COGNITIVE AND BRAIN AGING: INTERVENTIONS TO PROMOTE WELL-BEING IN OLD AGE. ROADMAP FOR INTERVENTIONS PREVENTING COGNITIVE AGING

EDITED BY: Pamela M. Greenwood, Carryl L. Baldwin, Thomas Espeseth, James Campbell Thompson, Xiong Jiang and Philip P. Foster

PUBLISHED IN: Frontiers in Aging Neuroscience

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ISSN 1664-8714
ISBN 978-2-88963-489-7
DOI 10.3389/978-2-88963-489-7

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COGNITIVE AND BRAIN AGING: INTERVENTIONS TO PROMOTE WELL-BEING IN OLD AGE. ROADMAP FOR INTERVENTIONS PREVENTING COGNITIVE AGING

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Citation: Greenwood, P. M., Baldwin, C. L., Espeseth, T., Thompson, J. C., Jiang, X., Foster, P. P., eds. (2020). Cognitive and Brain Aging: Interventions to Promote Well-Being in Old Age. Roadmap for Interventions Preventing Cognitive Aging. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-88963-489-7

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frontiers in Aging Neuroscience

EDITORIAL
published: 15 October 2019
doi: 10.3389/fnagi.2019.00268

Editorial: Cognitive and Brain Aging: Interventions to Promote Well-Being in Old Age

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Keywords: mindfulness, meditation, tDCS, neurofeedback, smartphone apps software, exergaming

Editorial on the Research Topic

Cognitive and Brain Aging: Interventions to Promote Well-Being in Old Age

ROADMAP FOR INTERVENTIONS PREVENTING COGNITIVE AGING

The Research Topic in Brief

Collectively, the studies of this book and the associated data sets provide an unprecedented resource for understanding the aging of the brain, the brain networks plasticity, and structure. A particular focus of this book is about the hippocampal and neocortical circuits with the emphasis on protective and enhancement factors of cognition. Major protective interventions evaluated are memory training programs, executive semantic processing of words, foreign-language learning, behavioral cognitive training, attention, mindfulness and transcendental meditation, transcranial direct current stimulation, neurofeedback, physical activity-aerobic exercise, dancing, and diet. There is also an analysis of the relation obesity-cognition and interventions of interest. The state-of-the-art training devices and software currently in clinical trials waiting for FDA approval are outlined. The relativity of the internal perception of time accelerating in aging brains is examined.

Cognition Defined

- ✓ ***Cognition*** is the study of mental processes of acquiring knowledge and understanding, enabling critical thinking, problem solving, language, creativity, social intelligence, and mastering fundamental concepts like the mere idea of number, time, quantity, causality, and justice (Piaget and Inhelder, 1947; Chomsky, 1964; Hauser et al., 2002; Piaget, 2009; Mattson, 2019).
- ✓ ***Psychological testing*** (psychometrics) evaluates human abilities, attitudes, traits, and learning evolution based on standards of objectivity, reliability, and validity (Piaget and Inhelder, 1947; Piaget, 2009). In this book, the authors are frequently studying and testing various aspects of memory processing and storage, such as episodic, working memory, and spatial memory. Logical thinking is also assessed via elaborated tasks: the term "fluid intelligence" is also referred to by the authors for logical problem solving (Greenwood and Parasuraman, 2016).
- ✓ ***Neuropsychological tests*** are specifically designed to determine the particular brain structure or pathway activated, e.g., cerebral imaging.

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Received: *15 July 2019*
Accepted: *17 September 2019*
Published: *15 October 2019*

Citation:
Foster PP, Baldwin CL, Thompson JC, Espeseth T, Jiang X and Greenwood PM (2019) Editorial: Cognitive and Brain Aging: Interventions to Promote Well-Being in Old Age. Front. Aging Neurosci. 11:268. doi: 10.3389/fnagi.2019.00268

Brain Mapping and Network Neuroscience

- ✓ ***Functional connectivity***. Cerebral imaging techniques such as MRI can measure intrinsic hemodynamic signals linked to neural activity (functional MRI or fMRI). The structure of the matrix can reveal what information is encoded in a region by comparing it to other similarity matrices, such as from human judgments or computational models. As you will see, some authors are reporting real-time results, in neurofeedback studies, used by the participant to change their strategy or behavior.
- ✓ ***High-resolution anatomical mapping***. What makes diffusion MR imaging (dMRI) so unique is that during their diffusion-driven motions, water molecules are focusing on tissue structures at a micrometer scale far beyond the standard millimetric MR imaging resolution (LeBihan, 2013). The non-invasive observation of the water diffusion–driven motion distributions thus provides unique hints to the delicate structural features and geometric organization of tissues and the changes with physiologic or pathologic states (**Figure 1**, MD: mean diffusivity). The dMRI data also provides a direct view of the displacements of water molecules further reflecting the brain tissue microarchitecture (Le Bihan, 2003; **Figure 2**). In their study, Burzynska et al., used the fractional anisotropy (FA), a prevalent measure of the directional dependence of diffusion, reflecting fiber orientation, density to characterize white fibers tracts. Diffusion tensor imaging, DTI, is a 3D modeling magnetic resonance technique enabling white matter, WM, tractography and producing neural projections images, mapping axonal trajectories **(Figure 2)**.
- ✓ ***Macro-networks***. Cerebral imaging provides a macroscopic cartography of evolving brain networks, related to the status creation-removal of synaptic connections in a macro-network (Foster, 2015). This is the first level of fractal scaling reflecting the number of projections to or from an area of the brain: regions of gray matter with high density of nodes and projections.
- ✓ ***Micro-networks***. Other fractal dimensions, at the sub-level of intra-cellular scale, via *micro-networks* or *interactome-networks* regulate the physiological mechanisms of the selection process in determining the preferential attachment of synapses and will affect by feedback the cartography of brain macro-networks (Foster, 2015).

What Is Aging?

- ✓ ***Hallmarks of cellular aging***. The time-dependent accumulation of cellular damage leading to a functional decline is considered to be the underlying starting point of aging. Hallmarks of the aging process such as genomic instability, telomere attrition, dysregulated energy metabolism, mitochondrial dysfunction, stem cell exhaustion shape the aging phenotype (Lopez-Otin et al., 2013; Mattson and Arumugam, 2018). Cellular senescence may be described as a durable arrest of the cell cycle coupled to stereotyped phenotypic changes and loss of functionality. In the brain, glial cell activation and inflammation are spreading (Mattson and Arumugam, 2018).
- ✓ ***Aging brain networks***. In another fractal dimension, on another scale, molecular networks of the human frontal cortex or the dorsal lateral prefrontal cortex, DLPFC, **Figure 3** are directly associated with cognitive decline and other large-scale transcriptomic changes in the aging brain (Mostafavi et al., 2018). Decreased Intra-network functional connectivity of the salience, visual and sensorimotor networks decreased with aging (Lyoo and Yoon, 2017).

Cognitive Decline Mitigated? Interventions

Types of Interventions [Stimulation/Action ↔ Effects on Brain]. This series of articles investigates the cognition performance in aging by neuropsychological tests related to cerebral imaging providing a status of the functional connectivity, brain networks and mapping. A first type of intervention is proposed, by stimulating the brain, *s*Brain (e.g., mental training, meditation and virtual reality/games), with direct effect on it, *e*Brain, noted as [***s*Brain → *e*Brain**]. The effect may be observed on the same function/task or same networks. Other [***s*Brain → *e*Brain**] experiments seek to have a more general effect impacting functions different from the stimulation/training task and networks known to be involved in the processing. A

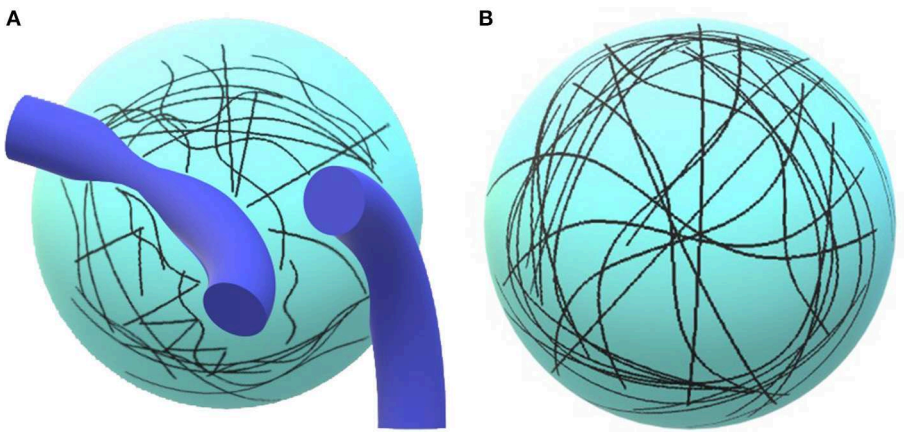

FIGURE 1 | Illustration of the concept. On **(A)**, the diffusion of water molecules is limited by tissues, e.g., vessels, axons, or dendrites. The trajectories are short. **(B)** Paucity of tissues, water molecules may freely diffuse and follow long trajectories.

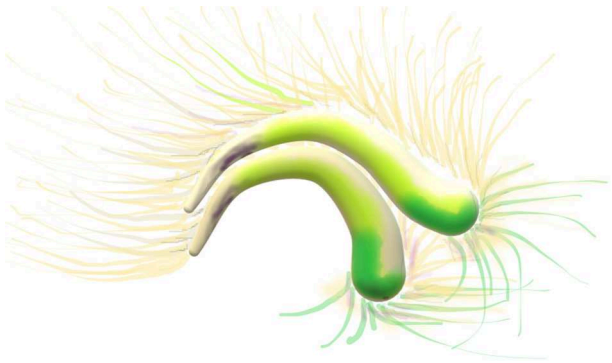

FIGURE 2 | Diffusion tensor imaging, DTI image. Cingulum: two arches, the two C's yellow, green and beige. Thin axonal projections from the bilateral arches are visible.

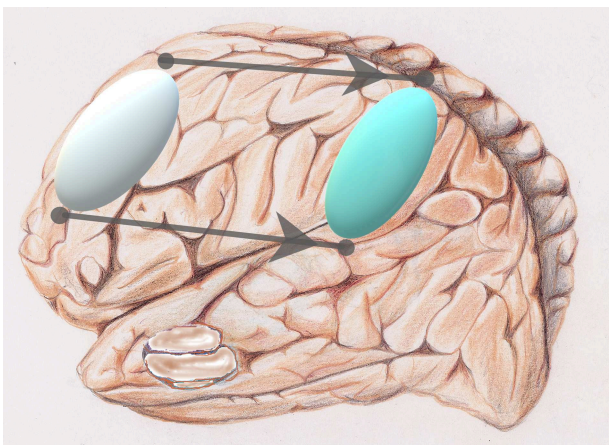

FIGURE 3 | Reorganization: via a sort of "network translation" from frontal (silver) to parietal (light blue) of a privileged activation during aging.

second type of intervention, physical exercise, seems to be playing an instrumental role in the cognitive enhancement. It is still unclear how all underlying mechanisms of the activation of the cardiorespiratory and skeletal muscle systems, *a*CRM, have an effect on the brain, *e*Brain, designated as [***a*CRM → *e*Brain**]. However, mental training, meditation or virtual reality (films, games) require only minimal motor activity and cardio-respiratory stimulation. Therefore, other potential paths [***s*Brain → *e*Brain**] molding brain networks are nonetheless essential. Practical details on how to implement the various types of training programs evaluated by the authors such as mental, [***s*Brain → *e*Brain**] (memory, attention, mindfulness, neurofeedback, etc.) and cardiorespiratory-physical exercise, [***a*CRM → *e*Brain**] (aerobic, dancing, etc.) may be found elsewhere in books, websites, institutions, or training centers.

MEMORY TRAINING PROGRAMS

Requena et al. found in a randomized controlled trial that time-extended programs [6-year training] in healthy older people significantly improve everyday memory in contrast with the usual intensive programs whose effects decline with time. The time-extended program involves a group memory therapy based on the Wilson's model with cognitive and emotional content. A first series of modules encompasses strategies to activate the working memory, retrospective, and prospective. A second series of modules, discussion groups emphasize the mood in a social environment. Personal perspective confronted with that of others strengthens the training process.

Working memory (wm) is the process to temporarily store, maintain, and organize task-relevant information. The wm is an essential element in the preservation of age-related language understanding (Payne and Stine-Morrow). In their study (Payne and Stine-Morrow), examined the effects of a novel home-based computerized cognitive training program targeting verbal working memory in healthy older adults. Participants in the wm training group showed non-linear improvements in performance on trained verbal working memory tasks.

REORGANIZATION: FRONTAL TO PARIETAL

Changes in synaptic connections are considered essential for learning and memory formation. However, it is unclear how neural circuits undergo continuous synaptic changes during learning while maintaining lifelong memories (Yang et al., 2009). Learning and novel sensory experience cause spine formation and pruning by a protracted process. Intensity of spine remodeling correlates with behavioral improvement after learning, underlying the essential role of synaptic structural plasticity in memory formation. The training-induced subset fraction of new spines along with long-lasting spines from the early development, surviving experience-dependent pruning, remains the structural basis for memory retention throughout the entire life. This is suggesting that lifelong memories are stored in stable connected synaptic networks (Yang et al., 2009).

Methqal et al. confirmed this observation, exploring the age-related, neuro-functional basis for executive semantic processing of words. Healthy aging is associated with neuro-functional reorganization that maintains cognitive performance. They employed a new word-matching task adapted for use in fMRI protocols. Such a task requires the flexible use of semantic relationship (or rules) supported by two executive processes with one invoking a higher-level of executive control. Results demonstrated that the shift in age-related brain activation from frontal to parietal regions (**Figure 3**) is a form of neuro-functional reorganization underlying executive processes during a word-matching task. Observing the maintain rule, which requires maintaining a given semantic rule through working memory updates, older adults demonstrated bilateral frontal activation, compared to more lateralized activations in younger adults. The posterior and dorsolateral prefrontal cortices were further recruited when older participants maintained and updated rule classifications in working memory. Disruption of one region results in shifting the recruitment in other parts of the network. Hence, a healthy aging brain recruits more than

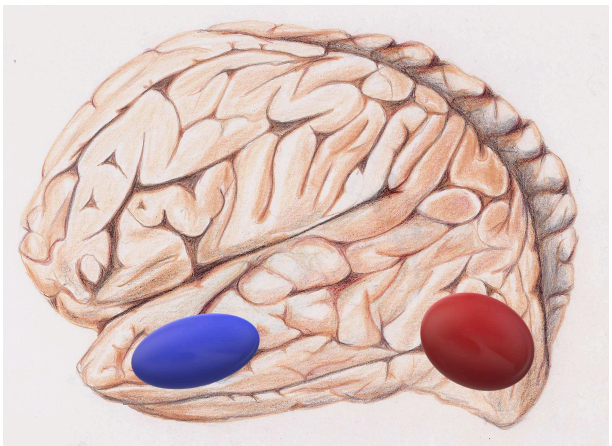

FIGURE 4 | The visual word form area, VWFA, is in red and the hippocampus in blue.

one pathway to preserve cognitive performance by recruiting the inferior parietal region when executive frontal resources are in high demand.

Jiang et al., developed a novel fMRI data analysis technique, local regional heterogeneity analysis, or H_{corr}, to estimate neuronal selectivity based on fMRI activation patterns (Jiang et al., 2013). In their new study, Jiang et al., investigated whether this cutting-edge H_{corr} technique can effectively assess neuronal selectivity across brain regions in elders. The H_{corr}-estimated neuronal selectivity may discriminate individual differences in behavioral performance on two cognitive functions, episodic memory, and letter verbal fluency (Jiang et al.). The authors assessed the neuronal selectivity for two brain regions (Jiang et al.), the hippocampus, which is associated with episodic memory and the visual word form area, VWFA, an area in the left ventral occipitotemporal cortex that is important for lexical aspects of language skills (Thielen et al.).

They identified a double dissociation: episodic memory performance correlates with neuronal selectivity in the hippocampus, but not VWFA (**Figure 4**), whereas verbal fluency shows the reverse pattern. This suggests a direct relationship between cognitive function and neuronal selectivity at the corresponding brain regions in healthy older adults. The authors conclude that age-related brain networks differences might not compensate for cognitive decline in healthy older adults (Jiang et al.). Rather, they may contribute to this decline.

NEAR TRANSFER

How "brain training" can improve cognition across several mental processes, as a general extension of its effects, measured as an improved performance on tasks differing from the trained tasks (transfer of training), is a debatable and hot topic (Souders et al.). Cognitive training, in the form of computer game training activities demonstrated some degree of success in the past and might result in broad transfer (Souders et al.). In their study, Souders et al., found that participants were learning specific skills and strategies from game training that later influenced steadily their performance on a similar task only. There was little evidence of transfer, even the near-transfer effect was weak (Souders et al.).

Shifting training in the elderly shows strong and long-lasting effects on the trained tasks albeit very little benefit in terms of generalization of ability to new tasks and activation of new brain networks (Gronholm-Nyman et al.). They made use of functions such as: (1) working memory updating, (2) inhibition of task-irrelevant responses, and (3) shifting between tasks and mental sets. In the computer setting that they used they found limited evidence for near transfer, and no far transfer based on an extensive test battery evaluating other executive domains such as fluid intelligence, episodic memory, verbal fluency, or visuomotor speed.

TRANSCRANIAL DIRECT CEREBRAL STIMULATION, TDCS

Passow et al., assessed the effect of behavioral cognitive training and state-of-the-art of non-invasive brain stimulation techniques such as transcranial direct current stimulation, *tDCS*, in the condition of cognitive aging. They focused on working memory and episodic memory functions. The *tDCS*-induced subthreshold changes in neuronal resting membrane potentials alter the cortical excitability and activity, dependent on the direction of the current flow (Passow et al.). Studies of stimulating the human motor cortex have shown that anodal *tDCS* facilitates, while cathodal *tDCS* reduces excitability. The repetitive transcranial magnetic stimulations over prefrontal brain regions cause modulatory effect on dopaminergic neurotransmission. Clearly, a "central executive brain network" is responsible for supervising the integration of information and for coordinating "slave systems" that are responsible for the short-term maintenance of information. The central executive is responsible inter alia for directing attention to relevant information, suppressing irrelevant information and inappropriate actions, and coordinating cognitive processes when more than one task is simultaneously performed.

ATTENTION, AS AN ESSENTIAL MECHANISM

Several studies published in this book investigate the role of attention in learning and preserving cognitive abilities. Attention is the process of selectively concentrating on a specific aspect of information, while disregarding the noise from other perceivable information. Specifically, Ayasse et al., found that eye fixations on a referenced object in a spoken sentence occurred as rapidly in elders than younger adults. However, in elders, the executive processing resources were slower in indicating the referenced object with a precise response (Ayasse et al.). Furthermore, the hearing process did not seem to play a limitation as would be expected in hearing-impaired elders.

Visual Spatial and Temporal Attentions

In contrast, visual search performance is thought to decline with age when the target is visually indistinct from distractors and a serial search is required (Callaghan et al.).

It is well-established that older adults require longer to process visual stimuli—i.e., have slower processing speeds and display an increased magnitude of the so-called "attentional blink" (Bateman et al., 2009; Callaghan et al.). Visual spatial attention aims the scrutiny to a particular location in space, whereas visual temporal attention focuses the attention to specific instants of time. The authors found larger switch-costs between temporal and spatial attention in older adults compared to younger (Callaghan et al.).

ATTENTION, AGING, AND BRAIN NETWORK REORGANIZATION

The degree of connectivity between the frontoparietal control network, FPN, and the default mode network, DMN, decreased with age from younger to older adults (**Figure 5**). The connectivity between FPN and dorsal attention network, DAN, remains stable across age groups (Avelar-Pereira et al.). This suggests that dynamic interactions of the FPN are stable across cognitive states. The DMN and DAN were anti-correlated with a task-dependent age-sensitivity. This anticorrelation increased from rest to task. Interestingly, the degree of DMN-DAN anticorrelation was associated to resting cerebral blood flow within the DMN. This implies that reduced DMN neural activity during rest underlies an impaired ability to achieve high levels of anticorrelation during a task (Avelar-Pereira et al.). Furthermore, there is a switching role for the FPN by dynamically interacting with DMN and DAN depending on task demands. Nodes changed their network affiliation and showed realignment from rest to task, implying a more flexible connectivity profile (Avelar-Pereira et al.). The authors found that older adults had lower FPN-DMN functional connectivity during both rest and the MSIT, but yet expressed greater FPN-DMN connectivity at rest compared to task (Avelar-Pereira et al.). The FPN serves as a switch to actively engage other networks and facilitate cognition in older adults. Normal aging is accompanied by a lower degree of flexible network interactivity (Avelar-Pereira et al.).

The overarching question is whether and how neurovascular coupling is produced during learning (Mitra and Raichle, 2016), i.e., correlating the brain network activation to the cerebral blood flow, CBF. Evidence for propagating low frequency activity underlies the neurovascular coupling and implies that the BOLD signal propagation is likely of neural origin (Mitra and Raichle, 2016). Vigilance creates an asymmetry with increase of left hemisphere activation in young adults. Aged-induced remodeling of brain networks underlying vigilance, the "hemispheric asymmetry reduction in older adults," or HAROLD model is supported by functional neuroimaging (Cabeza, 2002; Cabeza et al., 2002). In their study, Harwood et al., investigated whether the HAROLD brain networks age-induced reorganization, i.e., asymmetric reduction, or increase of bilateralization, result from a compensatory effect to attain a similar level of vigilance and cognitive performance compared to young adults (Harwood et al.). Making use of functional transcranial Doppler, fTCD, Harwood et al. found that CBF velocity, CBFV, declined during aging, and only young adults showed the typical right-lateralized CBFV pattern. Older adults showed greater left hemisphere activation consistent with the HAROLD model. However, the increased left hemisphere activation did not appear to be compensatory as the older adults performed at a significantly lower vigilance level compared to young adults.

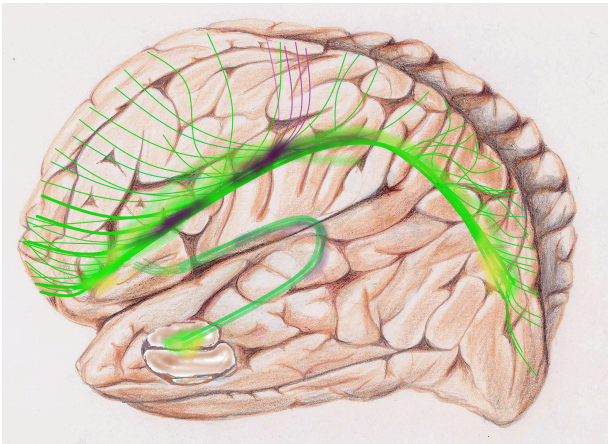

FIGURE 5 | Global tractography, sketch of diffusion tensor images, DTI, of the default mode network, DMN: is a set of areas active at rest. The upper C-shaped arch (green-yellow-purple) with widespread projection bundles (green-purple) is the cingulate cortex. The cingulum bundle radiates far-reaching antero-posterior connectivity from medial prefrontal lobe to the precuneus and other areas of the brain, e.g., frontal, parietal. The fornix, a lower and smaller C-Shaped arch is a major output projection tract of the hippocampus.

NEUROFEEDBACK

Neurofeedback (NFB) monitors real-time displays of brain activity, e.g., electroencephalography (EEG), to enhance brain function and behavioral performance on a positive self-regulating feedback mode. Characteristic brainwave measurement is training technique to enhance performance in athletes and musicians, creativity, attention and working memory (Daly and Wolpaw, 2008; Jiang et al.; Reis et al.). Typically, EEG theta oscillations are related to hippocampal activity during working memory (Tesche and Karhu, 2000). Spatial attention is a constant theta-rhythmic sampling process implemented through gamma-band synchrony (Landau et al., 2015). Two striking studies in this book might disrupt the classic thoughts about near-transfer spreading and generalization of training to other brain networks and tasks (Jiang et al.; Reis et al.).

Reis et al., found cognitive performance improvements after 8 consecutive days of training in specific tasks. NFB training led to the ability to uniquely up-modulate both alpha and theta frequency bands and seemed to produce positive effects

in cognitive performance. The analysis of the EEG acquired before and after NFB training, during the computerized battery, revealed that only the participants under NFB training were able to increase alpha and theta rhythms from pre- to post-training. Remarkably, Reis et al., identified a positive correlation between a successful (theta) NFB training and a better performance in specific tasks, as well as an increased alpha activity between pre- and post-training. Considering the overall functional system brain networks, it entails that EEG-NFB training might be *generalized and not restricted to the region of training or limited to a near-transfer* (Reis et al.).

In their article "Tuning Up the Old Brain with New Tricks," Jiang et al., are assessing how NFB training of older brains may be aiming to match those of younger brains during attention/working memory tasks. Jiang et al., conclude that NFB associated with new neurological measurements, e.g., "neuromarkers" such as event-related potentials and connectivity, is providing new hope for brain and cognitive training in the growing older population. This is a promising roadmap for future work.

MINDFULNESS AND TRANSCENDENTAL MEDITATION

Mindfulness is the psychological process of capturing a person's attention to the present moment. Practice of meditation trains to focusing on the present instant clearing the mind form past experiences and future possibilities (**Figure 6**). Mindfulness is derived from "*sati*," a *Sanskrit* word, meaning "awareness," based on "*Zen*" in the Buddhist tradition. Spiritual leaders such as the Dalai Lama and Thích Nhãt Hạnh gave rise to the popularity of mindfulness in the modern western culture. Mindfulness, as a modus operandi to mitigate cognitive impairment is described in two articles of this book.

Mindfulness training positively influences three essential domains of aging: (1) behavioral and neural correlating with attentional performance; (2) psychological well-being; and (3) systemic inflammation (Fountain-Zaragoza and Prakash). The scientific focus on mindfulness training is still recent, with limited randomized controlled trials utilizing active comparison conditions. Based on preliminary results, transcendental meditation seems to be more efficient than mindfulness, but both were worthier than relaxation or absence of treatment. Mindfulness and transcendental meditation associated with cognitive training, similarly improved word fluency. This preliminary evidence for cognitive benefits following transcendental meditation, has direct parallels with the current mindfulness training approaches (Fountain-Zaragoza and Prakash). Preliminary cross-sectional evidence suggests that mindfulness is associated with enhanced psychological well-being, measured as self-reported depressive symptoms, quality of life, and stress, in the elderly (Fiocco and Mallya, 2015) and emotion regulation mediates the relationship between mindfulness and reduced perceived stress across age (Prakash et al., 2015). Emotional distress and/or psychopathology can be accompanied by changes in inflammatory processes, which are further entailing several health issues. Participating in a mindfulness-based stress reduction program led to significant down-regulation of the pro-inflammatory gene *NF-κB* in leukocytes and the NF-κB (Creswell et al., 2012; Fountain-Zaragoza and Prakash).

Active experiencing (AE) is a form of mindfulness training improving attentional control to mitigate cognitive decline with via an immersive acting program. Unlike mindfulness meditation, participants in AE have a specific task to engage and follow instructions during every rehearsal. Episodic memory is particularly vulnerable to decline in aging (Banducci et al.). In their study, Banducci et al. identified specific gains in episodic recall from AE compared to active individuals ("control" group), albeit they found no other evidence of AE-intervention gains in cognition. AE produced greater gains persistent up to 4 months after AE-intervention. Intervention conditions were similar in magnitude across gains in working memory, executive function and processing speed (Banducci et al.).

FOREIGN-LANGUAGE

Because most cognition processing, or at least some of them, appear to eventually be accessible to sharing with others, via word-description (Hauser et al., 2002), the paramount question is where is the neuroanatomical location recruited by the language? It entails the hypothesis that the activation in a new language of areas of the brain in a broader sense may enhance the brain training [$_{s}$**Brain** → $_{e}$**Brain**], leading to better results of cognition preservation in older adults. Foreign-language acquisition has been shown to demonstrate structural neuroplasticity in children, adults, and elderly, even after short-term language training (Hosoda et al., 2013; Pliatsikas et al., 2015, 2017). In a community-dwelling, *not immersion* in a foreign country, learning a foreign language later in life could thus strengthen cognitive functioning in older adults as Ware et al., investigated in their study. The cognitive and loneliness perception scores did significantly improve in their study albeit language learning became a benefit as a social activity. Participants noted that differences in foreign language fluency encouraged seeking for help and fostered social interaction (Ware et al.). These results are not surprising. According to Noam Chomsky past the very earliest developmental stages, much of further acquisitions will be gained by imitation (Chomsky, 1964). Therefore, it takes more than practice for a second language to share native-like features such as easiness, fluency.

PHYSICAL ACTIVITY AND COMMUNICATION BRAIN-BODY: UNPICKING THE RIDDLE OF CAUSE AND EFFECT

Two postulates about [***a*CRM → *e*Brain**] and [***s*Brain → *e*Brain**] may be formulated. *A first postulate*: strikingly, the activations of the cardiorespiratory and skeletal muscle systems, *a*CRM, seem to produce *a generalized effect on the brain,* *e*Brain, [***a*CRM → *e*Brain**], *across broad aspects of cognitive performance* (Colcombe

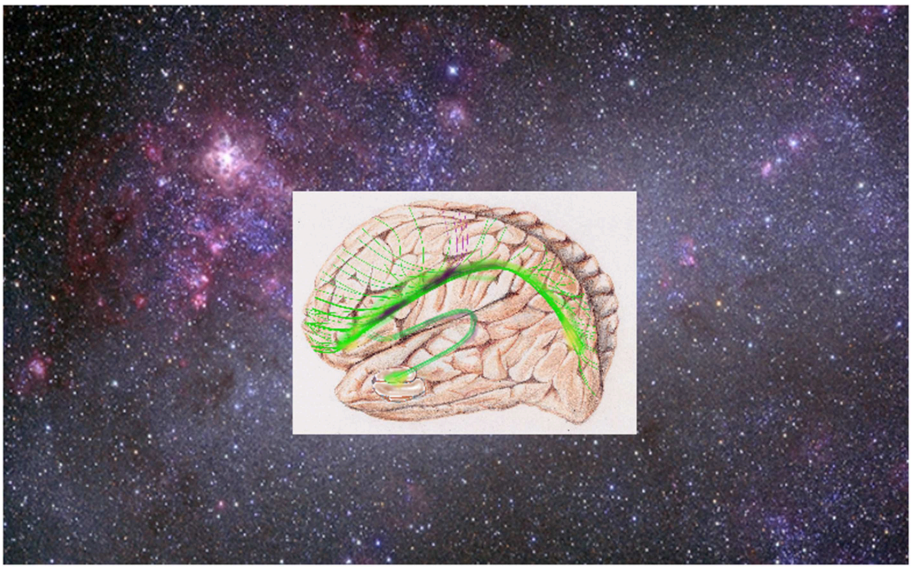

FIGURE 6 | Transcendental meditation: "it is sometimes qualified as a cosmic state of mind, harmonious with the rhythm of nature and cosmic life. The transcendental meditation brings the individual into a wider cosmic dimension and consciousness" (Yogi, 1973). Photo: Credit NASA, Goddard Space Flight Center and Penn State University.

et al., 2004, 2006; Foster et al., 2011; Foster, 2015; Jonasson et al.). Would an exercise-induced overall downregulation of brain amyloid β (Aβ) levels by increased clearance via the choroid plexus (Carro et al., 2002; Adlard et al., 2005) be producing this general effect? A deficient clearance of $A\beta_{1-42}$and $A\beta_{1-40}$ in the brain via the choroid plexus also contributes to Alzheimer's disease-related amyloidosis deposition (Carro et al., 2002, 2006; Mawuenyega et al., 2010; Foster et al., 2011). *A second postulate*: In contrast, task-induced direct stimulation of the brain, *s*Brain (e.g., mental training, meditation, and virtual reality/games), [***s*Brain → *e*Brain**], seems to produce localized effects to the brain, *e*Brain, *restricted to the networks associated to the task-training* (Anguera et al., 2013; Foster, 2015; Gronholm-Nyman et al.; Souders et al.). Indeed, the [***s*Brain → *e*Brain**] modality appears to produce localized effects with little or absence of near-transfer, and no broad-transfer, i.e., absence of gain on tasks differing from training and on non-activated brain networks. Further studies to the ***[sBrain → eBrain]-postulate*** are necessary to investigate how to cross these boundaries.

Supporting the first postulate a study demonstrated that aerobic exercise has the potential to broadly improve cognition and reduce brain atrophy in older adults (Jonasson et al.). They concluded that aerobic exercise in sedentary older adults has the potential to comprehensively improve cognition, rather than circumscribed to a specific skill/brain network, as captured by a "cognitive score" across cognitive capabilities based on episodic memory, processing speed, working memory updating, and executive function tasks. A one-time intervention, limited span of 6-month aerobic training, seemed insufficient to produce a notable direct effect on the prefrontal cortical thickness (Jonasson et al.). Rather, aerobic fitness at baseline was specifically related to larger thickness in dorsolateral prefrontal cortex (DLPFC), and hippocampus volume. The increased thickness appeared to be positively associated with increased aerobic fitness over a long time span (>12 months). It may be hypothesized that exercise-induced increased cortical thickness or reduced cortical thinning phenomenon localized to DLPFC (Jonasson et al.) and its potential further extension to other regions of the cortex is a slow process, undetectable within 6-months, requiring an extended period of time.

However, aerobic performance (VO_{2max}) may not be the limiting factor; other factors closely related to aerobic performance might be involved, e.g., cardiorespiratory health status, [***a*CRM → *e*Brain**], or else [***s*Brain → *e*Brain**]. The level of physical exercise inherent to dancing may be insufficient to produce an increase in aerobic fitness (VO_{2max}) albeit the exercise-induced elevation of heart rate, cardiac output. The perfusion may have been sufficient to produce changes in protein expression (brain-derived neurotrophic factor, BDNF; cytokines; insulin-like-growth factors, IGF-1 and IGF-2) improving cognitive plasticity (Chen et al., 2011; Foster et al., 2011; Foster, 2013). Dancing involves the moving, spinning, swaying, swinging, twisting, rocking, in a three-dimensional space which underlies brain activation of the path-integration maintaining permanent visual tracking of the direction and distance from reference points (landmark) during 3-D navigation in the environment and thus requires the activation of hippocampal and entorhinal networks (Foster, 2013). In dancing, information from the body position, movement (e.g., limbs, head, and trunk), and accelerations are integrated in the CNS along with instructions from the vestibular system and cerebellum, all of which contributing to create a spatial representation in real-time. In this case, the activation cascade becomes [***a*CRM → *s*Brain → *e*Brain**], *a*CRM being only a modus vivendi, instrumental at

automatically operating the indirect *s*Brain activation causing the expected cognitive effects, *e*Brain (Foster, 2013, 2015). Therefore, the absolute (VO_{2max}) value may bear a variable-spectrum of influence, from high to absence in preserving or promoting cognitive performance. Clearly, depending on several cofactors, the activations of the cardiorespiratory, skeletal muscle systems, and movements trigger other cognitive performance promoters.

In the study by Burzynska et al., (VO_{2max}) played little or no influence. They focused on the white matter (WM) microstructure integrity, since the degeneration or loss of axons and myelin is considered as a central mechanism underlying age-related cognitive decline (Gunning-Dixon and Raz, 2000). Extensive and concurrent decreases in FA, and modification of other dMRI factors are associated to WM degeneration, loss of myelin or axonal integrity. Burzynska et al., observed a decline in WM integrity across the majority of brain regions unless 6-month dance-intervention was performed. A one-time intervention, limited span of 6-month dancing seemed insufficient to produce an effect on post-intervention processing speed. Walking alone, walking associated with nutrition, or being an active elder produced no effect and were insufficient to prevent the decline of WM, including in the fornix. Therefore, preventing age-induced "WM structural disconnection" or improving WM integrity is key in preserving cognitive performance necessary for independent functioning in the elderly (Burzynska et al.).

OBESITY: HOW MUCH CAN WE LEARN ABOUT THE BRAIN?

We may deduce remarkable insights on the body–brain connections by analyzing the physiopathology of obesity. The thorough examination by Stillman et al., in their review "effects of obesity and behavioral interventions on neurocognitive aging" (Stillman et al.) provides clues to the [***a*CRM → *e*Brain**], [***s*Brain → *e*Brain**], [***a*CRM → *s*Brain → *e*Brain**], and **diet** postulates.

Gray Matter Reduction

Several studies demonstrated that physical activity [***a*CRM → *e*Brain**], is associated with increased gray matter (GM) volume in the hippocampus and prefrontal cortex (Colcombe et al., 2004; Erickson et al., 2011). The obesity-induced reduction of GM volume is found in several brain regions, including the hippocampus, prefrontal cortex, and other subcortical regions (Stillman et al.). They identified a characteristic role of excess body fat in the atrophy of GM, independently of other variables such as other comorbid conditions, e.g., diabetes.

White Matter in Obesity: Quantity vs. Quality?

Indeed, the structural integrity of the WM tracts in the connectome is reduced in obesity, recent DTI work has shown an obesity-induced decrease in FA. This pattern is associated with demyelination in models of inflammatory disorders, underlying a systemic increase in circulating inflammatory cytokines reported in obesity. Presence of white matter hyperintensities (WMH) might be indication of demyelination processes (Stillman et al.).

In summary, obesity is associated with an altered integrity of GM and WM in a process similar to that observed in normal aging and obesity is likely to accelerate brain aging (Stillman et al.).

Functional Brain Activation

Stillman et al., analyze how obese adults consistently exhibit hyperactivation to food compared to non-food elements in the limbic-orbitofrontal areas (fMRI) associated with decision making, satiety, motivation, and reward compared to healthy-weight controls. This hyperactivation interferes and potentially disrupts brain networks involved in executive functioning and memory. Physical activity may not be a necessary component to interventions designed to reverse obesity-related neurocognitive dysfunction. Cognitive performance seems related to cardiovascular fitness rather than to weight and adiposity. Clearly, weight loss may not be a requirement to mitigate the negative neurocognitive consequences of obesity.

Physical activity [***a*CRM → *e*Brain**], has consistent effects on the hippocampus and prefrontal cortex, as well as the white matter tracts connecting these regions (Stillman et al.). Physiologically, physical activity operates in the reverse direction to obesity.

Dietary interventions do not increase cardiovascular fitness, yet improve cognitive performance (Stillman et al.). Dietary restriction such as intermittent fasting into the lifestyle improves cognitive capabilities and neuronal resilience (Mattson, 2019).

The "obesity paradox," valid for the elderly group [>73 yrs.], referred to as the "oldest old," the classic scheme does not strictly apply. Higher BMI appears to bear protective effects on the cognitive performance in "oldest old" (Hainer and Aldhoon-Hainerova, 2013; Stillman et al.).

FDA CLEARANCE FOR MEDICAL SOFTWARE/DEVICE

Approximately 20 companies designing computerized cognitive training (CCT) will conduct clinical trials to prove their efficacy and obtain the green light from Food and Drug Administration (FDA) clearance as a medical software/device (Motter et al.). In their survey, Motter et al. are describing the state-of-the-art cognitive training, the clinical trials, and the future trends.

HOW AND WHY DOES OUR INTERNAL PERCEPTION OF TIME VARY WITH AGE?

Who has not heard elders say, "*time has just been flying by*," "*time seems to whiz by faster and faster as we get older?*" In a paper the authors (Turgeon et al.), highlight that a hallmark of normal aging is the increased noise and temporal uncertainty as a result of impairments in attention and memory. The authors present the potential reduction in accuracy of the central timing by underlying mechanisms of

dopamine-glutamate interactions in cortico-striatal circuits. In relation to these observations, the authors propose potential interventions that may reduce the prospect of age-related declines in timing consciousness.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

EDITORIAL
published: 14 January 2020
doi: 10.3389/fnagi.2019.00353

Editorial: Cognitive and Brain Aging: Interventions to Promote Well-Being in Old Age

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Keywords: cognitive aging, brain plasticity, cognitive training, physical exercise, multidomain interventions

Editorial on the Research Topic

Cognitive and Brain Aging: Interventions to Promote Well-Being in Old Age

This Research Topic is dedicated to the memory of Raja Parasuraman who passed away prematurely on March 22, 2015, ending a remarkable career spanning both diverse and intersecting research areas. Over the course of his career Raja used a variety of techniques ranging from behavioral studies, signal detection theory, electrophysiology, fMRI, and genetic analysis to contribute to different disciplines including human factors, cognitive neuroscience, and the intersection of the two in his founding of the field of neuroergonomics. He maintained an interest in cognitive aging throughout most of his career, studying the effects of not only disease states, such as Alzheimer's, but also interindividual differences in cognitive performance through cognitive genetics and cognitive training. This Research Topic celebrates the aspects of Raja's contributions that are related to cognitive aging and brain aging. Some of Raja's contributions in this area include work examining age-related changes in visuospatial processing and working memory, the role of the genetics of apolipoprotein E (APOE) in cognitive aging, in particular in Alzheimer's disease, and methods for supporting healthy cognitive aging. This work culminated in a book co-authored with Pam Greenwood entitled, "*Nurturing the Older Brain and Mind*" published by MIT Press (Greenwood and Parasuraman, 2012). Considered together, the contributions to this special issue build on Raja's work and, importantly, show a way for the field to move forward in the future.

Interventions are needed to ameliorate age-related cognitive decline which is a risk factor for the devastation of dementia, robbing older people of their well-being and shortening their lives. Interventions aimed at cognitive decline are the focus of this Research Topic dedicated to Raja Parasuraman. In recent years, cognitive aging research has pivoted from simply cataloging age-related cognitive decline to seeking interventions aimed at slowing or delaying that decline and improving quality of life in old age. Efforts to develop interventions to ameliorate cognitive aging rely on assumptions that interventions can heighten brain integrity and/or induce compensation for age-related decline in brain integrity. These assumptions are supported by evidence that aerobic exercise increases (a) adult-onset birth and integration of new neurons (neurogenesis) (Anacker and Hen, 2017; Kempermann, 2019) and (b) hippocampal blood flow in a manner related to improved recall (Pereira et al., 2007; Maass et al., 2015). These assumptions are also supported by evidence of cortical reorganization in older people following cognitive training (Maguire et al., 2000; Taub et al., 2002; Greenwood, 2007). This evidence of cortical reorganization related to training raises questions about the ability of the brain respond adaptively to age-related declines.

OPEN ACCESS

Edited and reviewed by:
Thomas Wisniewski,
New York University, United States

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Received: *31 October 2019*
Accepted: *04 December 2019*
Published: *14 January 2020*

Citation:
Baldwin CL and Greenwood PM (2020) Editorial: Cognitive and Brain Aging: Interventions to Promote Well-Being in Old Age. Front. Aging Neurosci. 11:353. doi: 10.3389/fnagi.2019.00353

CAN THE AGING BRAIN COMPENSATE FOR DECLINING INTEGRITY?

One of the important questions in cognitive training is whether the aging mind and brain exhibit active compensatory processes capable of countering cognitive decline. Two papers in this Research Topic address this question. Jiang X. et al. used a novel fMRI analysis method (local regional heterogeneity analysis) that showed individual differences in neuronal specificity were related to individual differences in task performance in a region-specific manner. They found that better neuronal specificity is associated with better task performance. Those findings are consistent with Baltes' notion that aging is not accompanied by compensation, but rather by neural "de-differentiation" accompanied by noise in information processing (Baltes, 1997). Also observing evidence refuting the existence of compensation, Harwood et al. in a cerebral blood flow study found that healthy older people showed greater left than right hemisphere activation during a vigilance task but still performed at a significantly lower level of vigilance compared to young adults. Alongside this evidence that older brains are not intrinsically able to compensate for declining brain integrity, is evidence that aerobic exercise interventions can improve brain integrity (Pereira et al., 2007; Maass et al., 2015).

AGE-RELATED COGNITIVE DECLINE IS RELATED TO CHANGES IN BRAIN NETWORKS

Although the aging brain does not appear to compensate, *per se*, it does appear capable of reorganizing functionally. We previously argued that during aging the brain undergoes change in cortical representation through changes in processing strategy (Greenwood, 2007). Consistent with that view, several contributors to this topic found that age-related decline in executive function is related to changes in intrinsic brain networks. Several of the interventions considered in this topic are aimed at modulating intrinsic brain networks (Passow et al.; Reis et al., discussed in the next section). Avelar-Pereira et al. found that in both young and older adults the frontal parietal control network (FPN), thought to play a role in cognitive control and flexible switching from internal thoughts to external stimuli, was more closely coupled with the default mode network (DMN) at rest and more closely coupled with the dorsal anterior network (DAN) during task performance. Although the FPN-DMN connectivity was reduced in older adults under both conditions, the connectivity patterns between the FPN-DAN during task performance were similar in young and older adults. Interestingly, Avelar-Pereira et al. also found that reduced cerebral blood flow (CBF) in the DMN predicted the amount of DMN-DAN anticorrelation during task performance. Further, the observed anticorrelation was associated with better behavioral performance. Thus, Avelar-Pereira et al. found that human cerebral blood flow affected the integrity of brain function, consistent with previous human and animal work on aerobic exercise and brain plasticity (Pereira et al., 2007; Maass et al., 2015).

Callaghan et al. presented confirming behavioral evidence of age-related deficits in cognitive control. They compared age groups across the adult lifespan and found that ability to switch between spatial and temporal attention undergoes a decline starting in midlife. Methqal et al. examined age-related changes in executive control in a semantic association and rule switching task using behavioral performance and fMRI. Results provide further support for greater age-related changes in high level executive control tasks (e.g., like those that involve task switching) relative to more continuous task performance. Results of Methqal et al. also indicate that the shift in age-related activation from frontal to parietal regions can be viewed as a form of neurofunctional reorganization.

INTERVENTIONS

Electrophysiological Interventions

That large-scale intrinsic brain networks undergo reorganization late in life suggests that electrophysiological interventions might have a normalizing effect. Two papers in this Research Topic do find benefits of such interventions on working memory: non-invasive brain stimulation (Passow et al.) and neurofeedback training to heighten certain EEG spectra (Reis et al.; Jiang Y. et al.) and to heighten attention and working memory (Jiang Y. et al.). Passow et al. argued that aging is accompanied by deficient neuronal gain control due to reductions in signal-to-noise within and between cortical networks. They reviewed evidence that non-invasive brain stimulation in the form of transcranial direct current stimulation (tDCS) alters patterns of brain electrophysiology in older people. They argued that anodal tDCS combined with cognitive training can improve cognition in older people by increasing functional connectivity in the fronto-striatal-parietal circuitry. Reis et al. took another approach to training brain electrophysiology. They found that an intensive alpha and theta neurofeedback protocol improved working memory (n-back) performance of older healthy people. Both of these studies are in the same vein as a recent high-profile demonstration that a form of non-invasive brain stimulation similar to tDCS can synchronize neuronal firing between prefrontal and temporal cortex with short-term benefits for working memory in older people (Reinhart and Nguyen, 2019). Overall, these non-invasive electrophysiological methods have considerable promise for improving working memory in healthy older people.

Cognitive Interventions

Cognitive interventions have long been used as a means to improve cognition in older people. One of the fundamental questions in the cognitive training literature concerns whether training transfers to untrained domains and abilities—termed "far transfer" (reviewed in Greenwood and Parasuraman, 2016). Far transfer of training is considered by many researchers to be the most important goal of cognitive training. In the sizeable working memory training literature, far transfer is usually assessed in fluid ability (Gf), most commonly in Raven's Progressive Matrices scores (e.g., Au et al., 2014). A number of reviews and meta-analyses of cognitive training have been

conducted, with results showing mainly small to medium effect sizes of far transfer (Simons et al., 2016), including in older people (Karbach and Verhaeghen, 2014; Melby-Lervag et al., 2016). The papers in this Research Topic are consistent with that literature. Payne and Stine-Morrow found that 3 weeks of home-based working memory training induced both near transfer and far transfer to various language functions. Souders et al. tested a large older sample using an active control condition and found that a "gamified" puzzle training intervention induced some near transfer but no far transfer. Similarly, Grönholm-Nyman et al. also found significant near transfer, but not far transfer from set shifting training in older people. Ware et al. did not find transfer from a language learning program. The finding of weaker or no evidence of far transfer is consistent with meta-analyses of working memory training in older people finding larger effect sizes for near transfer than far transfer (Karbach and Verhaeghen, 2014). Considered together with other evidence that cognitive training can have very durable effects (e.g., Willis et al., 2006; Anguera et al., 2013), this suggests that intervention research could also focus on durable near transfer. Although relatively neglected in the cognitive training literature, near transfer could help dementia patients learn and retain skills needed for daily tasks (de Werd et al., 2013).

Mindfulness Interventions

Several of the contributors to this topic recognized the need to promote well-being in older people in addition to improving their cognition. Mindfulness training with the goal of promoting sustained attention in the context of "non-reactivity and acceptance" (Kabat-Zinn, 1990) has long been advocated as a tool to promote mental health. Two studies in this special topic examined mindfulness in older people. Fountain-Zaragoza and Prakash reviewed the topics of mindfulness disposition (trait mindfulness) and mindfulness training (mindfulness experience), pointing out both findings and weaknesses in the existing literature. Weaknesses include the need for standardized training protocols, including the need to assess transfer of training more broadly to include everyday function. Banducci et al. showed that older people exhibited improved their episodic memory recall after 4 weeks of the novel intervention of "active experiencing," a tool used by actors that involves mindfulness. Although there have been previous studies using an active experiencing intervention, Banducci et al. used a rigorous intent-to-treat analyses and a non-imputation approach to missing data. Overall, these reviews show that mindfulness as an intervention has promise but is not yet supported by a body of rigorous investigation.

Physical Exercise Interventions

As discussed previously in this editorial, this topic adds to the growing evidence that cognitive function in aging must be considered in the context of physical fitness. In observational studies, self-reported aerobic exercise level has been related to cognitive performance, gray matter volumes (Schultz et al., 2015), and AD biomarkers (Okonkwo and Kinsella, 1969). In this Research Topic, Thielen et al. extended that previous work to changes in both functional connectivity and inflammation, processes known to undergo age-related alteration. Higher compared to lower self-reported aerobic exercise was associated with increased encoding-related functional connectivity in a brain network linked to episodic memory (mPFC, thalamus, hippocampus precuneus, and insula). Further, based on evidence of a role for inflammation in Alzheimer's disease (McGeer and McGeer, 2001), systemic inflammation was assessed. Increased connectivity was related to decreased in interleukin 6, suggesting lower inflammation in those with higher self-reported aerobic exercise levels.

Burzynska et al. reported that an older group randomly assigned to learn complex social dance sequences showed that integrity of the fornix (the major output tract of the hippocampus) increased over 6 months. In contrast, fornix integrity decreased in an older group randomly assigned to walking, to walking plus nutrition, or to active control. Jonasson et al. also examined brain structure changes over a 6 month exercise intervention and found that only the group randomly assigned to aerobic exercise showed improved cognition (on a composite measure of episodic memory, processing speed, updating, and executive function) as well as showing an association between cognitive score and dorsolateral PFC cortical thickness. A group assigned to stretching and toning did not show those effects. The results of two contributors (Burzynska et al.; Jonasson et al.) are consistent with the above-discussed evidence of the importance of aerobic exercise for hippocampal blood flow and adult neurogenesis for cognition in old age (Pereira et al., 2007; Maass et al., 2015). Finally, Stillman et al. reviewed the complex relation between physical activity and obesity. Obesity is a risk factor for dementia, making the recent increase in adult obesity in the US to nearly 40% very concerning. Yet the relation between obesity and physical activity is complex. Exercise interventions alone are largely ineffective at reducing obesity. Benefits on neurocognitive function after an exercise intervention depend on cardiovascular fitness rather than on adiposity. Nevertheless, combined dietary and exercise interventions are effective in counteracting the negative effects of obesity by increasing metabolic function, decreasing inflammation, and increasing neural plasticity. Specifically, dietary interventions do improve neurocognitive function despite having no effect on cardiovascular health. There is increasing recognition of the importance of diet in aging brain health, a topic we will return to at the end.

Design Issues in Intervention Research

Several design issues are important for development of effective interventions against cognitive aging. A problem that looms over all training interventions is the design of control conditions, an issue addressed by Motter et al.. Their review article discussed major factors to control for when developing an active control condition, namely expectancy, engagement, motivation, novelty, and therapist interaction. They then frame their discussion in terms of the desirable qualities of an active control condition, and how lack of attention to these factors has hindered interpretation of the results of training studies in many previous investigations.

Another design issue concerns the effort put forth by participants. It appears that for benefits from interventions to

be realized, additional effort is needed by the participant. Ayasse et al. found that despite poorer hearing acuity in the older group, sentence comprehension was as rapid in an older as in a younger group. However, the older group expended greater effort as measured in the pupillary response. These findings fit co-author Wingfield's previous work on the decremental effects of age-related hearing impairments on cognition. The finding of Ayasse et al. on a compensatory effect of increased effort suggest a direction for future work explicating the role of increased effort in other training domains.

Another design issue for cognitive interventions is the length of training. Most cognitive training studies have trained over weeks only, but the well-known Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study added periodic booster training found effects on cognitive function 5 years after reasoning training (Willis et al., 2006) and 10 years after reasoning and speed of processing training (Rebok et al., 2014). In this Research Topic, Requena et al. trained regularly for 6 years using techniques and strategies for improving working memory and mood in an everyday memory context. Although far transfer *per se* was not assessed, Requena et al. found effects on memory after 6 years, thereby partially confirming the findings of the ACTIVE study for reasoning and speed of processing training. However, the duration of the interval between training and testing used by Requena et al. was not clear. Also finding durable effects, Gronholm-Nyman et al. trained on set-shifting for only 5 weeks, but also found that benefits of training on memory were retained at the 1 year follow up test. Souders et al. also emphasized the need for additional long duration studies such as Requena et al. or at least assessment after a long delay. Requena et al. discuss potential benefits of using a booster training approach in light of the apparent success of that approach in the ACTIVE study. Considered together with the ACTIVE study, these studies in our Research Topic emphasize the benefits not only of cognitive training that is long-term, but also of longer-term assessment of effects of training regardless of training duration.

CONCLUSIONS

Considered together, the papers on cognitive aging in this Research Topic dedicated to Raja Parasuraman suggest the field of cognitive aging is undergoing a "sea change, into something rich and strange" (The Tempest, Act I, scene 2, Shakespeare, 1610). Parasuraman, a lover of Shakespeare and of bringing diverse perspectives and scientific communities together to forge new conceptual ground, would be pleased with the spirit and direction of this special issue.

Although cognitive aging research groups have typically each focused on only one type of intervention (cognition or diet or exercise), there may be synergism in combined interventions. A recent large scale study found that cognitive decline in aging can be slowed by a 2-year intervention of combined aerobic exercise, specific cognitive training and social stimulation, plus adoption of a Mediterranean diet. Participants were low-cognitive functioning but non-demented older people (Ngandu et al., 2015). Similar results from multidomain interventions have been reported in older people showing cognitive decline (Schelke et al., 2018) and in patients with "mild cognitive impairment" (MCI), a precursor state to Alzheimer's disease (Rovner et al., 2018). This evidence is consistent with Stillman et al. in showing the interrelatedness of diet and physical fitness on neurocognitive health. Despite a number of failed clinical trials on specific vitamins and supplements on cognitive aging (e.g., vitamin E, fish oil, etc.), the complex Mediterranean diet (involving high consumption of vegetables, legumes, fruits and nuts, cereals, olive oil and fish, moderate consumption of ethanol, and low consumption of red meat) appears to be effective, with greater adherence to the diet yielding greater cognitive benefits (Féart et al., 2009; Martínez-Lapiscina et al., 2013). The effectiveness of these multi-domain interventions points to the previously-mentioned importance of cardiovascular health (e.g., blood flow) in supporting neural plasticity late in life (Pereira et al., 2007; Maass et al., 2015; Avelar-Pereira et al.). It also points to the relative paucity of theoretical and empirical work on underlying mechanisms of combined effects. Importantly, although it is early days, the effectiveness of these comprehensive interventions stands in contrast to the failure of drug trials aimed at Alzheimer's disease and Mild Cognitive Impairment (Servick, 2019). Importantly, there are now several ongoing large scale multi-dimensional trials (USA POINTER, Baker, 2018) modeled on the Finnish FINGER study (Ngandu et al., 2015).

This Research Topic raises another important question. If cognitive interventions induce far transfer with small effect sizes but induce near transfer with medium to large effect sizes, perhaps cognitive interventions should also focus on durable near transfer. Rather than aiming interventions at improving cognitive globally in far transfer, the focus could be on interventions that improve specific cognitive skills and abilities regardless of far transfer. Near transfer from updating training to working memory would be important for daily functioning in the face of cognitive aging. Such an approach is currently being used to help dementia patients learn and retain skills needed for daily tasks (de Werd et al., 2013).

To summarize the main themes of this Research Topic, it appears that while the aging brain cannot compensate for declining integrity (Jiang X. et al.; Harwood et al.), brain and cognition in older people can benefit from aerobic exercise (Burzynska et al.; Jonasson et al.; Thielen et al.) and dietary interventions (Stillman et al.). Further, certain types of cognitive training have been shown to have very durable effects (Requena et al.; Grönholm-Nyman et al.) and also to more strongly induce near transfer than far transfer (Payne and Stine-Morrow; Grönholm-Nyman et al.). This points to durable near transfer as a useful aim for cognitive aging interventions. A recent innovation in the field shows that electrophysiological interventions have the potential to normalize large-scale networks in aging (Passow et al.; Reis et al.). Finally, the somewhat fragmented field of various cognitive and brain aging interventions may be unified by long-term multidomain interventions, the importance of which was emphasized by Stillman et al..

By its diverse contributions, this research topic reifies the sea change just beginning to transform research efforts to ameliorate

cognitive and brain aging. The status quo can be characterized as separate research communities each focused narrowly on cognition, on exercise, or on diet. What is needed is collaboration across scientific fields to investigate possible synergisms involved in combined interventions involving cognitive training, aerobic and resistance exercise training, and diet. The Finnish FINGER and the USA POINTER studies are leading the way to an approach which allows investigation into possible synergisms. Such a change has the potential to forge new conceptual and theoretical ground in line with the spirit of this special issue.

AUTHOR CONTRIBUTIONS

PG and CB contributed equally to the writing of this editorial.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

REVIEW
published: 18 May 2016
doi: 10.3389/fnagi.2016.00102

Cognitive Aging and Time Perception: Roles of Bayesian Optimization and Degeneracy

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This review outlines the basic psychological and neurobiological processes associated with age-related distortions in timing and time perception in the hundredths of milliseconds-to-minutes range. The difficulty in separating indirect effects of impairments in attention and memory from direct effects on timing mechanisms is addressed. The main premise is that normal aging is commonly associated with increased noise and temporal uncertainty as a result of impairments in attention and memory as well as the possible reduction in the accuracy and precision of a central timing mechanism supported by dopamine-glutamate interactions in cortico-striatal circuits. Pertinent to these findings, potential interventions that may reduce the likelihood of observing age-related declines in timing are discussed. Bayesian optimization models are able to account for the adaptive changes observed in time perception by assuming that older adults are more likely to base their temporal judgments on statistical inferences derived from multiple trials than on a single trial's clock reading, which is more susceptible to distortion. We propose that the timing functions assigned to the age-sensitive fronto-striatal network can be subserved by other neural networks typically associated with finely-tuned perceptuo-motor adjustments, through degeneracy principles (different structures serving a common function).

Keywords: interval timing, attention, clock, memory, decision-making, striatal beat-frequency model

OPEN ACCESS

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Received: *14 February 2016*
Accepted: *20 April 2016*
Published: *18 May 2016*

Citation:
Turgeon M, Lustig C and Meck WH (2016) Cognitive Aging and Time Perception: Roles of Bayesian Optimization and Degeneracy. Front. Aging Neurosci. 8:102. doi: 10.3389/fnagi.2016.00102

INTRODUCTION

We often hear that time flies by as we get older, but that idea is most applicable to our retrospections on years gone by e.g., Gallant et al. (1991), Hinton and Meck (1997a), Ukraintseva (2001), Wearden (2005), Friedman and Janssen (2010), Sucala et al. (2010), Janssen et al. (2013); (cf., McAuley et al., 2006). Our ability to time intervals in the milliseconds-to-minutes and extending into the hours-to-days range of circadian timing (Lewis and Miall, 2009) relies largely on different neural systems (Hinton and Meck, 1997b; Buhusi and Meck, 2005; Buonomano, 2007; Agostino et al., 2011; Hass and Durstewitz, 2016). Age differences in the temporal window of integration and performance on various timing tasks in the milliseconds-to-minutes range are often quite subtle or nonexistent (e.g., Rammsayer et al., 1993; Horváth et al., 2007), and in many cases almost completely accounted for by age differences in other cognitive functions such as attention and working memory (Krampe et al., 2002; Wittmann and Lehnhoff, 2005; Desai, 2007; Ulbrich et al., 2007; Bartholomew et al., 2015) and/or in circadian rhythms (Meck, 1991; Lustig and Meck, 2001; MacDonald et al., 2007; Halberg et al., 2008; Anderson et al., 2014; Golombek et al., 2014).

The age differences that do exist have traditionally been explained using an information-processing framework, typically with an attentional gate and/or switch that allows pulses that mark the passage of time to accumulate and be passed to working memory, where they are compared with standard values drawn from reference memory (Meck, 1984; Zakay and Block, 1997; Vanneste and Pouthas, 1999; Vanneste et al., 2001; Lustig, 2003; Allman et al., 2014b).

However, the neurophysiological plausibility of these pacemaker-accumulator models has been called into question (Matell and Meck, 2000; van Rijn et al., 2014). More current timing models instead emphasize the role of neural oscillations in providing the "raw material" analogous to the pulses or ticking of the clock, and the coincidence detection of patterns in those oscillations that mark relevant durations (e.g., Matell and Meck, 2004; Lustig et al., 2005; Allman and Meck, 2012; Merchant et al., 2013). A related development is the proposal that Bayesian processes govern decisions about time when a participant is comparing the current duration to the stored values of some previously timed standard (e.g., Jazayeri and Shadlen, 2010; Cicchini et al., 2012; Shi et al., 2013; Gu et al., 2015a; Shi and Burr, 2016; van Rijn, 2016). To our knowledge, these theoretical proposals have not yet been integrated into the broader literature on aging and time perception. Here, we take the first steps towards such an integration, and address the question of whether age differences in interval timing reflect "nothing more" than age differences in general cognition (especially attention and working memory). Alternatively, there may be fundamental age differences in the quality of timing information that older adults may attempt to compensate for via attention, working memory, as well as increased reliance on environmental support and timing circuitries other than cortico-striatal timing circuits.

The idea that attention influences our perception of time is intuitive and is reflected in popular culture, e.g., "time flies when you're having fun" but "a watched pot never boils". In other words, the less attention that is paid to the time dimension, the slower one's internal clock runs relative to the passage of physical time. This leads to the under-estimation and over-production of intervals relative to physical time (i.e., a person with a slow internal clock may perceive a 5-s stimulus as lasting only 3 s, and when asked to produce a 3-s interval, instead produce a 5-s one). Supporting this intuitive understanding of the relation between attention and time, laboratory studies consistently find that interval-timing performance is highly sensitive to attentional manipulations (e.g., divided attention and distraction) and that timing tasks and other tasks (e.g., memory search) that also load on attention and working memory show mutual interference (e.g., Penney et al., 1998, 2014; Bherer et al., 2007; Brown et al., 2015; Fortin and Schweickert, 2016). Not surprisingly, then, most studies comparing young and older adults on interval-timing tasks find that the presence and size of young adults' performance advantage depends heavily on attention and memory demands (see review and discussion by Block et al., 1999; Lustig, 2003; Balci et al., 2009; Lustig and Meck, 2009; Szymaszek et al., 2009; Krampe et al., 2010; Bisiacchi and Cona, 2016).

On the other hand, it would be surprising if older adults showed no decline in timing *per se*, as the dopaminergic functions and cortico-striatal circuits that support our sense of time (e.g., Hinton and Meck, 2004; Matell and Meck, 2004; Meck and Malapani, 2004; Lustig et al., 2005; Meck and N'Diaye, 2005; Meck et al., 2008a; Merchant et al., 2013; Agostino and Cheng, 2016) are among the most sensitive to age-related decline (e.g., Rubin, 1999; Raz et al., 2010; Seidler et al., 2010; Abedelahi et al., 2013; Bauer et al., 2015; Kleerekooper et al., 2016). Most reviews emphasize the age differences observed in timing when demands on attention and working memory are high. However, age differences are also found in situations where the opportunity for such processes to make a contribution appears to be quite low. For example, Turgeon and Wing (2012) tested healthy adults across ages 19–98 on a series of unpaced timing tasks where performance relies largely on internal representations and the opportunity to detect and correct errors is relatively low (see also McAuley et al., 2006). These included spontaneous motor tapping (SMT), where the participant is simply told to tap at their most comfortable pace, serial interval production (SIP), where the goal is to tap at a rate of 1 s and $\frac{1}{2}$ s, but no external standard is presented, fastest regular tapping (FRT), where the goal is to tap regularly as quickly as possible, and continuation tapping (CT), where participants first tap in rhythm to an external stimulus, but are then asked to continue tapping at that rate when the stimulus is discontinued. Across all of these tasks, greater age was associated with longer and more variable tapping rates, indicating a slower and more variable internal clock. Additional analyses indicated that these increases were reflective of clock rather than motor variance. In most cases, the increases with age were quite subtle until advanced age (75+ years), suggesting that previous studies failing to find age effects (e.g., Surwillo, 1964; Arenberg, 1968; Salthouse et al., 1979; Block et al., 1998) may have suffered from a lack of power due to smaller participant numbers and older adults who were primarily in the "young-old" (under 75 years) age range. See Kołodziejczyk and Szelsg (2008) for a study of temporal order judgments including centenarians.

In a similar manner, Ramos et al. (2015, 2016) measured tactile temporal discrimination thresholds (TDT) in healthy individuals from 18 to 79 years of age. The TDT was measured as the individual's ability to discriminate two short (0.2 ms) tactile stimuli from each other as a function of the inter-stimulus interval (ISI). Consequently, the TDT is the shortest ISI that allows a participant to reliably perceive successive stimuli, tested using 6 trials of alternating ascending and descending limits. No effect was observed for gender, race, ethnicity, or handedness, and the reproducibility of the results was good. The overall finding was that every year of increased age was associated with a 0.66 ms increase in TDT. These findings were discussed in terms of models for interval timing involving clock, memory, and decision stages (Allman and Meck, 2012) with the conclusion that age-related effects at the clock stage were most likely to account for the data. The slowing down of an internal clock as a function of age would be expected to lead to the ISI separating the 0.2 ms duration electrical stimulations to be subjectively shorter, making it more difficult to separate sequential stimulus presentations. This finding is of interest given the potential

importance of TDT as a behavioral screen for various genetic components of neurological dysfunction (e.g., Conte et al., 2010, 2012, 2014, 2015).

On the one hand, the results of these relatively simple tapping and duration discrimination tasks, which would seem to minimize the involvement of attention and memory processes, seem to point to a "true" age difference in clock speed and time perception. In a seeming paradox, however, there is little evidence that the accuracy and precision of magnitude estimations decline with age on more difficult or "cognitively based" duration discrimination or production tasks once age differences in general intelligence/cognitive function (attention, working memory, resource-sharing, and processing speed) are taken into account (e.g., Salthouse, 1996; Wearden et al., 1997; Greenwood and Parasuraman, 2003; Baudouin et al., 2004; Wearden, 2005; Hancock and Rausch, 2010; Lambrechts et al., 2013; Bartholomew et al., 2015). For example, in the largest timing study to date, evaluating 647 participants, Bartholomew et al. (2015) found that both discrimination and production were strongly correlated with scores on a general cognitive battery; more importantly, after controlling for cognitive scores, timing performance was unrelated to age. However, a potential caveat is that the age range of participants was limited to 18–67 years, precluding the observation of potential aging effects on timing accuracy and precision that may only become evident or independent of cognitive processes sometime after approximately 75 years of age (c.f., Turgeon and Wing, 2012).

These patterns could be explained in two ways. From a "timing-centric" perspective, they may reflect that "timing is everything", that is, a hallmark of general intelligence and cognitive function that may fundamentally underlie other cognitive functions. This view receives some support from the increasing interest in oscillatory function in general cognition (for reviews, see Siegel et al., 2012; Henry and Herrmann, 2014). Alternatively, timing may depend on the interaction and output of those cognitive functions. Teasing apart these two possibilities is an important challenge for current research, and the explanation may differ depending on the level of analysis. However, in either case, the proposition that interval timing and cognition are intricately linked leads to two predictions. First, the scalar property—reflecting the proportional relationship between the mean of the duration being timed and the standard deviation (SD) of these estimates (i.e., coefficient of variation [CV] is constant)—is the hallmark of interval timing (e.g., Gibbon and Church, 1984a,b; Gibbon et al., 1984; Church, 2003; Buhusi and Meck, 2005; Cui, 2011). This suggests that there should be a similar relationship between sources (e.g., clock, memory, and decision) and forms of variability (e.g., Bernoulli, Gaussian, or Poisson distributions) for other cognitive processes (e.g., Gibbon, 1992; Rakitin et al., 1998, 2005; Cordes et al., 2001; MacDonald and Meck, 2004; Baudouin et al., 2006a,b; Jazayeri and Movshon, 2006; Rakitin and Malapani, 2008; Cordes and Meck, 2014; Namboodiri et al., 2014; Gu et al., 2015b) given the need for the synchronization of oscillatory processes among brain areas for information transfer (e.g., Cheng et al., 2008b; Buehlmann and Deco, 2010; Gu et al., 2015b). Second, from a translational perspective, engaging in mental and physical exercises that require precise timing, balance, and motor coordination during practice (e.g., musical drumming, piano playing, flamenco dancing, video gaming, etc.) should improve not only our sense of time, but also other cognitive processes (e.g., Krampe and Ericsson, 1996; Lustig et al., 2009; Donohue et al., 2010; Anderson et al., 2012, 2013; Cicchini et al., 2012; Kattenstroth et al., 2013; Szabo et al., 2013; Bamidis et al., 2014; Benoit et al., 2014; Szelag and Skolimowska, 2014; Dallal et al., 2015; Kshtriya et al., 2015). Moreover, recent results suggest that rhythmical training exercises can counteract the lengthening errors of total duration in rhythmic reproduction observed after 60 years of age (Iannarilli et al., 2013). Earlier findings, however, provide a note of caution by indicating that moderate levels of skill do not protect against the negative age-related decline in temporal processing and that a certain level of expertise needs to be achieved in order for benefits to be observed (Krampe et al., 2001, 2002; Krampe, 2002).

AGE AND TIMING PERFORMANCE: DECLINE, PRESERVATION, AND COMPENSATION

One interpretation of the above statements is that age differences in cognition (e.g., attention, memory, and decision-making) provide more proximal and parsimonious explanations of age differences in timing than does the proposal that older adults generally have a slower internal clock (e.g., Block et al., 1998; Lustig and Meck, 1998, 2001, 2002, 2005, 2011; Lustig, 2003; Bherer et al., 2007; Gooch et al., 2009; cf., Ragot et al., 2002; Pouthas and Perbal, 2004; Moni et al., 2014). Nonetheless, numerous brain areas (e.g., caudate and frontal lobes) tend to atrophy as a consequence of normal aging and the shrinkage of these neural networks is a mediator of reduced dopamine-related temporal processing (e.g., Rubin, 1999; Cheng et al., 2006, 2007; Li et al., 2010; Coull et al., 2011; Gu et al., 2015a). As noted above, the cortico-striatal circuits that support our sense of time (e.g., Matell and Meck, 2004; Lustig et al., 2005; Meck and N'Diaye, 2005; Meck, 2006a,b,c; Meck et al., 2008a; Merchant et al., 2013) are one of the most sensitive neural networks in terms of age-related changes, suggesting that decreases in clock speed *per se* and increases in temporal variability should also be associated with normal aging (e.g., Bäckman et al., 2010; Hurley et al., 2011; Klostermann et al., 2012).

Age-related changes in brain and behavior likely involve long-term dynamic interactions between neural degeneration and recovery processes both within "canonical" regions involved in timing by both young and old adults, possibly involving compensatory sprouting within the damaged pathways (Song and Haber, 2000), buffering of noisy and sustained environmental perturbations (Domijan and Rand, 2011), and compensatory recruitment of other neural networks (Cabeza et al., 2002). This last form of compensation has been referred to as "degeneracy" (Edelman and Gally, 2001; Whitacre, 2010; Whitacre and Bender, 2010), namely, the ability of different brain regions and networks to produce the same or highly similar output, especially when the primary or canonical circuits are dysfunctional or impaired (e.g., Meck, 2002a; Jahanshahi

et al., 2010; Lewis and Meck, 2012; Jones and Jahanshahi, 2014, 2015; Harrington and Jahanshahi, 2016). We will use the term "*de-generacy*" as suggested by Mason et al. (2015) to minimize the common association between *degeneracy* and *degeneration*[1]. De-generacy is apparent in many of our neural systems, including vision, hearing, movement, etc. and is distinctive from redundancy in that structurally different mechanisms are involved in the former and multiple copies of identical mechanisms are involved in the latter (Mason, 2010). In the simplest sense, de-generacy can be thought of as a strategy by which the organism protects itself against loss of a vital function by having distribution of function in combination with structural variation. When it comes to purely neural systems, however, de-generacy can be more complex and subtle. It is unlikely that any two separate neural systems perform a given function in exactly the same way unless they have an almost identical neural architecture (as in the examples listed above). Instead, it is becoming increasingly apparent that the brain frequently provides several alternate routes to any given goal, with each of these drawing upon quite separate machinery (Price and Friston, 2002; Brandtstädter and Rothermund, 2003). Evidence for this type of "synergistic replication" comes both from patients with brain damage and from neuroimaging studies of normal, healthy participants. The former group frequently show a remarkable resiliency, still performing well on tasks such as semantic judgment and motor control even when the regions that are most strongly associated with these functions have been fully resected. Similarly, the huge variability in functional imaging results show that different participants perform the same task in different ways (e.g., using different neural systems). These data have been elegantly explained as evidence for de-generacy (Price and Friston, 2002; Noppeney et al., 2004). Furthermore, the proponents of this approach argue that such de-generacy is highly adaptive because it allows flexibility at an evolutionary level: if no single system is 100% essential, then it is more feasible to experimentally alter them without causing fatal side effects (Whitacre, 2010, 2012; Whitacre and Bender, 2010, 2013). The applicability of this line of thought to time perception should be obvious—it is very difficult to completely abolish time perception, especially as a result of focal, unilateral brain lesions where redundancy from the opposite hemisphere is likely to contribute to recovery (Lewis and Meck, 2012). Moreover, it has been proposed that de-generacy occurs as an active monitoring process during sleep, much like the sleep-dependent consolidation of temporal rhythms and other memories (e.g., Cheng et al., 2008b, 2009; Soshi et al., 2010; Lewis et al., 2011; Lewis and Meck, 2012; Scullin and Bliwise, 2015).

Regardless of the proximal cause of aging (Blagosklonny, 2012), de-generacy could explain why timing dysfunctions are likely to be less obvious in normal aging and/or during the initial stages of neurodegenerative disorders such as Parkinson's and Huntington's diseases than in experimental subjects with targeted bilateral brain lesions or genetic manipulations (e.g., Liu et al., 2002; Meck and Benson, 2002; Meck, 2006a,b; Desai, 2007; Centonze et al., 2008; Wild-Wall et al., 2008; Balci et al., 2009; Meck et al., 2012a; Church et al., 2014). That is, older adults (and these other patient populations) may be able to recruit alternative cognitive processes and neural networks to maintain performance, at least until those alternatives also "break down" under cognitive demand or due to age-related (or disease-related) physical declines (e.g., Paulsen et al., 2004). This would also explain the seeming paradox that on the one hand, age differences are quite reliable on the simplest timing tasks that attempt to minimize cognitive involvement (i.e., there is little or no opportunity for these alternative processes/networks to intervene), but on the other hand, once one enters the "cognitive realm", age differences tend to increase with demands on functions such as attention and working memory (i.e., the task demands eventually exceed the ability of older adults to compensate). Interestingly, the effects of de-generacy and the application of a Bayesian decision rule would lead to the "migration" of temporal memories towards each other and violation of the scalar property of interval timing whereby longer durations are timed with less variability than shorter durations (e.g., Malapani et al., 1998; Rakitin et al., 2006; Shi et al., 2013; Gu et al., 2015a).

As we grow older, the speed of our internal clock seemingly winds down over the course of a day and take longer to recover than when we were younger. This "fatigue effect" has been proposed to be the result of the gradual depletion of striatal dopamine as a function of sustained cognitive engagement during skill learning acquisition (Kawashima et al., 2012) and is facilitated by certain dopamine-related disorders such as normal aging, adult attention deficit hyperactivity disorder, and Parkinson's and Huntington's diseases (e.g., Malapani et al., 1998; Meck, 2005; Balci et al., 2009; Allman and Meck, 2012; Gu et al., 2015a). This more rapid depletion in dopamine function is accompanied by our sense that the external world is going faster, when in fact it may be our internal clock that is going slower, thereby suggesting to us that sequences of events are occurring in a shorter amount of time than would typically be expected (see Cooper and Erickson, 2002). An example of this "fatigue effect" was reported by Malapani et al. (1998) in their study of Parkinson's disease patients and aged-matched controls trained and then tested on a duration reproduction procedure without feedback (see Yin et al., 2016a for procedural details). Over the course of a 2 h session, healthy aged participants

[1]In neural Darwinism (Edelman and Gally, 2001), the term *degeneracy* refers to the concept of heteromorphic isofunctionality (i.e., different structures subserving the same function). On the other hand, *degeneration* is a term much more familiar to the lay public; it refers to deleterious decay, including that of neural structures. In a seemingly paradoxical way, de-generacy is a highly adaptive feature of complex biological systems like the brain given the inevitable degenerative processes (i.e., degeneration at many levels of neural organization) that ensues with their aging. Unlike *redundancy* (same structures subserving same functions), the structural diversity arising from de-generacy in the nervous system is highly conducive to functional plasticity or pluripotentiality (one structure subserving different functions). In Mason's words: "A key corollary of degeneracy is that, because it entails diversity at the structural level, different circumstances may elicit different outputs from the same degenerate set. Thus, one-to-many structure-function relationship has been dubbed *pluripotentiality*" (Mason, 2015). In sum, de-generacy (many-to-one structure-function relationship) is as essential for the emergence of complexity through evolution, and by extension the brain, as is pluripotentiality.

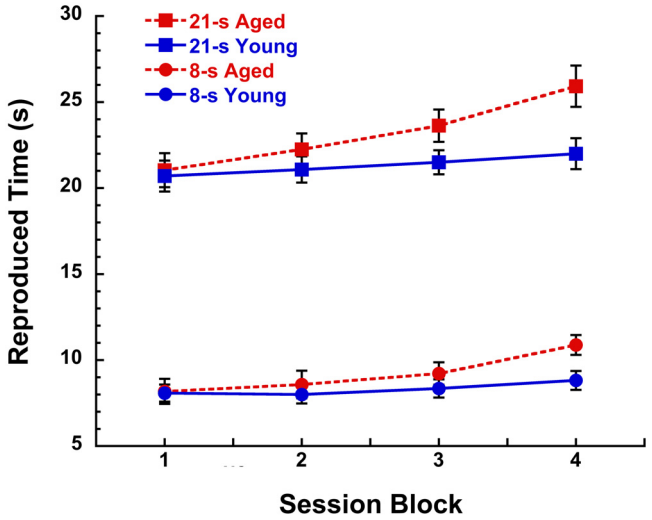

FIGURE 1 | Reproduced time (s) in a peak-interval procedure with 8-s and 21-s target durations for young (19–28 years, *n* = 7) and aged (67–90 years, *n* = 12) participants as a function of 30 min blocks during a 2 h session without feedback. Participants received training with inter-trial interval feedback prior to the discontinuation of feedback during the test phase. Data are taken from test sessions described by Malapani et al. (1998) and Rakitin et al. (1998). See Lustig and Meck (2005), Lake and Meck (2013), and Yin et al. (2016a) for a review of the benefits of the peak-interval procedure.

showed proportional rightward shifts in the reproduction of 8-s and 21-s target durations that increased as a function of 30-min session blocks as illustrated in **Figure 1**. In contrast, young participants (Rakitin et al., 1998) demonstrated a much smaller trend that didn't reach significance. This relative discrepancy between physical and psychological measurement is what most influences our sense of time in every day life (e.g., McAuley et al., 2006; Matthews et al., 2014; Wearden et al., 2014; Matthews and Meck, 2016).

Like memory and intelligence, our sense of time is multifaceted and some timing abilities are likely more resilient to the aging process than others. Timing tasks that do not involve controlled attention and working memory, or at least do so with a very minimal load (e.g., remembering the current task instructions like "tapping every second") are more indicative of our ability to perceive and produce temporal intervals than those that do (e.g., reproducing a series of intervals of a complex rhythm in the correct order). Even within less cognitively demanding (or low level) timing tasks, there is substantial heterogeneity in how performance varies with age. Results from paced and unpaced tapping tasks, respectively reported in Turgeon et al. (2011) and Turgeon and Wing (2012), demonstrate that timing error detection and correction abilities are preserved into advanced age, despite a reduction in timekeeping abilities. Indeed, individuals in their 8th and 9th decades of age were as sensitive to the presence of unpredictable temporal perturbations (a sound happening slightly later than it should have were the sequences completely regular, the rhythm being preserved from that point on) as those in their 3rd decade of age. Specifically, the just detectable phase shifts varied from 5 to 15% of Inter-Onset Interval (IOI) across individuals independently of age.

Weber fractions were estimated for intervals spanning a wide portion of the pulsation zone (i.e., IOIs of 300, 600 and 900 ms), that is, intervals that while repeated evoke the sensation of a pulse (or rhythm) and a tendency to move in unison with it (i.e., entrainment). Hence, the high sensitivity to deviations from regularity in old age is likely to reflect adjustments in motor preparedness (i.e., when to perform the next move). Indeed, when tapping in time with the sounds of sequences containing such unpredictable perturbations, elderly participants were as efficient in adjusting for the timing of their taps (i.e., within 1–3 tone(s) from the phase-shift location) as their young counterparts; whether these errors were consciously detectable or not. This suggests that predictable timing mechanisms, that is, the neural processes allowing an individual to generate accurate predictions as to when the next event or series of events should happen and adjust behavior accordingly, are quite resilient to the aging process (cf., Bornkessel-Schlesewsky et al., 2015). In contrast, the same elderly individuals are more variable in tasks depending mainly on the integrity of an internal clock, like tapping regularly as fast as possible (fastest regular rate of FRT) or at the most comfortable rate referred to as SMT.

Other timing tasks showing a clear increase in variability with age were: SIP and the continuation part of synchronization-continuation (SC). While SIP involved tapping every second or half of a second (i.e., twice as fast), SC requires tapping at a regular rate after the pacing sequence ends at the same rates as sensorimotor synchronization (SMS) task, i.e., IOIs of 300, 600 and 900 ms. Moreover, the age-related increased variability in CT could not be attributed to motoric factors (see Figure 5 in Turgeon and Wing, 2012). Interestingly, even though elderly participants tended to produce longer intervals when asked to tap every second or every half second (i.e., age-related impairment in timing accuracy), relative timing accuracy did not decline with age, that is, they produced taps twice as fast for the 0.5-s target interval as for the preceding 1-s one to the same degree as young participants. This is consistent with the use of the just-produced slow sequences as a baseline reference for the adjustment of the ongoing "twice-as-fast" rate. Accordingly the initial 1-s SIP trials are more likely to reflect an internal representation of an interval of 1 s than the subsequent 0.5-s SIP trials in which the just-produced series of slower taps serve as highly useful external cues forming a 1–2 ratio with the current target interval of half a second. These results are in general agreement with the use of all available contextual information (in this case that of concurrent and/or previous event sequences) to improve precision (reduce temporal uncertainty) as predicted by Bayesian models of interval timing (Shi et al., 2013; Gu et al., 2015a). As we will discuss below, Bayesian optimization models can be fruitfully integrated with more general theories of neurocognitive aging in order to provide a new perspective on when (and how) age differences in timing performance

are and are not likely to be observed (De Ridder et al., 2014).

A BAYESIAN DECISION THEORY PERSPECTIVE

The idea of increased noise and variability in older adults coordinates with Bayesian decision theory to explain patterns of age differences and preservation in timing performance. From this perspective, the proposal would be that older adults build an internal representation of both the experimentally imposed distribution of signal durations (the *prior*) and of the error (the *loss function*). This means that when participants are asked to reproduce or compare a recently presented signal duration they incorporate the knowledge of the distribution of previous durations into the perception of the current duration, thus biasing the reproduction towards the mean of the distribution of all durations experienced within a particular context (e.g., Jazayeri and Shadlen, 2010; Acerbi et al., 2012; Cicchini et al., 2012; Gu et al., 2015a). In Bayesian models of this sort, it is hypothesized that a tradeoff exists between accuracy and precision, such that the distribution of durations within a particular context is used to optimize timing performance by reducing uncertainty at the cost of accuracy. In this case, the implicit knowledge of the underlying distribution of durations from which a sample is drawn would be useful when the current clock reading is unreliable due to the effects of variability which may result from age-related declines in dopaminergic function and clock speed (e.g., Malapani et al., 1998; Lake and Meck, 2013; Gu et al., 2015a; Cheng et al., 2016). This explains how the inter-mixing of the memories of previous trials signal durations with the current trial's clock reading could bias performance (Penney et al., 1998; Gu and Kukreja, 2011; Gu and Meck, 2011; Matell and Kurti, 2014; van Rijn et al., 2014). Under challenging or stressful conditions, however, this statistical analysis provides an efficient strategy for reducing variability in the presence of high levels of uncertainty that may accompany age-related declines in temporal processing (Gu and Kukreja, 2011; Shi et al., 2013; Gu et al., 2015a). In order to justify such an approach, however, one must first demonstrate that older adults do in fact have a slower and/or more variable internal clock. Unfortunately, previous applications of Bayesian decision models have made this assumption without providing direct evidence of such effects (e.g., Sato and Aihara, 2011; Gu et al., 2015a).

A SLOWER/NOISER CLOCK: DIRECT EVIDENCE IN SUPPORT OF A BAYESIAN OPTIMIZATION APPROACH TO AGE DIFFERENCES IN TIMING

Regular tapping at the most comfortable rate (i.e., SMT procedures) has been assumed to reflect the natural resonance (or referent) period of the internal clock (McAuley et al., 2006). Variability in SMT is thus a good indicator of how noisy the clock becomes with age. When asked to tap at a rate that feels comfortable and natural for 30 s, older people produced longer inter-tap intervals (ITI) than younger people (see **Figure 2A**—Turgeon and Wing, 2012); this is consistent with a slowing of their internal clock (Vanneste et al., 2001). In addition, age was associated with relatively large increases in variability. Compared to the variability in tapping performance for the 15 youngest participants (age 19–30 yrs) who were quite stable (*SD* = 65 ms or 12% of mean of 549 ms), those produced across the 15 eldest participants (age 78–98 yrs) varied almost twice as much (*SD* = 177 ms or 21% of mean of 839 ms).

Within-trial variability as measured by the CV for each of the 60 participants (3 trials at the beginning and 3 trials at the end of the study) increased with age (see **Figure 2B**—Turgeon and Wing, 2012), age accounting for 13% and 11% of the variance among CV scores at the beginning and end, respectively. As most of the age-related changes observed in this study occurred at the top end of the age spectrum, we performed a more focused analysis for the 26 participants aged between 58–98 years for whom we have measures of general cognitive abilities using the Mini Mental State Examination (MMSE — Folstein et al., 1975). This additional analysis of the Turgeon and Wing (2012) data allowed for the examination of both the within-trial CV and the inter-trial SD as a function of age and MMSE at the beginning of the study when participants performed without practice and at the end of testing after having completed a variety of unpaced and paced tapping tasks. The results from these additional analyses (as illustrated in **Figure 2**) provide further evidence for a noisier internal clock in older adults, even when taking into account general cognitive abilities (MMSE scores) and practice effects (beginning vs. end of study measures).

Notably, even in this supposedly minimally-cognitive timing task, the effects of attention and memory can be seen and may interact with age. Although the MMSE is a rough measure of general cognitive abilities, the score accounts for a substantial proportion of the variance at the beginning of testing, namely 27% of the variance among within-trial CV (**Figure 2B**) and 48% among inter-trial SD (**Figure 2D**). In contrast, MMSE no longer predicts variability within or across trials at the end of testing, only 5–6% of the variance being accounted for by the MMSE. That general cognitive abilities contribute to a reduction in variability on the very first task seems plausible as older adults with high MMSE scores are more likely to understand the instructions rapidly, while those with lower MMSE scores might require a bit longer to "get into the swing" of tapping tasks. For instance, they might need to be reminded to be as regular as possible and maintain the same pace for the whole half-a-minute period. The lack of a relationship between MMSE and variability at the end of testing suggests that practice overcame any initial cognitive challenges of the SMT task. Interestingly, the predictive effect of Age on within-trial CV (**Figure 2A**) and inter-trial-SD (**Figure 2C**) is actually higher at the end (43–48% of variance accounted for) than at the beginning (27–28% of variance accounted for). This suggests that despite the age-related decline in performance due to general cognitive factors, there is an increased variability within and across trials arising from slower and less reliable timing mechanisms consistent with our

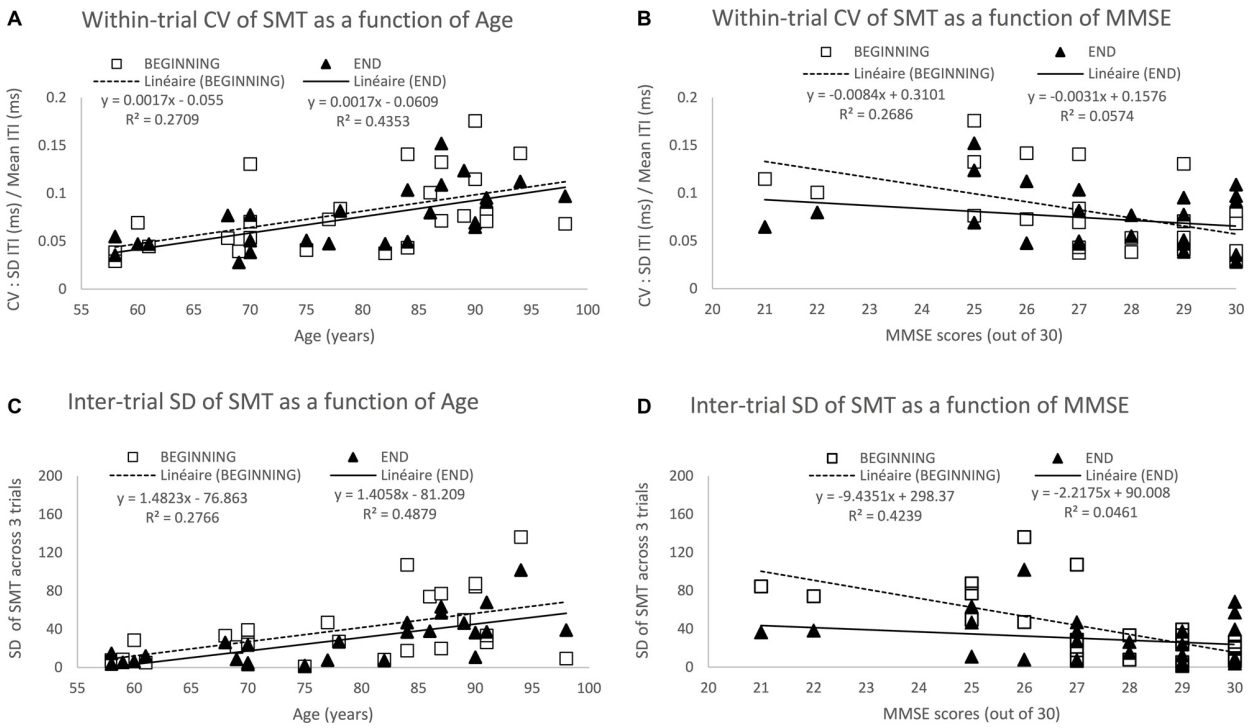

FIGURE 2 | Spontaneous motor tempo (SMT) across age and its associated variability at the beginning and end of testing. The top two panels show the mean coefficient of variation (CV) across the first 3 trials (beginning) and the last 3 trials (end), each CV equaling to the standard deviation (SD) of inter-tap intervals (ITI) divided by its mean on a given 30-s trial) across Age **(A)** and mini mental state examination (MMSE) scores **(B)**. The bottom two panels show the SD of the mean ITI across the 3 trials at the beginning and end of the study across Age **(C)** and MMSE scores **(D)**. Data represent additional analyses of the findings reported in Turgeon and Wing (2012).

earlier discussion of dopamine depletion and cognitive "fatigue effect" across a session. On a methodological front, these findings point to the importance of including enough trials and analyzing performance only after it has stabilized to increase the likelihood of testing "true" age differences in timing while minimizing artifacts and confounds due to individual or group differences in task acquisition and learning.

The age-related increase in inter-trial variability in combination with the age-related decrease in precision (i.e., increase of CV with age) on SMT as well as other unpaced tapping tasks reported by Turgeon and Wing (2012) is *consistent with a noisier and less reliable clock in older participants with otherwise intact predictive timing mechanisms*—as assessed from error detection and correction performance, with the external sound sequence providing some "feedback" that reduces uncertainty. The fact that age does not predict relative timing accuracy in SIP (see **Figure 3C**—Turgeon and Wing, 2012) provides further evidence that when a temporal context is available (i.e., a target period with a simple 2:1 ratio in SIP or a pacing sequence in SMS), it is used to compensate for a slower, more variable internal clock in an aging nervous system as opposed to effects on motor variability (e.g., Wing and Kristofferson, 1973).

Procedural limitations (e.g., limited range of durations and the use of magnitude estimation or reproduction procedures allowing for the calibration and rescaling of stimulus durations) as well as inadequate statistical power and improper control for general intelligence factors may have precluded the observation of age-related decreases in clock speed in numerous reports (e.g., Surwillo, 1964; Arenberg, 1968; Salthouse et al., 1979; Block et al., 1998). In general, the observation of age-related rightward horizontal shifts in psychometric timing functions is consistent with the internal clock slowing down if trial-by-trial and/or session-by-session analyses show appropriate temporal dynamics as a function of within-session feedback (e.g., Vanneste et al., 2001; Lustig and Meck, 2005; Rakitin and Malapani, 2008) and/or between-session train and test conditions (e.g., Meck, 1983, 1996, 2005; Malapani et al., 1998; Lake and Meck, 2013). Moreover, the observed reversals in duration categorization around the point of subjective equality for pairs of anchor durations and larger modality differences would be expected to occur with age-related decreases in clock speed as a result of duration discriminations becoming more difficult with a slower, less precise clock that normally exhibits differential sensitivity to auditory and visual stimuli (e.g., Penney et al., 1998, 2000, 2005; Cheng et al., 2008a, 2011) particulary when timing multiple signal durations concurrently (e.g., Lustig and Meck, 2001, 2002; Buhusi and Meck, 2009a,b; McAuley et al., 2010; Todorov et al., 2014). In contrast, systematic changes in temporal accuracy (e.g., horizontal rightward shifts

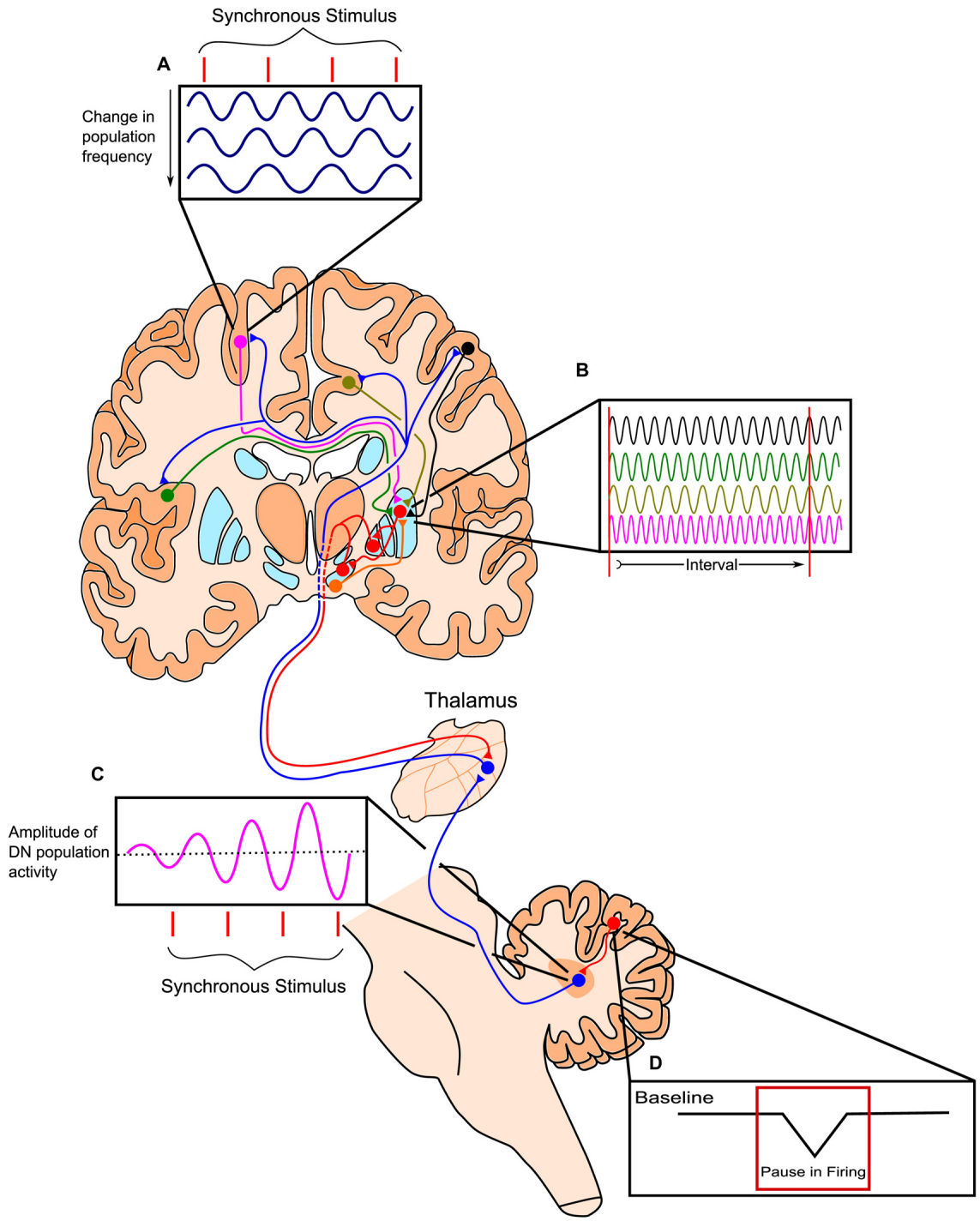

FIGURE 3 | Outline of the Striatal Beat-Frequency (SBF) model of interval timing with the incorporation of a cerebellar adjustment mechanism into the time code. (A) At the start of a to-be-timed signal a phasic pulse of dopamine from the ventral tegmental area (VTA) synchronizes cortical oscillations. Cortical oscillations in areas such as the prefrontal cortex (PFC) can be modulated with synchronous stimuli possibly through efferents from the thalamus. **(B)** These dispersed cortical neurons synapse onto medium spiny neurons (MSNs) within the striatum, which are activated at specific target durations based on the oscillatory activity pattern of synapsing projections. These neurons project from non-motor regions in the thalamus such as the caudal portion of ventralis lateralis, pars caudalis (VLcc) and receive extensive inputs from the cerebellar dentate nucleus (DN). **(C)** The DN also exhibits changes in population activity in response to synchronous stimuli, which may drive the modulation seen in cortical regions of the cerebrum. **(D)** The change in DN activity is likely modulated by decreases in tonic Purkinje cell activity (pauses) allowing for the precise tuning of timing mechanisms through disinhibition. Adapted from the initiation, continuation, adjustment, and termination (ICAT) model of temporal integration described by Lusk et al. (2016) and Petter et al. (submitted).

in psychometric timing functions that are gradually acquired over the course of the lifespan and maintained in the face of corrective feedback) are indicative of age-related decreases in memory storage speed (K*) resulting in proportional increases in the durations stored in long-term memory (e.g., Meck, 1983, 1996, 2002a,b, 2006c; Meck and Church, 1985, 1987; Meck et al., 1986; Meck and Williams, 1997; Lejeune et al., 1998; McCormack et al., 1999, 2002; Lustig, 2003; Meck et al., 2008b; Balci et al., 2009; Oprisan and Buhusi, 2011).

In summary, the findings reviewed here lend support to the application of Bayesian models of optimization in order to account for decision-making made under increased levels of uncertainty in the aging brain as a function of age and cognitive fatigue. Moreover, it appears justified to assume a slower and/or noiser internal clock as a contributing factor to this uncertainly above and beyond any age-related changes in attention and memory.

STRIATAL BEAT-FREQUENCY (SBF) MODEL: NEUROBIOLOGICAL BASIS FOR BAYESIAN TIMING

The striatal beat frequency (SBF) model of interval timing accounts well for much of the pharmacological, neurophysiological, and psychological data on timing and time perception (e.g., Matell and Meck, 2000, 2004; Coull et al., 2011; Oprisan and Buhusi, 2011, 2013, 2014; van Rijn et al., 2011; Allman and Meck, 2012; Buhusi and Oprisan, 2013; Oprisan et al., 2014; Kononowicz, 2015; Kononowicz and van Wassenhove, 2016). The SBF model proposes that time perception is largely subserved by connections between the striatum, cortex, and thalamus, with the dorsal striatum being specifically crucial for proper timing abilities (Meck, 2006a,b). According to this model, the start signal to time a stimulus is marked by the phasic release of dopamine from dopaminergic midbrain projections to the cortex and dorsal striatum (Matell and Meck, 2004; Gu et al., 2011). This neurotransmitter release causes oscillatory cortical neurons to synchronize their firing and resets activity in the dorsal striatum. Thousands of these oscillating cortical neurons converge on individual medium spiny neurons (MSNs) in the striatum. As ensembles of cortical glutamatergic pyramidal neurons oscillate with varying intrinsic frequencies, their oscillations fall out of phase after the initial synchronizing action of dopamine. The different cortical oscillation frequencies result in input activation patterns to striatal neurons that vary with the time elapsed from the cortical synchronization event (e.g., van Rijn et al., 2014; Gu et al., 2015b; Hashimoto and Yotsumoto, 2015; Murai et al., 2016). Each MSN in the striatum is thought to integrate these oscillatory cortical inputs and respond to select patterns of cortical neuronal firing, based on previous reinforcement through long-term potentiation (LTP). In the striatum, cortical firing results in long-term depression, unless there is a concurrent release of dopamine in which case LTP may occur. This dopaminergic input, originating from the dorsal midbrain, and the LTP it induces along this pathway, may strengthen connections with cortical inputs active at the time of reinforcement or feedback. In this way, striatal neurons may become specialized in responding to specific temporal intervals, as the threshold for firing is reduced when the correct cortical inputs are present. Prior to learning, the delivery of an unexpected reinforcement or feedback causes a phasic surge of dopamine release in the striatum that may represent the dopaminergic input necessary for LTP. Striatal output influences activity of the thalamus via a direct and an indirect pathway, which have opposing effects on thalamic activity. In turn, the thalamus has excitatory projections to the cortex, which then project back to the striatum, completing the cortico-thalamic-striatal loop (Buhusi and Meck, 2005; Agostino et al., 2011). The direct and indirect pathways of the basal ganglia are suggested to play a role in the start, stop, and resetting of the timing process, though further research is necessary to elaborate the proposed roles of these pathways in anticipatory timing, intertemporal choice, and temporal discounting (Wiener et al., 2008; Kim and Zauberman, 2009; Cui, 2011; Löckenhoff et al., 2011; MacDonald et al., 2012; Agostino et al., 2013; Heilbronner and Meck, 2014). In addition to cortico-striatal circuits, cortico-cerebellar circuits provide feedback and fine tuning of the processes described above for the cortico-striatal circuits as illustrated in **Figure 3** (see Cheng et al., 2016; Lusk et al., 2016; Petter et al., submitted).

As described above, the SBF model provides the necessary neurobiological substrates and neural firing properties in order to identify sources and forms for increased variability associated with aging effects on timing and time perception (e.g., Meck and Malapani, 2004; Buhusi and Oprisan, 2013; Oprisan and Buhusi, 2014; Cheng et al., 2016). For example, a slower clock with increased variability in clock speed could be accounted for by the effects of tonic and phasic dopamine release from the ventral tegmental area (VTA) to the frontal cortex. This would involve specific changes in the period, variability, resetting, and phase of cortical oscillatory processes being monitored by striatal median spiny neurons in the dorsal striatum (e.g., Oprisan and Buhusi, 2011; Gu et al., 2015b; Kononowicz, 2015; Cheng et al., 2016; Kononowicz and van Wassenhove, 2016).

DE-GENERACY IN PREDICTIVE TIMING MECHANISMS AS A POTENTAIL ROUTE FOR COMPENSATION

Though not specifically addressed by the SBF model, diminished striatal functioning might also engage brain circuits that compensate via de-generacy mechanisms (Lewis and Meck, 2012), wherein different anatomical networks are engaged (Meck, 2002a; Merchant et al., 2013). De-generacy in timing systems is plausible since time-related cell activity is not only found in the basal ganglia, but also the cerebellum, thalamus, posterior parietal cortex, prefrontal cortex (PFC), and the supplementary motor area (SMA and preSMA; Merchant et al., 2013; Strenziok et al., 2013; Lusk et al., 2016; Petter et al., submitted). Timing in different behavioral contexts is also associated with different neural architectures. For example, explicit timing is thought to depend on the striatum and basal

ganglia, whereas activation of the SMA, inferior cortex, and cerebellum is considered to be more task specific. In contrast, implicit perceptual timing is associated with a different set of brain regions, most frequently the parietal cortex (e.g., Coull and Nobre, 2008; Coull et al., 2011)—although the cerebellum has been argued to be involved in both explicit and implicit motor timing as well as explicit and implicit perceptual timing, perhaps distinguished from the striatum along a discrete vs. dynamic or duration-based vs. beat-based dimension (e.g., Liverence and Scholl, 2012; Teki et al., 2012; Breska and Ivry, 2016; Petter et al., submitted). Similarly, cortico-cortical systems are more engaged when timed movements are externally paced, whereas the striatum is engaged when movements are self-paced or internally timed (Taniwaki et al., 2003).

The results reported by Turgeon and colleagues (Turgeon et al., 2011; Turgeon and Wing, 2012) provide evidence that the adjustment component of timing is preserved up until the 9th decade of age in healthy, aged brains, that is, those without any diagnosed pathologies. By *adjustment timing*, we mean the adaptive use of predictable intensity fluctuations or temporal dynamics (e.g., the abrupt rise of intensity or onsets of the regularly-spaced events of a metronome) to initiate an action (e.g., when to jump) or series of actions (e.g., when to switch directions when running an obstacle course) and/or regulate an ongoing act/behavior (e.g., in a jazz performance, a double bass player delaying the plucking of a chord following a missed beat by the drummer). Predictability in temporal dynamics is inherent to rhythmic patterns (beat-based timing); however, it is also present whenever the signal provides enough information to generate expectations as to *what should happen when* (perceived and/or produced events). For instance, well-trained contemporary musicians or dancers can learn complex arrhythmic patterns; that is, they can prepare, initiate and smoothly execute the right moves at the right time despite the lack of metrical structure (present in most western music) or non-metrical regularity (as in speech prosody). Adjustment can also be made in the timekeeper's settings. For instance, the detection of a phase shift in an otherwise perfectly regular sequence presumably leads to a resetting of the clock period, even if no external movement is produced. Of course, the correct detection of temporal perturbations is not informative *per se* for the underlying internal timekeeping parameters. However, the fact that the same participants with the same sequences correct for these errors rapidly when asked to tap in time with the sounds of the pacing sequence is a strong indicator of a resetting of the period of the internal clock following the detection of a phase-shift perturbation. It's important to note, however, that apart from the age-related effects observed for auditory duration discrimination, the effects of variable rhythmic grouping on temporal sensitivity is greatest among older listeners independent of hearing loss. Such findings have implications for speech discrimination in degraded/noisy environments in terms of identifying deficits in temporal processing that are unrelated to the loss of hearing sensitivity associated with normal aging (Gordon-Salant et al., 2011; Fitzgibbons and Gordon-Salant, 2015).

CONCLUDING REMARKS

Our review of the literature suggests that there are fundamental age-related changes in the functioning of the cortico-thalamic-basal ganglia circuits that implement timing in the hundredths of milliseconds-to-minutes range. There are also instances of at least partial compensation that can in many cases mask age-related declines in timing and time perception and allow older adults to perform as well or nearly as well as young adults until the load of either cognitive demands or physical decline pushes them past their threshold for being able to compensate. Reuter-Lorenz and colleagues (e.g., Reuter-Lorenz and Lustig, 2005; Reuter-Lorenz and Cappell, 2008; Lustig et al., 2009; Lustig and Jantz, 2015) have referred to this as the compensation-related utilization of neural circuits (CRUNCH) hypothesis. Despite age-related declines in cognitive functions such as attention and working memory, older adults are still able to rely on these processes by recruiting additional cognitive resources and capitalizing on the availability of external cues that serve as environmental support. This leads to an increased reliance on predictive timing circuits, monitoring deviations from expectations (i.e., temporal errors) and allowing for adaptive corrections (i.e., online adjustments) to the parameters of internal timekeeping mechanisms and/or external movements like the olivocerebellar and parietofrontal networks (e.g., Turgeon and Wing, 2012; Gu et al., 2015a; Petter et al., submitted).

As a consequence of the above observations, we propose that: (1) as the functioning of MSNs in cortico-thalamic-basal ganglia circuits serving as coincidence detectors of patterns of cortical oscillations become more variable and therefore less reliable with age (see Allman and Meck, 2012), cortico-cerebellar or hippocampal regions that are less affected by the aging process are recruited to influence and/or take over some of these timing functions through de-generacy principles (e.g., Meck, 2002a; Merchant et al., 2013; Lusk et al., 2016; Petter et al., submitted); (2) the dynamic adjustments performed by error correction pathways implement Bayesian optimization principles, namely to estimate the likelihood of an actual event distribution (*prior* function) with as much relevant data as possible and to minimize error (*loss* function), that is the disparity between predicted (via internal clock) and actual (via external feedback) interval series (e.g., Jazayeri and Movshon, 2006; Jazayeri and Shadlen, 2010; Shi et al., 2013; Gu et al., 2015a).

It is important to note that the interplay among the regulation of multisensory integration, clock speed, feedback, and brain dopamine levels that contributes to distortions and preservations in time perception and timed performance are relevant not only to normal aging, but also to the timing differences associated with psychosis, dementia, and other types of neurodegeneration (e.g., MacDonald and Meck, 2005; Meck, 2005; Bonnot et al., 2011; Allman and Meck, 2012; Lake and Meck, 2013; Piras et al., 2014; Gu et al., 2015a; Bedard and Barnett-Cowan, 2016). The overall conclusion is that normal aging is commonly associated with reductions in the speed and increased variability in the operation of a core timing circuit supported by distributed dopamine-glutamate and GABA interactions in cortico-striatal circuits (e.g.,

Buhusi and Meck, 2002; Tseng and O'Donnell, 2004; Cheng et al., 2006, 2007, 2016; Merchant et al., 2013; Matthews et al., 2014; Terhune et al., 2014). These age-related changes in interval timing and relative time-sharing function at the level of multiple time scales, systematically affecting reaction time and unpaced finger tapping, the playing of sports and musical instruments, consciousness, retrospective and prospective memory processes, and other types of time, number, and reward-based decision making (e.g., Tulving, 2002; Fortin, 2003; Zakay and Block, 2004; Buonomano, 2007; Buhusi and Meck, 2009a; Fortin et al., 2009; Nyberg et al., 2010; Meck et al., 2012b; Turgeon and Wing, 2012; Aagten-Murphy et al., 2014; Allman et al., 2014a; Bermudez and Schultz, 2014; French et al., 2014; MacDonald, 2014; MacDonald et al., 2014; Wolkorte et al., 2014; Zakay, 2014; Yin et al., 2016b).

Given that senescence is observed in natural populations of animals—affecting their foraging strategies based, in part, on interval timing and the setting of temporal horizons (Bateson, 2003; MacDonald et al., 2007), the understanding of age-related changes in timing and time perception would appear to have widespread implications for bio-gerontology, emotional regulation, time-based prospective memory and other types of temporal cognition (e.g., Löckenhoff and Carstensen, 2007; Löckenhoff, 2011; Alexander et al., 2012; Nussey et al., 2013; Anderson et al., 2014; Fingelkurts and Fingelkurts, 2014; Matthews and Meck, 2014, 2016; Tucci et al., 2014; Vanneste et al., 2015; Lake, 2016; Lake et al., 2016; Mather, 2016). By providing a foundation for evaluating brain aging effects on timing and time perception we are now better prepared to evaluate the need for and effectiveness of interventions designed to alleviate age-related declines in temporal cognition (Roberts and Allen, 2016).

AUTHOR CONTRIBUTIONS

MT, CL, and WHM jointly wrote the review article.

ACKNOWLEDGMENTS

The authors would like to thank Melissa Allman, Penny Lewis, Devin McAuley, and John Wearden for previous discussions on this and related topics. We would also like to thank Nicholas Lusk and Elijah Petter for their illustration of cortico-striatal and cortico-cerebellar timing circuits.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 09 June 2016
doi: 10.3389/fnagi.2016.00135

Six-Year Training Improves Everyday Memory in Healthy Older People. Randomized Controlled Trial

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Purpose of the study: Everyday memory of older persons does not improve with intensive memory training programs. This study proposes a change in these programs based on a time-extended and massive intervention format.

Design and Methods: The sample of 1007 healthy older persons (mean age 71.85; SD = 5.12) was randomized into 2 groups. The experimental group followed an extended 6 years of training (192 sessions over 192 weeks) whereas the control group received an intensive training (3 sessions per week for a total of 32 sessions in 11 weeks). The program included cognitive and emotional content whose effects were assessed with the Rivermead Behavioral Memory Test (RBMT) and with the Mini-Mental State Examination (MMSE). Both groups were evaluated initially, after 32 sessions, and again after 6 years.

Results: The relative improvements measured with Blom's derivative showed that everyday memory and mental status of the experimental group were significantly better both in the short (Δ% 8.31 in RBMT and Δ% 1.51 in MMSE) and in the long term (Δ% 12.54 in RBMT and Δ% 2.56 in MMSE). For everyday memory and mental level, the overall gain estimate representing the mean difference in pre-post change between time-extended and intensive groups was 0.27 (95% CI: 0.13–0.40) and 0.54 (95% CI: 0.40–0.67), respectively. Time-extended programs have significantly improved everyday memory in contrast with the usual intensive programs whose effects decay with time. There are also significant increases in mental level scores while daily life functionality is preserved in all subjects who completed the training.

Implications: These results suggest that it is possible to preserve everyday memory in the long term with continuous training and practice. Massive and time-extended formats may contribute in the future to a paradigm shift in memory programs for healthy older people.

Keywords: older adult, everyday memory, long-term, training, randomized, trial

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Annette N. Boles, Texas Tech University Health Sciences Center, USA
Emma V. Ward, Middlesex University, UK

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Received: *24 March 2016*
Accepted: *27 May 2016*
Published: *09 June 2016*

Citation:
Requena C, Turrero A and Ortiz T (2016) Six-Year Training Improves Everyday Memory in Healthy Older People. Randomized Controlled Trial. Front. Aging Neurosci. 8:135. doi: 10.3389/fnagi.2016.00135

INTRODUCTION

The exponential growth of an aged population in the early 21st century means that not only has their overall life expectancy increased, but a far greater proportion are reaching this advanced life expectancy. Retirement thus occupies about one third of our whole lifetime and often coincides with the reduction of physical (Mullen et al., 2012) or cognitive activity (Bamidis et al., 2014),

and/or a reduction in social activities (Wrosch et al., 2013). Therefore, aging societies face the challenge of preserving the autonomy of older people until the end of their lives. Since the brain and cognition remain plastic even in older age, this collective can improve their memory skills through instruction and practice (Mayr, 2008), even if some cognitive standards decline.

Early memory training approaches used mono-factorial techniques such as visualization or organization, cognitive re-structuring, concentration, faces and numbers, mnemonic techniques (Lachman et al., 1992), or the loci method (Rose and Yesavage, 1983). Ulterior mono-factorial approaches implement not only memory techniques but also train other related support processes such as attention, reasoning, and processing speed. In cognitive-training studies such as Advanced Cognitive Training for Independent and the Vital Elderly (ACTIVE), subjects are distributed into different groups, each of them training a particular process. The evaluation of each process as a laboratory task allows the measurement and comparison of the effect of both trained and non-trained processes. Yet, as evidence has accumulated regarding their benefits, interest in multifactorial approaches has increased since the efficacy of a given cognitive component may depend upon the activation and interaction of various processes (Gross et al., 2012).

Multifactorial programs are a jumble of several methods based on the observation that real-world tasks rarely depend on a single component of cognition. Accordingly, the cognitive-training approach was to train a range of cognitive processes, that are likely involved in many everyday tasks and that decline with age. For instance, the everyday activity of cooking requires a variety of cognitive processes including planning, attentional (executive) control, and working memory. Significant examples of multifactorial programs are centered on prospective memory training which is needed in daily life to remember errands and appointments or accurately remember medical information. These programs incorporate discussion groups which provide opportunities to overcome emotional alterations caused by erroneous beliefs about memory (Phillips and Ferguson, 2013). Additionally, the mutual support given by the group improves training performance (Wilson, 1992). Both mono-factorial and multifactorial programs are generally carried out in an intensive fashion, that is, 1–15 sessions given over 6–8 weeks.

Memory training programs have immediate beneficial effects over trained and distal processes and seem to be momentarily transferred to daily life activities. A recent meta-analysis on intensive memory-training programs shows that the tendency towards memory improvement does not seem to be associated with the specific trained content but rather with their diversity and repetition which also produces more solid effects on everyday life. The effects during the middle and long term of multifactorial programs is not known, hence the effect of their transfer and the persistence of their training benefits are also ignored. Concerning mono-factorial programs, their benefits are also immediate and since these improvements decay after 2 years, reinforcement sessions have been proposed as a means to maintain the longitudinal positive effect of mono-factorial programs. In particular, the ACTIVE program, a major randomized trial on cognitive training for older adults, shows gains in the training group as opposed to the control even 5 years after training. However, in the 10-year evaluation of the ACTIVE program, we found reinforcement sessions preserve certain improvements with respect to the basal line in some cognitive functions (reasoning and speed-of-processing), but not everyday memory which decays under the basal line. Therefore, the longitudinal follow-up of current intensive programs has made it evident that their benefits with regard to memory decline over time, principally because the majority of the participants do not continue to employ the techniques they have learned (Cohen-Mansfield, 2014).

The key to preserving everyday memory gains over time is the variety of content (Gross et al., 2012), the repetition of the training, and the number of sessions (Rebok et al., 2014). Our conceptual proposal is to set up a time-extended training program to train for both cognitive and emotional content, while simultaneously practicing them in real life. The objectives of this study were to contribute to the knowledge of the effect of time on mental level and everyday memory through the analysis of the effect of a time-extended training program vs. an intensive program as control.

MATERIALS AND METHODS

Participants

The initial candidate group consisted of 1756 subjects older than 65 years. They were all living independently and enjoyed good functional and cognitive status. The participants were recruited through members of the city's senior community centers for the retired established at the Ponferrada Town Hall, an urban district in the province of León, Spain. Of the total subjects interested in participating, 592 were excluded. Ninety-five percentage of the remaining participants completed the training intervention. Baseline characteristics are shown in **Figure 1** according to intervention groups.

Finally, the study included 711 subjects in the experimental group and 296 in the control group (**Figure 1**). The demographic characteristics of the experimental group were: 617 women and 94 men whose ages ranged from 65 to 83 years old (average: 71.76, standard deviation (SD): 5.05); educational level: 95 had obtained a university degree, 136 had completed secondary school, and 480 had only finished primary school; marital status: 350 were married, 290 were widowed, 62 were single, and 9 were divorced. In the control group, the age range was from 65 to 83 years old (average: 71.85, SD: 5.12); 253 women and 43 men; educational level: 46 had obtained a university degree, 62 had completed secondary school, and 188 had only finished primary school; marital status: 173 of them were married, 90 were widowed, 27 were single, and 6 were divorced.

The exclusion criteria were: self-reported diagnoses of Alzheimer's disease, severe sensory impairment (sight and/or hearing), moderate dependence (help needed to perform

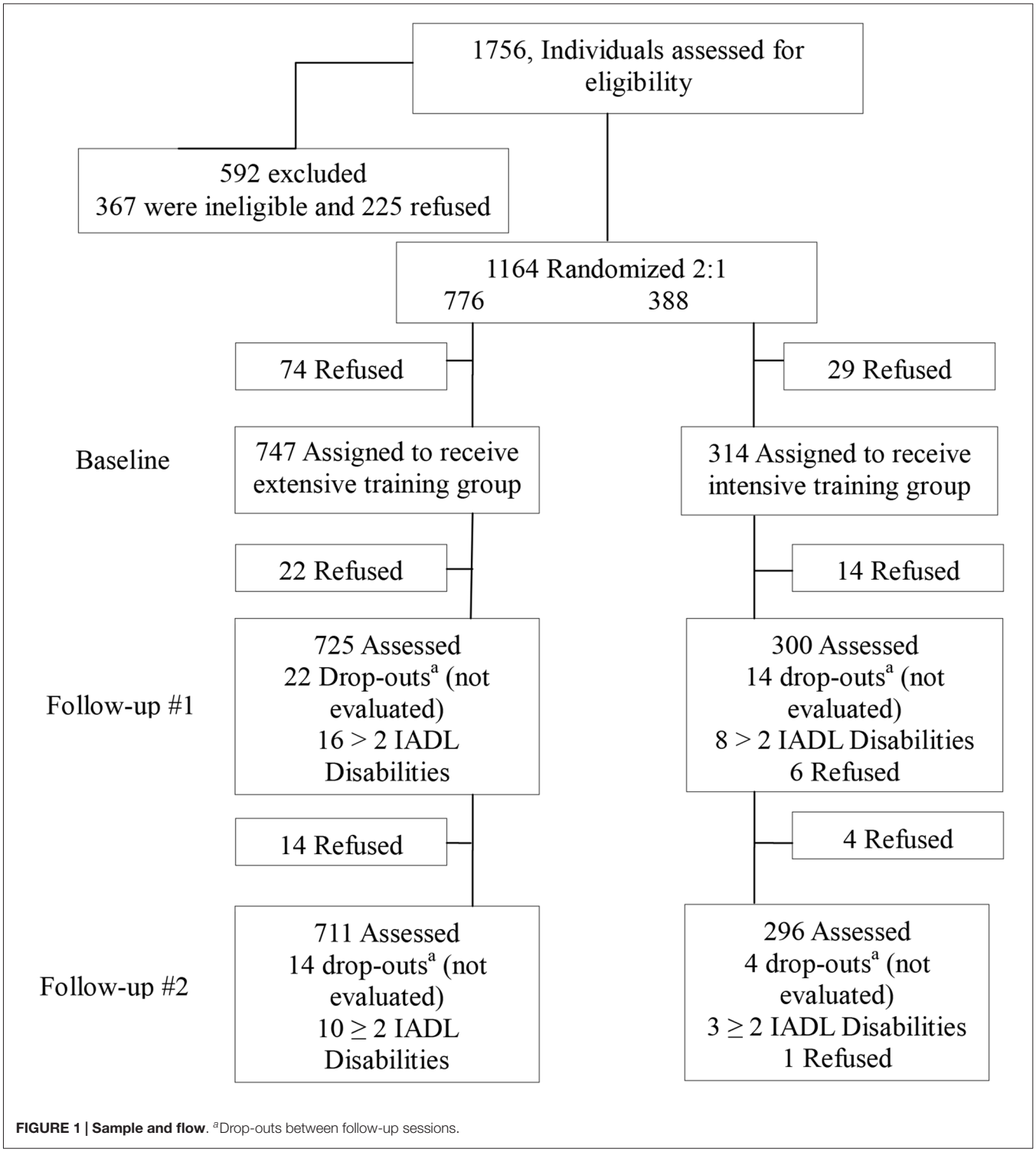

FIGURE 1 | Sample and flow. [a]Drop-outs between follow-up sessions.

Instrumental Activities of Daily Living (IADLs) more than twice a day) reported by the social worker, or unavailability during the study period. Written, informed consent was obtained from all the participants after they received both verbal and written information about the study.

The trial was approved by the Ethical Hospital Service of León and Technical Committee of the City Council of Ponferrada. Subjects who did not meet the inclusion criteria were referred to a family doctor for further evaluation and check-ups.

Procedure

Memory Training Program

The initial recruitment began in January 2006 with informative talks given in senior citizen community centers where the study was carried out. Those who signed up as prospective participants were later contacted by telephone and evaluation and appointments were scheduled. The evaluations lasted for approximately 90 min and involved the completion of a socio-demographic questionnaire and the administration of the tests chosen for this study. The initial response was greater than anticipated. Since we were limited by the capacity of the senior citizen community centers, this problem was overcome by publicly drawing lots of the interested subjects in order to decide who was to participate.

The subjects chosen were then randomized into two groups: extensive training (experimental) and intensive training (control). A randomized controlled procedure with a 2:1 allocation ratio was carried out combined with stratified randomization by age, sex and mini-mental state examination (MMSE) scores. It was decided that any subject who abandoned the study at any stage or who did not attend at least 80% of the sessions, would be excluded from the statistical analysis. This intervention has been registered[1] and assigned the reference[2]. The control group received 32 intensive sessions, at a frequency of three times weekly for 11 consecutive weeks in 2006. The experimental group received 192 sessions, at a frequency of once weekly for 32 weeks from October to May each year between 2006 and 2012.

The program was carried out in two phases: the first phase analyzed the differences between the extended and intensive training programs after both groups had received 32 sessions; and the second phase analyzed the effect of the additional 160 sessions of training only received by the experimental group. In all, three assessments were performed: at baseline, after 32 training sessions (follow-up #1), and a final evaluation of both groups in year 6 (follow-up #2). In the case of the control group, follow-up #1 took place after 32 sessions at the 11th week, and follow-up #2 at the 6th year. In the case of the experimental group, follow-up #1 occurred after 32 sessions at the 32nd week, and follow-up #2 took place after the last (6th) year after receiving an additional 160 sessions in 160 weeks.

The training group in the time-extended program was comprised of a working group (which focused on common tasks) and a discussion group (which fostered active participation and experience exchange). Memory training program sessions were based on *the Group Memory Therapy Model* and on the *Memoria Mejor* (MM) program (Requena, 2002, 2005). The training program included the instruction of eight qualified psychologists (M.A. or Ph.D.). Therapists used register sheets for each participant on which correct/failed exercises were checked and registered relative to each training module: homework, group sessions, and attendance. This data was collated in therapists' monitoring sessions at the end of each module. Further details on the administration, intervention, and monitoring of the memory training are offered[3].

Group Memory Therapy

Wilson's model includes cognitive and emotional content which we organized into 11 modules, the first nine of which addressed techniques and strategies to improve working memory both retrospective and prospective. During the last two modules, the affect of mood was addressed in the discussion groups.

Module I: How does the memory work?

The objectives of the memory program were explained as well as issues regarding the different types of memory and memory in older age. This module included home exercises so that participants could accurately measure their own performance in different memory tasks.

Module II: Making it easier to remember

External aids such as temporary storage (e.g., shopping list), long-term storage (e.g., address book), planning (e.g., calendar) or organizing one's space (e.g., keeping each thing in its appropriate place) were explained.

Module III: Concentration

This module dealt with maintaining concentration skills such as having brief periods of rest during reading, suppression of external distractions (e.g., working in a calm room or doing one thing at a time), or working against one's intrusive thoughts (e.g., verbalizing the action during its performance).

Module IV: Practice makes perfect

Information to be learned by the experimental subjects was presented in group settings (e.g., names of people or objects). Each group member identified information to learn and remember such as people's names, objects, or dates. One of those elements was selected to practice daily using worksheets. This exercise was spaced throughout the day using a rule of doubling the time interval in between practice sessions (e.g., the exercises commenced at 10:30 am, 10:32 am, 10:36 am, 10:44 am, and so on: Wilson and Moffat, 1992).

Module V: Remembering to run errands

The group focused on exploring ways to reduce the chance of forgetting (e.g., method of Loci). The procedure consisted of creating an itinerary (almost always a sequence of rooms) that was very familiar to the subject. This itinerary was linked to tasks or issues that the experimental subject wished to remember (e.g., to do errands or make phone calls).

Module VI: Remembering information

Practicing this module entailed tasks such as recalling a newspaper article or recent news seen on television. Homework related to this was also given (e.g., fill-in-the-blank exercises on paper regarding the news).

[1] www.controlled-trials.com

[2] http://www.isrctn.com/ISRCTN46109513

[3] http://www.isrctn.com/ISRCTN46109513

Module VII: Active listening and expressing ideas
Cards with sequences of listening activities as well as instructions for expressing ideas were given to the participants. Each group member gave a presentation about a freely chosen topic. The cards were distributed among the group members to maintain a minimal rate of conversation and also help them to remember the presentation's main issues.

Module VIII: Making the best use of my memory
Exercises within this module were designed to stimulate mental skills that reinforce memory. They included sensory stimulation exercises (e.g., improving visual acuity using a photograph), voluntary attention (e.g., identifying a misspelled word), intellectual structuring (e.g., re-ordering a disorganized text), language (e.g., word puzzles) or calculations (e.g., Sudoku).

Module IX: Exercising memory strategies
Training subjects were required to engage in categorization activities by grouping information. In order to remember a list of words, the subject had to organize them into different categories which required a degree of abstraction. During practice, a disorganized list of elements was given. Next, the participants had to sort the list into different categories. Finally, those words had to be remembered without naming the categories.

Module X: Confronting others' problems
Many of the group members share similar worries including cognitive, emotional, family, economic, and legal problems. The group was encouraged to discuss the problems or struggles that were proposed by the psychologist or a group member. If any particular group member required specific information, he or she was referred to a social worker at the senior citizens community center.

Module XI: Emotion and memory
This module concentrated on the relationship between mood and memory performance (or more precisely the self-perception of memory performance). The therapy group discussed the relationship between confidence in one's memory and factors like depression, good vs. bad days, and anxiety. Relaxation and auto-instructional training were proposed to aid memory when lapses occur.

Pastimes in the MM Program

Pastimes in the MM Program were selected from journals and magazines by the older people themselves (Requena, 2002, 2005). Exercises improve linguistic, numeric, spatial and constructive tools. Pastimes are: (1) alphanumeric code; (2) extraction of words from other words; (3) word completion from missing vocals; (4) recognition of misplaced words; (5) alphabet soups; (6) peseta/euro conversion; (7) tangram (5 levels of difficulty); (8) domino; (9) magic stair; (10) crosswords combined with labyrinths; (11) knight moves; (12) operations with addresses; (13) calculation of prizes of fruit; (14) letter puzzles (1 level of difficulty); and (15) colors and forms layout patterns. Pastimes are also ordered in levels of difficulty with at least six individual exercises for each type of exercise. Exercise types with training, reinforcement, and solutions are available at the web address given below[4]. The contents of the 32 training sessions were organized in the following way: the first 11 training sessions corresponded with the 11 modules. Each of the first nine pastimes occupied a session (from the 12th to the 20th), while the remaining pastimes occupied two training sessions each (from the 21st to the 32nd). With regard to the 160 refresher sessions only received by the experimental group, they were distributed in 32 sessions during the following 5 years after the treatment (1 weekly session from October to May). The contents of refresher had different individual exercises but were organized in the same manner as the training sessions.

The temporal distribution of training sessions was as follows: sessions were held over 75 min in groups of between 8 and 10 people, 60% of this time was set aside for modules and pastimes, 30% of the session involved debate and discussion concerning the difficulty of the exercises and its daily life application, while the remaining 10% of the session was dedicated to solving doubts raised by homework exercises which were repetitions of already trained abilities.

Measures

A number of instruments was used to evaluate the psychological effects of the extended training. The Mini-Mental Cognitive Examination (MEC-35) test is the Spanish adaptation (Lobo et al., 1979; Lobo, 1987) of the MMSE (35 items; Folstein et al., 1975). This test is widely used to quantify intellectual deterioration or mental level and its progression over time since it can be used repeatedly and thus document an individual's response to training or treatment. Mental level is measured with tasks involving orientation, attention, concentration, language, calculation, constructive praxia, and work memory. A measure equal or higher than 1.5 times the SD with respect to the subject's normative levels (age and education), implies a sucessful mental level. The MMSE has an 84.6% sensitivity and an 82% specificity (Saz and Lobo, 1993).

Memory was evaluated through the standardized measure Rivermead Behavioral Memory Test (RBMT; Wilson et al., 1985). The RBMT is a battery designed to tap the participant's memory doing everyday tasks. There is evidence that favors the use of the RBMT in older adults and for neuropsychological assessment of memory impairment (Cockburn, 1996). The RBMT assesses different types of memory such as associative memory, prospective memory, visual memory, verbal memory, topographic memory, control, and recognition strategies which produces a global score from 0 to 12 points. A Spanish version of the RBMT has been used and validated with the Wechsler Memory Scale.

Statistical Analysis

The scores for each cognitive or functional measure were normalized using the Blom transformation (Blom, 1958;

[4]http://envejecimientoentodaslasedades.unileon.es/primera-generacion.html

Lehmann, 1975), the most commonly used rank-based inverse normal transformation. Homogeneity for the experimental and control groups at baseline was analyzed using two-sample *t*-tests for transformed measures and age, and using χ^2 (chi squared) tests to assess sex and educational level. In order to evaluate the effects of the memory program, a repeated-measures-mixed-effects model was used, with the group as the between-subjects factor (experimental and control) and the repeated measures were the MMSE and RBMT. Mental status and everyday memory were measured at baseline, post-training (follow-up #1), and at the follow-up evaluation (follow-up #2). A Bonferroni *post hoc* analysis was completed. All statistical analyses were carried out using SPSS 22 statistics software.

Effect Size Calculation

Effect size was defined as "gain" in order to adapt to standard usage in the relevant literature (Gross et al., 2012; McDaniel et al., 2014; Rebok et al., 2014). Training gain was calculated in three stretches, follow-up #1 − baseline, follow-up #2 − baseline, and follow-up #2 − follow-up #1. Average differences were divided by the pooled SD to place gain values of all memory training programs in the same scale. The same calculations were performed to obtain control group gains.

Retest-adjusted gains were also calculated as experimental improvement from baseline to year 6 minus control improvement from baseline to year 6 divided by the intra-subject SD of the composite score. The first set of effect sizes were standardized differences in mental level and everyday memory change between baseline and follow up #1 and follow up #2 assessments. In contrast, retest-adjusted effect sizes or gains represent everyday memory and mental level change attributable to training by adjusting for a retest effect in control.

Improvement

A first assessment of the long-term change in mental level (as measured by MMSE) and everyday memory is given by the relative percentage increase in these measures at the two time points evaluated: follow-up #1 and follow-up #2. This measure is defined by: Δ% measure follow-up-up # 1 equal to intermediate measure minus baseline measure divided by baseline measure and multiplied by 100. The same calculation to follow-up #2 was repeated.

The values of these increases for the MMSE and RBMT scores along the period of study are shown in **Table 1**. The columns represent the average increase/decrease of each measure in relation to the baseline scores for each group. For example, from the baseline values the MMSE scores increased in the experimental group an average of 1.51% and 2.56% in follow-up sessions #1 and #2 respectively. By contrast, in the control group this average value remained virtually unchanged during follow-up session #1 (0.06%) and had decreased slightly in follow-up session #2 (−0.20%). This divergent tendency was also evident for the RBMT measures.

TABLE 1 | Mean values, standard deviations (SDs) and mean relative percentage increases for mini-mental state examination (MMSE) and rivermead behavioral memory test (RBMT) at baseline and follow-up sessions.

		MMSE	SD	RBMT	SD
	Baseline	29.35	0.98	7.26	2.26
Training group	Follow-up #1	29.78	0.94	7.70	2.27
($n = 711$)	Follow-up #2	30.09	0.89	7.98	2.31
	Baseline	29.32	1.09	7.22	2.26
Control group	Follow-up #1	29.32	0.94	6.97	2.29
($n = 296$)	Follow-up #2	29.25	1	7.04	2.15
Mean relative percentage increases			**Δ% MMSE**		**Δ% RBMT**
	Follow-up #1		1.51%		8.31%
Training group	Follow-up #2		2.56%		12.54%
	Follow-up #1		0.06%		−2.42%
Control group	Follow-up #2		−0.20%		−0.87%

MMSE, Mini-Mental State Examination; RBMT, Rivermead Behavioral Memory Test; SD, Standard deviation.

Effects of the Memory Training Program

To evaluate the effects of this intervention program, a repeated-measures model was used. When the plot of the means for Normal Blom composite of the Mini-Mental State Examination (NMMSE) was analyzed (**Figure 2**), it appeared that the experimental and control groups exhibited divergent behavior during the follow-up period.

There is also a clear NMMSE * group interaction. Statistical analysis highlighted the significant differences among NMMSE scores through the follow-up period ($F_{(2,1946)} = 92.12$, $p < 0.001$ $\eta^2 = 0.125$). The interaction of the NMMSE * group was very significant ($F_{(2,1946)} = 139.31$, $p < 0.001$ $\eta^2 = 0.194$) and there were significant differences between the NMMSE scores in both groups ($F_{(1,1005)} = 53.28$, $p < 0.001$ $\eta^2 = 0.05$).

When the means of Normal Blom composite of the Rivermead; Behavioral Memory Test (NRMBT) scores were plotted (**Figure 2**), it again seemed that the experimental and control groups exhibited divergent behavior during the follow-up period and that an NRBMT * group interaction was present. The statistical analysis showed significant differences among NRBMT scores during the follow-up period ($F_{(2,1951)} = 24.26$, $p < 0.001$ $\eta^2 = 0.045$) and a strongly significant NRBMT * group interaction ($F_{(2,1951)} = 69.76$, $p < 0.001$ $\eta^2 = 0.107$). There were also significant differences between the NRBMT scores in both groups ($F_{(1,1005)} = 14.97$, $p < 0.001$ $\eta^2 = 0.015$; see **Figure 2**).

Means and SDs of transformed measures and age at baseline are shown in **Table 2**. NMMSE and NRBMT represent the transformed values of these measures. None of the comparisons between the means of the two groups reflected statistically significant differences when subjected to a *t*-test (all $p > 0.73$). Also, the groups were homogeneous with regard to gender ($\chi^2_1 = 03$, $p = 0.58$) and educational level ($\chi^2_2 = 1.563$, $p = 0.458$).

The *post hoc* analysis indicated that there were significant differences between the means of the NMMSE scores for both groups in the follow-up #1 and follow-up #2 sessions. There were also significant differences among

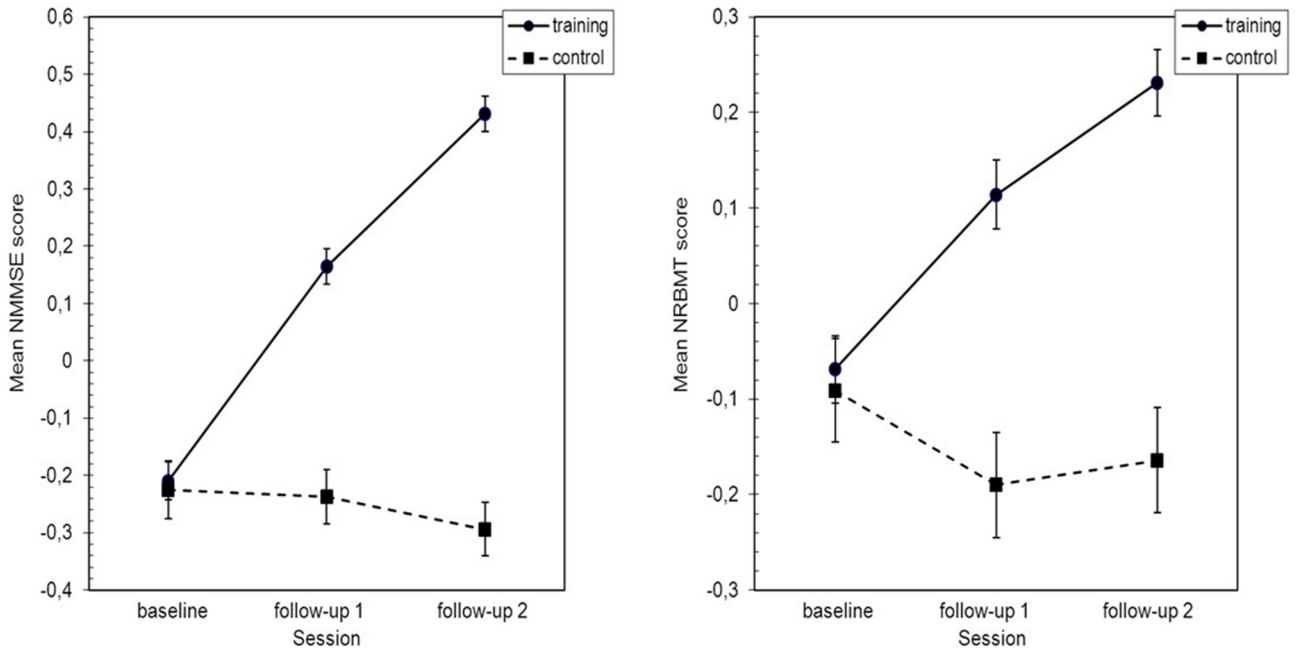

FIGURE 2 | Standarized means plot of normal blom composite of the mini-mental state examination (NMMSE) and normal blom composite of the rivermead behavioral memory test (NRMBT) scores. Error bars indicate SEM. NMMSE, Normal Blom composite of the Mini-Mental State Examination; NRBMT, Normal Blom composite of the Rivermead Behavioral Memory Test; SEM, Standard Error of mean.

TABLE 2 | Multiple comparisons for normal blom composite of the mini-mental state examination (NMMSE) and normal blom composite of the rivermead behavioral memory test (NRBMT).

		NMMSE			NRBMT		
	Session	**Mean**	**SD**	**95% CI**	**Mean**	**SE**	**95% CI**
Training group	Baseline	−0.210	0.033	(−0.274, −0.147)	−0.069	0.035	(−0.138, −0.000)
	Follow-up #1	0.164	0.031	(0.104, 0.224)	0.114	0.036	(0.044, 0.184)
	Follow-up #2	0.431	0.031	(0.371, 0.491)	0.231	0.035	(0.162, 0.300)
Control group	Baseline	−0.225	0.05	(−0.324, −0.126)	−0.091	0.054	(−0.198, 0.015)
	Follow-up #1	−0.237	0.047	(−0.331, −0.144)	−0.190	0.055	(−0.298, −0.082)
	Follow-up #2	−0.294	0.047	(−0.387, −0.201)	−0.164	0.055	(−0.271, −0.057)
	Session	**Gains**	**SD**	**95% CI**	**Gains**	**SE**	**95% CI**
Training group	Follow-up #1−baseline	0.421	0.051	(0.320, 0.522)	0.186	0.051	(0.086, 0.286)
	Follow-up #2−baseline	0.721	0.053	(0.618, 0.824)	0.309	0.051	(0.208, 0.409)
	Follow-up #2−Follow-up #1	0.310	0.051	(0.210, 0.411)	0.119	0.051	(0.019, 0.219)
Control group	Follow-up #1−baseline	−0.014	0.082	(−0.175, 0.147)	−0.106	0.082	(−0.267, 0.056)
	Follow-up #2-baseline	−0.083	0.082	(−0.244, 0.079)	−0.078	0.082	(−0239, 0.082)
		−0.070	0.082	(−0232, 0.091)	0.027	0.082	(−0.134, 0.186)
Retest adjusted gain	Follow-up #2−follow-up #1	0.537	0.069	(0.401, 0.673)	0.269	0.069	(0.134, 0.219)

Means, standard errors (SE), effect size (gain), retest effect and 95% confidence intervals (CI). NMMSE: Normal Blom composite of the Mini-Mental State Examination. NRBMT: Normal Blom composite of the Rivermead Behavioral Memory Test. Gain: Effect size defined as the mean difference between the post-training and pre-training scores for the trained group divided by the pooled standard deviation (SD). Positive effect sizes indicate improvement. Retest-adjusted gain was defined as training improvement from baseline to year 6 minus control improvement from baseline to year six divided by the pooled standard deviation. CI, Confidence Interval.

the means of the baseline, intermediate, and final NMMSE scores in the experimental group. No significant differences were found among the means of NMMSE scores in the control group. All of these comparisons were made using the Bonferroni test at the 5% level and the results of these comparisons are shown in **Table 2**.

The *post hoc* analysis emphasised the significant differences between the means of NRBMT scores in both groups at the follow-up #1 and follow-up #2 sessions. There were significant

differences between the means of NRBMT values at baseline and in the 2nd follow-up sessions but not between the follow-up #1 and follow-up #2 sessions in the experimental group. No significant differences were found among the means of NRBMT scores in the control group. All comparisons were made with the Bonferroni test at the 5% level of significance, as shown in **Table 1**.

Longitudinal gains with respect to the three measures of time and retest-adjusted gain, are also shown in **Table 2**. The interpretation of data follows Cohen's values, which describe an effect size of 0.2 as small, 0.5 as medium, and 0.8 as large (Brown and Prescott, 2006). Because the analyses included three comparisons, a corrected significance level of $p < 0.05$ was used.

Descriptive Analysis of Cognitive Subdomains in the Follow-Up Period

Global RBMT measures include 12 items distributed in five subdomains: "names" (items 1 + 2), "prospective memory" (items 3 + 4), "recognition" (items 5 + 7), "short-term memory" (items 6 + 8 + 10), and "orientation" (items 9 + 11 + 12). Statistical analyses of standardized means plots are shown in **Figure 3**.

In view of the plots, control and training groups differ significantly in the baseline scores in the subdomains "names," "prospective memory," and "recognition" ($p < 0.001$), therefore results concerning these subdomains should be interpreted with caution. The subdomain "names" exhibits a divergent behavior between the two groups in the follow-up #2, but the differences shown in the baseline do not allow one to interpret the differences observed.

Regarding the subdomains "prospective memory" and "recognition" which had higher baseline scores in the control group, 2 facts are worth mentioning: the divergent trend in both groups and the strongly significant differences at follow-up session #2 ($p = 0.009$ and $p < 0.0001$ respectively) were again noted.

Finally, the "short-term memory" and "orientation" subdomains are homogeneous in the baseline ($p = 0.597$ and $p = 0.961$ respectively) with significant differences found in follow-up session #2 ($p < 0.001$ in both cases) but not in the follow-up session #1 ($p = 0.525$ and $p = 0.48$ respectively).

Plots and p-values displayed come from the repeated measures analyses for each subdomain, once such measures were Blom-transformed. The analysis of subdomains is therefore consistent with the global RBMT score, that is, with the long-term gradual improvement.

The MEC-35 test contains five subdomains: orientation, short-term memory, attention, concentration and calculation, and language and construction. The first two subdomains have already been analyzed with RBMT items, while the three final ones have been statistically analyzed; their standardized means plot is shown in **Figure 4**.

Control and training groups differ significantly in the baseline scores in the subdomain "concentration and calculation" ($p = 0.018$), whereas the other two were homogeneous in baseline ($p = 0.29$ and $p = 0.175$). For these two subdomains, the evolution along the follow-up period was similar for both groups up to follow-up #1. From here on, the behavior was divergent with significant differences in follow-up #2 ($p < 0.001$ in both cases). Results relative to "concentration and calculation" clearly showed the stabilization of scores along the follow-up period in the control group and the significant growth of these scores along the follow-up period in the training group ($p < 0.001$ in both times). In addition, differences between groups shown at follow-up #2 for this subdomain were close to the significance ($p = 0.058$).

DISCUSSION

As far as we know, this is the first study to analyze the effects of a time-extended memory training program which included cognitive and emotional content for older adults. The extended format resulted in significant short and long-term improvement in everyday memory and mental level (as measured by MMSE), in contrast with the usual intensive format whose effect on memory decays with time. All participants have preserved independent performance in IADLs with respect to the basal line.

The behavior of the variables "mental level," MMSE, and "everyday memory," RBMT, at follow-up are remarkably divergent between the experimental (extended program) and the control groups (intensive program; see **Figure 2**). The descriptive analysis of that behavior shows that the average percentage increase in MMSE scores in the experimental group reaches 1.51% and 2.56% after 32 weeks and 6 years respectively. On the other hand, in the control group the above-mentioned average remains invariant and decreases slightly (0.20%) at both periods (see **Table 2**). The average relative percentage increase in RBMT scores in the experimental group was 8.31% and 12.54% after 32 weeks and 6 years respectively, while in the control group this percentage decreased on average 2.42% and 0.87% at both periods (see **Table 2**).

In the first phase of our study, both experimental and control groups were given the same total number of sessions and the same content but with different formats: extended and intensive, respectively. The extended form of the training resulted in a significant gain in both mental level (0.421) and everyday memory (0.186) in relation to their corresponding baseline scores (follow-up #1−baseline), against the invariance or non-significant decrease of both scores with the intensive training (mental level: −0.014, everyday memory: −0.106). In the second phase of the study, only subjects in the experimental group received further sessions in an extended format. Now, MMSE scores exhibit gains of 0.721 with respect to those obtained at the baseline (follow-up #2−baseline) while RBMT scores show gains of 0.309 in relation to the base line (follow-up #2−baseline). Again the intensive training or control group did not show any gains in both measures: −0.083 (follow-up #2−baseline).

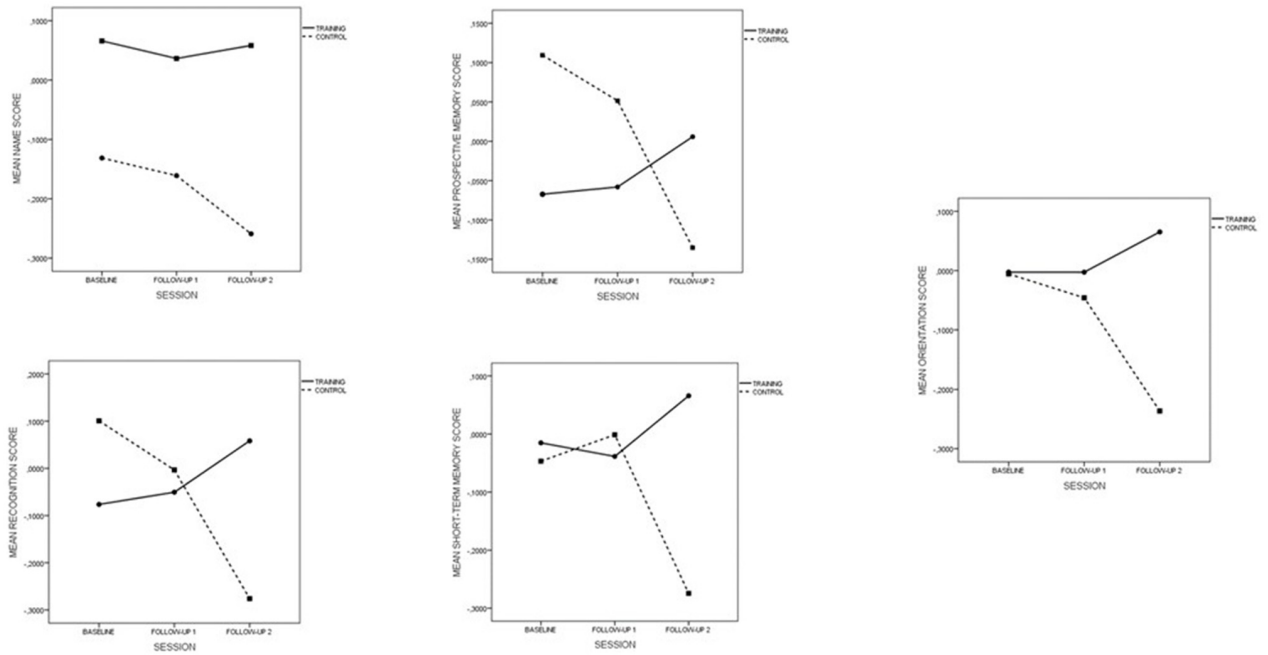

FIGURE 3 | RBMTs Subdomains in the follow-up period.

These results can first be compared with short term training, since immediate effects of cognitive multifactorial programs are well known in the literature. For example, in the meta-analysis on memory programs for healthy older adults, the overall gain of memory was 0.31 (Gross et al., 2012), and 0.14 in the research on the combined effects of cognitive and erobic memory training (McDaniel et al., 2014). The only longitudinal program with which to compare results on long-term memory is the mono-factorial trial ACTIVE, whose immediate memory improvement is well established, but which decays after 6 months (Neely and Bäkman, 1993) or after 2 years (Ball et al., 2002). Intensive programs with booster sessions such as ACTIVE preserve memory levels after five years (performance gains of 0.23), but not longer (Willis et al., 2006; Goh et al., 2012). The recent 10 years follow-up study with ACTIVE shows improvement in reasoning and processing speed, but benefits are dispelled in everyday memory which decays under the basal line with gains of 0.06 (Rebok et al., 2014). In contrast, the overall gain of our time-extended training after 6 years was 0.54 for mental level and 0.27 for everyday memory, which are manifestly higher than any intensive program (see **Table 2**). As ACTIVE researchers acknowledge, it is possible that more extensive practice or greater dosing are required to reach durability in memory performance (Rebok et al., 2014).

The long term decay of memory in ACTIVE shows that either a multifactorial program, or more reinforcement sessions, or more extended duration of the training, or all three conditions together are required to reach durability in memory performance as verified by the results of this study. Probably, the long term preservation of memory requires not only the repetition of reinforcement sessions, but also a multifactorial and durable program. Moreover, preserving memory in the long term depends not only on variables internal to the memory program, but also on the posterior practice of trained abilities in real life (Bennett et al., 2014). Contrasting with most intensive programs, the time-extended program includes a module devoted to home tasks promoting the continued practice of trained content in real-world situations.

Significant post-training differences measured at follow-up #1 after receiving the same number of sessions leads us to conclude that the temporal format of the program determines the training effect on healthy older people. However, the extended format itself is an insufficient condition for the long-term success of memory programs since leisure activities and IADLs also have this format but do not systematically improve the cognitive measures of older people. This is the case of formative leisure activities which happen to be associated with the preservation of everyday memory while non-formative leisure activities like card games do not sustain the preservation of memory. (Requena and López, 2014). Similarly, the retrospective and prospective memory training is associated with benefits to IADLs such as cooking, while verbal memory practice is not.

Therefore, the continuous improvement in mental level and everyday memory during the program is not only explained by the temporal format, but also by the explicitly multifactorial nature of the training. This approach is based on the observation that both cognitive and real-world daily functions rarely depend on a unique cognition

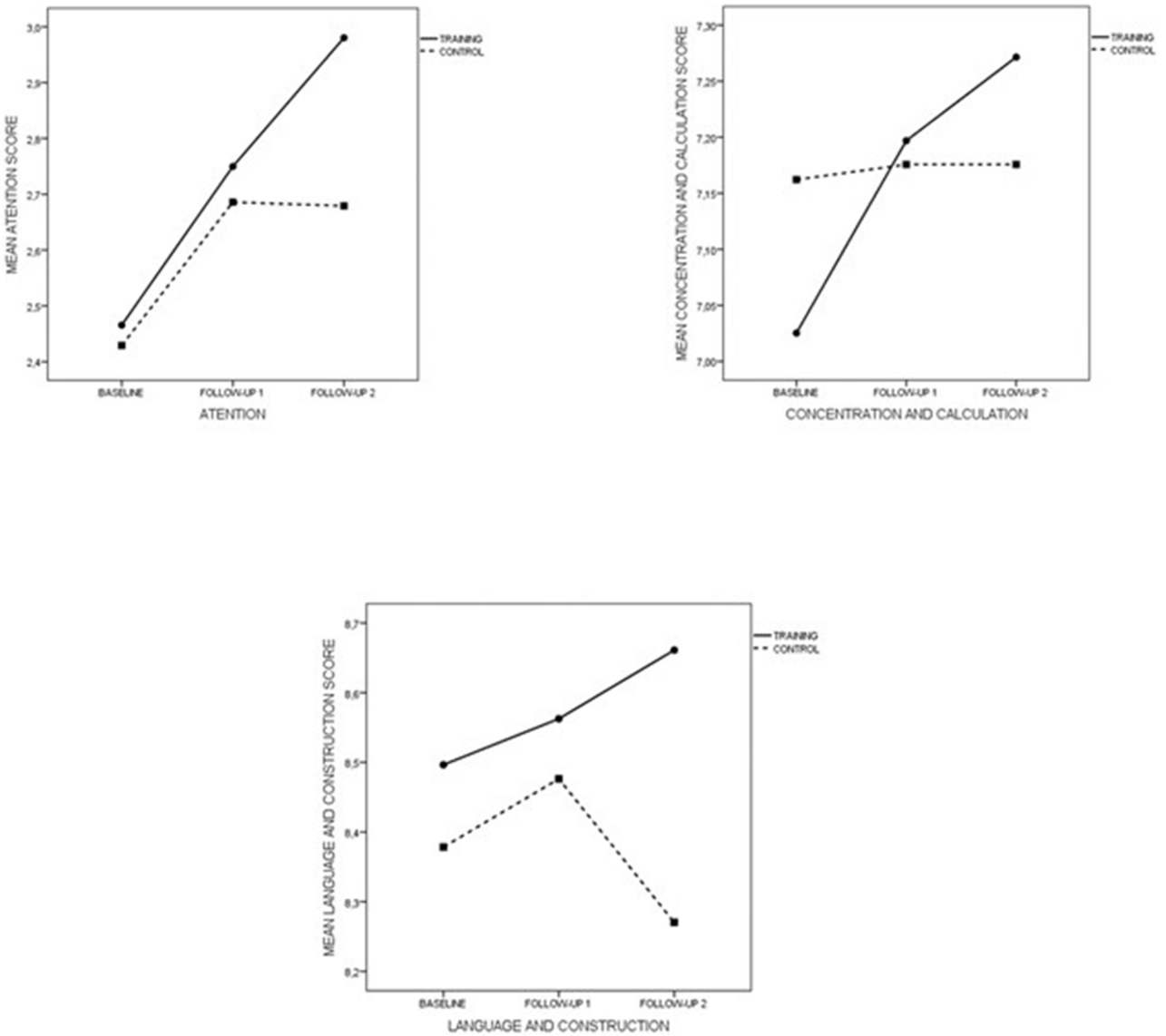

FIGURE 4 | MMSEs Subdomains in the follow-up period.

component. For example, the daily activity of cooking requires a variety of cognitive processes including planning, attention, work memory, and prospective memory (Craik and Bialystok, 2006). In this regard, a key component of our cognitive training was to train a wide variety of cognitive abilities which are involved in many daily tasks and which decay with age. This multifactorial nature of the program explains why the same divergent tendency is observed in the experimental group as with the control group which has already been observed on global MMSE and RBMT scores (see **Figures 3**, **4**). Contrastingly, ACTIVE was designed to analyze the benefits of mono-factorial programs over specifically trained cognitive abilities. Viewed in this way, it is not surprising that improvements in reasoning and processing speed led to improved performance measures of memory and IADLs after training and reinforcement sessions. These results are consistent with the thesis that multiple cognitive abilities are more likely to have an effect on IADL performance.

Special consideration should be given to the high compliance of the experimental group with the intervention program, since 95% of participants completed the training. In contrast, the ACTIVE retention rate was 44% among subjects who were booster-trained and 20% among subjects who were non-booster-trained. The low withdrawal rate of the experimental group may be due to either the intrinsic opportunity for social interaction or having the obligation of "something to do" (Morack et al., 2013). These aspects are reflected

in our sample characteristics: lack of activity, availability, and scarcity of other opportunities to exercise cognitive and social functions (Zinke et al., 2014). On the other hand, special attention has been paid to strengthening the attendance and dealing with ruminations and false beliefs about memory in discussion groups in the extended program.

In summary, the results at 6 years demonstrate that a time-extended program with emotional and cognitive content has beneficial effects on everyday memory, mental level, and IADL function. The research has some limitations due to its multifactorial character since there is an inherent difficulty in attributing particular improvements to specific properties of the program. Future research on time-extended memory programs will determine how to adjust the measures and training into everyday functional tasks. Another concern is the practical sustainability of the intervention in terms of its costs.

AUTHOR CONTRIBUTIONS

CR has conceived and defined the investigation; involvement includes all research phases: design methodology, sample collection, monitoring, implementation of the program in memory training and preparation of the article. AT has claimed responsibility for the statistical analysis of research. TO has collaborated in the methodology and writing of the article.

FUNDING

This research has been partly founded by the Ayuntamiento de Ponferrada (Spain).

ACKNOWLEDGMENTS

Our gratitude to Jana White (Adult Learning Center Spartanburg SC).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 07 July 2016
doi: 10.3389/fnagi.2016.00157

An Alpha and Theta Intensive and Short Neurofeedback Protocol for Healthy Aging Working-Memory Training

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The present study tested the effects of an intensive and short alpha and theta neurofeedback (NF) protocol in working memory (WM) performance in a healthy elder population and explored the effects of a multimodal approach, by supplementing NF with cognitive tasks. Participants were allocated to four groups: NF ($N = 9$); neurofeedback supplemented with cognitive training (NFCT) ($N = 8$); cognitive training (CT) ($N = 7$) and sham neurofeedback (Sham-NF) ($N = 6$). The intervention consisted in 30-min sessions for 8 days. The NF group presented post intervention increases of alpha and theta relative power as well as performance in the matrix rotation task. In addition, a successful up training of frontal theta showed positive correlation with an improvement of post-training alpha and a better performance in the matrix rotation task. The results presented herein suggest that an intensive and short NF protocol enables elders to learn alpha and theta self-modulation and already presents moderate improvements in cognition and basal EEG. Also, CT group showed moderate performance gains on the cognitive tasks used during the training sessions but no clear improvements on neurophysiology and behavioral measurements were observed. This study represents a first attempt to study the effects of an intensive and short NF protocol in WM performance of elders. The evidence presented here suggests that an intensive and short NF intervention could be a valid alternative for introduction of older populations to NF methodologies.

Keywords: EEG, neurofeedback, healthy aging, cognitive training, working memory, alpha, theta

OPEN ACCESS

Edited by:
Carryl L. Baldwin, George Mason University, USA

Reviewed by:
Ramesh Kandimalla, Emory University, USA
Laura Lorenzo-López, University of A Coruña, Spain

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Received: *04 April 2016*
Accepted: *15 June 2016*
Published: *07 July 2016*

Citation:
Reis J, Portugal AM, Fernandes L, Afonso N, Pereira M, Sousa N and Dias NS (2016) An Alpha and Theta Intensive and Short Neurofeedback Protocol for Healthy Aging Working-Memory Training. Front. Aging Neurosci. 8:157. doi: 10.3389/fnagi.2016.00157

INTRODUCTION

Modern societies have been witnessing a significant increase in life expectancy. Therefore, an increase in the burden of age-related conditions has been observed, namely in cognitive performance. The most documented cognitive changes in the aging brain are slower processing speed (Salthouse, 1996), poor encoding of information into episodic memory (Balota et al., 2000) and a deficit in inhibitory processing (Kramer et al., 1994). Also a considerable decline in executive functions such as working memory (WM) (Grady, 2000), attention (Madden, 1990; Connelly et al., 1991) and cognitive flexibility (Cepeda et al., 2001) were documented. WM is described as the ability of short-term retention of information, while allowing

it to be prioritized, modified, utilized and protected from interference. WM is an essential feature in human cognition and it is typically reduced in older adults.

The most prevalent rhythm in the adult electroencephalogram (EEG) is the alpha (8-12 Hz). Alpha oscillations are related to the psychological state and cognitive performance of the subjects (Adrian and Matthews, 1934; Klimesch, 1997, 1999). In frontal sites, alpha activity might be caused by thalamic and anterior cingulate cortex activity, which addresses attention and WM processing. Another important EEG rhythm is the theta (4–8 Hz) and its activity is related to cognitive performance, especially during memory tasks. Lower theta activity is related to resting state, unless in sleepy stages (Vaitl et al., 2005), and enhanced activity is related to memory encoding and retrieval (Jacobs et al., 2006; Cavanagh et al., 2012; Itthipuripat et al., 2013), proving its relationship with hippocampus functioning (Cantero et al., 2003).

Neurology and electrophysiology studies found differences in the brain through aging. Indeed, age-related poorer cognitive performance might be paired with some registered EEG differences, as a slower general EEG activity (Giaquinto and Nolfe, 1986; Breslau et al., 1989; Prichep, 2007), an enhanced parietal and temporal delta (Breslau et al., 1989), and changes in coherence (Prichep, 2007) mainly between frontal and parietal structures that share attentional and information processing pathways. In a study performed by Dias et al. (2015) EEG spectral power and coherence were related to age-related performance decline on the Wisconsin Card Sorting Test (WCST) (Dias et al., 2015). Hence, the relationship between cognitive performance and EEG signals suggest that EEG features in specific cortical sites may be used as targets of neuromodulation strategies.

Neurofeedback (NF) is a brainwave training technique that has been used to enhance performance in athletes and musicians, creativity, attention and WM (Gruzelier, 2014b). It has also been used in several clinical conditions such as attention deficit hyperactive disorder (ADHD) (Heinrich et al., 2007), autism spectrum disorder (Coben et al., 2010), depression (Hammond, 2005) and epilepsy (Egner and Sterman, 2006). NF acts by giving feedback to the subject about his electrophysiological state and directing it to the desired activity (Vernon, 2005; Hammond, 2011). The focus on NF as a tool to increase physical and cognitive performance (commonly referred as peak performance training) is growing. Most studies focus on alpha and theta training in healthy adult populations, stressing its effects in attention and WM improvements (Angelakis et al., 2007; Lecomte, 2011). In terms of protocol duration, greater results are observed in longer NF protocols with 10 sessions on average (Lecomte, 2011) and with resting days between sessions. Studies showed that in a healthy population upper-alpha training had positive effects on mental rotation task performance (Bauer, 1976; Hanslmayr et al., 2005; Zoefel et al., 2011). Also, other study reported better cognitive performance in a WM task in the participants who were able to modulate upper-alpha in a NF up-training protocol (Escolano et al., 2011).

The studies dedicated to NF intervention in elderly populations for preservation of cognitive functions are still sparse, with very small samples, distinct protocols and provide conflicting evidence (Angelakis et al., 2004; Babiloni et al., 2007; Lecomte, 2011; Becerra et al., 2012; Wang and Hsieh, 2013; Gruzelier, 2014a; Staufenbiel et al., 2014). Importantly, however, these studies revealed that NF learning could be successfully applied to aged individuals. Following such evidence, alongside with other studies that linked alpha rhythm to attention processes and theta to WM performance, herein we studied the effects of an 8-days combined alpha and theta intensive NF training in EEG modulation and cognitive performance in older adults, especially in WM tasks. Considering the importance traditionally attributed to cognitive training on clinical settings (Lustig et al., 2009), as well as the advantages generally highlighted on multimodal approaches of cognitive enhancement, the combination of traditional cognitive tasks and NF methodologies seem to afford the advantage of supplying the subject with two types of performance assessment. Thus, besides a sham-NF group, two extra groups were additionally included: an experimental group that supplements NF with traditional cognitive tasks; and cognitive training group controlling for the effects of cognitive tasks alone. In order to assess the results of all training methodologies, EEG and cognitive evaluations were done before and after training. Cognitive performance during training and its translation to attention, resources mobilization and working-memory gains were the main outcomes evaluated on each training approach.

METHODOLOGY

Participants Recruitment and Characterization

For this study, 34 right-handed healthy participants (16 males and 18 females) aged above 55 years (mean age of 65.97 $\pm$ 6.63 years), were recruited from a Health Care Centre from Braga, Portugal. Only participants without any diagnosed dementia, cerebrovascular or neurological pathology were invited to take part in the study. All participants were asked about their educational background, current or previous occupations as well as prescribed medication. The participants did not present a high academic level (mean years of schooling: 6.69 years $\pm$ 3.71 years) and were mostly retired. The cohort was established in accordance with the principles expressed in the Declaration of Helsinki and the work was approved by the national ethical committee and by local ethics review boards. (Ethics Subcommittee for Life and Health Sciences of the University of Minho Ethics Committee of Hospital de Braga, Portugal). All the participants sign a voluntarily informed consent for the use of the collected data.

Initially the participant's neuropsychological profile was assessed by a team of trained psychologists, using a battery of cognitive tests to measure cognitive state and psychological tests to assess the presence of depressive symptoms. Geriatric Depression Scale (GDS), Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE) were comprised in this battery. At the end of the study, all participants completed a questionnaire about their general opinion of the study.

EEG Acquisitions

All EEG signals were acquired with the QuickAmp®, Brain Products, GmbH or the ActiCHamp®, Brain Products, GmbH. Both systems use the international 10–20 system with 32-channels standard electrode layout with ground and reference electrodes. The whole system was constituted by: Ag/AgCl active electrodes, a cap – actiCAP or EASYCAP (Brain Products, GmbH) – electrolyte gel and straps to keep the cap in place. Ground was located at forehead and reference was FCz channel when using QuickAmp equipment and Cz when using the ActiCHamp equipment. For each participant, the same equipment was used through all the sessions.

Experimental Design

All the participants followed a 12-day protocol accordingly to the diagram in **Figure 1**. During the intervention, participants were sited in an illuminated and acclimatized room, distancing 50–80 cm from a 17-inch computer screen with touch technology. All the stages of the study were conducted in Hospital of Braga.

Participants were randomly allocated to four experimental groups according to the diagram presented in **Figure 2**. From the initial 34 participants, 1 dropped out and 3 outliers were excluded from the analysis which results in a final $N = 30$ participants. The participants were divided in the following groups; (i) NF ($N = 9$); (ii) NF supplemented with cognitive training (NFCT, $N = 8$), (cognitive training consisting of four different tasks: Corsi-Block Tapping Task – Forward and Backward; and n-Back Task– 1-Back and 2-Back); (iii) cognitive training alone (CT, $N = 7$) and (iv) sham neurofeedback (sham-NF, $N = 6$).

During the sessions, EEG signals were acquired continuously using the BCI++ platform (Perego et al., 2009), sampled at 500 Hz from the Fp1, Fp2, Fz and Pz channels. The NF and sham-NF protocols were divided in 6 5-min blocks and preceded by a 3-min active baseline. The NFCT protocol consisted in 3 5-min NF blocks (also preceded by a 3-min active baseline) and 5 3-min blocks of the above-described cognitive tasks (each task was headed by a 1-min eyes open baseline). The CT protocol only consisted of 10 3-min blocks of the cognitive tasks (each one also headed by a baseline). The training sessions had a duration of 30-min for all experimental groups.

In order to guarantee that all participants presented a minimum attention level to perform the tasks, in the first 2 days they were submitted to a modified version of the Arrow Flanker Test adapted from the Psychology Experiment Building Language (PEBL; Mueller and Piper, 2014). All participants scored above 93.5% accuracy in the second test day and as a result, no subject was excluded from the study based on attention deficits.

After all the training sessions were completed a questionnaire regarding the participant's general opinion about the study was applied. On a scale of 1 to 4 (being 3 "like" and 4 "like very much" to participate on the study) all participants answered with 3 or 4.

Participants Pre- and Post-Training Evaluations

All participants were characterized before and after the training protocol. At the same time, 32-channel EEG signals were acquired while participants performed 4 modified computerized cognitive tests: Stroop Test, Matrix Rotation Test, Trail-Making Test and Auditory Backward Digit Span Test, also adapted from PEBL (Mueller and Piper, 2014). The EEG signals acquired

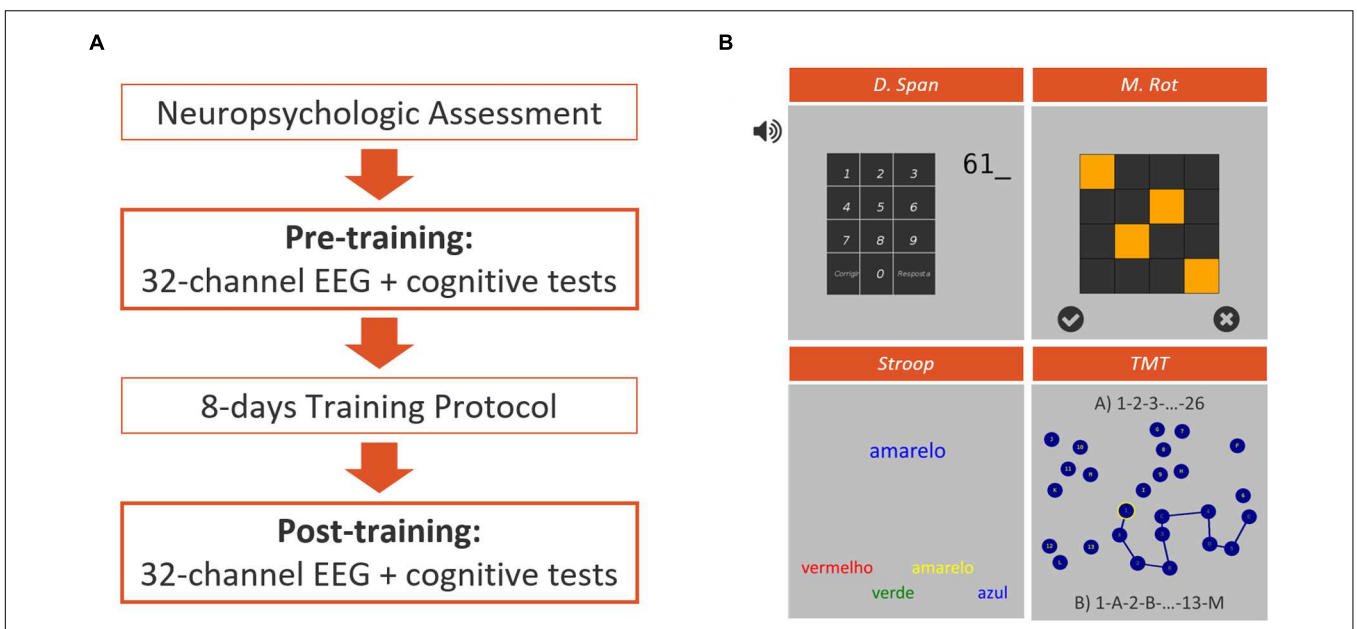

FIGURE 1 | Experimental design **(A)** representation of the different phases of the intervention protocol featuring a traditional neuropsychological assessment, a pre- and post-training sessions for EEG assessment simultaneously to the performance of a computerized test battery, and 8 days of intensive training. **(B)** Representative screenshots of the four computerized tests applied on pre- and post-training assessment sessions, featuring the Auditory Backward Digit Span Test (D. Span), the Matrix Rotation Test (M. Rot), the Stroop Test and the Trail-Making Test (TMT).

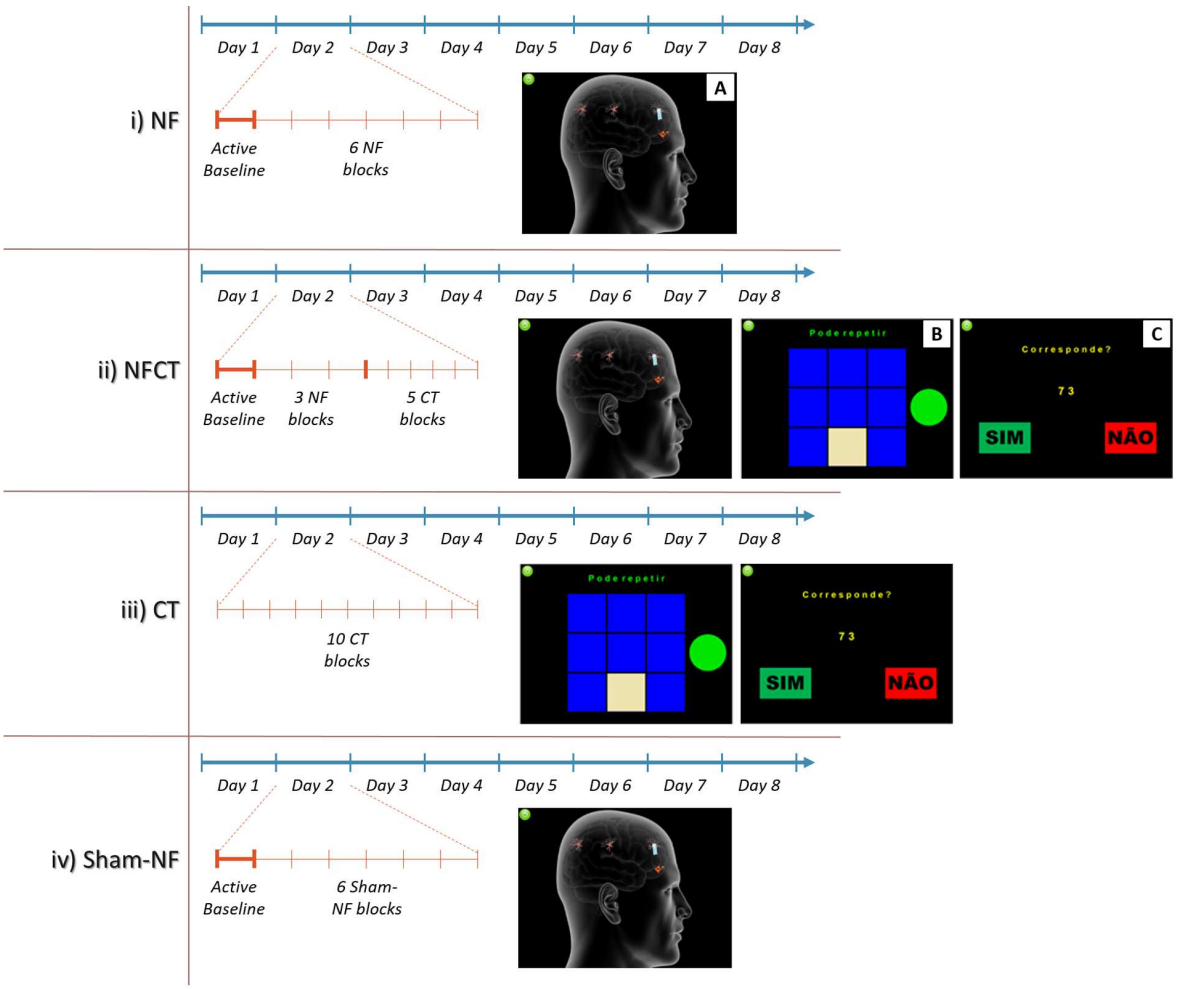

FIGURE 2 | Representation of the implemented 8-days training intensive and short NF protocol featuring four groups: NF, NFCT, CT and Sham-NF. The NF group (i) performed 4 days of alpha and 4 days of theta training. Each day involved an active baseline followed by six blocks of NF **(A)**. The NFCT group (ii) performed NF supplemented with cognitive tasks [Corsi Block-Tapping Task **(B)** and n-Back Task **(C)**]. Each day consisted in an active baseline followed by 3 blocks of NF (similar to **A**) and 5 blocks of NC tasks. The CT group (iii) performed, each day, 10 blocks of the abovementioned NC tasks. The Sham-NF group (iv) followed the same protocol structure as applied to the NF group.

during the cognitive tests were synchronized with PEBL using OpenVibe software (Renard et al., 2010). All cognitive tests were preceded by a 1-min eyes-open baseline, where the participants were instructed to relax and minimize blinking and body movements while staring at the center of a gray computer screen.

To study the training effects on WM we used a measure of the mean accuracy for the Matrix Rotation and a combined measure of memory span and number of correct trials for the Digit Span. Differences between the pre- and post-training were calculated to evaluate the individual alterations induced by the different intervention protocols.

Neurofeedback

The NF task used in this study was fully designed and implemented by our team using BCI++ (Perego et al., 2009), a platform for custom development of C++ and Matlab® (Mathworks, Natick, MA, USA) based game paradigms and processing algorithms.

Online signal processing

All NF training sessions were preceded by a 3-min active baseline. In this baseline, the power spectrum density (PSD) average was calculated for both alpha and theta rhythms. Alpha band was adjusted to the individual alpha peak frequency (IAPF) and set as IAPF $\pm$ 2 Hz. Theta was set from 4Hz to IAPF-3 Hz. The active baseline PSD was used as a participant-specific reference for the following NF training session and updated for each day of training. During the NF training, PSD was calculated online in 1 s windows and updated to the participant every 200 ms. Feedback was calculated as the ratio of the PSD calculated at Fz to the baseline PSD.

Artifact contaminated signals influence the NF learning outcome since their power affects frequency bands often used

for NF training. Thus, data windows showing contamination of ocular artifacts, like eye blinks and saccades, were detected online and discarded from feedback whenever the signal amplitude of the Fp1 (vertical eye movements) or Fp2–Fp1 (horizontal eye movements) exceeded an adjustable threshold (the values ranged from 60 to 100 μV). In this case, the feedback was suppressed and the length of the bar did not change.

Neurofeedback paradigm

The NF virtual scenario consisted in the representation of a human head, three neurons and a flame, as depicted in **Figure 2A**. The feedback was given through a blue bar (symbolizing water) coming out of the neuron that must be increased by the participant in order to reach the flame. The blue bar length mirrored the aforementioned PSD ratio. Three neuronal cells indicated the three levels of the game (i.e., easy, medium and hard). The maximum length of the bar corresponded to 95% of the maximum amplitude measured during the active baseline, in a specific rhythm.

To assure comparability, the active baseline and the training use the same virtual scenario. During the baseline, the blue bar was locked to the first level and its length was randomly assigned. The subject was asked to count the number of times the bar reached the flame in order to maintain an active mental state (Zoefel et al., 2011; Enriquez-Geppert et al., 2014).

Cognitive Training Tasks

For the cognitive training, two WM cognitive tasks were implemented as illustrated on **Figure 2B**, the Corsi Block-Tapping Task, adapted from PEBL, and on **Figure 2C** the n-Back Task. In the Corsi Block-Tapping Task a sequence of up to nine identical spatially separated blocks is highlighted and the participant has to reproduce it, in either forward or backward order. If the sequence is reproduced correctly the next sequence is increased by one block, if not, it is decrease by one block. Each block has 15 trials.

In the n-Back Task the participant is continuously presented with digits and has to indicate whether or not the current digit matches the one n instance before (1-back – 1 instance before; 2-back – 2 instances before). Each block has 65 trials.

Off-Line Signal Processing

All EEG data collected was processed off-line using EEGLAB, a MATLAB toolbox (Delorme and Makeig, 2004). Firstly, EEG signals acquired during the pre- and post-training evaluation sessions were filtered using high-pass (>0.2 Hz) and low-pass (<35 Hz) filters. To filter the signals, we used EEGLAB function *eegfilt* that implements a two-way least-squares FIR (finite-duration impulse response) digital filter with order calculated by default as 3*(sample rate/low cut off frequency). Channels with contaminated or compromised data due to physiological (e.g., muscle activity, ECG, respiratory and skin artifacts) and extra physiological artifacts (e.g., interference originated from other equipment, alternating current or the electrodes) were then discarded and thereafter interpolated from neighboring channels. Then ocular artifacts were detected and removed using an algorithm based on independent component analysis (ICA; Makeig et al., 1996). The signal was segmented in 1-s windows both for baseline and activity records. The segments that contained artifacts were rejected from further analysis. Values above 50 μV and below −50 μV were marked as artifacts and segments with a difference between the lowest and highest amplitudes higher than 60 μV were also considered artifacts. Channels were grouped in four pools, frontal region on left hemisphere (FL), frontal region on right hemisphere (FR), parietal region on left hemisphere (PL) and parietal region on right hemisphere (PR). The average of three channels per area were considered for analyses (FL pool: FC5, F3 and FC1 electrodes; FR pool: FC6, F4 and FC2 electrodes; PL pool: CP5, P3 and CP1 electrodes; PR pool: CP6, P4 and CP2 electrodes. The PSD and coherence between signal pairs were calculated for each segment in both baseline and activity periods. PSD was calculated for Fz channel and for the four pools of channels. Coherence was calculated between the pools FR-FL, FR-PL, FR-PR, FL-PL, FL-PR, and PR-PL. Alpha and theta bands were adjusted according to the participant's alpha peak frequency using the same methodology applied in training sessions. Relative PSD were also calculated based on the ratio of the mean PSD of each frequency band to the broadband (i.e., 0.2 – 35 Hz) PSD.

In order to assess the subject ability to modulate EEG rhythms, alpha and theta PSD were calculated for each day of training. Because only 4 EEG channels (i.e., Fp1, Fp2, Fz and Pz) were acquired during training, the ICA-based approach to ocular artifacts correction was not an option. The artifact rejection and segmentation was performed as explained for the EEG signals acquired on pre- and post-training. In each day, the PSD mean of the four best blocks (blocks in which the participants could reach a higher alpha or theta power) was calculated. The mean value of baseline PSD for the 8 days of training was subtracted to the block-wise PSD values. Alpha and theta PSD gradients were extracted from the linear regression of the baseline-corrected PSD values for the 4 days of training. Following the same approach, relative PSD differences were also calculated based on the ratio of the mean PSD on each band to the broadband (i.e., 0.2 – 35 Hz) PSD. Relative PSD gradients were calculated likewise.

The performance measures in the cognitive training were also assessed. A combined measure between the span and number of correct answers (score) in Corsi-Block tapping task and the percentage of correct answers in n-Back task (i.e., accuracy), were extracted for the 8 days of training of participants from groups NFCT and CT. A linear regression of the performance measures daily series was extracted similarly to NF linear regressions in order to obtain the performance gradients.

Statistical Analysis

Non-parametric tests were used for all statistical analyses. For comparisons between groups the Kruskal–Wallis ANOVA was used. For testing for positive or negative effects of the intervention (testing if the median is greater or smaller than 0) the one-sample Wilcoxon signed-rank test was used. Kendall's Rank Correlation Coefficient Test was performed to observe statistical dependence between measures. All statistical analyses were performed using OriginLab® (OriginLab, Northampton, MA, USA) and significance was considered for p-values below 0.05.

TABLE 1 | Kendall correlation coefficients between digit span score and matrix rotation accuracy in the pre-training cognitive battery and various measures of the neuropsychological assessment implemented at the start of the protocol ($N = 34$).

	MMSE	MOCA	D. Direct	FAS (Ad.)	Codif.	CLOX
D. Span Score (Pre)	0.38**	0.27*	0.47***	0.34**	0.31*	0.33*
M. Rot Acc. (Pre)	0.46***	0.50***	0.48***	0.55***	0.40**	0.32*

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

RESULTS

Table 1 shows the positive correlations found between the traditional neuropsychological tests (MMSE, MOCA, D.Direct, FAS, Codif., and CLOX) and the computerized versions of Digit Span and Matrix Rotation Tests. The other two tests (Trail-Making Test and Stroop Test) did not correlate to any measures of the traditional neuropsychological battery.

Figure 3 represents the differences in performance between pre- and post-intervention for all experimental groups in Digit Span Test and Matrix Rotation Test. In the Digit Span Test, NF, NFCT and CT groups tended to increase the score when comparing pre- and post-intervention but these increases were not statistically significant (NF: p-value = 0.219; NFCT: p-value = 0.191; CT: p-value = 0.500). In the Matrix Rotation Test all groups but the CT tended to increase accuracy (NFCT: p-value = 0.063; Sham-NF: p-value = 0.25); however, only NF participants significantly increased their performance (p-value = 0.039).

Figure 4A represents the training gradients of absolute PSD values for NF, NFCT and sham-NF groups across the 4 days of alpha and the 4 days of theta training (see EEG signal processing section). The positive values obtained in the NF group indicate that this group was able to increase both frequency bands activity during NF training. Only alpha band activity increased significantly (p-value = 0.014), whereas theta band activity did not, although close to significance (p-value = 0.064). Interestingly, the NFCT group did not show any important tendency and the Sham-NF group did not achieve significant changes. **Figure 4B** represents the training gradients of relative PSD values during training. These results indicate that the relative power of alpha and theta bands was significantly increased in the

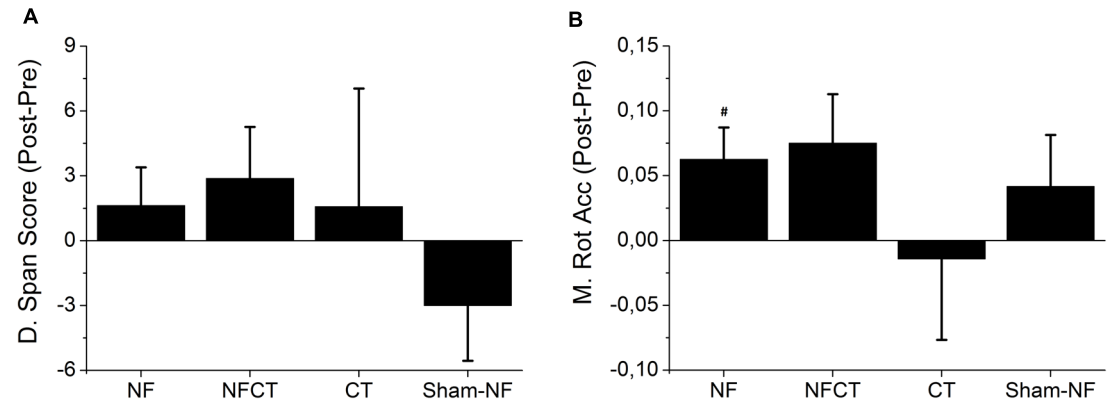

FIGURE 3 | Representation of the mean difference between pre- and post-training performance in the cognitive tests. (A) Digit Span Test Score and **(B)** Matrix Rotation Test Accuracy, for all experimental groups: NF ($N = 8$), NFCT ($N = 8$), CT ($N = 7$) and Sham-NF ($N = 6$). NF group presented a statistically significant increase in Matrix Rotation Accuracy (p-value = 0.039). $^{\#}p < 0.05$.

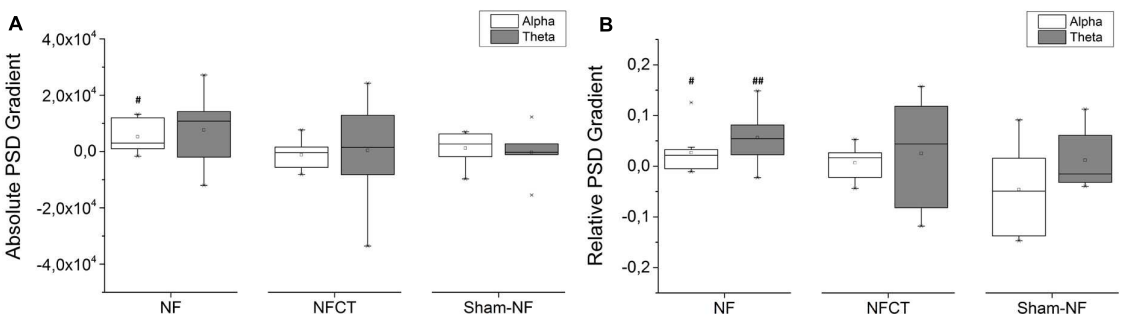

FIGURE 4 | Representation of the 4-day variation of alpha and theta gradients during training; (A) absolute PSD and **(B)** relative PSD, for NF ($N = 9$), NFCT ($N = 8$) and Sham-NF ($N = 6$) groups. NF group presented a statistically significant increase in absolute alpha (p-value = 0.014) and in relative alpha and theta (p-value = 0.027 and 0.006, respectively). $^{\#}p < 0.05$, $^{\#\#}p < 0.01$.

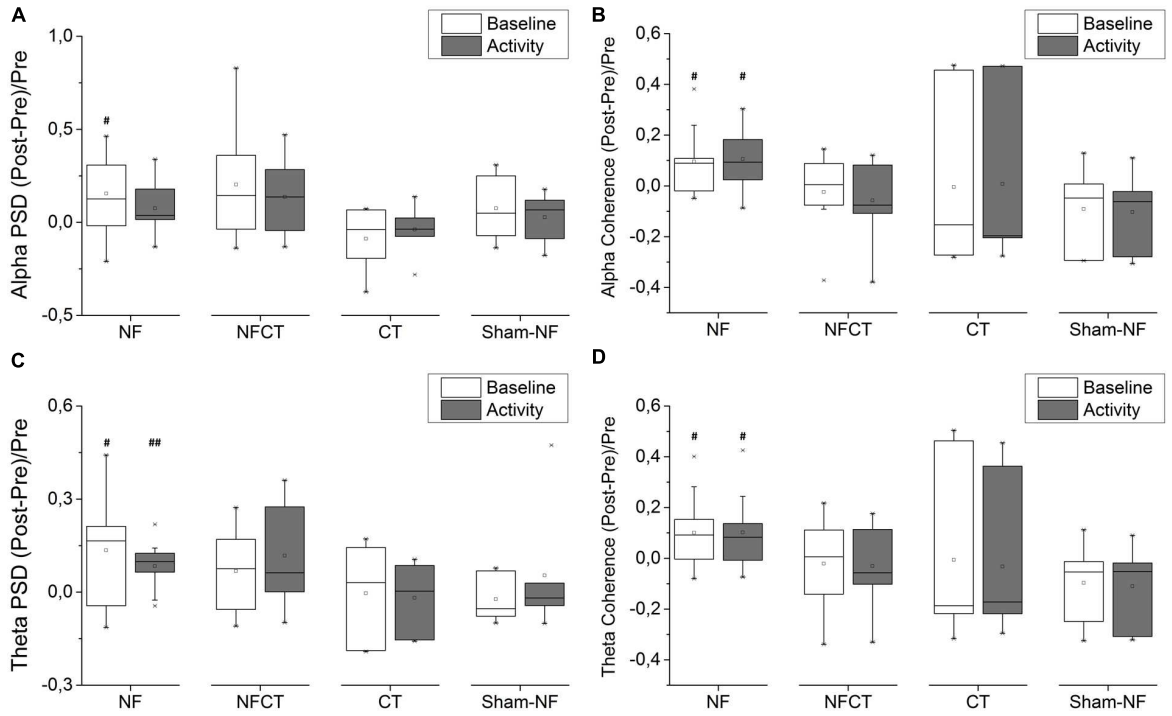

FIGURE 5 | Evolution of frontal EEG power spectral density (PSD) and frontal spectral coherence from pre- to post-training phase; (A) alpha and **(C)** theta PSD, on baseline and activity periods, in Fz channel, for NF ($N = 9$), NFCT ($N = 8$), CT ($N = 7$) and Sham-NF ($N = 6$) groups; NF group presented a statistically significant increase in basline alpha (p-value = 0.049) and both baseline and activity theta (p-value = 0.037 and 0.010, respectively, $^{\#}p < 0.05$, $^{\#\#}p < 0.01$); for **(B)** alpha and **(D)** theta frontal spectral coherence (between FL and FR channel pools), for all four experimental groups. NF group presented a statistically significant increase in both baseline and activity alpha (p-value = 0.037 and 0.027, respectively) and in both baseline and activity theta (p-value = 0.049 and 0.049, respectively, $^{\#}p < 0.05$).

NF group (p-value = 0.027 and 0.006 respectively), but not in NFCT or sham-NF groups.

Figure 5 represent the results obtained from the EEG acquired before and after the 8 days of training. **Figures 5A,C** represent relative PSD measured in the Fz electrode in alpha and theta bands, respectively. Only the NF group could increase significantly the PSD in both theta (during baseline – p-value = 0.037 and activity – p-value = 0.010) and alpha (during baseline – p-value = 0.049) rhythms. Although not statistically significant, NFCT presented a tendency to increased relative PSD values in theta (during baseline – p-value = 0.125 and activity – p-value = 0.055) and alpha (during baseline – p-value = 0.074 and activity – p-value = 0.098) rhythms. No statistically significant results were obtained using the absolute PSD measures. **Figures 5B,D** represent coherence measured between frontal sites (frontal left – FL and frontal right – FR) in alpha and theta bands, respectively. Again, only the NF group was able to significantly increase alpha and theta coherence in baseline (p-value = 0.037 and 0.049, alpha and theta respectively) and activity (p-value = 0.027 and 0.049, alpha and theta respectively) records.

Figure 6A represents the positive correlation found between theta gradient during NF training and Matrix Rotation accuracy differences between pre and post NF intervention (Correlation Coef. = 0.617, p-value = 0.040). **Figure 6B** represents the positive correlation between theta gradient and alpha PSD differences between pre and post NF intervention (Correlation Coef. = 0.556, p-value = 0.037). **Figure 6C** represents the positive correlation between this alpha PSD and the above mentioned matrix rotation accuracy, both measures representing differences between pre and post NF intervention (Correlation Coef. = 0.694, p-value = 0.021). Additionally, a positive correlation was found between the theta gradient and the difference between pre- and post-training in the Digit Span score (Correlation Coef. = 0.718, p-value = 0.016; not shown). Reliability analyses were applied on all three measures (i.e., relative theta PSD gradient, alpha PSD and Matrix Rotation accuracy) analyzed on **Figure 6**, and the Cronbach's α resulted in 0.823 (standardized α = 0.922) when only NF subjects were considered. The Cronbach's α analyzed exclusively for NFCT and Sham-NF subjects resulted in 0.509 and 0.297, respectively. These results suggest that the participants that were able to better modulate theta across the 4 days of training uniquely increase their WM performance, translated in an increase in accuracy in the matrix rotation test (**Figure 6A**) and in score in Digit Span from the pre- to the post-intervention moments. Besides, we also found that only these participants enhanced their background alpha activity in Fz location from pre- to post-training periods (**Figure 6B**). Predictably, the subjects with highest accuracy gains in Matrix Rotation also

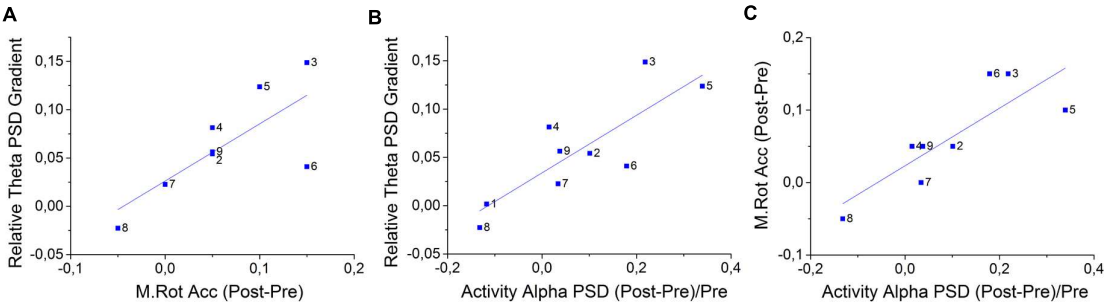

FIGURE 6 | Correlations between the Fz relative theta gradients, accuracy gains on the Matrix Rotation Test and improvements of post-training Fz alpha PSD for all NF group's participants ($N = 8$). Specifically, the positive correlations between **(A)** relative theta gradient and M. Rot. accuracy (Kendall's $\tau = 0.617$, p-value $= 0.040$) **(B)** relative theta gradient and post-training alpha PSD during activity periods ($\tau = 0.556$, p-value $= 0.037$) and **(C)** M. Rot. accuracy gains and post-training alpha PSD ($\tau = 0.694$, p-value $= 0.021$); Additionally, there is a non-represented positive correlation between the relative theta training gradient and score gains in the D. Span task ($\tau = 0.718$, p-value $= 0.016$); In-plot dots represent participants.

obtained highest improvements in background alpha PSD (**Figure 6C**).

Figure 7 presents the results of cognitive training performance from the participants of NFCT and CT groups. The participants from CT group have shown performance gains during both forward (p-value $= 0.004$) and backward (p-value $= 0.004$) Corsi tasks as well as during 1-back (p-value $= 0.007$) and 2-back (p-value $= 0.004$) tasks. The participants from NFCT group only presented performance gains for the forward version of Corsi task (p-value $= 0.006$). CT participants over performed NFCT participants in the 2-back task (p-value $= 0.016$).

DISCUSSION

The goal of this study was to assess the effects of an intensive alpha and theta NF protocol in WM performance in a healthy population above 55 years old, as well as to initially explore the benefits of a multimodal cognitive training approach, by supplementing NF protocols with traditional cognitive tasks. Importantly, these subjects were cognitively assessed before the intervention, using traditional neuropsychological scales (MMSE, MOCA, D.Direct, FAS, Codif., and CLOX) and the computerized versions of Matrix Rotation and Digit Span Tests; the results (**Table 1**) show statistically significant correlations between the tests, which provides confidence about the behavioral results of the adapted computerized tests used for WM assessment.

The NF group showed improvements in the Digit Span and Matrix Rotation performance after eight consecutive days of training (**Figure 3**), but only the latter presents statistically significant differences. Together with the fact that the NF group was uniquely able to modulate both alpha and theta frequency bands in respect to the broadband spectrum (**Figure 4**), it seems that a specific up-modulation of alpha or theta activity may have had positive effects in cognitive performance. This

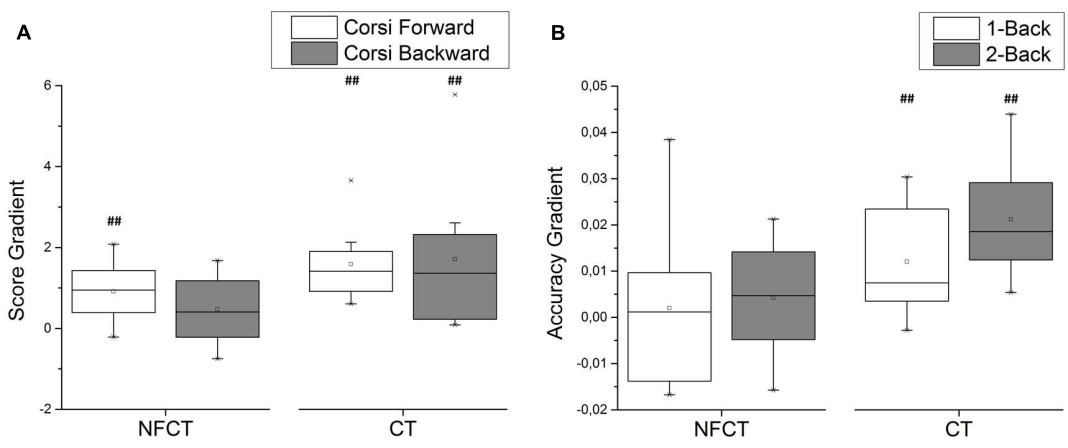

FIGURE 7 | Cognitive training performance for NFCT and CT groups. (A) The participants from CT experimental group have shown performance gains during both forward (p-value: 0.004) and backward (p-value: 0.004) Corsi tasks as well as during 1-back (p-value: 0.007) and 2-back (p-value: 0.004) tasks. **(B)** The participants from NFCT group only presented performance gains for the forward version of Corsi task (p-value: 0.006). CT participants over performed NFCT participants in the 2-back task (p-value: 0.016).

finding comes in line with other studies that have already shown the relationship between a successful upper-alpha training and mental rotation enhancement (Hanslmayr et al., 2005) and alpha training and a better performance in a Matrix Rotation task (Riečanský and Katina, 2010). The participants that underwent NF training supplemented with cognitive training (i.e., NFCT group) presented a tendency to increase performance in Matrix Rotation Accuracy (**Figure 3**). Although these results may suggest a potential advantage of a combined cognitive training approach, their failure to show significance is likely due to the reduced dosage of NF training blocks in comparison to the NF group. In fact, the NFCT group only performed 3 5-min blocks of NF in each training session in order to maintain the total training time of 30 min per day. That amount of NF training seems insufficient to fully promote NF learning in all participants. In addition, the implemented cognitive training tasks *per se* seemed to have failed in endorsing cognitive enhancement. Indeed, the CT group did not increase the performance in matrix rotation or digit span scores after the 8 days of intensive cognitive training.

The absolute PSD gradients across the 4 days of alpha and 4 days of theta training (**Figure 4**) show that the NF group presented a tendency to increase PSD in both alpha and theta rhythms but the increase was only statistically significant in alpha. Sham-NF subjects, although not receiving a real feedback of their own EEG signals, also tended to increase the absolute value of alpha power, but not theta power. This could be explained by the nature of the protocol itself and the engagement of attention processes that are often associated with the alpha rhythm. As the subjects must pay attention to the visual stimulus presented in the computer screen, it is possible that even the sham-NF participants had increase alpha rhythm even without receiving the real feedback of their own EEG signals. Also, alpha was reported as being a dominant rhythm in the adult EEG (Klimesch, 1999) and this could explain why its enhancement may be easier, especially when compared to theta which is an EEG pattern more common in sleepy stages or cognitive demanding tasks (Vaitl et al., 2005). Interestingly, the NFCT group presents a theta PSD gradient highly variable across participants, which may be also due to insufficient NF training dosage.

The relative PSD gradients across the 4 days of alpha and 4 days theta training show that only the NF group presented an increased PSD in both frequency bands. Given that the relative alpha and theta are calculated as a ratio of the PSD on a frequency band to the broadband PSD, the increase in relative PSD could be explained by an energy specificity improvement in the underline alpha and theta bands during NF training. In contrast, the Sham-NF group did not improve neither alpha nor theta relative bands, showing the inability of unspecific-feedback to effectively modulate EEG rhythms. The issue of specificity is an assumption inherent to NF practice and it contrasts with an alternative view that suggests that only a generalized learning process is trained. Although our results suggest an energy specificity improvement in the NF group, the evidence is mixed for both specific and generalized effects. Taking into account that NF is a complex process that requires attention, motivation and learning effort, that could explain why it could involve different EEG rhythms besides the target ones (Gruzelier, 2014c).

The analysis of the EEG acquired before and after training, during the computerized battery (**Figure 5**), revealed that only the participants from the NF group were able to increase alpha and theta rhythms in the Fz location from pre- to post-intervention. NFCT group showed only a tendency to increase Fz alpha and theta during baseline and activity, which points to the need of a NF protocol with enough sessions to promote learning and alterations in EEG during task and resting states. The analysis of EEG acquired during the pre- and post-intervention also revealed, in the NF group, an improvement in spectral FL-FR coherence in alpha and theta bands during both activity and baseline. Nevertheless, this improvement did not correlate with NF training success or with cognitive performance improvements. Topological specificity in NF has little support in the literature. However, studies with elder populations provided evidence for frontal locus changes following NF training (Angelakis et al., 2004; Becerra et al., 2012), as a result of the higher engagement of frontal lobes in executive functions and learning. However, in the view of the brain as a group of functional system networks it should be expected that the effects of EEG NF training might be generalized and not restricted to the region of training (Becerra et al., 2012; Gruzelier, 2014b).

The positive correlation between a successful theta NF training and a better performance in matrix rotation task in the NF group, as well as an increased alpha activity between pre- and post-training in these subjects (**Figure 6**), were relevant findings of the present study. The results of these three measures, together with their internal consistency in the NF group, seems to indicate that a successful theta NF training following the proposed protocol could have led to the improvement of alpha EEG and performance in a task involving WM during a computerized battery. These results could indicate that the promoted changes in the alpha PSD could have been triggered by a successful theta up-training and might have enabled a better performance in matrix rotation task, which involves short-term memory and attention abilities. However, these results should be carefully analyzed, since these are correlations, and additionally no statistical significance was found between different groups.

Regarding cognitive training, only the CT group was able to follow cognitive training and improve performance on tasks (**Figure 7**). Again, the failure of NFCT participants to follow training may be due to the reduced dosage in comparison to the CT group. Yet, and although the participants from CT group were able to achieve highest score gradients on Corsi and n-Back tasks, those accomplishments did not translate into either better cognitive performance or post-pre EEG effects. On the other hand, NFCT participants did not show evidence of cognitive enhancement during training but they tended to increase PSD from previous to posterior training moments. These results might suggest that evident training improvement might not be a requirement for achieving effective cognitive gains.

The results presented herein suggest that an intensive no-interval NF training protocol may be adequate for an appropriate learning of EEG modulation. This protocol triggered

some alterations in basal EEG that seem to support a better performance in tasks involving short-term memory and attention skills. This is in line, with empirical evidence presented in the literature that seems to indicate that an 8–10-session intervention might be sufficient for young healthy participants (Angelakis et al., 2007); herein, we show that the same applies to elder subjects (Lecomte, 2011). Although positive results have been herein shown for elders, more training sessions might be advisable for an aged population in order to promote enduring effects. The explanation could be the reduced neuroplasticity observed in elder individuals (Goh and Park, 2009) thus, impairing the mnesic processes necessary in a learning process.

CONCLUSION

In essence, the major conclusions of this study are, firstly, the moderately positive results on EEG modulation during intensive no-interval 8 NF sessions and their outcome in terms of WM in healthy elder subjects. Multimodal cognitive training approach failed to prove efficacy but revealed promising insights to future study designs aiming to combine NF with cognitive tasks. We also conclude, in line with other studies, that age does not exclude elderly people from learning NF.

AUTHOR CONTRIBUTIONS

JR and AMP, contributed to all stages of the work including the acquisition, analysis, and interpretation of data for the work, drafting the work and final approval for publishing. LF, NA, and MP contributed for the acquisition and interpretation of data for the work, revising the manuscript for important intellectual content and final approval. NS and NSD are mainly responsible for the conception and design of the work, contributed for the interpretation of data for the work, revised the work critically for important intellectual content and also gave final approval of the version to be published.

FUNDING

This work was co-sponsored by FCT – Foundation for Science and Technology and Compete Program with the project reference FCOMP-01-0124-FEDER-021145 (PTDC/SAU-ENB/118383/2010) and Agência Nacional de Inovacão "DoIT – Desenvolvimento e Operacionalização da Investigacão de Translacão" (project no. 13853, PPS4-MyHealth), funded by Fundo Europeu de Desenvolvimento Regional (FEDER) through the Programa Operacional Factores de Competitividade (POFC).

ACKNOWLEDGMENTS

We are thankful to Unidade de Saúde Familiar S. João de Braga and to all the study participants. We also want to thank Daniela Ferreira, Cristiana Merendeiro, Carlos Portugal-Nunes, Nadine Santos, Teresa Castanho, Liliana Amorim and Pedro Moreira for aid in participant recruitment and psychological characterization.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

OPINION
published: 02 November 2016
doi: 10.3389/fnagi.2016.00249

Clinical Trials to Gain FDA Approval for Computerized Cognitive Training: What Is the Ideal Control Condition?

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Keywords: cognitive training, active control, placebo, mild cognitive impairment, engagement

The explosive growth of mobile technologies combined with the rapid rise of aging populations fearful of their risk for Alzheimer's disease has led to a number of marketed products aimed at enhancing cognitive health. However, an increasing number of product claims that are not substantiated has led regulatory agencies, such as the Federal Trade Commission (FTC), to issue warnings or penalties against some companies. Therefore, it is likely that a number of computerized cognitive training (CCT) companies will conduct clinical trials to prove their efficacy to gain Food and Drug Administration (FDA) clearance as a medical software/device. This raises a number of issues such as optimal trial design for establishing efficacy. The type of control condition is unique issue for CCT, given the variety of non-specific known to produce beneficial effects on cognition that are difficult to isolate from the content of the program. These include participant expectancy, engagement, motivation, novelty, and therapist interaction. We herein discuss the types of non-specific factors, desirable qualities of an active control condition, and the nuances that exist between previously used control conditions within the context of CCT for mild cognitive impairment.

OPEN ACCESS

Edited by:
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George Mason University, USA

Reviewed by:
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Received: *21 April 2016*
Accepted: *12 October 2016*
Published: *02 November 2016*

Citation:
Motter JN, Devanand DP, Doraiswamy PM and Sneed JR (2016) Clinical Trials to Gain FDA Approval for Computerized Cognitive Training: What Is the Ideal Control Condition? Front. Aging Neurosci. 8:249. doi: 10.3389/fnagi.2016.00249

EXPECTANCY

One nonspecific factor is expectancy, which refers to the participant's anticipation of positive or negative treatment effects. Expectancies come in two major forms: outcome expectancy, which is the belief that the treatment itself will result in a particular outcome, and response expectancy, which is the participant's subjective response to the treatment. Expectancies of both kinds impact outcomes across modalities, including psychotherapy (Goossens et al., 2005; Smeets et al., 2008; Weinberger, 2014), pharmacological interventions (Rutherford et al., 2010), and neurosurgery (Freeman et al., 1999). Long known to produce clinically significant outcomes, the belief that one will symptomatically improve is met with high response rates. For example, a meta-analysis of randomized placebo-controlled trials of antidepressants found the placebo effect to be responsible for the majority of observed change, in depression symptoms, with a response rate of 50% for those receiving medications compared to 30% for groups assigned to the placebo condition (Walsh et al., 2002).

Further evidence for the contribution of expectancy to treatment effectiveness can be found in the different response rates across different trial designs. Greater response rates have been observed in comparator trials between two drugs than in placebo-control trials in late-life depression (Sneed et al., 2008). This discrepancy may be a consequence of participants in comparator trials knowing they will receive treatment, while participants in placebo-controlled trials are hoping they are assigned to the treatment arm (and hence have lower expectations). This finding has been extended in middle-aged and adolescent depression (Rutherford et al., 2011) as well as in schizophrenia

(Rutherford et al., 2014). Although these groups are diverse in terms of presenting ailment, consistent among them is that degree of expected improvement coincides with magnitude of actual improvement.

Rutherford et al. (2010) elaborated on a model of expectancy effects driving the differences in response rates between types of trials in which the orbitofrontal cortex (OFC), rostral anterior cingulate cortex (rACC), and nucleus accumbens (NAC) generate and maintain expectancies (Rutherford et al., 2010). The OFC and rACC are active during anticipation of pain and unpleasant experiences (Petrovic et al., 2005). Placebos lower activation of these regions which coincides with reduced severity of experienced pain (Wager et al., 2004). This analgesic effect may be partially explained by heightened opioid activity in the OFC and rACC that follows placebo administration and correlates with reported pain alleviation (Wager et al., 2007). Activation of the NAC, on the other hand, occurs in anticipation of reward. Greater activation of the NAC occurs with expectancy of analgesia and is correlated with placebo-induced pain reduction (Scott et al., 2007). Taken together, heightened expectancy of relief attenuates appraisal of negative experiences to a clinically significant degree.

In addition to altering perception of negative symptoms, raising expectancy increases participant's belief of self-efficacy in their functioning, making them more confident in their own capability to perform tasks. Judgments of high self-efficacy are associated with greater exerted effort in the face of challenges, as well as lengthened persistence (Bandura, 1982). A systematic review of placebo responses found self-efficacy and locus of control to be significant predictors of symptom improvement (Horing et al., 2014). The impact of response expectancy on cognition is particularly important in trials of CCT, given the use of performance-based outcome measures. In trials of CCT, participants are told that improvement in their cognitive functions is possible as a benefit from their involvement in the study. This creates an expectation of better performance following training, which is known to create positive cognitive outcomes. Indeed, participants who enrolled in a trial of CCT via a flyer suggesting CCT will improve working memory and fluid intelligence had greater post-training performance than participants who enrolled via a non-suggestive flyer, despite participating in the same program (Foroughi et al., 2016). Similarly, in a trial of healthy adults randomly assigned to a placebo pill or no-pill condition, those who took the placebo pill described as a "cognitive enhancer" had greater performance on tests of attention and delayed recall, though no effect was found in five secondary outcome measures (Oken et al., 2008). Given the potential effect of expectancy on cognitive performance, and the wide use of neuropsychological tests as primary outcomes in CCT trials, treatment, and comparison conditions must be balanced in terms of anticipated improvement.

ENGAGEMENT

How well a CCT program captivates and sustains attention will affect the capability of subjects to participate and focus during training. How engaging a task is depends on numerous factors, including usability, focused attention, positive affect, esthetics, endurability, richness, and control (Wiebe et al., 2014). These characteristics can be independent of the main program content. For example, a 2-back task necessitates working memory ability by nature of the design alone. By adding auditory feedback, sound effects, colorful animations, score tracking, and countdown timers, the task becomes more attractive to the participant. Such design elements create a nonspecific cognitive load, are not unique to CCT, yet make the CCT condition more interesting than the comparison group. When comparing an engaging CCT task to either waitlist or uninteresting control activities, it becomes impossible to isolate the central treatment effect.

MOTIVATION

Whereas engagement may be understood as emotional or attentional investment during a task, motivation is a global personal orientation to the activity (Wiebe et al., 2014). A participant may believe that cognitive improvement is contingent upon active involvement in their training. Numerous cognitive training platforms track then share performance data with participants. Following conclusion of a module, participants are shown their score, typically alongside a report of previous attempts. Congratulatory messages for surpassing earlier records are common. This positive feedback and potential for goal-setting behavior creates an environment where the participant is motivated to perform well.

Participant's beliefs about the malleability of their intelligence will affect their performance as well. In a study evaluating performance on tests of general knowledge, participants who held the believe that intelligence is malleable corrected more errors in their responses during retesting than participants who believed that intelligence is fixed (Mangels et al., 2006). When given negative feedback following errors, participants who believed in fixed intelligence demonstrated reduced memory-encoding activity in the temporal lobe. This suggests that one's attitude toward learning will affect the amount of effort placed in training tasks. This is particularly important for older adults with MCI, whose motivation toward the task may be increased by the prospect of preventing further cognitive decline.

NOVELTY

The novelty effect is the tendency for improved performance due to interest in a fresh experience, rather than the content. A review of educational research found that when not controlled, novelty effects create an increase in test scores. On average, performance increases due to novelty by 50% of a standard deviation for the first 4 weeks, and by 20% of a standard deviation after 8 weeks (Clark and Sugrue, 1991). Novel experiences may also simply be remembered better than familiar ones. On tasks of explicit recognition, subjects show higher accuracy in identifying novel words from a studied list than familiar words viewed multiple times (Tulving and Kroll, 1995; Habib et al., 2003). Given that CCT consists of tasks not encountered in everyday life, and prior familiarity with training protocols is grounds for excluding participants, there is ample opportunity for sheer novelty of

the task to constitute a considerable portion of any measured effects.

ACTIVE CONTROLS

To address these issues, studies have employed active controls, where the comparison condition completes an activity designed to account for non-specific factors. This type of control condition aims to determine whether the benefits of such mental exercise are unique to CCT or can be obtained by any stimulating activity. Commonly used active controls include crossword puzzles, word searches, newspapers, and questionnaires. Active controls alleviate ethical issues of placebo-controlled treatments, as both the treatment and comparison condition may expect improvement. Although active controls are methodologically superior to waitlist conditions, differences in effect sizes between active control conditions and passive control conditions are not consistently observed (Karbach and Verhaeghen, 2014; Au et al., 2015), and the nature of the active control task may not account for all non-specific effects. Given the diversity of CCT paradigms and quantity of non-specific factors, researchers have argued that there is no universally applicable active control condition for all design cases (Boot et al., 2013). Instead, the control condition must be reasonably related to the tasks of the CCT condition such that participants expect improvement in the same cognitive domain regardless of their group assignment.

Table 1 contains a list of studies of CCT in patients with mild cognitive impairment (MCI). Most studies use waitlist control conditions (Rozzini et al., 2007; Finn and McDonald, 2011) or control conditions that do not account for engagement and motivation in the task (Galante et al., 2007; Talassi et al., 2007; Gagnon and Belleville, 2012; Herrera et al., 2012; Carretti et al., 2013; Gaitan et al., 2013). In such designs, the treatment condition is at an unfair advantage because patients assigned to CCT have a greater chance of improvement simply because the tasks are engaging and motivating whereas those assigned to waitlist control lose interest and motivation. Even when active control conditions have been used in previous studies of CCT in MCI, they are not consistently computerized (Talassi et al., 2007; Herrera et al., 2012; Carretti et al., 2013; Gaitan et al., 2013) and consist of CCT tasks of invariable complexity (Gagnon and Belleville, 2012; Gaitan et al., 2013). Comparing CCT that scales in difficulty with participant performance to CCT that remains at a fixed difficulty does not determine whether effects are specific to CCT or can be obtained with any engaging computerized game. Further, trials of scaling difficulty fail to take into account the novelty of experience they introduce, beyond just harder problems.

The CCT conditions themselves vary considerably, both by targeted cognitive domains and whether they are administered alone (Galante et al., 2007; Barnes et al., 2009; Finn and McDonald, 2011; Rosen et al., 2011; Gagnon and Belleville, 2012; Herrera et al., 2012; Carretti et al., 2013; Gooding et al., 2016), or as part of a wider intervention (Rozzini et al., 2007; Talassi et al., 2007; Gaitan et al., 2013). If CCT is administered alongside additional therapies, the magnitude of participant's expectancy, engagement, and motivation may be greater than if they were treated with CCT alone. Such nuances in design will impact the magnitude of the observed differences between the training and control groups, and the measured effect sizes across trials. One needs to consider the nonspecific factors present in both the CCT and control conditions in order to accurately interpret the results.

MODEL CONTROL CONDITIONS

An adequate comparison condition must be matched for engagement, motivation, training time, computer interface, and novelty of stimuli. Preferably, the control group should account for nonspecific factors without introducing neurocognitive demands. If it does create specific effects, their impact on cognitive functioning should be known before comparing it to a CCT group. By using a CCT group, an active control group, and a passive control group, the relative contributions of each nonspecific factor can be estimated (Greenwood and Parasuraman, 2016). There is no "one size fits all" control condition. Instead, the selection of a control condition must be made in view of the content of the CCT platform and the specific research question.

An example of a well-balanced active control condition is a CCT program targeting domains of cognition that are different from those being targeted in the CCT program of the intervention condition. Should one group find greater improvement in cognitive domains of interest that transfer to untrained domains and quality of life, this can be taken as evidence that the content of CCT matters more than the non-specific factors. Participants in the active control group must expect the same types of cognitive benefits as those in the training group, principally by the control group and training group having identical descriptions of anticipated effects.

Another active control condition is one that incorporates non-adaptive versions of CCT. These programs use the same types of tasks as those in the experimental training condition, though they do not scale in difficulty with participant performance. When compared with adaptive versions of the same procedure, the tasks are balanced on participant expectancy and motivation, and practice effects can be ruled out. However, scaling difficulty introduces novelty, both in terms of activities encountered and strategies necessary for completing the task. Further, participants who complete the same task at unchanging difficulty may become less engaged as they reach their peak performance early. Controlling for practice effects is particularly important in older adults with cognitive impairment, given their propensity toward greater practice effects than their cognitively-stable peers (Suchy et al., 2011).

Remedial skills training has also been used as an active control condition. In these groups, participants discuss top-down strategies aimed at compensating with cognitive deficits. Such designs make it difficult to disentangle the plasticity of representations (knowledge, skills) from plasticity of processes (cognitive ability, brain function, brain structure, Fissler et al., 2015). It is possible that improvement following CCT is due to familiarity with neuropsychological tests and not due to improvement in underlying cognitive capacities. For example, learning to chunk numbers may improve digit span score, but may reflect one's ability to apply knowledge of cognitive strategies rather than one's actual attentional capacity. Comparisons

TABLE 1 | Studies of CCT for MCI.

Study name	Treatment condition	Control condition	Control Weaknesses
Barnes et al., 2009	Processing speed and auditory processing CCT ($n = 22$)	Audio books, reading online newspapers, visuospatial computer games ($n = 25$)	Heterogeneous control tasks, not matched for engagement
Carretti et al., 2013	Working memory CCT ($n = 10$)	Memory discussion and questionnaires ($n = 10$)	Control group not computerized, unequal socialization opportunities
Finn and McDonald, 2011	Attention, processing speed, visual memory, and cognitive control CCT($n = 12$)	Waitlist ($n = 13$)	Non-active control condition
Gaitan et al., 2013	CCT + pen and paper cognitive training ($n = 37$)	Pen and paper cognitive training ($n = 23$)	Control group not computerized, not matched for engagement
Galante et al., 2007	Attention, memory, language, abstract reasoning, and visuo-spatial CCT ($n = 7$)	Life history and current event discussion ($n = 4$)	Heterogeneous control tasks, not matched for engagement, not computerized, small sample
Gagnon and Belleville, 2012	Variable priority divided attention tasks ($n = 13$)	Fixed priority variable attention tasks ($n = 13$)	Does not account for engagement, novelty
Gooding et al., 2016	Milieu-based attention, memory, and executive function CCT ($n = 23$) Attention, memory, and executive function CCT ($n = 31$)	BrainAge, Sudoku, crosswords ($n = 20$)	Heterogeneous control activities, different CCT vs. control interface
Herrera et al., 2012	Short-term memory CCT ($n = 11$)	Fact searching, crossing out letters, sentence construction ($n = 11$)	Heterogeneous control tasks, not entirely computerized, not matched for engagement
Rosen et al., 2011	Processing speed and auditory processing CCT ($n = 6$)	Audio books, reading online newspapers, visuospatial computer games ($n = 6$)	Small sample size, heterogeneous control tasks, not matched for engagement
Rozzini et al., 2007	Attention, memory, language, abstract reasoning, and visuo-spatial CCT + cholinesterase inhibitors ($n = 15$)	Cholinesterase inhibitors only ($n = 22$) And Waitlist ($n = 22$)	Non-active control condition
Talassi et al., 2007	CCT, occupational therapy, and behavioral training ($n = 54$)	Physical rehabilitation, occupational therapy, and behavioral training ($n = 13$)	Heterogeneous control tasks, not matched for engagement, not computerized

between cognitive remediation and CCT are useful for balancing expectancy, motivation, and novelty, but offer little insight into the precise mechanism of any observed cognitive improvement.

LOOKING FORWARD

Future studies would benefit from inclusion of measures to evaluate non-specific factors as covariates. For example, the User Engagement Scale measures aspects of engagement, usability, and satisfaction on a 5-point Likert scale and comprises both negative ("I felt annoyed when on this site," "the game was confusing") and positive ("I really had fun," "It was really worthwhile") items (Wiebe et al., 2014). The Immersive Experience Questionnaire provides ratings of temporal distortion, challenge, emotional involvement, enjoyment, and attentional involvement in the task (Jennett et al., 2008). Expectancy can be evaluated using the Credibility and Expectancy Scale (Devilly and Borkovec, 2000). The CES asks participants to report how logical the therapy seems, how successful they expect the treatment to be, and whether they would recommend the treatment to a friend. Two factors, credibility, and expectancy, have been found within the CES, with expectancy ratings successfully predicting treatment outcome in a randomized controlled trial of cognitive therapies for generalized anxiety disorders.

Until CCT can be found to improve cognitive and everyday functioning after accounting for each non-specific factor, its future as a treatment remains uncertain. What is more certain is the usefulness of being generally mentally active. Indeed, high levels of mental activity may be associated not only with higher cognitive performance, but reduced risk of dementia. A systematic review of 22 population studies found mental exercises may reduce overall incident dementia risk by 46% (Valenzuela and Sachdev, 2006). Whether CCT is the same as any other form of mental activity or represents a unique method for augmenting cognitive processes shall be a continuing topic of investigation.

AUTHOR CONTRIBUTIONS

JM: Manuscript conceptualization and design, writing of article. DD: Manuscript conceptualization and design, critical revision. PD: Manuscript conceptualization and design, critical revision. JS: Manuscript conceptualization and design, writing of article, critical revision. All authors have contributed to and have approved the final manuscript.

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Conflict of Interest Statement: PD has received grants and advisory/speaking fees from several pharmaceutical and technology companies including antidepressant manufacturers. He owns stock in several companies whose products are not discussed here. DD has received fees for scientific advisory boards from AbbVie, Lundbeck, and Intracellular Therapeutics.

The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 26 December 2016
doi: 10.3389/fnagi.2016.00319

Aerobic Activity in the Healthy Elderly Is Associated with Larger Plasticity in Memory Related Brain Structures and Lower Systemic Inflammation

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Edited by:
Xiong Jiang, Georgetown University, USA

Reviewed by:
Christian Gonzalez-Billault, University of Chile, Chile
Douglas Watt, Quincy Medical Center/Cambridge Health Alliance, USA

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Received: *05 September 2016*
Accepted: *09 December 2016*
Published: *26 December 2016*

Citation:
Thielen J-W, Kärgel C, Müller BW, Rasche I, Genius J, Bus B, Maderwald S, Norris DG, Wiltfang J and Tendolkar I (2016) Aerobic Activity in the Healthy Elderly Is Associated with Larger Plasticity in Memory Related Brain Structures and Lower Systemic Inflammation. Front. Aging Neurosci. 8:319. doi: 10.3389/fnagi.2016.00319

Cognitive abilities decline over the time course of our life, a process, which may be mediated by brain atrophy and enhanced inflammatory processes. Lifestyle factors, such as regular physical activities have been shown to counteract those noxious processes and are assumed to delay or possibly even prevent pathological states, such as dementing disorders. Whereas the impact of lifestyle and immunological factors and their interactions on cognitive aging have been frequently studied, their effects on neural parameters as brain activation and functional connectivity are less well studied. Therefore, we investigated 32 healthy elderly individuals (60.4 ± 5.0 *SD*; range 52–71 years) with low or high level of self-reported aerobic physical activity at the time of testing. A higher compared to a lower level in aerobic physical activity was associated with an increased encoding related functional connectivity in an episodic memory network comprising mPFC, thalamus, hippocampus precuneus, and insula. Moreover, encoding related functional connectivity of this network was associated with decreased systemic inflammation, as measured by systemic levels of interleukin 6.

Keywords: physical activity, elderly, memory, fMRI, functional connectivity, interleukin-6, inflammation

INTRODUCTION

It is a well-known phenomenon that our neurocognitive abilities change with age but there are remarkable differences in the timing and trajectory of these changes (Hedden and Gabrieli, 2004; Hofer and Alwin, 2008). Investigating the effects of lifestyle factors may be highly informative for the development of interventions to reduce or delay age-related cognitive decline. Among these lifestyle factors physical exercise both enhances and preserves cognitive function in the elderly (Dustman et al., 1984; Colcombe and Kramer, 2003; Smith et al., 2010; Bherer et al., 2013). Additionally, physical exercise appears to significantly reduce the risk of adults developing

dementing diseases in later years (Laurin et al., 2001; Hamer and Chida, 2009; Middleton et al., 2010; Llamas-Velasco et al., 2015). Even patients already suffering from mild cognitive impairment or dementing disorders improve in cognitive functioning after a physical exercise intervention (Heyn et al., 2004; Lautenschlager et al., 2008). Hence, physical exercise is a promising low-cost treatment to improve neurocognitive function that is accessible to most elderly.

There is general agreement that memory performance declines from early to late adulthood, and that such age-related memory impairments do not involve every domain of Memory (Grady and Craik, 2000). Decrements are typically slight in implicit memory tasks, immediate memory tasks, and in many recognition memory tasks (Grady and Craik, 2000). In contrast, age-related memory losses are substantial in episodic memory tasks involving cued or free recall (Anderson and Craik, 2000; Balota et al., 2000; Grady and Craik, 2000; Nyberg et al., 2012). In this regard, it has been shown that episodic memory (Chalfonte and Johnson, 1996; Naveh-Benjamin, 2000; Naveh-Benjamin et al., 2003, 2004), and in particular the memory for face-name or face occupation associations (Naveh-Benjamin et al., 2004; James et al., 2008; Hayes et al., 2015), is markedly reduced in the elderly. However, recent elderly studies have shown that the engagement in physical activity can counteract those episodic memory losses (Zlomanczuk et al., 2006; Hayes et al., 2015). For instance, Hayes et al. (2015) showed that engagement in physical activity, is positively associated with performance on the face-name association task. However, the neuronal correlates of this effect in terms of brain activation and functional connectivity have not yet studied. Sperling et al. (2003) examined the pattern of brain activation during the encoding of face-name associations in young and elderly. The authors showed that elderly, compared to young adults, have greater activation in parietal regions but less activation in both superior and inferior prefrontal cortices and the hippocampus, a brain region known to be essential in episodic memory (Burgess et al., 2002). One may hypothesize that engagement in aerobic physical activities has a positive effect on these brain regions affecting encoding related brain activation in and functional connectivity between these brain regions. Anatomically, the hippocampus is strongly connected to prefrontal regions as medial prefrontal cortex (mPFC; Preston and Eichenbaum, 2013) which, in turn, have reciprocal connections to several thalamic nuclei that are indirectly or directly reciprocally connected to the hippocampus in monkey (Aggleton et al., 2011). Moreover, a recent fMRI study revealed functional connectivity between hippocampus, mPFC and thalamus during episodic memory retrieval in young adults (Thielen et al., 2015). Therefore, we hypothesize that face association learning (encoding) is associated with the hippocampal-thalamus-mPFC axis and that engagement in aerobic physical activity has a positive effect on activation and functional connectivity within this memory network.

There is evidence that aerobic physical activity is associated with reduced systemic inflammation (Elosua et al., 2005; Autenrieth et al., 2009). There is also evidence that age related episodic memory decline is associated with inflammation (Simen et al., 2011). An association between inflammation and memory impairment has been reported in both, rodents, and human studies (Heyser et al., 1997; Gemma et al., 2005; Barrientos et al., 2006, 2009; Hilsabeck et al., 2010; Simen et al., 2011; Harrison et al., 2014, 2015). Thus, there seems to be an interaction between physical activity, inflammation and aging related memory decline. In this regard, it has been reported that inflammation affects the functioning of the hippocampus. For instance, peripheral injection of the bacteria *Escherichia coli* – leading to increased inflammation – produces both retrograde and anterograde amnesia in 24 month old, but not 3-month-old rats for memories that depend on the hippocampus (Barrientos et al., 2006). Recent studies in human have linked hippocampal activation and functional connectivity to systemic inflammation (Harrison et al., 2014, 2015). It was shown that induced (*S. typhi* vaccination) inflammation causes a reduced medial temporal cortex glucose metabolism and selectively impaired spatial episodic, but not procedural, memory (Harrison et al., 2014). Moreover, induced inflammation blocked functional connectivity between the substantia nigra and hippocampus that occurred during novelty processing in noninflammatory states (Harrison et al., 2015). Thus, it seems that inflammation has pronounced effects on hippocampus both, in terms activation and connectivity. Therefore, we assume that inflammation is inversely related to encoding related activation and functional connectivity within the hippocampal-thalamus-mPFC axis. Interleukin-6 (IL-6) has been recognized as an active player in inflammation (Rincon, 2012). IL-6 is both an anti-inflammatory and pro-inflammatory cytokine and can be released from different cell types as for instance astrocytes, muscle or fat cells (Gruol and Nelson, 1997; Nybo et al., 2002). IL-6 released from muscle tissue during or immediately after a bout of exercise exert anti-inflammatory effects by suppressing pro-inflammation factors. For instance, elevations in skeletal muscle derived IL-6 trigger an anti-inflammatory cascade by lowering the release of pro-inflammatory cytokines (e.g., IL-1β) via the stimulation of their antagonistic receptors (Nimmo et al., 2013). Moreover, exercise-related IL-6 triggers the release of IL-10, an anti-inflammatory molecule, which directly inhibits the synthesis of different pro-inflammatory mediators, particularly of the monocytic lineage, such as TNF-α, IL-1α, IL-1β, IL-8, and macrophage inflammatory protein-1α (Petersen and Pedersen, 2005) At rest, the release of IL-6 from skeletal muscle is minimal, with the majority being produced from adipose tissue and leucocytes, which is thought of as pro-inflammatory (Fischer, 2006; Nimmo et al., 2013). Moreover, studies revealed that regular engagement in physical activities is associated with lower systemic IL-6 levels at rest. For instance, Elosua et al. (2005) reported a negative relation between interleukin-6 to both physical fitness and leisure time related physical activity in the elderly. Lower levels of the pro-inflammatory IL-6 may reduce the risk of adults developing neurodegenerative diseases (Laurin et al., 2001; Hamer and Chida, 2009; Middleton et al., 2010; Llamas-Velasco et al., 2015). For instance, IL-6-treated hippocampal neurons showed tau hyperphosphorylation (Quintanilla et al., 2004), a hallmark of Alzheimer's disease. Moreover, neurons subjected to chronic IL-6 treatment exhibit increased sensitivity to NMDA receptor mediated neurotoxicity

(Qiu et al., 1998). In addition, it has been shown that IL-6 can have negative effects on synaptic plasticity. For instance IL-6 affects synaptic plasticity in the CA1 region of the hippocampus by causing a marked decrease in the expression of long term potentiation (LTP), the cellular model of learning and memory (Gruol and Nelson, 1997; Tancredi et al., 2000). However, we should note that IL-6 has not only destructive but also a beneficial potential. In this regard, numerous studies provide evidence for an IL-6 involvement in neuronal survival, protection, and differentiation (Hirota et al., 1996; Gadient and Otten, 1997; März et al., 1997; Loddick et al., 1998).

In the light of the aforementioned findings, we hypothesized that aerobic physical activity does not only improve episodic memory (Hayes et al., 2015) but that this effect goes along with changed brain activation and connectivity in the hippocampal-thalamus-PFC axis which in turn is inversely related to inflammation as measured with systemic IL-6 at rest. Therefore, this cross sectional study examined the effects of aerobic physical activity engagement on the performance on a face association task and related brain activation and functional connectivity in the elderly. Moreover, we hypothesized that systemic IL-6 levels are reduced in individuals that engage in aerobic physical activity which in turn is related to the functional effects, especially those that are related to the hippocampus.

MATERIALS AND METHODS

Subjects

Thirty-two healthy elderly, right-handed volunteers (16 males, mean age 60.4 ± 5.0 *SD*; range 52–71 years) were examined. None of the subjects reported a history of neurological or psychiatric diseases and all were free of psychotropic medication. Participants had normal or corrected-to-normal vision. Exclusion criteria were febrile illness within 7 days prior to study participation and severe somatic diseases, such as thyroid dysfunction, hypercortisolism, or adrenal dysfunction as well as diabetes mellitus type I and type II with an HBA1c > 8%, subjects with regular medication other than diabetes type 2 related medication. Written informed consent was obtained according to the local medical ethics committee.

Procedure

Assessments were carried out during 1 day. Before scanning, each subject scored the Physical Activity Scale for the Elderly (PASE; Washburn et al., 1993) questionnaire and a blood sample was taken to define plasma levels of IL-6. Since there is strong evidence for an increased level of IL-6 immediately after a bout of exercise that last at least 90 min (Leggate et al., 2010; Nimmo et al., 2013), it is important to note that the participants had not engaged in physical exercise on the day of testing. In addition, to account for potential differences between groups, each subject performed a standard neuropsychological test battery. The neuropsychological assessment included (1) the German version of the *Auditory Verbal Learning Test* (VLMT; Lux et al., 1999) to assess verbal episodic memory, (2) the *Brief Visuospatial Memory Test-Revised* (BVMT-R; Benedict et al., 1996; Benedict, 1997) and (3) the *Paired Associates Learning* (PAL; Torgersen et al., 2011) as measures of visuospatial episodic memory. (4) the *Trail Making Test* (Tombaugh, 2004; Bowie and Harvey, 2006) version A (TMT-A, visuoperceptual abilities; Sánchez-Cubillo et al., 2009) and B (TMT-B, working memory; Sánchez-Cubillo et al., 2009) and (5) the *Intra- and Extra-dimensional Shift* (IED; Égerházi et al., 2007) to assess cognitive flexibility and executive functions as well as (6) the *Controlled Oral Word Association Test* (COWAT; Baldo et al., 2006) to assess for verbal fluency. The *Mehrfachwahl-Wortschatz-Intelligenztest* (MWT-B; Lehrl, 2005) was conducted to estimate subject's general educational status as measurement for IQ. Both, the PASE and the neuropsychological test battery were performed before the blood sampling to ensure that the participants were not engaged in any physical activities for 90 min.

Physical Activity Assessment

The Physical Activity Scale for the Elderly (PASE; Washburn et al., 1993) provides a measure of physical activity regarding the past 7 days and is composed of the individual engagement in activity like sports, gardening, household activity, etc. Physical activity is commonly described by the following four dimensions: (1) frequency, (2) duration, (3) intensity, and (4) type of activity (Caspersen et al., 1985). Any assessment of physical activity should ideally measure all of these dimensions and account for day-to-day variation (Warren et al., 2010). The PASE questionnaire measures all dimensions and is therefore an appropriate measurement to assess physical activity level. Since we aimed at elucidating the effects related to aerobic physical activity we used the "strenuous sport" PASE sub-score to assess the aerobic physical activity level. Based on the finding that the PASE has demonstrated good validity in a couple of evaluations as for instance peak oxygen uptake, systolic blood pressure and measurements assessing physical fitness (Washburn et al., 1993, 1999; Harada et al., 2001) we assume that in particular this subscore has the potential to measure variations in aerobic capacity.

IL-6 Assessment

Blood samples were collected in EDTA tubes from the cubital veins between 9:00 am and 12:00 am in the fasting state and processed within 2 h by centrifugation at 1600 *g* for 15 min at RT. Plasma aliquots (500 μl) were stored in Matrix™ tubes (Thermo Fisher Scientific, Inc., Waltham, MA, USA) at −80° until IL-6 determination. IL-6 was determined in duplicate with the Human IL-6 Quantikine™ HS (high-sensitivity) ELISA Kit in 1:2 prediluted plasma. All readings were acquired in the dual wavelength mode at 467/650 nm on a Tecan Infinite Pro™ microplate reader (Tecan, Switzerland) with the Magellan™ data analysis software and corrected for background. Standard curves were generated on the basis of a four parameter logistic (4-PL) curve-fit.

fMRI Design

An associative face-profession encoding task (Theysohn et al., 2013) was performed during fMRI scanning (**Figure 1**). Five blocks of an episodic memory condition (face-profession

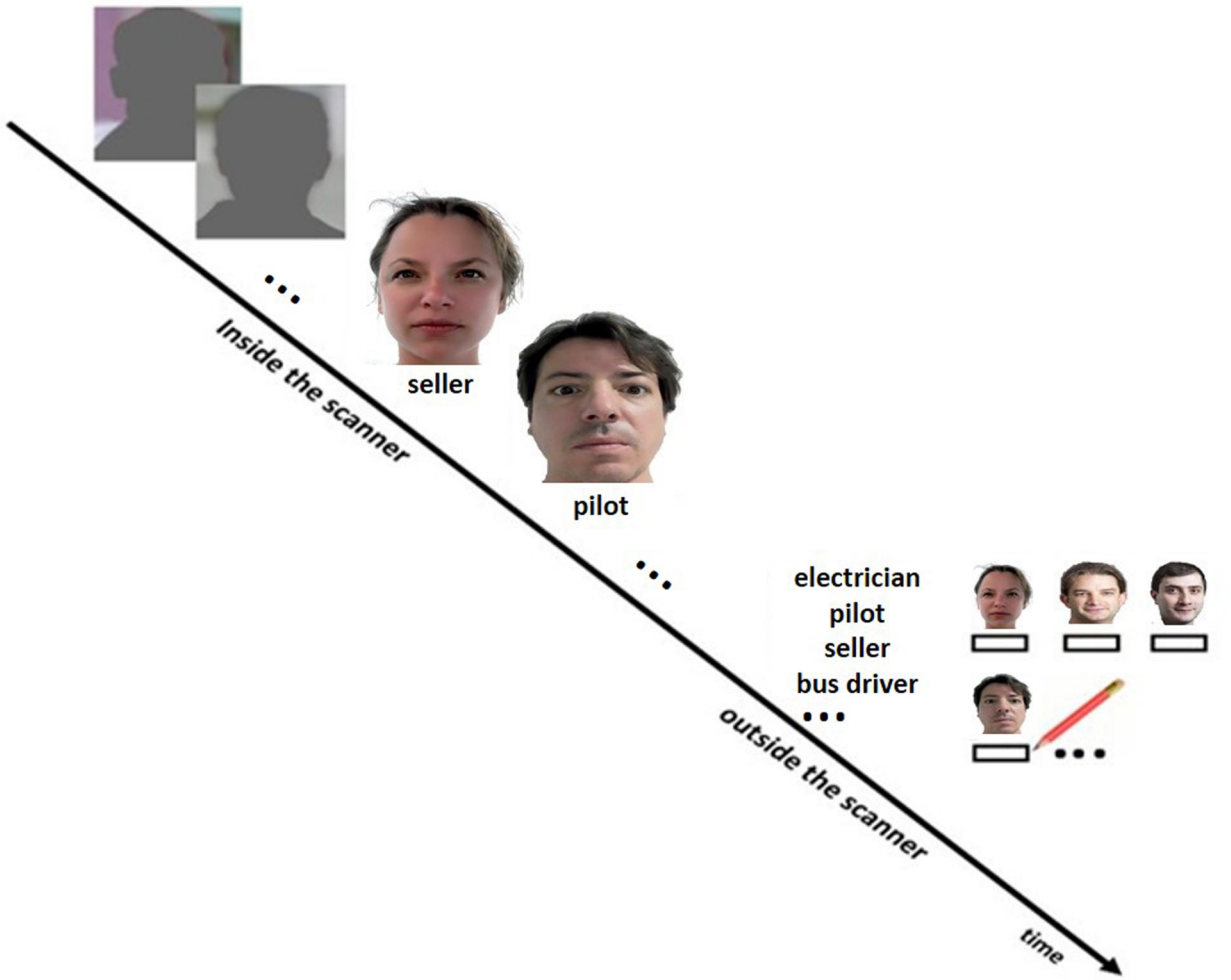

FIGURE 1 | Design of the face profession association task. During scanning, subjects performed the face-profession association task and a visuo-motor control task. The participants were instructed to memorize the face-profession associations for a subsequent memory test and to judge whether the face fitted well with the underlined profession or not. A simple visuo-motor task was used as control condition, in which subjects were required to judge whether the ears of a shadow-masked face contour were closer to the left or the right shoulder. Thereafter, subjects performed a recall test for the associated profession outside the scanner. Therefore, the participants were provided with a list on which all professions were listed and the faces (printed on papers in A4 format) seen during scanning. The participant had to write down the associated professions below the faces.

encoding task) consisting of four stimuli as described below were interleaved by five blocks of a control condition consisting of six stimuli whereby each block lasted 22.8 s. During the episodic memory condition, a series of four novel faces uniquely associated with occupational titles were shown. Each face with its associated occupational title underneath was displayed at the center of the screen for 5.7 s. Subjects were instructed to memorize face-profession associations for a subsequent memory test and to judge whether the face fitted well with the underlined profession or not. A simple visuo-motor task was used as control condition, in which each block (as in the episodic memory condition) started with the presentation of a brief instruction for 2.0 s, and followed by showing a series of six shadow-masked face contours with the presentation time of 3.8 s each. Subjects were required to judge whether the ears of a shadow-masked face contour were closer to the left or the right shoulder. We have chosen an "active" control task to avoid mental processes that are related to memory formation. In other words, during the visuo-motor task the participants could not spend effort to remember the faces and related occupations in order to improve memory. After the fMRI task subjects performed a recall test for the associated profession outside the scanner whereby they were presented with all the faces (printed on papers in A4 format) and had to write down the associated profession. To simplify this task, participants were also provided with a list on which all professions were listed. Stimuli, consisted of 20 portraits (half males) and 20 familiar professional names, were standardized according to several criteria, such as no strong emotional facial expression, direct gaze contact, no glasses, no beard, no headdress, etc. The

order of stimuli presentation was randomized for each subject. Length of familiar professional names ranged from 7 to 15 letters (mean length $\pm$ *SD* = 10.65 $\pm$ 2.77). For the control condition, 30 color photographs showing shadow-masked face contours (with shoulders) served as stimuli.

MRI Data Acquisition

Image acquisition was performed on a whole-body 7 T MR system (Magnetom 7T, Siemens Healthcare, Germany) using a 32-channel Rx/Tx head coil (Nova Medical, Wilmington, MA, USA). We used a T1 weighted MPRAGE sequence for structural image acquisition with a TR = 2.5 s, TE = 1.44 ms, flip angle = 6°, slice thickness = 0.7 mm, resolution = 0.7 mm^3, FOV 236 mm × 270 mm. Functional volumes were acquired using a T2*-weighted gradient echo 3D EPI sequence with ascending slice acquisition order, acceleration factor 8 (GRAPPA $R = 4*2$), TR = 3.0 s, TE = 20 ms, flip angle = 15°, matrix size 192*192*96, slice thickness = 1.5 mm, resolution = 1.5 mm^3, and a FOV of 288 mm × 288 mm.

fMRI Data Analysis

The native structural T1 images were segmented into gray and white matter components. The output of the segmentation was then used to create a group specific template in SPM8 by using diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL), which is registered to the Montreal Neurological Institute (MNI) space. Functional images were realigned, and the individual mean images were coregistered with the corresponding structural MRI by using normalized mutual information optimization. Then, the functional images were spatially normalized and transformed into a common space (group specific DARTEL template), as well as spatially filtered by convolving the functional images with an isotropic 3D Gaussian kernel of 6 mm FWHM. Regressors of interest were formed by creating a box-car function for both conditions (face-profession task/control task) convolved with the canonical hemodynamic response function. On the first level, a GLM was conducted with these two regressors, together with the six motion parameters derived from realignment procedure.

To investigate the effects of aerobic physical activity on the memory network, we performed psychophysiological interaction (PPI) analyses embedded in SPM8 (Friston et al., 2007). First eigenvariate values were extracted (physiological factor) from 5-mm spheres centered around the maxima within the clusters indicative of significant main effects (face-profession task > control task). A box-car function (weighted with +1 for face-profession and −1 for the control condition) was temporally convolved with the canonical hemodynamic response function (psychological factor). An interaction factor (PPI) was calculated as an interaction term of physiological and psychological factors. For each seed region, a first level GLM was conducted including the face-profession and control task regressors, the PPI regressors (physiological, psychological, and interaction factors) as well as the six motion regressors derived from realignment procedure during preprocessing of the functional scans.

Activation Analysis (Main Effect of Memory)

To assess the main effect of memory encoding, the subject-specific contrast images (face-profession condition over control condition) from all participants ($N = 32$) were used as inputs for the second-level random effects analysis. The results of the second level random effects analyses were thresholded at $P = 0.001$ and thereafter cluster-size statistics were used as test statistic. Only clusters at $P \leq 0.05$ (family-wise error corrected for multiple comparisons) were considered significant.

Activation Analysis (Effects of Aerobic Physical Activity)

The subject-specific contrast images (face-profession condition over control condition) were used as inputs for the second-level random effects analysis. Age, gender, and MWT-B IQ scores were included in the model as covariates of no interest. We did a GLM analyses in SPM8 to probe differences in brain activation due to aerobic physical activity [aerobic (+) group vs. aerobic (−) group]. Given the prior findings regarding the hippocampus, a bilateral hippocampus region of interest (ROI) was defined by means of the WfU-Pickatlas (Maldjian et al., 2003, 2004) as reduced search space. Thus we performed, whole brain and ROI (hippocampus) analyses. The outcomes of the second level group analyses were thresholded at $P = 0.001$ and thereafter cluster-size statistics were used as test statistic. Only clusters at $P \leq 0.05$ (family-wise error corrected for multiple comparisons) were considered significant.

Functional Connectivity Analysis

We conducted separate PPI analyses (mPFC and precuneus), based on the outcome of the initial activation analyses (main effects). The subject-specific contrast images for the interaction term (PPI.ppi) were used as inputs for the second-level group analyses [aerobic (+) vs. aerobic (−)] with age, gender, and MWT-B IQ scores as covariates of no interest. As previous, we performed a whole bran and ROI analysis (hippocampus). The results of the second level group analyses were thresholded at $P = 0.001$ and thereafter cluster-size statistics were used as test statistic. Only clusters at $P \leq 0.05$ (family-wise error corrected for multiple comparisons) were considered significant.

Correlation Analysis

Pearson's partial correlations analyses were performed by means of SPSS (IBM 21) software, with age, gender and MWT-B IQ score as variables of no interest. To assess the relations between brain activation/connectivity parameters and IL-6, we extracted the mean beta values of the clusters that revealed a significant effect of aerobic physical activity. For this purpose, we used MarsBaR toolbox to create separate masks of the significant clusters (see **Figures 2B,C**) which in turn were used in the REX toolbox to extract the analyses specific (PPI mPFC, PPI precuneus, or activation) mean beta-values of each cluster for all subjects. The mean *b*-values of the fMRI (activation/PPI) clusters and IL-6 concentration were then used for Pearson's partial correlation

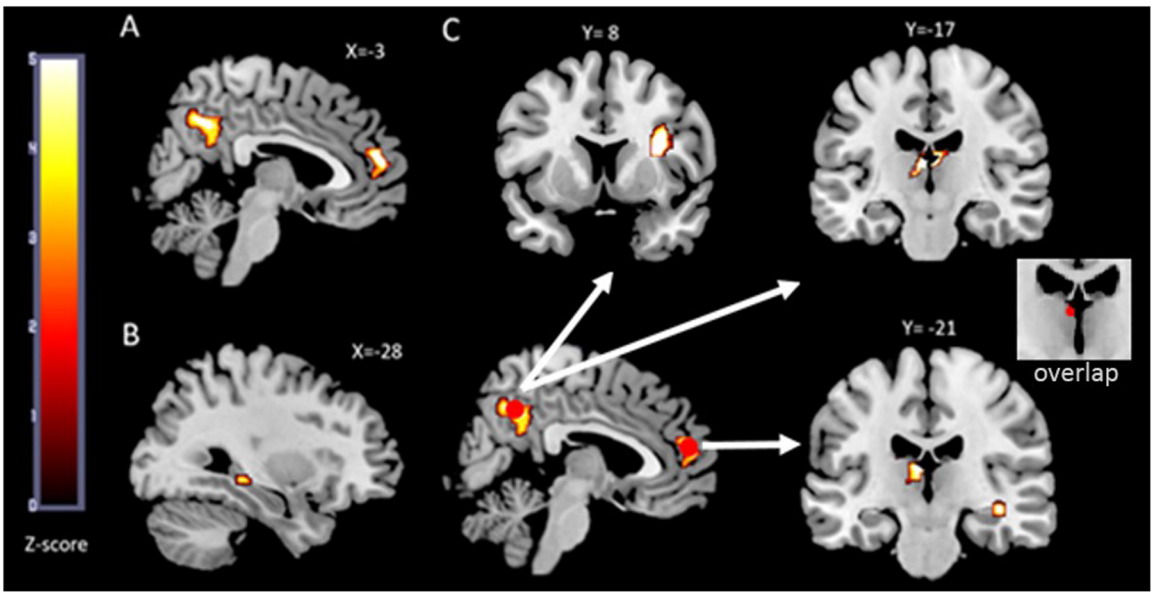

FIGURE 2 | fMRI results. The functional maps are overlaid on the MRIcron template brain (ch256). In **(A)** an illustration of the two brain regions that showed a main effect (face-profession task over control task) in the *whole group* analysis is depicted. Both, the precuneus cluster and the mPFC cluster extend into both hemispheres and served as seed regions in the functional connectivity analyses. In **(B)** the left hippocampus region that was more activated in the aerobic (+) group compared to the aerobic (−) group is illustrated. The outcome of the performed psychophysiological interaction (PPI) analyses is depicted in **(C)**. The two red circles are the seed regions which are spheres of 5 mm centered around the maxima within the clusters depicted in **(A)**. The white arrows indicate increased functional connectivity's between precuneus and thalamus, precuneus and right insula, mPFC and right hippocampus as well as between mPFC and left thalamus in the aerobic (+) group.

analyses with Benjamini and Hochberg (1995) correction for multiple testing.

RESULTS

Characteristics of the Sample

We grouped the subjects according to the PASE subscore "strenuous sport." Subjects in the aerobic (+) group scored on average 9.01 (SD = 4.7) whereas the subjects in the aerobic (−) group did not engage in any strenuous physical activities. No significant differences were found on relevant group characteristics, such as age and gender. However, the aerobic (−) group revealed a higher MWT-B IQ score compared to the aerobic (+) group (**Table 1**). Regarding the neuropsychological assessment, we found that the aerobic (+) group performed better on the TMT-A/B and the COWAT (**Table 2**). With respect to the fMRI memory task, we found a significant difference in performance (number of correct remembered face-profession associations) between the aerobic (+/−) groups. The aerobic (+) group revealed a significantly increased memory performance compared to the aerobic (−) group (see **Table 1**). This effect remained stable if corrected for MWT-B score, age, and gender.

Subjecting the blood parameter scores (IL-6) to a ANOVA a statistical significant effect of aerobic physical activity on IL-6 was observed ($F(1,30) = 7.70$, $P < 0.009$) when dividing groups according to their aerobic physical activity level (+/−). This effect remained stable if corrected for MWT-B score, age and gender. A *post hoc* t-test revealed that the aerobic (+) subjects had significantly lower levels of IL-6 compared to the aerobic (−) group (**Table 1**).

TABLE 1 | Group differences in the aerobic (+/−) groups are depicted.

	Aerobic physical activity		*P*
	Aerobic (−) Mean (*SD*)	**Aerobic (+) Mean (*SD*)**	
Demographics			
Gender	9 M/7 W	7 M/9 W	0.480
Age	61.19 (4.87)	59.75 (5.19)	0.426
MWT-B (IQ score)	116 (13.52)	106.69 (11.53)	0.045*
Blood parameter			
IL-6 (pg/ml)	1.98 (1.45)	0.89 (0.59)	0.009*
fMRI-Task			
Face-professional task (remembered items)	2.62 (1.82)	5.62 (3.57)	0.006*

*In the top relevant group characteristics (age, gender, and IQ) are shown. Below the group characteristics, the group differences of the parameters of interest (blood parameter and fMRI task) are depicted. *Significant.*

MRI Analyses

fMRI (Activation)

Whole brain analysis revealed a *main effect* of memory encoding in the bilateral precuneus (maxima at MNI = −2 −61 40

TABLE 2 | Group differences in the aerobic (+/−) groups are depicted.

	Aerobic physical activity		*P*
	Aerobic (−) Mean (*SD*)	Aerobic (+) Mean (*SD*)	
Neuropsychology			
VLMT-recognition (remembered items)	10.50 (2.65)	10.19 (4.26)	0.805
VLMT-delayed recall (remembered items)	8.53 (2.53)	9.12 (3.13)	0.570
BVMT-recognition (remembered items)	9.81 (1.97)	10.63 (1.70)	0.223
BVMT-delayed recall (remembered items)	7.5 (3.03)	9 (2.53)	0.139
PAL-stages completed	7.73 (0.5)	8 (0.0)	0.104
TMT-A (time)	40.19 (10.14)	31.88 (6.81)	0.011*
TMT-B (time)	99.44 (26.41)	80.56 (22.69)	0.038*
IED-stages completed	14.20 (5.58)	18 (16.99)	0.408
COWAT-correct produced	43.56 (11.33)	53.94 (12.53)	0.020*

*The aerobic (+) group scored better on tests assessing visual processing speed (TMT-A), working memory (TMT-B) and verbal fluency (COWAT) but not on tests assessing verbal LTM (VLTM), visuospatial LTM (BVMT-R/PAL) or cognitive flexibility/executive functions (IED). *Significant.*

FWE corrected, $P < 0.03$) and bilateral medial prefrontal cortex (maxima at MNI = −6 48 6 FWE corrected, $P < 0.05$; **Figure 2A**).

While the whole-brain analysis did not reveal significant differences between the aerobic + vs − group, the ROI analysis, however, revealed significantly increased activation in the left hippocampus (maxima at MNI = −29 −33 −6, FWE corrected, $P < 0.03$) in the aerobic (+) group (**Figure 2B**).

Functional Connectivity

Seed ROI mPFC (**Figure 2C**): The whole brain analyses revealed a stronger mPFC-left thalamus functional connectivity (maxima at MNI = −3 −17 13, FWE corrected, $P < 0.02$) in the aerobic (+) group compared to the aerobic (−) group. Regarding the ROI approach, an increased mPFC-right hippocampus functional connectivity (maxima at MNI = 37 −21 −11, FWE corrected, $P < 0.05$) was found in the aerobic (+) relative to the aerobic (−) group.

Seed ROI precuneus (**Figure 2C**): In the aerobic (+) group a pattern of increased functional connectivity was found comprising the bilateral thalamus (maxima at MNI = −4 −16 10 FWE corrected, $P < 0.01$) and the right insula (maxima at MNI = 32 8 17 FWE corrected, $P < 0.02$) when compared to the aerobic (−) group.

Correlation Analyses

The functional parameter that revealed a significant association with IL-6 (see **Table 3**) were the functional connectivity between mPFC/hippocampus and precuneus/insula. We found that mPFC-hippocampal functional connectivity correlated negatively with IL-6 ($r = -0.46$; $P = 0.009$). As did the precuneus-insula functional connectivity ($r = -0.45$; $P = 0.011$). In line with lesser inflammation in the presence of better connectivity within the memory network, we also found a negative correlation between hippocampal activation and IL-6 concentrations ($r = -0.39$; $P = 0.033$), which, however, did not survive the Benjamini and Hochberg correction for multiple comparisons.

TABLE 3 | Correlation matrix of aerobic physical activity effects on fMRI parameter (activation and functional connectivity) and IL-6 concentration.

	IL-6
fMRI (activation)	
Left hippocampus	$r = -0.39$*
fMRI (connectivity)	
mPFC to thalamus	$r = -0.27$
mPFC to hippocampus	$r = -0.46$**
Precuneus to thalamus	$r = -0.33$
Precuneus to insular	$r = -0.45$**

The black correlations indicate the Benjamini and Hochberg corrected correlations.
**Uncorrected significant.*
***Benjamini and Hochberg corrected significant.*

DISCUSSION

The present study aimed to combine immunological and functional imaging parameters to investigate multifactorial protective mechanisms of physical activity in healthy elderly. More precisely, we assessed the potential impact of the engagement in aerobic physical activity on changes in a network of brain regions mediating episodic memory functions and the associations to inflammation. As a marker for inflammation we indexed IL-6 since this cytokine displays the most marked response to acute exercise compared to other inflammation marker as for instance TNF-R, TNF alpha, IL 1 beta, IL-1ra, or IL-10 (Petersen and Pedersen, 2005).

Behaviorally, the aerobic (+) group had an elevated memory performance for face-profession associations compared to the aerobic (−) group, which is in line with the recent finding of Hayes et al. (2015). This finding was paralleled by better scores on tests assessing visual processing speed (TMT-A), working memory (TMT-B), and verbal fluency (COWAT) but not on tests assessing verbal episodic memory (VLTM), visuospatial episodic memory (BVMT-R/PAL) or cognitive flexibility/executive functions (IED). Note, we found only in the face-association task but not on the other episodic memory tasks an effect of physical exercise. This results are only partly in line with the findings of Hayes et al. (2015), which showed also no effect on verbal episodic memory but on visuospatial episodic memory. This may be related to methodological differences since Hayes et al. (2015) measured the level of physical activity via accelerometry. Moreover, Hayes et al. (2015) showed that the face-association task seems to be more sensitive to physical activity in older adults, since physical activity level accounted for 29.6% of the variance in the face-association task compared to 13.3% of the variance on the neuropsychological tests of visuospatial episodic memory. Regarding brain activation (main effect),

we found face-profession encoding related activation in the medial precuneus and the mPFC. While in line with other studies, we also found an activation in ventral temporal areas and lateral parietal as well as lateral frontal areas, these clusters failed to reach significance in the whole brain analysis, mirroring the findings from Theysohn et al. (2013), which used the same experimental paradigm and 7 Tesla scanning in healthy young adults. It is important to note, that dissimilar to Theysohn et al. (2013), there was signal dropout in the ventral temporal cortices, reducing the size of the activation cluster in the hippocampus so that the hippocampal clusters did not reach significance in the whole brain analyses. As aforementioned, based on anatomical connections and previous fMRI reports we assumed the mPFC-thalamus- hippocampus axis to be involved in the given memory task and that the engagement in aerobic activity increases functional connectivity in this axis. Therefore, we used the mPFC region as seed region in the PPI analyses. The precuneus is assumed to be involved in visual imagery and working memory occurring in episodic memory (Fletcher et al., 1996; Halsband et al., 1998; Cavanna and Trimble, 2006). Given the rich anatomical connectivity to several thalamic nuclei (Cavanna and Trimble, 2006) and reports of aging related changes in precuneus functions (Sperling et al., 2003; Gould et al., 2006; Mevel et al., 2011; Yang et al., 2014; Kleerekooper et al., 2016), we used the precuneus region as a second seed region in the PPI analyses. Note, since our preliminary hypothesis was focused on the mPFC-thalamus-hippocampus axis, the analyses regarding the precuneus cluster have an exploratory characteristic. In the following paragraphs, the effects of self-reported engagement in aerobic physical activity on brain activation/functional connectivity and the relation to inflammation will be discussed.

Whereas behavioral effects of physical activity/fitness on episodic memory have been frequently studied its relation to functional parameter as memory related brain activation or functional connectivity are still poorly understood. Here, we provide first evidence that engagement in aerobic physical activity is associated with episodic memory related brain activation and functional connectivity. More precisely, we found that the aerobic (+) group revealed stronger BOLD *activation* in the left hippocampus and a stronger *functional connectivity* between mPFC and left thalamus/right hippocampus during memory encoding. The thalamus has been described as an important structure regarding mPFC-hippocampus "communication" during memory processes. Evidence from human imaging studies as well as animal data revealed that the mPFC-thalamus-hippocampus axis is strongly associated with memory encoding (Xu and Südhof, 2013) memory consolidation (Thielen et al., 2015) and memory retrieval (Aggleton and Brown, 1999; Davoodi et al., 2009, 2011; Aggleton et al., 2010; Loureiro et al., 2012). Here, we show for the first time, that engagement in aerobic physical activity is associated with increased activation and functional connectivity in the mPFC-thalamus-hippocampal axis when elderly learn new face-occupation associations. Unfortunately, we could not observe a relation between the functional effects and performance on the face-profession task. However, in contrast to event related designs, blocked designs (as used here) are not able to distinguish between successful vs unsuccessful encoding processes.

In addition, we found that the aerobic (+) group revealed a stronger *functional connectivity* between precuneus and bilateral thalamus/left insula. The precuneus is assumed to be involved in visual imagery occurring in episodic memory (Fletcher et al., 1996; Halsband et al., 1998; Cavanna and Trimble, 2006). Interestingly, both seed regions (precuneus and mPFC) revealed increased functional connectivity to the thalamus that overlaid in the midline/dorsomedial thalamus. Therefore, the precuneus/thalamus connectivity might reflect support of the mPFC-thalamus-hippocampus axis with information regarding the visual representation of the memory. The insula, has been functionally divided into a posterior, ventroanterior and dorsoanterior part (Wager and Feldman-Barrett, 2004; Chang et al., 2013). In the present study, we found precuneus functional connectivity to the dorsoanterior insula, a region that is commonly activated in tasks that require executive control of attention, including those that require manipulation of information in working memory (Wager and Smith, 2003), shifting attention and response inhibition (Wager et al., 2004). Hence, the underlying function of the precuneus/insula connectivity may be related to executive manipulations of information in the working memory. To summarize, as hypothesized, the engagement in aerobic physical activity increased activation and functional connectivity within the mPFC-thalamus-hippocampus axis in the elderly. Interestingly, we found that the engagement in aerobic physical activity increases also task related functional connectivity in a precuneus-insula network that appears to interact with the mPFC-thalamus-hippocampus axis via the thalamus. Thus, we provide initial evidence that the thalamus has the potential to connect different networks, probably involved in different aspects of episodic memory encoding, a function that is boosted due to the engagement in aerobic activity.

Finally, we assessed whether systemic IL-6 concentrations are related to the functioning within the episodic memory network. In this regard, Harrison et al. (2014, 2015) have shown that induced inflammation causes a reduction in hippocampal glucose metabolism and functional connectivity during memory related processes. In the present study, we found an inverse relation between mPFC-hippocampus functional connectivity and circulating IL-6. In addition, a negative correlation between hippocampal activation and IL-6 could be observed. However, this correlation did not survive the Benjamini and Hochberg correction for multiple comparisons. Regarding the functional connectivity between mPFC and thalamus there was no relation to IL-6 which may be related to the heterogeneity of IL-6 distribution within the brain. For instance, rodent studies revealed high levels of IL-6 mRNA and IL6 receptor mRNA expressions in some brain regions, including the hippocampus, if compared to other brain regions (Schobitz et al., 1993; Gadient and Otten, 1994; Aniszewska et al., 2015). Together, we found that the functioning in the mPFC-thalamus-hippocampus axis is negatively related to inflammation, extending the previous findings of Harrison and colleagues to episodic memory

processes in the elderly. Interestingly, we found also an inverse relation between IL-6 and the functional connectivity between precuneus and insula. This is in line with recent studies that showed an association between inflammation and the insula in human (Hannestad et al., 2012; Labrenz et al., 2016). For instance, Labrenz et al. (2016) induced inflammation with lipopolysaccharide in healthy young adults and measured inflammation produced changes in resting state functional connectivity. They found a strong reduction between insula-precuneus functional connectivity, which was most pronounced for the anterior part of the insula. In the present study, we reveal for the first time that encoding related functional connectivity to the insula is associated to inflammation as measured with IL-6. Altogether, we provide new evidence that self-reported engagement in aerobic physical activity predict the strength of brain activation and functional connectivity in an episodic memory network composed of hippocampus, mPFC, thalamus, precuneus, and insula. Within this network, it appears that the circulating inflammatory marker IL-6 is inversely related to mPFC/hippocampal and precuneus/insula functional connectivity extending previous research that showed high affinity of inflammation on these brain regions. With respect to memory performance, we could not observe a relation between the amount of remembered associations and IL-6 levels, which may be attributed to the small sample size.

Some limitations should be acknowledged in this study. First, due to susceptibility artifacts, there was signal dropout in the ventral temporal cortices which reduced the size of the activation clusters (main effect) in this areas. Thus we cannot rule that these clusters would have reached significance in the absence of this artifact. Second, we did not assess the individual levels of physical fitness. Therefore, the findings we report here in relation to aerobic physical activity cannot transferred directly to aerobic capacity (fitness). For instance, a participant that reported 3 h of jogging may have run a distance that was much less than that of another participant that reported also 3 h of jogging. Moreover, physical activity is socially desirable behavior that might be overreported because of a social desirability bias. Third, this study had a non-randomized design so any number of third variables could have influenced the results. Fourth, our preliminary hypothesis did not include the involvement of the precuneus in the given task rendering the second PPI analysis more exploratory. Furthermore, we used IL-6 only as a measure of inflammation which does not represent the whole complexity going on in inflammatory processes. To date, many different markers of inflammation have been discovered. Therefore, to get a more comprehensive understanding, future studies should also indexing other inflammatory marker as for instance NF Kappa B, TNF alpha, and IL-10. In addition, we cannot determine whether the IL-6 effect is related to cells in the CNS (e.g., astrocytes) or cells in the periphery as for instance muscle or fat cells. In this regard, Nybo et al. (2002) showed that IL-6 release from the CNS is increased after a bout of exercise. However, the net release of IL-6 from the CNS appears to be manyfold lower than that released from muscles (Steensberg et al., 2001; Nybo et al., 2002). Future studies should use controlled experimental designs (e.g., Nybo et al., 2002) to determine the effects of physical activity on CNS released IL-6.

CONCLUSION

We assessed the impact of the engagement in aerobic physical activity on immunological and functional imaging parameters in healthy elderly in a between-subject cross-sectional design. We replicated prior findings regarding better memory functioning and decreased IL-6 concentration in aerobic active elderly subjects. In addition, we provide new evidence for an effect of aerobic physical activity on episodic memory related activation and functional connectivity. Moreover, we demonstrate that episodic memory related hippocampal and insula functional connectivity is inversely related to circulating IL-6 extending previous findings of inflammation effects on network properties. Future studies should try to replicate the current findings in a prospective intervention set-up to assess the impact of physical activity on the given parameters and their relations over time.

AUTHOR CONTRIBUTIONS

J-WT (data acquisition, analysis, and writing), CK (data acquisition and writing), BM (writing), IR (Neuropsychology), JG (Interleukin 6), BB (writing), SM (fMRT sequences), DN (MRT, supervisor), JW (supervisor), and IT (analysis, writing, and supervisor).

ACKNOWLEDGMENT

J-WT was supported by the ICEMED grant to DN, IT and JW from the Helmholtz Alliance, Germany.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 10 January 2017
doi: 10.3389/fnagi.2016.00329

Effort Not Speed Characterizes Comprehension of Spoken Sentences by Older Adults with Mild Hearing Impairment

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In spite of the rapidity of everyday speech, older adults tend to keep up relatively well in day-to-day listening. In laboratory settings older adults do not respond as quickly as younger adults in off-line tests of sentence comprehension, but the question is whether comprehension itself is actually slower. Two unique features of the human eye were used to address this question. First, we tracked eye-movements as 20 young adults and 20 healthy older adults listened to sentences that referred to one of four objects pictured on a computer screen. Although the older adults took longer to indicate the referenced object with a cursor-pointing response, their gaze moved to the correct object as rapidly as that of the younger adults. Second, we concurrently measured dilation of the pupil of the eye as a physiological index of effort. This measure revealed that although poorer hearing acuity did not slow processing, success came at the cost of greater processing effort.

Keywords: speech comprehension, aging, hearing loss, cognitive effort, eye tracking, pupillometry

OPEN ACCESS

Edited by:
Carryl L. Baldwin,
George Mason University, USA

Reviewed by:
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Jingwen Niu,
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Received: *17 August 2016*
Accepted: *19 December 2016*
Published: *10 January 2017*

Citation:
Ayasse ND, Lash A and Wingfield A (2017) Effort Not Speed Characterizes Comprehension of Spoken Sentences by Older Adults with Mild Hearing Impairment. Front. Aging Neurosci. 8:329. doi: 10.3389/fnagi.2016.00329

INTRODUCTION

The early literature on mental performance in adult aging was largely one of cataloging age-related deficits—most notably, ineffective learning and poor memory retrieval for recent events. It is the case that aging brings changes to the neural structures and network dynamics that carry cognition (Burke and Barnes, 2006; Raz and Kennedy, 2009), with behavioral consequences that include reduced working memory capacity and a general slowing in a number of perceptual and cognitive operations (Salthouse, 1994, 1996; McCabe et al., 2010). This deficit view of aging raises an intriguing paradox when applied to the everyday comprehension of spoken language. This paradox arises from the fact that natural speech runs past the ear at rates that average between 140–180 words per minute (Miller et al., 1984; Stine et al., 1990), that correct word recognition requires matching this rapidly changing acoustic pattern against some 100,000 words in one's mental lexicon (Oldfield, 1966; see also Brysbaert et al., 2016), and that one must maintain a running memory of the input to connect what is being heard with what has just been heard, and to integrate that with what is about to be heard (van Dijk and Kintsch, 1983).

Given the well-documented cognitive changes that accompany adult aging, surely, understanding spoken language should be among the hardest hit of human skills. Yet, barring significant neuropathology or serious hearing impairment, comprehension of spoken language remains one of the best-preserved of our cognitive functions (Wingfield and Stine-Morrow, 2000;

Peelle and Wingfield, 2016). Underlying this success, however, one may still ask: (1) whether such comprehension occurs as rapidly for older adults relative to younger adults; and (2) whether older adults' success at speech comprehension requires more effort compared to younger adults. These two questions have not heretofore been easy to answer.

A common approach to addressing the first of these questions has been to measure the relative speed with which younger and older adults can indicate the answer to a comprehension or semantic plausibility question after a sentence has been heard. These studies have typically employed a verbal or manual response, such as a key press, to indicate the moment the meaning of the sentence has been understood. Such measures have uniformly implied that older adults are slower in processing speech input than younger adults (e.g., Wingfield et al., 2003; Tun et al., 2010; Yoon et al., 2015). Less clear, however, is the extent to which such off-line, after-the-fact overt responses serve as a true measure of when comprehension has actually occurred (Caplan and Waters, 1999; Steinhauer et al., 2010).

Eye-Gaze as a Measure of Processing Speed

To address this question, we took advantage of the finding that an individual's eye-gaze to a picture of an object on a computer screen can be closely time-locked to its reference in a spoken sentence, such that eye-tracking can serve as a useful technique for studying real-time (in-the-moment) speech comprehension (Cooper, 1974; Tanenhaus et al., 2000; Huettig et al., 2011; Wendt et al., 2015; Huettig and Janse, 2016).

Since our question pertains to age differences, it is also fortunate that there are only minimal age differences in the velocity of saccadic eye movements (Pratt et al., 2006). We thus reasoned that measuring both overt responses and eye-gaze responses would allow us to determine whether the assumption that age-related slowing extends to speech comprehension is necessarily correct, or whether estimates of age differences in speed of comprehension have been exaggerated by slowing in the response measures themselves.

Our research strategy was to present younger and older adults recorded sentences that referred to a particular object, with their task being to select, as quickly as possible, the correct one of four pictured objects displayed on a computer screen. Our contrast would be the potential age difference in the time to indicate the referenced object with an overt, off-line selection response, vs. the moment the participants' eyes fixated on the referenced object as an on-line measure of when the referenced object was actually understood.

In the original "visual world" eye-tracking paradigm participants viewed objects on a computer screen with instructions such as "put the apple that is on the towel in the box". Using an eye-tracking apparatus that recorded where the eye was fixated on the computer screen, it was found that the participants' eye gaze moved from object to object as the sentence was being understood as it unfolded in real time (Tanenhaus et al., 1995; see also Cooper, 1974). Subsequent research has recorded time-locked eye-gaze for participants instructed to look at a target picture (e.g., "look at the candle") to measure the speed of isolating a named target from competitor objects (Ben-David et al., 2011), and tracked eye-gaze when participants have been asked to point to a named object (Hadar et al., 2016) or printed word (Salverda and Tanenhaus, 2010) displayed on a touch screen, or to select a named object by clicking on the correct object picture using a computer mouse (Allopenna et al., 1998). In the present study we used the latter as our overt response measure.

Pupil Dilation as a Measure of Processing Effort

Pertaining to our second question, a number of behavioral methods have been proposed to measure processing effort. One may, for example, assess the degree of effort by the degree to which conducting a speech task interferes with a concurrent non-speech task (e.g., Naveh-Benjamin et al., 2005; Sarampalis et al., 2009; Tun et al., 2009). Although informative, such dual-task studies are prone to trade-offs in the momentary attention given to each task that may complicate interpretation. Ratings of subjective effort have shown mixed reliability, as well as being an inherently off-line measure (McGarrigle et al., 2014).

To avoid these pitfalls we took advantage of an unusual feature of the pupil of the human eye. Beyond the reflexive change in pupil diameter in response to changes in ambient light, and the discovery that the pupil enlarges with a state of emotional arousal (Kim et al., 2000; Bradley et al., 2008), pupil diameter also increases with control of attention (Unsworth and Robinson, 2016) and increases incrementally with an increase in the difficulty of a perceptual or cognitive task (Kahneman and Beatty, 1966; Beatty, 1982; see the review in Beatty and Lucero-Wagoner, 2000). Importantly, when used while participants are listening to a sentence, pupillometry has the critical advantage of allowing an index of processing effort that does not interfere with performance on the speech task itself (e.g., Kuchinsky et al., 2013; Zekveld and Kramer, 2014).

MATERIALS AND METHODS

Participants

Participants were 20 younger adults (6 men, 14 women) ranging in age from 18 to 26 years (M = 21.2 years) and 20 older adults (5 men, 15 women) ranging in age from 65 to 88 years (M = 73.6 years). The younger adults were university students and staff and the older participants were healthy community-dwelling volunteers. All participants were self-reported native speakers of American English, with no known history of stroke, Parkinson's disease, or other neurologic involvement that might compromise their ability to perform the experimental task.

All participants were screened using the Shipley vocabulary test (Zachary, 1986) to insure that any potential age differences in the experimental task would not be due to a chance difference in vocabulary knowledge. As is common for healthy older adults (Kempler and Zelinski, 1994; Verhaeghen, 2003), the older adults

in this study had an advantage in terms of vocabulary knowledge relative to the younger adults (*M* older = 16.6, *SD* = 2.43; *M* younger = 13.8, *SD* = 1.71; $t_{(38)} = 4.01$, $p < 0.001$).

Audiometric evaluation was carried out for all participants using a Grason-Stadler AudioStar Pro clinical audiometer (Grason-Stadler, Inc., Madison, WI, USA) by way of standard audiometric techniques in a sound-attenuated testing room. The younger adults had a mean better-ear pure tone threshold average (PTA) of 7.6 dB HL (*SD* = 4.1) averaged across 500, 1000, 2000 and 4000 Hz, and a mean better-ear speech reception threshold (SRT) of 11.4 dB HL (*SD* = 3.9). The older adults had a mean better-ear PTA of 24.7 dB HL (*SD* = 8.7), and a mean better-ear SRT of 25.9 dB HL (*SD* = 8.0). As is typical for their age ranges (Morrell et al., 1996), the older adults as a group had significantly elevated thresholds relative to the younger adults ($t_{(38)} = 6.14$, $p < 0.001$). None of the older adults were regular users of hearing aids.

Vision screening was conducted using a Snellen eye chart (Hetherington, 1954) at 20 feet and the Jaeger close vision eye chart (Holladay, 2004) at 12 inches. All participants had corrected or uncorrected visual acuity at or better than 20/50 for both near and far vision.

This study was carried out in accordance with the approval of the Brandeis University Committee for the Protection of Human Subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Stimuli

Speech Materials

The stimuli consisted of 44 sentences recorded by a female speaker of American English. The sentences were spoken with natural prosody and speech rate. The spoken sentences were recorded on computer sound files using Sound Studio v2.2.4 (Macromedia, Inc., San Francisco, CA, USA) that digitized (16-bit) at a sampling rate of 44.1 kHz. Root-mean-square (RMS) amplitude was equated across sentences. Each of the sentences made reference to a picturable object that always formed the last word of the sentence. The waveform of an example sentence is shown in **Figure 1A**.

Because listeners may continually update their understanding of a sentence as it is being heard, it is possible for the referent of a sentence to be understood before the sentence has been fully completed (Huettig, 2015; Padó et al., 2009). To take this into account, we determined the knowledge point (KP) for each sentence; the point at which a *cloze* procedure conducted in a control study showed that both younger and older adults would know the likely identity of the sentence-final word. As illustrated in **Figure 1A**, for this example the KP occurred at the word *door*.

The KP was determined for each sentence using a cloze procedure with a separate group of participants (27 younger adults, 9 males and 18 females; *M* age = 20.2, *SD* = 1.20, and 26 older adults, 7 males and 19 females; *M* age = 72.3 years, *SD* = 5.56). Each sentence was presented visually, one word at a time, as participants viewed four object pictures, one of which would be the last word of the sentence being presented. As each word of the sentence was presented participants were asked to indicate if possible which object was being referenced by the sentence. The KP for each sentence was operationally defined as the earliest word in a sentence at which at least 90% of the participants knew the target word. For the majority of sentences, the KP was the same for younger and older adults. (Fifty-five sentences were initially constructed. In 10 sentences the KP differed by one word between the age groups. These sentences were not used in the main experiment, resulting in 44 sentences with age-invariant sentence-final word agreement that would serve as stimuli).

Visual Stimuli

For each trial the participants were presented with an array of four pictures of objects displayed in the four corners of a 1280 × 1040-pixel computer screen. Each object was surrounded by a 100-pixel diameter black ring to indicate the area within which the participant would be asked to place the computer cursor to indicate his or her selection. A 50-pixel red fixation circle was centered on the computer screen. Pictures were selected predominantly from the normed color image set of Rossion and Pourtois (2004), supplemented by images taken from clip art databases selected to match the Rossion and Pourtois images in terms of visual style.

In all cases, one of the pictures corresponded to the final word of the sentence that would be heard (*target picture*). The other three pictures (*lure pictures*) were always unrelated to the sentence meaning. None of the lure pictures were phonological competitors for the respective target word, and each set of lure pictures came from distinct functional categories. **Figure 1B** shows an illustrative stimulus array for the example sentence shown in **Figure 1A**.

Procedure

Participants were seated 60 cm from the computer screen with their head placed in a custom-built chin rest to stabilize head movement. Each trial began with the participant positioning the computer cursor on the red fixation circle. This was followed by a 2 s display of the particular four-picture array for that trial to allow the participant to familiarize himself or herself with the pictures and their positions on the computer screen. After the 2 s familiarization period the fixation circle turned blue. This signaled the participant to click on the fixation circle to initiate the sentence presentation. The participant's instructions were to listen carefully to the sentence and to choose the picture that they believed corresponded to the last word of the sentence as soon as they believed they knew the word. They were to indicate this by using the computer mouse to move the cursor from the fixation circle to the target object and clicking on the mouse to confirm the selection. The computer recorded the moment in time that the participant "clicked" on the correct picture with the mouse (*overt response time, ORT*). Instructions were to respond as rapidly as possible.

Throughout the course of each trial the participant's moment-to-moment eye-gaze position on the computer screen and changes in pupil size were recorded via an EyeTrac 6000 (Model 6 series, Applied Science Laboratories, Bedford, MA,

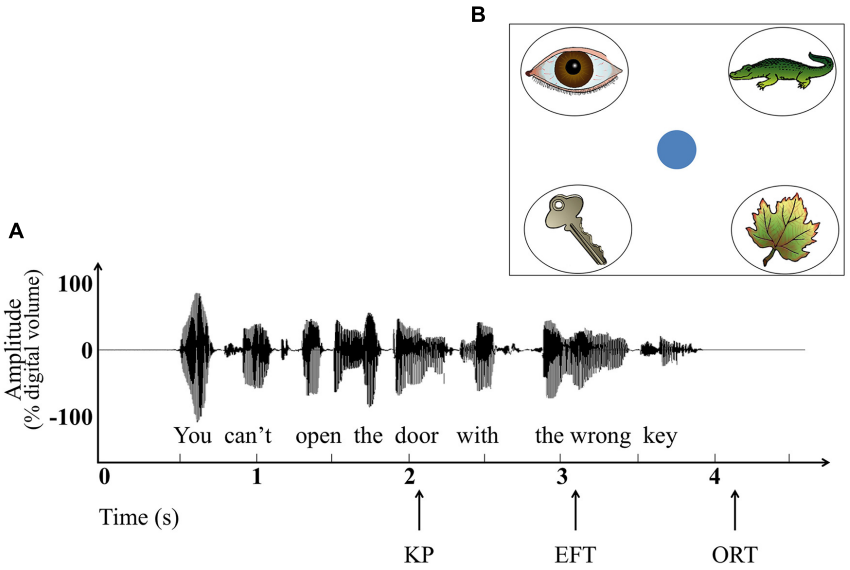

FIGURE 1 | Experimental stimuli and procedures. (A) Waveform of an example sentence showing the *knowledge point* (KP) based on a cloze procedure, the relative times after the KP that participants' eye-fixation indicated knowledge of the target object (*eye fixation time*; *EFT*), and when the target picture was selected with the computer mouse (*overt response time*; *ORT*). **(B)** An example picture array. Depicted in the bottom left corner is the target picture (key), while the other three pictures represent unrelated lures.

USA) eye-tracker that was situated below the computer screen and calibrated using EyeTrac software. These data as well as computer mouse movements and response-selection mouse-clicks were recorded via Gaze Tracker software (Eye Response Technologies, Inc., Charlottesville, VA, USA) at a rate of 60 Hz. The sentences and pictures were presented via a custom MATLAB (MathWorks, Natick, MA, USA) program.

The sentences were presented binaurally over Eartone 3A (E-A-R Auditory Systems, Aero Company, Indianapolis, IN, USA) insert earphones. To insure audibility sentences were presented at 25 dB above each individual's better-ear SRT. The main experiment was preceded by three practice trials using the same procedures as used in the experiment. None of these sentences or pictures was used in the main experiment.

RESULTS

Eye Fixations and Overt Response Times

With our procedures we thus had two measures for each sentence presentation: the *ORT*, indicating the participant's understanding of the sentence by the speed with which they placed the computer cursor and "clicked" on the referenced object on the computer screen, and the *eye fixation time* (EFT): the time point at which the participant's eye first fixed longer on the correct target picture than on the lures. This latter measure was based on prior studies using eye-tracking (Huettig et al., 2006; Wendt et al., 2014). For each trial, the proportion of time spent fixating on each of the three lures (averaged over the three lures) was subtracted from the proportion of time spent fixating on the target picture in 200 ms time bins (Huettig et al., 2006; Wendt et al., 2014). The EFT was operationalized as the point at which this difference in proportions of fixations exceeded a 15% threshold for 200 ms or more (Wendt et al., 2014, 2015).

The EFTs and the ORTs were measured from the word representing the KP for that sentence. This measure was taken from the midpoint of the KP word to take into account the finding that word recognition often occurs before the full duration of a word has been heard, especially when heard within a sentence context (Grosjean, 1980; Wayland et al., 1989; Lash et al., 2013). Data for incorrect initial target selections were excluded from the analyses (M = 6.8% of trials for older adults; M = 4.8% of trials for younger adults).

The waveform of the example sentence in **Figure 1A** shows, along with the KP, the mean EFT on the correct picture, and the mean ORT represented by the mouse-click on the correct object picture. This example is typical in that, for the average participant, the eye fixated on the target picture before the full sentence had been completed, while the overt response occurred shortly after the sentence had ended.

Figure 2 quantifies these data for the younger and older participants. The results show both an expected finding and a less expected finding based on claims of generalized slowing in adult aging (Cerella, 1994; Salthouse, 1996). The vertical bars on the right side of **Figure 2** show the mean latency from the KP in a sentence to the overt response for the younger and older adults. These are exactly the results that would be expected based on generalized slowing in older adults, with the older adults showing significantly longer response latencies than the younger adults ($t_{(38)}$ = 4.65, $p < 0.001$). The two vertical bars on the left side of **Figure 2** show, for the same participants, the mean latencies from the KP to the time point

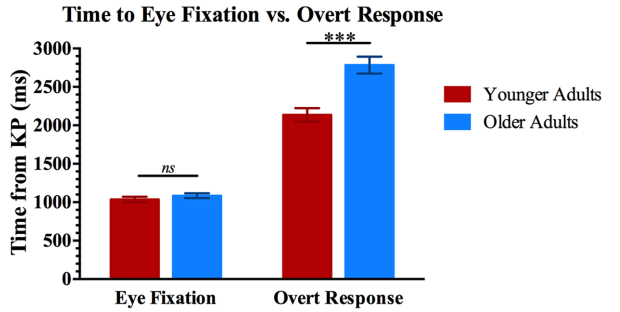

FIGURE 2 | Results for gaze time and overt responses. Two vertical bars on the left show mean latencies from the KP in a sentence to the time point when younger and older adults' eyes fixated longer on the target picture than on the lures (*EFT*). Two vertical bars on the right show the mean latency from the KP in a sentence to the selection of the correct target picture with a computer mouse (*ORT*). Error bars are one standard error. ***Significant pairwise differences, $p < 0.001$.

where listeners' eye gaze fixated more on the target picture than on the non-target lures. It can be seen that, by this measure, the older adults were no slower in knowing which object was being indicated by the sentence than the younger adults ($t_{(38)} = 1.01$, $p = 0.32$).

This dissociation between knowing the identity of the referenced object, as evidenced by the participant's eye movements to the target picture, and indicating this knowledge by an overt response, was supported by a 2 (Response type: EFT, ORT) × 2 (Age: Younger, Older) mixed-design analysis of variance (ANOVA), with response type as a within-participants factor and age as a between-participants factor. This confirmed a significant main effect of response type ($F_{(1,38)} = 447.19$, $p < 0.001$, $\eta_p^2 = 0.922$), and of age ($F_{(1,38)} = 18.69$, $p < 0.001$, $\eta_p^2 = 0.330$), with the dissociation of age effects on the two measures revealed in a significant Response type × Age interaction ($F_{(1,38)} = 20.51$, $p < 0.001$, $\eta_p^2 = 0.351$). That is, while older adults may appear slower in comprehending a spoken sentence using a measure that includes decision-making and an overt response (off-line measures that typify reports of age-related slowing in speech comprehension), the eye movement data reveal that the older adults' time to actually comprehend the semantic direction of a sentence was not significantly slower than younger adults'.

As previously noted, stimuli were presented at a loudness level relative to each individual's SRT (25 dB above SRT). This procedure was followed to ensure that the stimuli would be audible for all participants. Following the above-cited ANOVA, we conducted an analysis of covariance (ANCOVA) with better-ear PTA as a covariate. This analysis confirmed the same pattern of main effects and the Response type × Age interaction with these effects uninfluenced by hearing acuity. Although confirming that our presentation of the speech stimuli at an equivalent suprathreshold level for each participant was successful in ensuring audibility of the stimuli, this should not necessarily imply that those with better and poorer hearing acuity accomplished their success with equivalent listening effort.

Pupillometry Measures and Hearing Acuity

To explore the possibility that hearing acuity differences among the older adults may have affected processing effort, we separated the older adult participants into two subgroups based on a median split of hearing acuity.

The *normal hearing* older adult group consisted of the 10 older adults with better hearing acuity, having PTAs ranging from 10 dB HL to 24 dB HL. We use the term "normal" although this group includes individuals with a slight hearing loss (defined as PTAs between 15–25 dB HL; Newby and Popelka, 1992). Although representing thresholds elevated relative to normal-hearing young adults, this range is typically defined in the audiological literature as clinically normal hearing for speech (Katz, 2002).

The *hearing-impaired* older adult group consisted of the 10 older adults with relatively poorer hearing acuity, having PTAs ranging from 26 dB HL to 40 dB HL. These participants' PTAs lie within the range typically defined as representing a mild hearing loss (26–40 dB HL; see Newby and Popelka, 1992; Katz, 2002).

The left, middle, and right panels of **Figure 3** show better-ear audiometric profiles from 500 Hz to 4000 Hz for the young adults, the 10 normal-hearing older adults and the 10 hearing-impaired older adults, respectively. These data are plotted in the form of audiograms, with the *x-axis* showing the test frequencies and the *y-axis* showing the minimum sound level (dB HL) needed for their detection. Hearing profiles for individual listeners within each participant group are shown in color, with the group average drawn in black. The shaded area in each of the panels indicates thresholds less than 25 dB HL, a region, as indicated above, commonly considered as clinically normal hearing for speech (Katz, 2002).

The normal-hearing and hearing-impaired older adults were similar in age, with the normal-hearing older adults ranging in age from 65 to 88 years ($M = 73.1$ years, $SD = 7.17$) and the hearing-impaired older adults ranged in age from 68 to 81 ($M = 74.2$, $SD = 4.22$; $t_{(18)} = 0.40$, $p = 0.70$). The two groups were also similar in vocabulary knowledge as measured by the Shipley vocabulary test (Zachary, 1986; Normal-hearing $M = 16.3$, $SD = 2.21$; Hearing-impaired $M = 16.6$, $SD = 2.76$; $t_{(18)} = 0.27$, $p = 0.53$).

Pupil size was continuously recorded at a rate of 60 times per second using the previously cited ASL eye tracker (Model 6 series, Applied Science Laboratories, Bedford, MA, USA). routed through the presentation software (GazeTracker, Applied Science Laboratories, Bedford, MA, USA) to allow for pupil size measurements to be synchronized in time with the speech input. Measures of pupil diameter were processed with software written with Matlab 7 (Mathworks, Natick, MA, USA).

Eye blinks were determined by a sudden drop in vertical pupil diameter and were removed from the recorded data prior to data analysis. As is common in pupillometry studies, blinks were defined by a change in the ratio between the vertical and the horizontal pupil diameter. For an essentially circular pupil, the ratio would be approximately 1.0. During a blink or semi-blink the ratio quickly drops toward 0. All samples with a ratio differing more than 1 *SD* from the mean

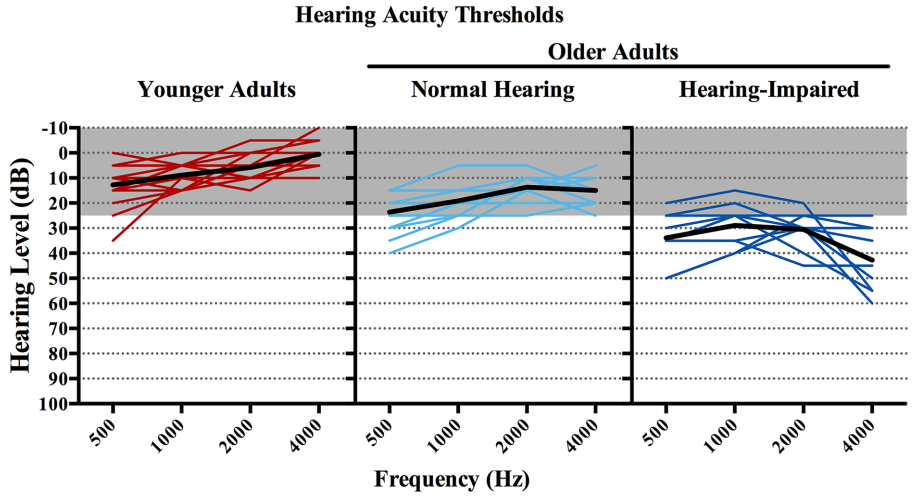

FIGURE 3 | Better-ear pure-tone thresholds from 500 Hz to 4000 Hz for the three participant group. Hearing profiles for individual listeners within each participant group are shown in color, with the group average drawn in black. The shaded area in each of the panels indicates thresholds less than 25 dB HL (the range considered clinically normal for speech; Katz, 2002).

were eliminated (Piquado et al., 2010; see also Zekveld et al., 2010; Kuchinsky et al., 2014; Winn et al., 2015; Wendt et al., 2016).

When comparing relative changes in pupil sizes across age groups it is necessary to adjust for *senile miosis*, where the pupil of the older eye tends to be generally smaller in size, to have a more restricted range of dilation, and to take longer to reach maximum dilation or constriction (Bitsios et al., 1996). To the extent that a change in pupil size is a valid index of processing effort, an absolute measure of a task-evoked pupil size change would thus tend to underestimate older adults' effort relative to that of younger adults.

To adjust for this potential age difference in the pupillary response, pupil sizes were normalized by measuring, for each individual prior to the experiment, the range of pupil size change as the participant viewed a dark screen (0.05 fL) for 10 s followed by a white screen (30.0 fL) for 10 s. Based on the individual participant's minimum pupil constriction and maximum pupil dilation, we scaled his or her pupil diameter according to the equation: $(d_M - d_{min}) / (d_{max} - d_{min}) \times 100$, where d_M is the participant's measured pupil size at any given time point, d_{min} is their minimum pupil size (measured during presentation of the white screen), and d_{max} is their maximum pupil size (measured during presentation of the black screen; Allard et al., 2010; Piquado et al., 2010). Pupil sizes were additionally adjusted to account for any trial-to-trial variability in pupil diameter (Kuchinsky et al., 2013; Wendt et al., 2016), using a baseline of the mean pupil diameter during a 2-s pre-sentence silence as the d_{min} in the above equation and the maximum post-sentence pupil diameter as the d_{max}.

Figure 4 shows the accordingly adjusted mean pupil sizes for the three participant groups over a 1-s time window preceding the point of participants' eye fixation on the correct object picture relative to the lure pictures. This time window was intended to capture the processing effort leading up to this moment (Bitsios et al., 1996).

A one-way ANOVA conducted on the data shown in **Figure 4** yielded a significant effect of participant group on pupil diameter ($F_{(2,37)} = 8.22$, $p = 0.001$, $\eta_p^2 = 0.308$), with Bonferonni *post hoc* tests confirming that the hearing-impaired older adults showed a significantly greater increase in relative pupil size leading up to their eye fixation on the correct object picture as compared to either the younger adults ($p = 0.003$) or the normal-hearing older adults ($p = 0.003$). The difference in relative pupil sizes between the young adults and the normal-hearing older adults was not significant ($p = 1.00$). This general pattern was seen for pupil sizes at the time of the overt response,

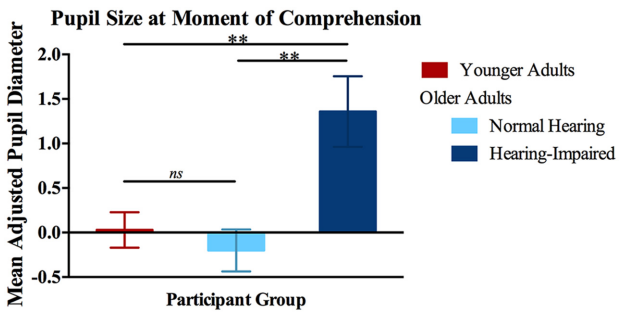

FIGURE 4 | Mean adjusted pupil diameter leading up to the moment of comprehension. Pupil diameters calculated over a 1-s window preceding participants' eye fixations on the target picture. Data are shown for younger adults (left vertical bar), older adults with normal hearing acuity (middle vertical bar), and older adults with hearing impairment (right vertical bar). Error bars are one standard error. **Significant pairwise differences, $p < 0.01$.

although the data were more variable and not statistically reliable.

DISCUSSION

It has been well documented that older adults are on average slower than their younger adult counterparts on a range of perceptual and cognitive tasks (Cerella, 1994; Salthouse, 1996), to include sentence comprehension when measured by decision latencies indicating that a sentence as been understood (e.g., Wingfield et al., 2003; Tun et al., 2010; Yoon et al., 2015). On the surface our present data would appear to be consistent with an extension of general slowing to spoken language comprehension, at least when comprehension was indexed by latencies to correct response selection. The eye-gaze data, however, tell a different story, one in which on-line comprehension of sentence meaning was accomplished as rapidly for healthy older adults as for younger adults.

Eye-Gaze as an On-Line Measure

The observed dissociation in this experiment between knowing and the speed of expressing this knowledge in sentence comprehension is consistent with the previously cited distinction suggested by Caplan and Waters (1999). This is the distinction between on-line interpretive processing of a sentence, which may be age-independent for adult listeners, vs. post-interpretive operations, such as planning an action or response, that may well be slower for older adults (see also Waters and Caplan, 2001; Evans et al., 2015). Also implied by this distinction is that an age-independence in on-line interpretive processing may be obscured in sentences that place a heavy demand on working memory for their comprehension. Such working memory demands are associated with sentences that express their meaning with more complex syntax, where older adults are known to show a differential increase in comprehension errors relative to younger adults (e.g., Carpenter et al., 1994; DeCaro et al., 2016) and an increase in the pattern of neural upregulation when comprehension is successful (Wingfield and Grossman, 2006; Peelle et al., 2010).

In this regard, we present our processing-speed data with two caveats. The first is that the sentences used in this study were heard in quiet, were presented at individually adjusted suprathreshold levels, and that they were intentionally, like most of the sentences we hear on a daily basis (e.g., Goldman-Eisler, 1968), grammatically straight-forward and lacking in the working memory demands associated with comprehension of sentences with complex syntax (Just and Carpenter, 1992; Carpenter et al., 1994). As such, these data present a best-case scenario for older adults who, at the perceptual level, have a special difficulty with speech heard in a noisy background (Humes, 1996; Tun and Wingfield, 1999) and who tend to show minimal age difference in comprehension accuracy for grammatically simple sentences (Wingfield and Stine-Morrow, 2000).

Although hearing impairment is known to interact with syntactic complexity when off-line measures of comprehension are employed (e.g., Wingfield et al., 2006), Wendt et al. (2015) have shown that effects of hearing impairment and syntactic complexity can also appear using eye-gaze as an on-line measure. In their experiment, participants heard syntactically simple sentences with a canonical subject-verb-object (SVO) word order, such as, "The little boy greets the nice father" or with the meaning expressed with a less canonical, object-verb-subject (OVS) word order, such as, "It is the nice father that greets the little boy". As sentences were being heard participants viewed two pictures side-by-side on a computer screen. For this example, one picture depicted a father greeting a little boy and the other depicted a little boy greeting a father. The participant's task was to indicate with a key press whether the picture on the left or the right of the screen matched the sentence. Wendt et al. (2015) found that eye-fixations to the correct picture tended to be longer for hearing-impaired participants when the relationship between agent and action was expressed with complex syntax.

It may thus be that an absence of age or hearing acuity effects on on-line comprehension speed as demonstrated in the present experiment for syntactically simple sentences might appear when listeners are presented with syntactically complex sentences that place a heavy demand on working memory for their resolution, and perhaps further affected by more challenging listening conditions such as the presence of background noise or especially rapid input rates that are known to place older adults and those with hearing loss at a special disadvantage (see Wingfield and Lash, 2016, for a review of age-related susceptibility to effects of background noise and input rate on speech understanding).

The second caveat is that, in addition to our use of sentences with non-complex syntactic constructions not expected to place significant demands on working memory (see for example Carpenter et al., 1994; DeCaro et al., 2016), the selection of the referenced object on each trial was from a closed set of four possible candidates. Within these constraints, however, the time to older adults' eye-gaze on the correct object demonstrated that the older adults understood which object was being referenced by the sentence before the sentence had been completed, and that they did so as rapidly as the younger adults.

An alternative to eye-gaze as a measure of on-line sentence processing has been to measure electrical brain activity using event-related potentials (ERPs) as a marker of sentence comprehension. Such studies have primarily focused on the finding that an N400 component of the ERP responds to a semantic violation in a sentence while a P600 component responds to a syntactic violation (see the review in Kutas and Federmeier, 2011). Although many studies have centered on written, as opposed to spoken sentences, and often with such sentences presented in a word-by-word fashion, studies have been conducted that have monitored ERPs as spoken sentences are being heard in real time. One such study in the speech domain revealed affects consistent with our finding of an age-dissociation between on-line vs. off-line measures of sentence comprehension (Steinhauer et al., 2010). These authors found that a P600 was elicited when the syntactic clause boundary in a sentence occurred in one position while the prosodic pattern indicated a different boundary position. They found that the P600 response to this inconstancy occurred as rapidly for older adults as for

younger adults, while an off-line measure (responding whether the sentence sounded natural) showed typical age-related slowing. In Caplan and Waters's (1999) terms, one would characterize this distinction as an age-invariance in on-line interpretive processing vs. the appearance age-related slowing in post-interpretive processing.

Pupillometry as a Measure of Processing Effort

As we saw, steps were taken to insure that the speech materials were presented at an audible sound level for all participants, such that differences in hearing acuity did not affect either the EFTs to the correct object pictures or the ORTs. This should not imply, however, that this success was achieved with equivalent effort for those older adults with normal hearing or impaired hearing acuity. Indeed, using the pupillary response as a physiological index of processing effort (Piquado et al., 2010; Kuchinsky et al., 2013; Zekveld and Kramer, 2014), however, we found that the older adults with hearing impairment achieved their success at the cost of greater processing effort than required either by the young adults or the older adults with normal hearing acuity.

The underlying connection between effortful processing and the task-evoked pupillary response (TEPR) remains a topic of active investigation. Current evidence suggests that task-related increases in pupil diameter are associated with activity of the *locus coeruleus*-norepinephrine (LC-NE) system, with the LC-NE system serving to modulate prefrontal attentional control (Unsworth and Robinson, 2016). Although pupil dilation is correlated with attention-relation neuronal firing in brain stem *locus coeruleus*, the specific chain of neural events underlying this correlation is complex and not yet fully understood (see "Discussion" Section in Kuchinsky et al., 2014).

At the behavioral level, however, increases in pupil size relative to baseline have been shown to serve as a reliable index of effortful processing, whether in response to listening effort attendant to a degraded speech signal (Zekveld et al., 2011; Kuchinsky et al., 2013; Zekveld and Kramer, 2014; Wendt et al., 2016), to increasing cognitive load in problem-solving and memory tasks (Hess and Polt, 1964; Kahneman and Beatty, 1966; Beatty, 1982) or recall of sentences that increase in length and syntactic complexity (Piquado et al., 2010).

The present study revealed larger adjusted pupil sizes in older adults with impaired hearing, relative to those with normal hearing acuity, in the time period just prior to the point where eye-fixations indicated knowledge of the object being referred to in the sentence. We take these data to support the likelihood that the hearing-impaired participants' successful comprehension was accomplished with greater effort than the equivalent success of the older adults with better hearing acuity.

This latter finding is especially important in the face of mounting evidence that successful perception of degraded speech can come at the cost of resources that would otherwise be available for encoding what has been heard in memory (Rabbitt, 1968, 1991; Murphy et al., 2000; Wingfield et al., 2005; Surprenant, 2007; Miller and Wingfield, 2010; Cousins et al., 2014) or for comprehension of sentences with complex syntax (Wingfield et al., 2006; DeCaro et al., 2016). This phenomenon represents a "hidden effect" of even a relatively mild hearing loss on older (and younger) adults' comprehension and recall of spoken input that goes beyond simply missing or mishearing occasional words (Piquado et al., 2012).

CONCLUSION

Taken together, our results show that although general slowing may be a hallmark of adult aging, its effects do not apply uniformly across all linguistic operations. Specifically, we found that eye fixations on a referenced object in a spoken sentence occurred as rapidly for older adults as for younger adults, although the older adults were slower in indicating the referenced object with an overt response. As we have indicated, this observed dissociation is consistent with Caplan and Waters (1999) distinction between immediate interpretive processing of sentence meaning that is age-independent, and age-sensitive post-interpretive processes that include decision-making and response selection. An additional finding in this study, however, was that even though the hearing-impaired older adults were no slower in on-line understanding of which object was being referenced by a sentence than older adults with better hearing, their success was accompanied by significantly greater processing effort as indexed by pupil dilation.

The prevalence of hearing impairment among older adults has led to an almost exponential increase in studies of listening effort; how it can be defined and measured (McGarrigle et al., 2014), the cascading effects of front-end perceptual effort on downstream cognitive operations include encoding what has been heard in memory (Wingfield et al., 2005), and a special appreciation for the role modern hearing aids can play in reducing listening effort beyond the historical focus on word recognition *per se* (Sarampalis et al., 2009). This growth of interest in the nature and cognitive costs of effortful listening is well represented in a recent collection edited by Pichora-Fuller et al. (2016).

We have cited studies showing that listening effort attendant to mild hearing loss can affect speech comprehension and effectiveness of encoding what has been heard in memory. Although many older adults may be unaware of this "hidden effect" of hearing impairment on comprehension and immediate memory, there is one consequence of hearing loss that many older adults do recognize. That is, even with a relatively mild hearing loss, many older adults report a sense of stress and end-of-the-day fatigue consequent to the continual effort needed to understanding daily conversational speech (Pichora-Fuller, 2006; Fellinger et al., 2007). This can, in turn, lead to avoidance of social interactions and reduced self-efficacy (Kramer et al., 2002).

In this latter regard, we emphasize the importance of maintaining task engagement by the older adult with or without hearing impairment, even at the cost of cognitive effort. The alternative would be to avoid all difficult tasks that would lead to a potential downward spiral to a general sense of lowered expectations and reduced self-efficacy. We suggest that this was not the case with the hearing-impaired older adults in our study.

An early finding in studies of digit- and word-list recall was that the progressive increase in pupil size as the size of a to-be-recalled list was increased may cease, or reverse, at the

point where a list becomes so long as to lead to a memory overload (Kahneman and Beatty, 1966; Peavler, 1974; Granholm et al., 1996). Such an effect can reasonably be interpreted as reflecting task disengagement by the participant when cognitive ability, or one's willingness to commit effort, is not up to task demands (Kuchinsky et al., 2014; Zekveld and Kramer, 2014). The larger pupil sizes relative to baseline observed for our older hearing-impaired listeners, relative to either the young adults or the better-hearing older adults, suggests that the hearing-impaired older adults in this study remained fully engaged in the experimental task.

Implications for Interventions

Although our focus is on aging, and age-related hearing loss, it should be noted that mental fatigue due to the continual effort required to successfully understand others' speech, and its potential effects on cognitive effectiveness, is no less a concern for young adults with hearing impairment (Hicks and Tharpe, 2002), many of whom report being unaware of their hearing loss (e.g., Le Prell et al., 2011).

The frequency-selective amplification and signal processing algorithms available in modern hearing aids can not only improve speech intelligibility, they can also reduce the resource drain associated with effortful listening (Sarampalis et al., 2009). Yet it is the case that two out of three older adults (age 65 and older), and 9 out of 10 younger adults with hearing loss do not use hearing aids, with the numbers especially large in the mild-to-moderate hearing loss range (National Academy on an Aging Society, 1999). Indeed, on average, 10 years pass from the time a person suspects they have a hearing impairment and the time they seek hearing healthcare (Davis et al., 2007).

Numerous studies have been conducted to discover why this most straightforward of interventions has such a low adoption rate. Although cost is certainly a factor, adoption rates remain low even in those countries where hearing aids are available at no cost (Hougaard and Ruf, 2011; Godinho, 2016). This signifies that there are other obstacles beyond cost that must be overcome if we are to increase adoption rates. In some cases, older adults see hearing loss as a natural part of aging and only seek hearing healthcare when the loss becomes severe (van den Brink et al., 1996). Studies have also stressed a stigma associated with wearing hearing aids that is not present, for example, for eyeglasses, with "ageism" an apparent part of this picture (see Hellström and Tekle, 1994; Lundberg and Sheehan, 1994; Levy and Myers, 2004; Jennings, 2005; Southall et al., 2010; Wallhagen, 2010).

It should also be acknowledged that there are "higher-level" auditory processing deficits (Humes, 1996) and attentional factors (Tun and Wingfield, 1995; Tun et al., 2002) that can impair listening effectiveness in older age. As such, setting realistic expectations with the aid of a knowledgeable and trusted audiologist is an essential piece of the full adoption picture. All of these factors have undoubtedly contributed to the discrepancy between hearing aid adoption rates and the dramatic pace of improvements in hearing aid technology.

Among the interventions available for age-associated performance declines, addressing the immediate (Wingfield and Lash, 2016) and long-term (Lin, 2011; Peelle and Wingfield, 2016) cognitive consequences of hearing impairment is among the most direct. The delay in seeking hearing healthcare thus remains a critical public health issue. Creativity in public education that highlights the benefits of reduced listening effort for ease of communication can be an important step in this regard.

AUTHOR CONTRIBUTIONS

NDA contributed to experimental design, data collection and analysis, data interpretation, and drafting and revisions of this manuscript. AL contributed to the conception of this work and experimental design, as well as revisions of this manuscript. AW contributed to experimental design, data interpretation, and drafting and revisions of this manuscript.

ACKNOWLEDGMENTS

This work was supported by the National Institutes of Health under award R01 AG019714 from the National Institute on Aging (AW). NDA and AL acknowledge support from NIH training grants T32 GM084907 and T32 AG000204, respectively. We also gratefully acknowledge support from the WM Keck Foundation. AL is now at Whittier College, Whittier, CA, USA.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 18 January 2017
doi: 10.3389/fnagi.2016.00336

Aerobic Exercise Intervention, Cognitive Performance, and Brain Structure: Results from the Physical Influences on Brain in Aging (PHIBRA) Study

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Studies have shown that aerobic exercise has the potential to improve cognition and reduce brain atrophy in older adults. However, the literature is equivocal with regards to the specificity or generality of these effects. To this end, we report results on cognitive function and brain structure from a 6-month training intervention with 60 sedentary adults (64–78 years) randomized to either aerobic training or stretching and toning control training. Cognitive functions were assessed with a neuropsychological test battery in which cognitive constructs were measured using several different tests. Freesurfer was used to estimate cortical thickness in frontal regions and hippocampus volume. Results showed that aerobic exercisers, compared to controls, exhibited a broad, rather than specific, improvement in cognition as indexed by a higher "Cognitive score," a composite including episodic memory, processing speed, updating, and executive function tasks ($p = 0.01$). There were no group differences in cortical thickness, but additional analyses revealed that aerobic fitness at baseline was specifically related to larger thickness in dorsolateral prefrontal cortex (dlPFC), and hippocampus volume was positively associated with increased aerobic fitness over time. Moreover, "Cognitive score" was related to dlPFC thickness at baseline, but changes in "Cognitive score" and dlPFC thickness were associated over time in the aerobic group only. However, aerobic fitness did not predict dlPFC change, despite the improvement in "Cognitive score" in aerobic exercisers. Our interpretation of these observations is that potential exercise-induced changes in thickness are slow, and may be undetectable within 6-months, in contrast to change in hippocampus volume which in fact was predicted by the change in aerobic fitness. To conclude, our results add to a growing literature suggesting that aerobic exercise has a broad influence on cognitive functioning, which may aid in explaining why studies focusing on a narrower range of functions have sometimes reported mixed results.

Keywords: aerobic exercise, cognition, executive function, plasticity, hippocampus, prefrontal cortex, freesurfer, transfer

OPEN ACCESS

Edited by:
Pamela M. Greenwood, George Mason University, USA

Reviewed by:
Ben Godde, Jacobs University Bremen, Germany
Patrick J. Smith, Duke University Medical Center, USA

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Received: *15 September 2016*
Accepted: *23 December 2016*
Published: *18 January 2017*

Citation:
Jonasson LS, Nyberg L, Kramer AF, Lundquist A, Riklund K and Boraxbekk C-J (2017) Aerobic Exercise Intervention, Cognitive Performance, and Brain Structure: Results from the Physical Influences on Brain in Aging (PHIBRA) Study. Front. Aging Neurosci. 8:336. doi: 10.3389/fnagi.2016.00336

INTRODUCTION

During the last two decades, numerous investigations have addressed the relationships between physical exercise and cognition (e.g., Khatri et al., 2001; Fabre et al., 2002; Legault et al., 2011; Langlois et al., 2013). Despite the wealth of literature showing how staying physically active may prevent cognitive decline (Yaffe et al., 2001; Sofi et al., 2011), dementia onset (Laurin et al., 2001; Yaffe et al., 2009), and improve brain-behavior relationship throughout the lifespan (Boraxbekk et al., 2016), there are also studies, e.g., a recent Cochrane review (Young et al., 2015), that have concluded that aerobic exercise, compared to active control training, had no added benefit on any cognitive function investigated. In contrast, several studies have shown that physical exercise positively influences a variety of cognitive processes, including controlled-processing (Chodzko-Zajko and Moore, 1994), processing speed (Dustman et al., 1994), executive control (Kramer et al., 1999), and visuospatial ability (Shay and Roth, 1992). The positive influence of physical exercise on cognition have also been supported by meta analyses (Colcombe and Kramer, 2003; Angevaren et al., 2008; Smith et al., 2011). Partially responsible for the somewhat equivocal results in the past may be that studies have translated results from an isolated task to reflect an effect on a cognitive domain (Blumenthal and Madden, 1988; Dietrich and Sparling, 2004; Oken et al., 2006), which has also been recognized by others (Roig et al., 2013). Some have even argued that to study plasticity related changes in cognition, several tasks tapping the same cognitive construct is critical for truly stating interventional effects (Noack et al., 2009). Another issue that may explain divergent findings is that designs, e.g., training protocols, and sample-specific characteristics, differ between studies (Etnier et al., 1997; Voelcker-Rehage and Niemann, 2013).

Parallel to examining cognitive functions in relation to exercise, studies have also started to examine the effects of exercise on brain structures; in particular in the hippocampus (Pereira et al., 2007; Erickson et al., 2011; Maass et al., 2014; Niemann et al., 2014; Thomas et al., 2016), and in frontal areas (Colcombe et al., 2006; Erickson et al., 2010; Flöel et al., 2010; Voss et al., 2013; Oberlin et al., 2016). One approach to study brain-behavior relationships stem from the underlying processes logic (Greenwood and Parasuraman, 2016), which implies that if there are observable structural changes in the brain from exercise, cognitive functions relying upon processing in those specific areas in the brain, may also benefit (Erickson et al., 2011; Voss et al., 2013; Burzynska et al., 2015). However, in the exercise literature mixed support for this hypothesis have been presented, with some studies failing to link exercise related differences in gray matter structure to cognitive changes (e.g., Colcombe et al., 2006; Burns et al., 2009; Ruscheweyh et al., 2011; Johnson et al., 2012), whereas others show a positive association between aerobic exercise, hippocampus gray matter morphology, and episodic memory performance (Erickson et al., 2009, 2011). Support for the association in regions of the brain besides the hippocampus is, however, scarce with two cross-sectional studies showing a link between aerobic fitness, executive functions, and prefrontal gray matter volume (Erickson et al., 2007; Weinstein et al., 2012, see also Voss et al., 2013; Oberlin et al., 2016 for frontal white matter structure, and Colcombe et al., 2004; Voelcker-Rehage et al., 2011, for cardiovascular responses in PFC and ACC, in relation to exercise-induced cognitive changes). Considering the general improvements on cognitive functions from aerobic exercise (Colcombe and Kramer, 2003; Angevaren et al., 2008). We decided to focus on three frontal regions that we predicted would undergo changes from exercise, and predict cognitive improvements according to the underlying processes logic. The dorsolateral prefrontal cortex (dlPFC) is involved in selecting and manipulating information in working memory whereas the ventrolateral PFC (vlPFC) is more involved in maintaining information in working memory (D'Esposito et al., 1999). The role of the anterior cingulate cortex (ACC) on the other hand is related to monitoring processes (Botvinick et al., 2004).

The aims of the present study were to investigate whether an aerobic exercise intervention (i) improves cognition in a general, non-construct-specific, sense, or specifically to certain cognitive constructs and (ii) alters cortical thickness or volume in brain structures important for cognition, specifically the dlPFC, vlPFC, ACC, and hippocampus.

MATERIALS AND METHODS

Participants

A total of 60 participants (64–78 years old) were recruited through an advertisement in the local newspaper. When applicants showed interest in participating in this study we contacted them to explain the purpose of the study as well as to verify that they were eligible to participate. Exclusion criteria included diabetes, medication known to influence dopamine, having a neurological disease, scoring below 27 on the mini-mental state examination (MMSE), having claustrophobia, or regularly performing moderately high to high-intensity exercise. A radiologist assessed structural images but no abnormality warranting exclusion was found. Participants provided written informed consent prior to the start of the study and were compensated with 1000 SEK for their participation. After baseline assessments, the participants were randomized into either an aerobic training group or an active stretching and toning control group. One female participant in the aerobic group had to discontinue training due to a foot injury, and one male participant in the control group due to a knee problem. Thus, the final sample included 29 participants in the aerobic training group and 29 participants in the active control (**Table 1**). The regional ethical committee in Umeå, Sweden, approved this study.

Procedure

After inclusion, each participant was scheduled for baseline data collection on six separate days. On day one, participants underwent aerobic fitness testing and body composition measurements (bone densitometry, not reported here). Neuropsychological testing was performed on three occasions on three separate days. On additional 2 days, scanning of the brain was made with magnetic resonance imaging (MRI, with T1

TABLE 1 | Sample characteristics.

	Aerobic		Control		
	N	Mean ± SD	N	Mean ± SD	Statistics
Females (%)	29	52	29	59	$\chi^2_{(1)} = 0.279, p = 0.597$
Age (years)	29	68.40 ± 2.54	29	68.97 ± 2.91	$t_{(55)} = 0.789, p = 0.434$
Education (years)	29	13.69 ± 3.49	29	13.69 ± 4.68	$t_{(52)} = 0.191, p = 0.575$
MMSE	29	28.96 ± 1.16	29	29.46 ± 0.64	$t_{(40)} = 1.977, p = 0.055$
Attendance (%)	29	85.13 ± 9.16	29	82.11 ± 10.43	$t_{(55)} = 1.227, p = 0.225$

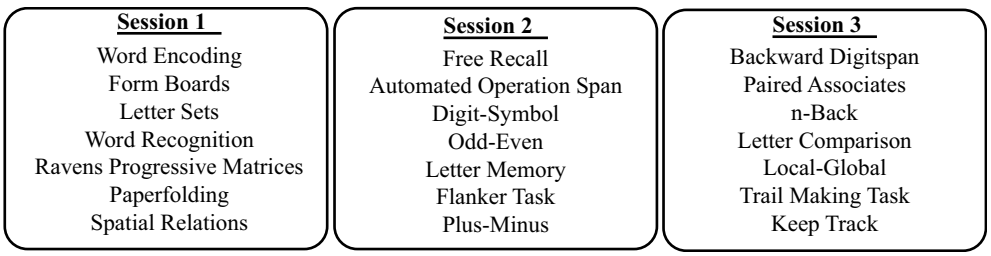

FIGURE 1 | Flow chart showing the neuropsychological test battery administration.

weighted imaging reported here, but also resting-state functional MRI, diffusion tensor imaging, anterior spin labeling, C2-C3 blood flow, and T2 weighted imaging), as well as positron emission tomography to measure dopamine D2 receptors (not reported here). In addition, several questionnaires about daily activities, sleep, motivation, subjective memory, and wellbeing were filled out but will not be reported here.

Aerobic Fitness

Aerobic fitness was estimated from a standardized graded cycle (Monark 839E, Monark Exercise AB, Sweden) ergometer test performed by an experienced tester at the Sport Science Lab at Umeå School of Sport Sciences. Every 3 min, the resistance was incremented by 30 W, with starting values being 30 W for females, and 40 W for males. Expired air was measured through a mouthpiece and analysis of O_2 uptake ($VO_2 = O_2$ ml/kg *min) was performed in an open system (Oxycon Pro, Erich Jaeger GmbH & Co, Würzburg, Germany) every 20 s. Heart rate was registered each minute with a Polar Sport chest transmitter (Polar H1, Kempele, Finland). Self-perceived exertion was assessed on a 15-point RPE-scale (ranging from 6 to 20) (Borg, 1970) at the end of each 3 min interval. The test was terminated at volitional exhaustion or when the self-perceived exertion was rated 15 or above at baseline, and 17 at follow-up. VO_2 peak was estimated as the highest VO_2 reached before test termination.

Aerobic Training

In the aerobic training group, participants trained in order to increase their VO_2 by walking or jogging on an athletic indoor track, cycling on stationary cycles, or using cross-trainers. Their heart rate (HR) was monitored while they exercised 3 days a week for 6 months (30–60 min per session). As training continued, heart rate (HR) load of each session was increased incrementally, from 40 to 80% of their estimated maximum HR.

Stretching and Toning Control Condition

In the stretching and toning control condition, participants performed circuit training involving various bodily exercises aimed to improve muscle strength, flexibility, and balance without influencing VO_2 to a large extent. They made between 6 and 10 repetitions per exercise and each exercise had various levels of difficulty.

Neuropsychological Test Battery

Testing was performed on three separate days and lasted between 60 and 90 min per session. On the first day, tests of reasoning and visuospatial ability were performed. Trials on those tasks were self-paced and served to accommodate participants to the testing situation and computerized testing. On all computerized tasks recording reaction times (RT), individual responses deviating by more than 2.5 standard deviations from the mean were excluded. In addition, RT on a given trial was included only for correct responses. Unless stated otherwise, the tasks were presented using the E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). Each task will be described under its respective cognitive domain but see **Figure 1** for a flow chart of the task order.

Episodic Memory

Word recognition

Participants were required to encode a list of visually presented words for later retrieval (Nyberg et al., 1996). A list containing 30 nouns was studied in the encoding phase, 3 s per word with an interstimulus interval (ISI) of 1 s. Approximately 25 min later, a

recognition phase commenced. Again, 30 words were presented, 4 s per word with an ISI of 1 s. Fifteen of the words were new, not from the original list presented during encoding, and 15 were words from the original list. With a key press, participants had to decide whether the word was presented in the original list or not. A practice block of five words was performed before the 30 nouns were studied. All words were different at baseline and post-intervention. The dependent measure was accuracy.

Free recall

In this task (Murdock, 1962), 16 Swedish nouns were visually presented, 3 s per word, with an ISI of 1 s. Immediately following the list presentation, participants were required, on a blank sheet, to write down as many of the 16 words as possible. Words were different at baseline and post-intervention. The dependent measure was the number of correctly recalled words.

Paired associates

In this task (Rohwer et al., 1967), word pairs comprised of Swedish nouns were studied. The word pairs were presented at a rate of 3 s per word pair, with an ISI of 500 ms. Two blocks of ten word pairs were performed. After each block, participants were presented with a sheet of paper where the first word in each word pair was printed. The task was to write down the word missing. Ten word pairs consisted of related nouns, e.g., head-nose, and the other ten of unrelated nouns, e.g., fork-flower. One practice block with five word pairs, three related and two unrelated, were performed before the two task blocks. Words were different at baseline and post-intervention. The dependent measure was the total number of correct words.

Processing Speed

Trail making task 2 and 3

D-KEFS (Delis-Kaplan Executive Function System) (Delis et al., 2001) pen and paper trail making task (TMT) series 2 and 3 measure processing speed. In series 2, subjects were instructed to connect the numbers 1 through 16, as quickly as possible, by drawing a line with a pen between consecutive numbers. In series 3, the letters A through P were to be connected. Participants were also instructed that lines could not cross. The dependent measure was the sum of the times in seconds taken to complete the two series.

Digit-symbol task

In a computerized version of the Wechler Adult Intelligence Scale-Revised (WAIS-R), Digit-Symbol task, an array of nine digit-symbol combinations was shown on the upper half of a screen. Digits were always sorted in ascending order. On the lower half, a single digit-symbol combination was presented and the task was to, as quickly as possible, indicate with a key press whether the same digit-symbol combination could be found in the array. A single practice block consisting of ten trials with feedback was performed prior to three consecutive task blocks of 30 trials each. The dependent measure was RT.

Letter comparison

In this simple choice RT task, two lowercase letters were simultaneously presented. The task was to, as quickly as possible with a key press, indicate whether the two letters were equal or not. A 10 trial practice block with feedback was performed before two 30 s task blocks. The dependent measure was RT.

Executive Function

Automated operation span

In the automated version of the operation span task (Unsworth et al., 2005), the goal was to memorize sequences of letters while judging simple mathematical operations true or false. These two tasks were practiced both separately and together before the real task begun. In four practice blocks, two and three letter sequences were displayed, 1 s per letter with an ISI of 250 ms. After each sequence, a response screen with 12 boxes containing a capitalized letter appeared. Using the mouse, the previously shown letters had to be selected in the correct order of appearance before the next block commenced. After four practice blocks of letter recall, 15 mathematical operations had to be solved. A mathematical operation [e.g., $(9/3) + 2 = ?$] was displayed in the center of the screen and participants were instructed to mentally solve the problem. When knowing the answer to the operation they were instructed to click the mouse to advance to the next screen. On the upper part of the screen a number appeared. If that number was the correct solution to the math problem (i.e., 5 in our example), a box stating "TRUE" had to be clicked, and if incorrect (e.g., 3), a box stating "FALSE." After solving the 15 equations, participants practiced for three blocks on the real task with two letter sequences, performing both math operations and letter recall. After each math judgment, a letter was presented for 1 s. When the two math problems had been solved, and their corresponding letters had been presented, the response screen with 12 boxes appeared. After selecting the boxes with the remembered letters, the next block commenced. For the 10 task blocks (2×3–7 letter sequences), participants were instructed to maintain at least 85% accuracy on the math equations, which was indicated in the upper right corner of the screen. This was done to ensure that participants did not simply memorize letters, which was the outcome. After each block, feedback was presented, stating the math performance and how many letters were correctly remembered. The dependent measure was the sum of correctly remembered sets multiplied by the respective set size.

Flanker task

In the Flanker task (Eriksen and Eriksen, 1974), five arrows were presented in the center of the screen for 2 s, with an ISI of 2 s. These arrows were either congruent (e.g., $< < < < <$) or incongruent (e.g., $< < > < <$). The task was to focus on the direction of the middle arrow, and indicate with a left arrow press if the arrow pointed toward the left, and a right arrow press if pointing toward the right. On 50% of the trials, the arrows were congruent, and on the other 50% they were incongruent. After a 17 trial practice block, four blocks of 17 trials were performed. The dependent measure was the cost in RT on incongruent compared to congruent trials.

Backward digit span

In this computerized version of the WAIS-R digit span backward task, a sequence of presented numbers, 1–9, had to be memorized

and responded to in backward order (answer to 5 9 2 is 2 9 5). Numbers were presented for 1 s, with an ISI of 250 ms, at the center of the screen. Pressing the corresponding keyboard numbers provided the response. Two sequences of two numbers with feedback served as practice. After practice, set length started with three numbers. If a correct response were given, the difficulty increased by one number, to a maximum of nine. If an incorrect response was given, the same sequence length was provided again. After two incorrect responses on a given sequence length the task was terminated. The dependent measure was the highest sequence length completed correctly.

Updating

Letter memory

In the Letter Memory task (Dahlin et al., 2008), a sequence of letters (A, B, C, or D) were pseudo-randomly displayed, 2 s per letter and with an ISI of 1 s. After the last letter was presented a response screen appeared and the task was to indicate the last four letters in the array by pressing the corresponding key. In other words, the task was not to remember the full length of the sequence but to consistently update working memory to hold the last four letters. Two practice blocks, 5 and 7 letter sequences, were performed with feedback, prior to 8 task blocks. The task blocks were 7, 9, 11, or 13 letter sequences that were performed twice. The dependent measure was accuracy.

N-back

In n-back (Kirchner, 1958) the task was to indicate with a key press within 2 s from stimulus onset, whether the digit presently on screen was the same digit as the digit presented 1 stimulus (1-back) or 2 stimuli (2-back) back. A 20-digit sequence was presented, 1.5 s per digit and an ISI of 500 ms. A practice 1-back block with feedback was performed prior to two 1-back task blocks. After 1-back, a practice 2-back block was performed prior to four task blocks. The dependent measure was 2-back accuracy.

Keep track

In the Keep Track task (Miyake et al., 2000), 15-word sequences were presented, 1.5 s per word with an ISI of 500 ms. Each word belonged to one of six categories: colors, metals, distances, countries, relatives, or animals. For each block, 2–4 target categories were displayed in boxes positioned in the lower part of the screen. The task was to recall the last seen word belonging to each of the target categories and write the answer on a sheet of paper. In two practice blocks with feedback, there were two target categories. In six subsequent task blocks, the number of target categories was either three or four. The dependent measure was the sum of correct blocks, times the number of target categories for each of those blocks.

Task-Switching

Trail making task 4

D-KEFS pen and paper trail making task (TMT) series 4 was used to measure task-switching ability. In series 4, subjects were instructed to, as quickly as possible, connect the numbers 1 through 16 and the letters A through P by drawing a line with a pen between consecutive numbers/letters. The task was to begin with the number 1, connecting 1 to letter A, from A to 2, from 2 to B, and so on. Participants were also instructed that lines could not cross. The dependent measure was the additional time taken to complete TMT 4 compared to completing TMT 2 and 3, i.e., the switching cost.

Odd-even

A cued task-switching paradigm was used (Rogers and Monsell, 1995; Jonasson et al., 2014). The target consisted of a letter-digit pair presented a few centimeters apart. On each trial, the sequence of events was as follows: fixation cross (1000 ms), task cue (250 ms), cue-target interval (1500 ms), and target (2000 ms). Task cues indicated the upcoming task, "Attend Letter" or "Attend Digit," the former indicating a consonant-vowel judgment, and the latter an odd-even judgment. The task cues were randomly alternated, such that there were a task switch on 50% of the trials, and a task-repeat on the other 50%. A practice block of 20 trials was completed with feedback, followed by three task blocks without feedback. Odd and consonant judgments were recorded with a left-arrow press, whereas even and vowel judgments were recorded with a right-arrow press. The dependent measure was the cost in accuracy between switch and no-switch trials.

Local-global

In this task, Navon figures were used (Navon, 1977), where a large figure (global level), is comprised of smaller figures (local level). The larger figure was always a circle or a triangle, comprised of smaller triangles or circles, respectively, such that both circle and triangle were represented either as a global object or as local objects. These were shown on screen for 3 s, with an ISI of 1 s. If the color of the figure was blue, the task was to judge whether the global figure was a circle (right button), or a triangle (left button). If the color of the figure was black, the task was to judge whether the local objects were circles (right button), or triangles (left button). On 50% of the trials the same rule was repeated, and on the other 50% a rule switch was required. A 20 trial practice block was first performed with feedback, followed by three task blocks. The dependent measure was the cost in accuracy between switch and no-switch trials.

Reasoning

Letter sets

On this reasoning task (Salthouse, 2005; Baniqued et al., 2013), the goal was to identify which of five alternative letter sets were odd. Four of the sequences shared some common rule not shared by the fifth, odd, letter set. Two practice problems were explained before the task commenced. Participants were instructed that they had 10 min to complete as many of the letter sets as possible. The dependent measure was the number of accurate trials, corrected for guessing.

Ravens progressive matrices

In this version of Ravens progressive matrices (Salthouse, 2005; Baniqued et al., 2013), a 3 by 3 array with patterns was presented. The pattern in the lower right corner was missing, and from eight alternatives, the pattern that will complete the array could

be found. After two practice trials with feedback, 10 min were provided to complete as many trials as possible, for a maximum of 18. A response was given by pressing the corresponding alternative's number on a keyboard. The dependent measure was accuracy, corrected for guessing.

Visuospatial Ability

Form boards

In form boards (Salthouse, 2005; Baniqued et al., 2013) the task was to produce a figure by combining 2–5 alternative pieces, similar to a puzzle. The target figure was displayed on the upper part of the screen, and the five pieces on the lower part of the screen. After having decided which non-overlapping pieces were required to produce the figure, each piece was selected with a mouse click. Participants were instructed on a practice trial, before they were given 8 min to complete as many figures as possible. The dependent measure was the number of accurate figures completed.

Paper folding

In this task (Salthouse, 2005; Baniqued et al., 2013), participants could see images of a square paper being folded in the upper part of the screen. After 3–4 folds, a number of holes were punched through all layers of the folding. The task was to mentally unfold the paper, and select the correct image showing the location of the holes. There were five alternatives and the response was given by clicking with the mouse on one of the five images. After a practice trial, 10 min were given to complete as many trials as possible, to a maximum of 12. The dependent measure was the number of accurate trials, corrected for guessing.

Spatial relations

In this task (Salthouse, 2005; Baniqued et al., 2013), a target figure was displayed on the upper part of the screen. The task was to select the figure, from five alternatives displayed in the lower part of the screen, which could be rotated to fit the target figure. After two practice trials, 10 min were given to complete as many trials as possible, to a maximum of 20. The dependent measure was the number of accurate trials, corrected for guessing.

Failed Task

Plus-minus

The goal of this task was to measure task-switching ability. Participants were presented with three sheets of paper on which the answers should be written, each with two columns of numbers ranging from 1 to 100. On the first sheet, the task was to add three to each number, on the second sheet, subtract three, and on the final sheet, alternate between adding three and subtracting three. Unfortunately, a considerable number of participants had problems writing numbers with a pencil within a reasonable time frame and therefore the task was removed from the analyses.

Magnetic Resonance Imaging Acquisition

Structural imaging was performed on a 3T General Electric scanner equipped with a 32-channel head coil. High-resolution T1-weighted structural images were collected with a 3D fast spoiled gradient echo sequence (180 slices with a 1 mm thickness, TR 8.2 ms, TE 3.2 ms, flip angle 12°, field of view 25 × 25 cm).

Brain Segmentation

Freesurfer (Fischl et al., 2002), version 6-beta (20151015) longitudinal stream (Reuter et al., 2012), was used to segment the brain into known anatomical structures. In the longitudinal stream a subject specific base template is created from several time points. Errors visually observed on the base template were manually edited prior to creation of the final longitudinal segmentation. For the subcortical segmentations, the volume (mm^3) of hippocampus was used as dependent measures. For the cortical segmentation, the dependent measure was cortical thicknesses (mm) from the Destrieux atlas (Destrieux et al., 2010).

Similar to Vijayakumar et al. (2014), a dlPFC region-of-interest (ROI) was produced by combining the bilateral superior and middle frontal gyri, a vlPFC ROI by combining the bilateral opercular, orbital, and triangular gyri, and an ACC ROI by combining the bilateral anterior and middle-anterior part of the cingulate gyri and sulci.

Statistical Analyses

Neuropsychological Test Battery

Each cognitive construct, episodic memory (EM), processing speed (PS), updating (UPD), task-switching (TS), executive function (EF), and visuospatial ability (SRS) constructs included three different tasks. The reasoning construct (RS) included two tasks. The cognitive tasks were first z-transformed and averaged to form the unit-weighted EM, PS, UPD, TS, EF, RS, and SRS constructs. Missing values were imputed based on the score on the completed tasks belonging to the same construct. For any participant, not more than one task score for any given construct was missing.

Confirmatory Factor Analysis

To confirm the underlying factor structure of the cognitive battery, confirmatory factor analyses (CFA) were performed with the lavaan package in R (http://CRAN.R-project.org/package=lavaan). CFAs were made with the EM, PS, UPD, TS, and EF tasks. Due to the small sample size, we considered a unit-weighted "Cognitive score" to be more reliable than the latent score of a general higher-level factor (Wolf et al., 2013), hence the "Cognitive score" was computed by averaging the constructs used in the CFA. The RS and SRS constructs involved self-paced tasks related to reasoning or problem-solving ability and were thus analyzed in two separate CFAs, one with a single factor and one with two factors. See Supplementary 1 for further CFA details.

Group Differences

Two-way repeated measures analysis of covariance (rmANCOVA) was performed to compare within and between groups differences in aerobic fitness. Two separate two-way repeated measures multivariate ANOVAs (MANOVA) were performed on the cognitive constructs from the CFA, and on the Freesurfer segmentations; dlPFC, vlPFC, ACC cortical thickness, and hippocampus volume. All analyses were conducted with age, gender, and education as covariates, and, unless stated otherwise, significant tests were also significant without the addition of covariates.

Associations of Aerobic Fitness, Cortical Thickness, and Cognitive Performance

To understand the specific influence of aerobic fitness on cortical thickness, hippocampus volume, and "Cognitive score," additional analyses were performed using linear regressions both at baseline and with changes over time. The regressions are reported with the covariates age, gender and education regressed out. One participant was excluded due to having an aerobic fitness > 3 SD above the mean. For the regressions involving cortical thickness and hippocampus volume, the freesurfer derived intracranial volume was regressed out. To analyze changes over time, delta scores were computed by subtracting baseline scores from post-intervention scores.

In order to understand the connection between aerobic fitness, cortical thickness, hippocampus volume, and cognitive performance, it is important also to examine the interplay between brain structure and cognitive performance. To that end, cortical thickness in dlPFC, vlPFC, and ACC were used as predictors for "Cognitive score." Due to the well-known influence of the EF measures on dlPFC, vlPFC, and ACC, we performed additional regressions as control analyses. Similarly, EM was specifically tested in relation to hippocampus volume.

RESULTS

Confirmatory Factor Analysis

Details for the CFAs are reported in Supplementary 1. In short, a five factor solution with a "Cognitive score" factor with loadings from EM, PS, UPD, and EF showed best fit, $\chi^2_{(50, N=118)} = 75.199$, $p < 0.012$, RMSEA = 0.065, CFI = 0.946, AIC = 3652.311, SRMR = 0.079. The loading from UPD to "Cognitive score" was highest, followed by EF, PS, and finally EM. Due to the small sample size we do not consider the estimated loadings to be reliable however [see e.g., (Wolf et al., 2013) who, based on simulation studies, recommend $n > 150$ when all (true) loadings are expected to be above.8]. Hence, instead of using a factor score, the EM, PS, UPD, and EF constructs were averaged to form a unit-weighted "Cognitive score."

Group Differences

Both groups had, compared to baseline, higher aerobic fitness after the intervention (**Table 2**, **Figure 2**). The rmANCOVA revealed a significant group by time interaction favoring the aerobic group, $F_{(1, 53)} = 5.215$, $p = 0.0264$, confirming the desired effect of the intervention.

Due to presence of six multivariate outliers we decided to conduct rmANCOVAs on the "Cognitive score" and the separate cognitive constructs instead of a MANOVA on the constructs (**Table 2**, **Figure 3**). A significant group by time interaction on the "Cognitive score" favored the aerobic group, $F_{(1, 53)} = 7.700$, $p = 0.0076$. There were no group by time interactions on EM, $F_{(1, 53)} = 2.707$, $p = 0.1058$, PS, $F_{(1, 53)} = 2.090$, $p = 0.1542$, UPD, $F_{(1, 53)} = 1.411$, $p = 0.2402$, and EF, $F_{(1, 53)} = 2.080$, $p = 0.1551$, or SRS, $F_{(1, 53)} = 2.439$, $p = 0.1243$. However, a significant interaction favoring the control group was seen on the RS construct, $F_{(1, 53)} = 5.219$, $p = 0.0264$, but only after controlling for age, gender, and education. For descriptive purposes, results for all tasks

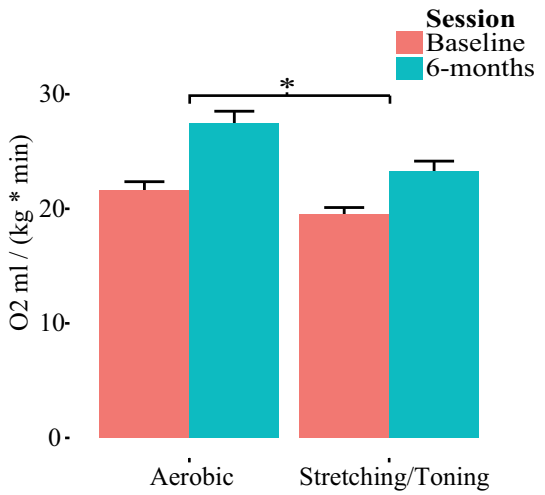

FIGURE 2 | Group by time differences in aerobic fitness (O_2ml/kg*min). Repeated measures of covariance, controlling for age, gender, and education revealed a group by time interaction favoring aerobic exercise. *$p < 0.05$.

TABLE 2 | Group differences between aerobic exercise ($n = 29$) and stretching/toning ($n = 29$) in cognitive performance and aerobic fitness.

	Aerobic		Control		Change	
	Baseline Mean ± SD	6-months Mean ± SD	Baseline Mean ± SD	6-months Mean ± SD	Aerobic δ_{RM}	Control δ_{RM}
Episodic Memory	−0.17 ± 0.50	0.08 ± 0.86	0.22 ± 0.87	0.17 ± 1.02	0.41	−0.08
Processing Speed	0.08 ± 0.61	0.37 ± 0.47	−0.12 ± 0.99	0.05 ± 1.04	0.76	0.40
Updating	−0.09 ± 0.49	0.10 ± 0.51	0.06 ± 0.61	0.12 ± 0.72	0.42	0.14
Executive Function	0.07 ± 0.71	0.50 ± 0.76	−0.06 ± 0.89	0.16 ± 0.91	0.79	0.45
Cognitive Score	−0.03 ± 0.42	0.26 ± 0.50	0.02 ± 0.62	0.13 ± 0.67	1.02	0.43
Aerobic fitness	21.60 ± 4.13	27.69 ± 5.53	19.50 ± 3.31	23.22 ± 5.06	1.73	1.20

*Cognitive constructs and "Cognitive score" are reported as z scores and aerobic fitness as VO_2 peak (O_2ml/kg*min). In addition, effect size δ_{RM} estimates for each test and group were calculated. The formula provided by Morris and DeShon (2002), Equation 8, was used as it takes into account the test correlation between time points when calculating the effect size for repeated measures.*

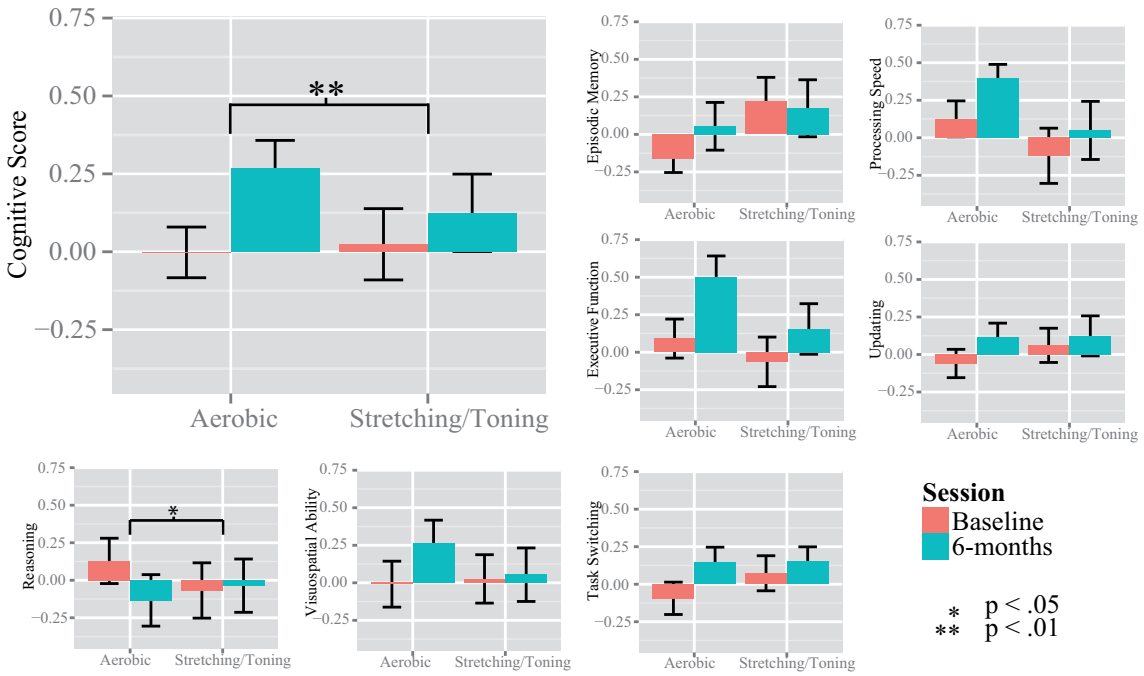

FIGURE 3 | Changes in cognition over time. The y-axis show the standardized z value for the unit-weighted cognitive constructs. The "Cognitive Score" was derived from the episodic memory, processing speed, updating, and executive function tasks. Significance bars are derived from repeated measures analysis of variance, within and between groups.

TABLE 3 | Cortical thickness and hippocampus volume per group and session.

		Aerobic Exercise		Control		
		Baseline	6-months	Baseline	6-months	Statistic
	N	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	*F*-test[a]
dlPFC	29	2.59 ± 0.12	2.58 ± 0.11	2.60 ± 0.12	2.60 ± 0.12	$F_{(1,53)} = 0.002$, $p = 0.964$
vlPFC	29	2.55 ± 0.11	2.53 ± 0.11	2.57 ± 0.11	2.57 ± 0.13	$F_{(1,53)} = 1.139$, $p = 0.291$
ACC	29	2.59 ± 0.13	2.56 ± 0.15	2.57 ± 0.09	2.56 ± 0.11	$F_{(1,53)} = 0.763$, $p = 0.386$
HPC	29	7462 ± 832	7430 ± 827	7683 ± 651	7668 ± 700	$F_{(1,53)} = 0.095$, $p = 0.760$

[a] *Two-way repeated measures analysis of covariance with group and session, controlling for age, gender, and education. dlPFC, dorsolateral prefrontal cortex (mm); vlPFC, ventrolateral prefrontal cortex (mm); ACC, anterior cingulate cortex (mm); HPC, hippocampus (mm^3).*

and constructs in the neuropsychological test battery, including within group rmANCOVAs, are reported in Supplementary Table 1.

The MANOVA with dlPFC, vlPFC, and ACC thickness, and hippocampus volume revealed no group differences in cortical thickness or hippocampus volume, $F_{(4,108)} = 0.128$, $p = 0.972$; Wilks' $\Lambda = 0.995$. There were no group interactions or significant effects of time in any of the regions, all $p > 0.05$ (**Table 3**).

Associations of Aerobic Fitness, Cortical Thickness, and Cognitive Performance

Additional analyses were conducted to understand possible associations between aerobic capacity, cortical thickness, and cognitive performance. Results of the regressions are reported in **Table 4**. At baseline, higher VO_2 peak was positively associated with dlPFC thickness, but was unrelated to vlPFC and ACC thickness as well as hippocampus volume (**Figure 4**). The change in VO_2 peak was positively associated with the change in hippocampus volume, but unrelated to change in cortical thickness (**Figure 5**).

"Cognitive score" at baseline was significantly associated with larger thickness in dlPFC ($p = 0.01$) and vlPFC ($p = 0.01$), but not to ACC, or to hippocampus volume (**Figure 4**). Following the 6-month training period the change in "Cognitive score" was positively associated with the change in dlPFC (**Figure 6**). The association between changes in "Cognitive score" and dlPFC thickness was driven by the aerobic group, showing a significant effect, $F_{(1,28)} = 4.828$, $p = 0.037$, $r = 0.39$, (**Figure 6B**) whereas the control group did not, $p = 0.34$.

Further analyses revealed construct specific influences in expected anatomical structures. Higher EF at baseline was

TABLE 4 | Associations between cortical thickness, aerobic fitness, and "Cognitive score".

	Change	Aerobic Fitness[a]		"Cognitive score"[b]	
	Mean ± SD	Cross-sectional	Longitudinal	Cross-sectional	Longitudinal
dlPFC	−0.01 ± 0.05	$F_{(1,56)} = 4.94$, $p = \mathbf{0.03}$, $r = 0.28$	$F_{(1,55)} = 1.12$, $p = 0.29$, r = −0.14	$F_{(1,57)} = 6.75$, $p = \mathbf{0.01}$, r = 0.33	$F_{(1,56)} = 4.76$, $p = \mathbf{0.03}$, r = 0.28
vlPFC	−0.01 ± 0.05	$F_{(1,56)} = 3.07$, $p = 0.09$, $r = 0.23$	$F_{(1,55)} = 1.52$, $p = 0.22$, r = −0.16	$F_{(1,57)} = 6.82$, $p = \mathbf{0.01}$, r = 0.33	$F_{(1,55)} = 0.15$, $p = 0.70$, r = 0.05
ACC	−0.02 ± 0.07	$F_{(1,56)} = 0.90$, $p = 0.35$, $r = 0.13$	$F_{(1,55)} = 2.05$, $p = 0.16$, r = −0.19	$F_{(1,57)} = 2.17$, $p = 0.15$, r = 0.19	$F_{(1,55)} = 0.37$, $p = 0.55$, r = 0.08
HPC	23.67 ± 140	$F_{(1,56)} = 0.49$, $p = 0.49$, r = −0.09	$F_{(1,55)} = 9.68$, $p = \mathbf{0.002}$, r = 0.39	$F_{(1,57)} = 1.14$, $p = 0.29$, r = 0.14	$F_{(1,56)} = 2.61$, $p = 0.11$, r = −0.21

Linear regressions with cortical thickness (mm) and hippocampus volume (mm^3) predicted by [a]aerobic fitness, and [b]"Cognitive score," controlling for age, gender, education, and intracranial volume. One outlier in baseline aerobic fitness and one outlier in cortical thickness change were removed. Associations were only considered significant (bold p-value) if significant both with and without covariates. dlPFC, dorsolateral prefrontal cortex; vlPFC, ventrolateral prefrontal cortex; ACC, anterior cingulate cortex; HPC, hippocampus.

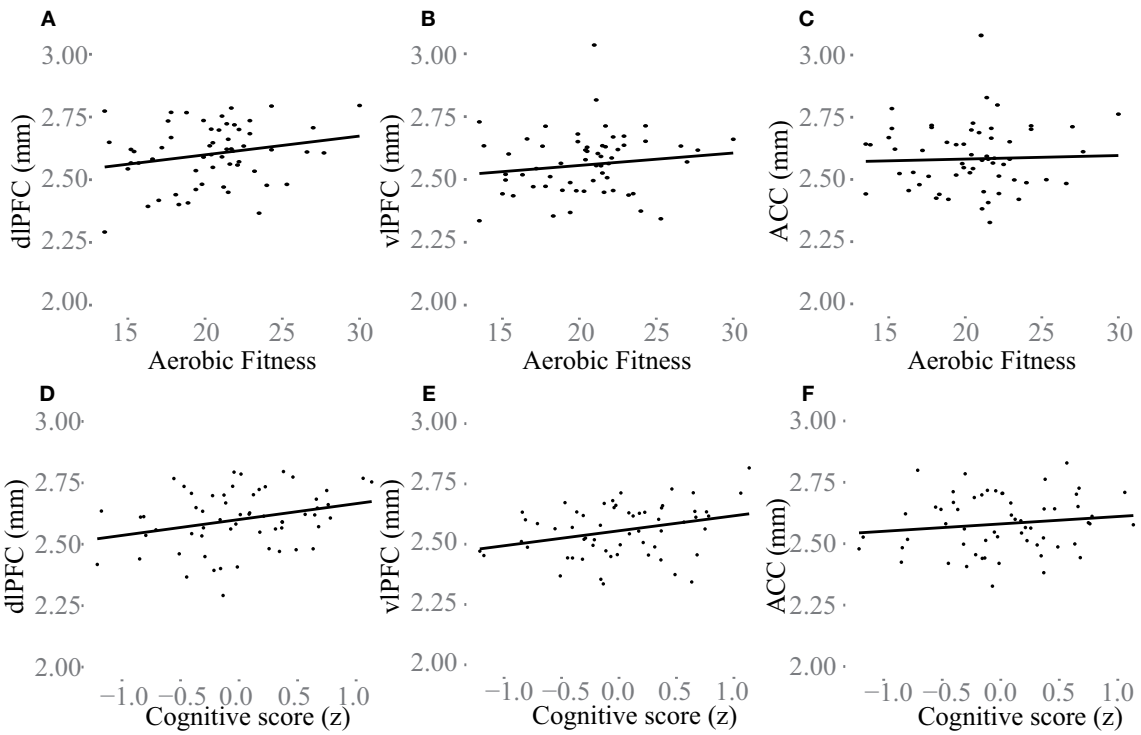

FIGURE 4 | Baseline associations between aerobic fitness (O_2ml/kg*min), "Cognitive score" (z) and cortical thickness (mm) in dlPFC (A,D), vlPFC **(B,E)**, and ACC **(C,F)**. In **(A–C)** aerobic fitness is plotted against cortical thickness, and in **(D–F)** "Cognitive score" is plotted against cortical thickness.

specifically associated with thickness in dlPFC, $F_{(1,57)} = 8.167$, $p = 0.006$, $r = 0.35$, vlPFC, $F_{(1,57)} = 5.596$, $p = 0.021$, $r = 0.30$, and ACC, $F_{(1,57)} = 8.309$, $p = 0.006$, $r = 0.36$, but not to hippocampus volume $F_{(1,57)} = 0.62$, $p = 0.44$, $r = 0.10$. Conversely, EM showed a specific association with larger hippocampus volume at baseline, $F_{(1,57)} = 4.661$, $p = 0.035$, $r = 0.28$, but not to cortical thickness. Over time, improved EF was positively associated with the change in dlPFC thickness specifically, $F_{(1,57)} = 4.761$, $p = 0.033$, $r = 0.28$. EM was unrelated to changes in cortical thickness and hippocampus volume.

DISCUSSION

The aims of the present study were to investigate the influence of aerobic exercise on cognitive performance, and brain structures derived using Freesurfer. We observed that sedentary older adults randomly assigned to aerobic exercise exhibited a broad improvement in cognitive performance, reflected by a cognitive score, compared to individuals assigned to stretching and toning control training. Regarding brain structures, the results were rather equivocal with no direct effect of the intervention, but with

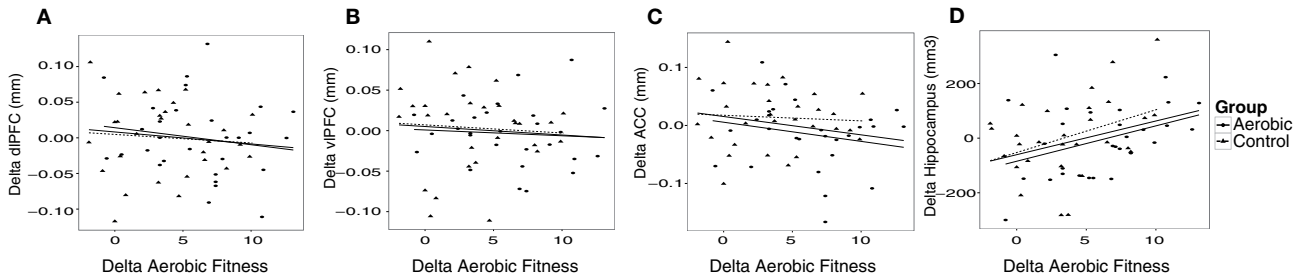

FIGURE 5 | The change in cortical thickness and hippocampus volume plotted against change in aerobic fitness (O_2ml/kg*min). Increases over time in cortical thickness (mm), hippocampus volume (mm^3) and aerobic fitness have positive values. Change in aerobic fitness is plotted against change in thickness in **(A)** dlPFC, **(B)** vlPFC, **(C)** ACC, and **(D)** hippocampus volume. Observations from the aerobic group are circles, and the regression line is the thinner line. Observations from the control group are triangles, and the regression line is dashed. The thicker regression line is for the full sample.

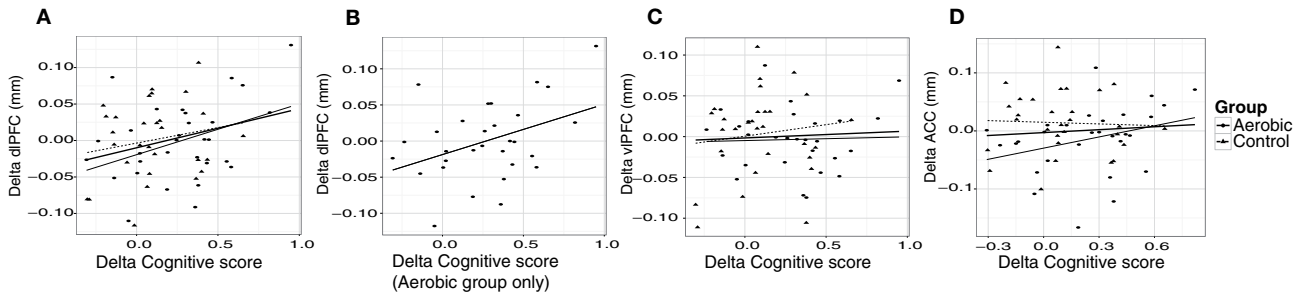

FIGURE 6 | Associations between changes in "Cognitive score" (z) and cortical thickness (mm). The change in "Cognitive score" is plotted against the change in thickness in, **(A)** dlPFC, **(B)** dlPFC for the aerobic group specifically, **(C)** vlPFC, and **(D)** ACC. Observations from the aerobic group are circles, and the regression line is the thinner line. Observations from the control group are triangles, and the regression line is dashed. The thicker regression line is for the full sample.

aerobic fitness predicting cortical thickness in PFC at baseline, but not over time, whereas hippocampus volume exhibited the opposite pattern, with no association at baseline, but a positive association over the 6-month training period.

Cognition

A considerable strength of the present investigation was the inclusion of several tests for each cognitive construct, providing the opportunity to investigate cognition in a broad sense. The CFA displayed good fit indices despite the small sample size, disregarding TS. Previous studies have generally had fewer tasks and/or investigated fewer constructs (Burns et al., 2009; Erickson et al., 2011; Legault et al., 2011; Thomas et al., 2016). Thus, the present observation that aerobic exercise compared to stretching and toning control training was more effective in improving cognition in older adults is an important contribution to a field showing equivocal results, owing at least in part, to a lack of robust test batteries enabling use of latent constructs. Different tasks have been used across studies and although the tasks are taken to represent the same cognitive constructs, this is not always the case, e.g., improved digit-symbol task performance in aerobically fit individuals could be taken to support the visuospatial hypothesis (Stones and Kozma, 1989), although this particular task is commonly viewed as a task measuring speed of processing (Salthouse, 1996). Thus, we support a general improvement in cognitive function which is in contrast to Young et al. (2015) but according to several other meta-analyses (Colcombe and Kramer, 2003; Angevaren et al., 2008; Smith et al., 2011). Our conclusion of an effect in a broad sense was further supported by our construct specific analyses. Compared to baseline, aerobic exercise resulted in improvements in several cognitive constructs; PS, UPD, EF, and SRS, with a trend also for EM (**Figure 3**, and Supplementary Table 1). The largest effect size was seen for EF, assimilating conclusions from an earlier meta-analysis (Colcombe and Kramer, 2003). The control group improved PS and EF abilities, albeit to a lesser degree, and not in the other cognitive constructs. This suggests that even low-intensity exercises aiming to promote strength, balance, and flexibility may have positive effects on cognitive functioning. Motor fitness and resistance training have been related to improved executive functioning (Liu-Ambrose et al., 2008; Voelcker-Rehage et al., 2010, 2011) and processing speed (Voelcker-Rehage et al., 2010, 2011), hence, group comparisons may mask aerobic exercise-induced changes to cognition due to training-induced improvements also in the control group. There was an interaction favoring the control group on the reasoning construct not expected a priori. However, there could have been a regression to the mean effect influencing this particular analysis (**Figure 3**), and the interaction was due to the aerobic group's worsened performance, rather than improved performance for the control group. In sum, our observations indicate that aerobic exercise, compared to stretching and toning control training

improves cognition generally, rather than being specific to any given component.

Prefrontal Cortical Thickness

Regarding aerobic exercise, fitness, and cortical thickness, results were rather equivocal. A direct effect of the intervention on cortical thickness in dlPFC, vlPFC, or ACC was absent. However, subsequent analyses indicated that aerobic fitness at baseline had a positive relationship with cortical thickness in dlPFC, partly consistent with previous cross-sectional data showing positive effects on PFC and ACC gray matter from aerobic fitness (Colcombe et al., 2003; Weinstein et al., 2012) and physical activity (Flöel et al., 2010). As the aerobic exercise group improved their aerobic fitness considerably compared to the control group one could have expected to find an effect from aerobic fitness in dlPFC over time, explaining also the improved cognitive performance, considering that "Cognitive score" predicted dlPFC thickness both at baseline and change over time in the aerobic group. However, one explanation is that the exercise-induced improvements in cognitive performance immediately after a period of training is not mainly due to gray matter changes, but may depend on altered cardiovascular responses (Colcombe et al., 2004; Voelcker-Rehage et al., 2011), white matter changes (Voss et al., 2013; Oberlin et al., 2016), functional connectivity (Voss et al., 2010, 2016), brain-derived neurotrophic factor (Leckie et al., 2014), or other molecular processes. Wheel-running for example, has been associated with alterations in dopaminergic markers in striatum (MacRae et al., 1987; Meeusen et al., 1997; Kim et al., 2016), and considering the influence of dopamine both on prefrontal and striatal function in relation to executive control functions, (Frank and O'Reilly, 2006; Cools and D'Esposito, 2011; D'Esposito and Postle, 2015) this could be a potential pathway for exercise-induced improvements in cognition.

Moreover, training duration may also be an important factor, where effects of exercise may be absent at 6-months, only to be revealed after 12 months (Voss et al., 2010). Duration could potentially explain why baseline levels, and not 6-month change, predicted cortical thickness, assuming that baseline fitness levels can be taken to represent an average fitness level, stretching further back in time than 6 months. It should also be noted that recent studies have shown that resistance training may also influence the brain, e.g., by altering cardiovascular responses in PFC and ACC (Voelcker-Rehage et al., 2011). The active control group likely improved both their motor fitness and muscle strength; hence, effects may be influenced also by factors we did not measure, and mask potential group comparisons. Future studies could include additional tests to control for changes in motor and muscle fitness. In sum, our analyses of cortical thickness are only partly consistent with the view that being aerobically fit at an older age preserves brain health in executive control regions (Kramer and Erickson, 2007; Prakash et al., 2015).

Hippocampus Volume

As opposed to the pattern observed in dlPFC, hippocampus volume did not show an association to aerobic fitness at baseline, as was presented by Erickson et al. (2009). Conversely, the change in aerobic fitness was positively associated with the change in hippocampus volume, replicating previous studies (Erickson et al., 2011; Thomas et al., 2016). This effect could be explained by increased neurogenesis (van Praag et al., 1999; van Praag, 2005) or angiogenesis (Pereira et al., 2007; Maass et al., 2014), as a function of aerobic fitness improvement. It should also be noted that resistance training has been linked to increased hippocampus volume (Niemann et al., 2014). Functionally, hippocampus volume was related to EM at baseline, but the change in hippocampus volume could not predict changes in EM. One explanation as to why hippocampus volume may not have been predictive of verbal EM over time is that new neurons may not have been incorporated in functional circuitry, considering that a large proportion of newborn hippocampal cells do not survive the first few weeks without environmental challenges (van Praag et al., 1999). An alternative explanation is that we used verbal memory tasks, and previous exercise studies finding a relation between EM and hippocampus used spatial memory tasks (Erickson et al., 2011; Maass et al., 2014), also in rodents (van Praag, 2005; Yau et al., 2012). Others, using verbal EM measures have also failed to find an association (Pereira et al., 2007; Thomas et al., 2016). Hence, spatial memory tasks could be more sensitive to structural changes in hippocampus (Bonner-Jackson et al., 2015).

Limitations

Despite using the gold standard for estimating VO_2 peak, we are limited in making firm claims concerning the absolute changes in VO_2 peak. We speculate that this may be due mainly to two factors. Firstly, different termination thresholds were used at baseline and at follow-up. Secondly, leg strength has an influence on estimated VO_2 peak when using a cycle ergometer test, (Diesel et al., 1990), and both training protocols were likely to influence leg strength. Including additional measurements on leg strength could have been informative and should be considered. In addition, including accelerometers or activity bracelets during the intervention period for monitoring everyday physical activity should be an important source of information for future studies.

Limitations of this study include only measuring two time points, 6 months apart. For instance, it appears as if hippocampus is sensitive to the timing of measurements, which was recently showed in a study observing that aerobic exercise may increase hippocampus volume within 6 weeks, while returning back to baseline values also within 6 weeks (Thomas et al., 2016). The time between aerobic fitness measurements and MRI acquisition in the present study was between 1 and 2 weeks, potentially introducing a source of noise. The issue of timing is also related to the lack of a clear understanding of the dose-response relationship between aerobic fitness and various brain indices (Prakash et al., 2015). For instance, Voss et al. (2010) found effects on functional connectivity in the default mode network and a frontal executive network only after 12 months, not after 6, suggesting that longer training or time between scans may be required to detect cortical changes.

Moreover, practice effects from repeated testing are a potential limitation affecting the cognitive results, but unlikely explain the improvements entirely despite the lack of interactions on specific

constructs; due to the long test-retest duration, comparably large effect sizes (Makizako et al., 2013; de Oliveira et al., 2014; Goldberg et al., 2015), and an active control group that may also have exhibited training-induced cognitive improvements (Liu-Ambrose et al., 2008; Voelcker-Rehage et al., 2010). Finally, although white matter has also been investigated in relation to physical activity (Voss et al., 2013; Hayes et al., 2015; Oberlin et al., 2016) we restricted this study to mainly gray matter thickness in frontal regions and hippocampus volume. On that note, Freesurfer may also be less specific than voxel-based morphometry, or diffusion weighted imaging, as Freesurfer assigns voxels to either gray or white matter, thereby limiting our ability to be specific about the exact changes captured in our ROIs. Nevertheless, cortical thickness from Freesurfer has shown to be predicitive of cognitive functioning in older adults (Burzynska et al., 2012), and concords with voxel-based morphometry when assessing atrophy (Lehmann et al., 2011).

CONCLUSION

In this study we conclude that aerobic exercise in sedentary older adults has the potential to improve cognition in a broad, rather than specific, sense, as captured in our "Cognitive score" based on episodic memory, processing speed, working memory updating, and executive function tasks. These results add to a growing literature suggesting that aerobic exercise has a broad influence on cognitive functioning, which may aid in explaining why studies focusing on a narrower range of functions have sometimes reported mixed results. In addition, dlPFC may be a key region of interest in frontal cortex for explaining exercise-induced effects on cognition, although larger studies are warranted. Cortical thickness in dlPFC predicted "Cognitive score" at baseline, as well as improvement in cognitive performance over time in the aerobic group only. That aerobic fitness is specifically related to increased cortical thickness or reduced cortical thinning of dlPFC in older adults was only given partial support however, with fitness showing a positive relation to dlPFC at baseline, but not over 6 months, despite the potential links to dlPFC and aerobic exercise via improved "Cognitive score."

AUTHOR CONTRIBUTIONS

LJ, LN, AK, KR, and CB designed the study; LJ and AL performed the statistical analyses; all authors contributed in revising the work and approved the final version of the manuscript.

FUNDING

Support was obtained from the Swedish Research Council (2012-00530), Västerbotten County Council and Umeå University, the Swedish Research Council for Sport Science and Umeå School of Sport Sciences to CB, and from the Kamprad Family Foundation to LN.

ACKNOWLEDGMENTS

We thank all participants taking part in this study, the training supervisor Peter Lundström, Urban Ekman for sharing the digit-symbol task, the staff at Umeå Center for Functional Brain Imaging, University Hospital of Northern Sweden, Umeå, the Sport Science Lab at Umeå School of Sport Sciences Umeå University, and the Graduate School of Population Dynamics and Public Policy (LJ).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnagi.2016.00336/full#supplementary-material

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

REVIEW
published: 03 February 2017
doi: 10.3389/fnagi.2017.00011

Mindfulness Training for Healthy Aging: Impact on Attention, Well-Being, and Inflammation

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The growing interest in mindfulness interventions for use in aging samples has been met with promising evidence of cognitive, emotional, and physiological benefits. The purpose of this review is to provide an overview of the impact of mindfulness training on three areas of functioning in older adults: behavioral and neural correlates of attentional performance, psychological well-being, and systemic inflammation. We have previously proposed that mindfulness training is uniquely suited as a rehabilitative tool for conferring both cognitive and emotional benefits for older adults. Specifically, mindfulness training's promotion of focused attention may mitigate the decline of attentional control abilities across late development and allow older adults to capitalize on their preserved emotion regulation abilities. Existing evidence points to some improvements in facets of attentional control in older adults, although some studies have shown no benefits in performance. Further, there is evidence of enhancements in both psychological and physical aspects of well-being, and accompanying improvements in systemic inflammation, following mindfulness training. The scientific investigation of mindfulness training is still relatively nascent, with only a limited number of studies, particularly randomized controlled trials utilizing active comparison conditions. It will be important for future research to incorporate placebo-controlled comparison groups to clearly establish the causal role of mindfulness practices in promoting holistic health in older adults.

Keywords: mindfulness training, healthy aging, attentional control, psychological well-being, systemic inflammation

OPEN ACCESS

Edited by:
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Reviewed by:
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Received: *01 November 2016*
Accepted: *16 January 2017*
Published: *03 February 2017*

Citation:
Fountain-Zaragoza S and Prakash RS (2017) Mindfulness Training for Healthy Aging: Impact on Attention, Well-Being, and Inflammation. Front. Aging Neurosci. 9:11. doi: 10.3389/fnagi.2017.00011

INTRODUCTION

Mindfulness training has gained increasing traction in recent years as a feasible and promising intervention for enhancing facets of both psychological and physical health across development. Broadly defined as the cultivation of sustained attention in a framework of non-reactivity and acceptance (Kabat-Zinn, 1982), mindfulness training involves direction of attention to either one or multiple phenomena as they arise. These techniques often fall into three component types: (1) focused attention meditation involves sustained attention to a single object while monitoring for and disengaging from distractions (Lutz et al., 2008); (2) open monitoring meditation involves attending to the detailed features of transient phenomena without selective focus on one object (Lutz et al., 2008); (3) loving-kindness meditation involves cultivation of a universal state of love and compassion toward oneself and others (Salzberg, 2002). Thus, engagement

in mindfulness practices requires the utilization of either narrowly focused attention (e.g., breath awareness or body scan practices) or broadly receptive attention (e.g., choiceless awareness or gratitude practices).

Training in such mindfulness practices has been evaluated for its prophylaxis for various metrics of overall health including, but not limited to, improvements in behavioral and neural metrics of cognitive functioning, particularly attentional control (Tang et al., 2015); regulation of affective experiences (Chiesa et al., 2013); reductions in overall levels of perceived stress and systemic inflammation (Creswell et al., 2012; Rosenkranz et al., 2013); and improvements in overall well-being and psychological health (Baer, 2003). Although the majority of these studies have been conducted in young adults and community participants, there is a growing interest in the application of mindfulness training as a preventative intervention targeting the elderly. This population is of particular interest given the age-related declines in social support, limitations to physical independence, and decrements in several domains of cognitive function.

We have previously proposed that mindfulness training is particularly useful in aging populations as it orients the practitioner, in an accepting and non-judgmental framework, to the mind's tendency to wander (Bishop et al., 2004), thereby promoting the use of attentional control and allowing older adults to capitalize on the preserved emotion regulation abilities that are observed with aging (Prakash et al., 2014). As a follow-up to this proposed paradigm recommending mindfulness training as a rehabilitative tool for conferring emotion-cognition benefits in older adults, this review provides a critical summary of the recent literature examining the impact of mindfulness training for behavioral and neural correlates of attentional control. One of Dr. Raja Parasuraman's seminal contributions to the literature, in collaboration with his colleagues, is the nuanced examination of age-related differences in the shifting, scaling, and maintenance of attentional control. This work detailing older adults' decrements in these areas, provides a theoretically-informed set of outcome variables for use in this population. Although there is some evidence that mindfulness yields benefits for attentional abilities with age, we believe future research examining the potential of mindfulness training in mitigating age-related attentional decrements can benefit tremendously from implementing measures derived from Dr. Parasuraman and colleagues' key findings. Further, given that successful aging is truly a metamorphosis of cognitive, affective, and physiological health, we go beyond reviewing the cognitive potential of mindfulness training to include a brief review of the existent literature examining alterations in psychological well-being and systemic inflammation resulting from mindfulness training in older adults (See **Figure 1**). An electronic search was conducted in *PubMed*, *PsychInfo*, and *Web of Science* using the keywords *mindfulness*, *older adults*, *aging*, *attentional control*, *cognition*, *well-being*, and *inflammation*. We then inspected the reference sections of all retrieved articles for a cross-reference. We included articles written in English that were published prior to September, 2016. Please see **Table 1** for a list of the reviewed studies and a brief summary of their findings.

MINDFULNESS AND BEHAVIORAL CORRELATES OF ATTENTIONAL CONTROL

Age-Related Alterations in Attentional Control

Attentional control is broadly defined as the ability to streamline information processing by selecting and amplifying task-relevant information while ignoring irrelevant, interfering information in order to conduct complex goal-oriented behaviors (Petersen and Posner, 2012). Attentional control thus encompasses a wide variety of cognitive processes ranging from those that operate upon information arising from external stimuli, such as orienting and discriminating, to those that require the use of internal information stored in working memory and long-term memory or that are dictated by internal task-sets (Chun et al., 2011). There is an extensive literature documenting age-related changes in attentional control processes, with aggregate evidence that older adults exhibit deficits on many tasks of attentional control (Hasher and Zacks, 1988; Parasuraman and Greenwood, 1998; Braver and West, 2008; Lustig and Jantz, 2015). The work of Dr. Raja Parasuraman and colleagues contributed substantially to our understanding of the deficits in various facets of attention that come with age. Greenwood and Parasuraman (1999) developed a two-component model of visual search that includes shifting and scaling, making use of cued-visual search tasks in order to elucidate age-related changes in the allocation of attention. These studies showed age-related decrements in voluntarily shifting of visuospatial attention from one hemifield to another following invalid location cues (Greenwood et al., 1993), as well as poorer attentional disengagement following invalid cues (Greenwood and Parasuraman, 1994). When the scale of spatial attention was systematically altered by the presentation of location precues of varying sizes (i.e., cueing a single letter, a column of letters, or the entire array), the ability to effectively adjust the focus of attention declined with age and was lowest for those over the age of 75 (Greenwood et al., 1997). Subsequent work showed that the performance benefits of valid precues observed in younger adults initially increased with age (ages 65–74), but then decreased with advanced age (ages 75–85), providing evidence that aging is associated with a decreasingly focused attentional beam (Greenwood and Parasuraman, 2004). Both the shifting and scaling of attentional focus, occurring very early in information processing, might be augmented by mindfulness training as practitioners develop more acute attention to present-moment experiences.

In addition to age-related declines in selective attention, age decrements in sustained attention have also been systematically evaluated. Employing vigilance tasks in which participants are asked to respond to targets and withhold responses to non-targets, older adults were found to exhibit decreased hit rates and increased false-alarm rates compared to young adults (Parasuraman and Giambra, 1991; Filley and Cullum, 1994), and these differences did not disappear with increased practice in older adults (Parasuraman and Giambra, 1991). Vigilance may also be parceled into two types, sensory and cognitive,

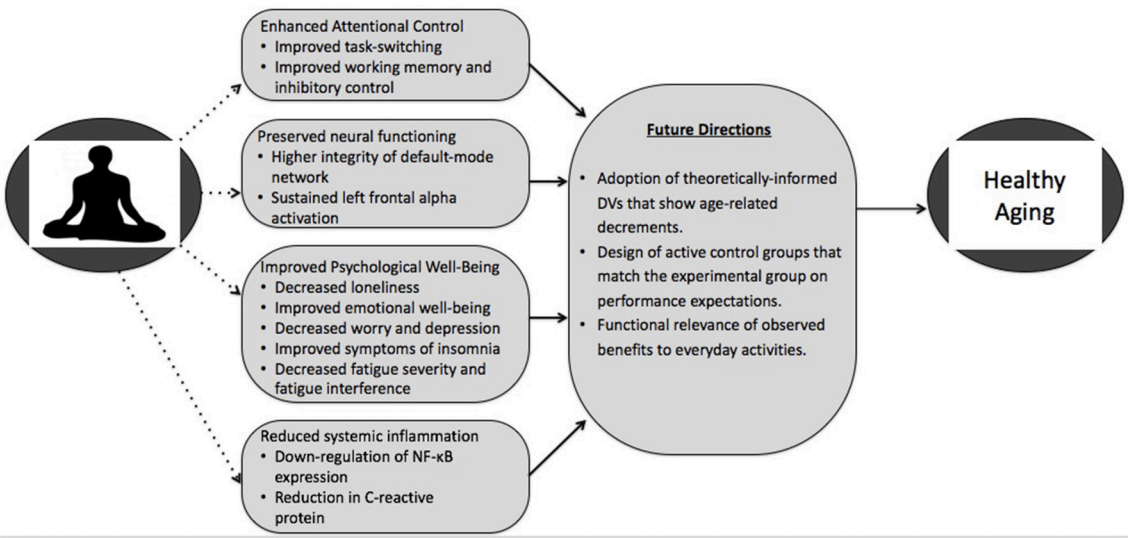

FIGURE 1 | An illustration of the known and examined potential mechanisms through which mindfulness training may exert its influence on healthy aging (dotted lines demonstrating a tentative link between mindfulness and various pathways). Given the infancy of this research and the lack of rigorous RCT designs, the evidence linking mindfulness training to improvements in attentional control, psychological well-being, and systemic inflammation, though promising, needs more conclusive support. Incorporation of the suggested future directions will aid in providing a more concrete, definitive test (represented by solid lines) for the efficacy of mindfulness training in promoting healthy aging.

that can be evaluated by presenting participants with pairs of digits and instructing them to discriminate between the physical size (sensory vigilance) or the numeric value of the digits (cognitive vigilance). Evaluations of these two conditions provided evidence that older adults exhibited lower detection rates than young adults on both task types, but that false alarm rates were greater in older adults, particularly in the sensory task (Deaton and Parasuraman, 1993). This suggests that older adults might experience significant declines in perceptual processes, which might relate to the deficits in visual selective attention outlined above. Work employing signal detection indices, which incorporate both hits and false alarms, has suggested equivalent overall vigilance across age groups for tasks requiring both automatic and effortful stimulus processing and no differences in sustained attention decrements over time (Berardi et al., 2001). Interestingly, older adults changed the strategy used for target detection during more difficult conditions such that they limited attention to one feature of the target, leading to decreases in overall sensitivity compared to young adults, but preventing vigilance decrements at higher demands.

There is relatively strong support for age-related declines in executive types of attention (e.g., Chao and Knight, 1997; Andrés and Van der Linden, 2000; Milham et al., 2002; Davidson et al., 2003a). Although a set of meta-analyses found limited age-related deficits in local task-switching and several selective attention tasks, including inhibition, negative priming, flanker, and Stroop tasks (Verhaeghen, 2011), there was evidence of age-related differences in tasks of divided attention, including dual tasking and global task-switching (Verhaeghen, 2011; Wasylyshyn et al., 2011). It is important to note that sustained and executive attentions rely in part on the efficient and accurate allocation of attention. Thus, all of these facets of attentional control might be meaningfully impacted by the focused attention practices incorporated in mindfulness training, allowing for the sharpening of attentional focus and conscious maintenance of goal-directed attention.

Mindfulness and Facets of Attentional Control

Given that attentional control is posited to be a primary skill that is utilized during and facilitated by engagement in mindfulness practices, and considering the reviewed evidence that attentional control abilities decline with age, there is an emerging literature examining the impact of mindfulness on attentional control abilities in older adults. Within the mindfulness and attention literature, researchers have primarily employed three study designs: (1) correlational studies examining associations between trait levels of mindfulness and performance on attentional tasks, (2) cross-sectional comparisons of individuals with extensive mindfulness experience (i.e., expert meditators) and meditation-naïve individuals on attentional tasks, and (3) longitudinal studies of change in attentional performance across mindfulness interventions.

A number of correlational studies have examined the associations among dispositional measures of mindfulness and various facets of attentional control in older adults. Across studies, older adults show higher levels of self-reported dispositional mindfulness compared with young adults (Frank et al., 2015; Prakash et al., 2015; Fountain-Zaragoza et al., 2016). However, existing cross-sectional studies have found non-significant association between mindfulness, working memory, and inhibitory control (Prakash et al., 2015) and both positive

TABLE 1 | Brief summaries of reviewed studies categorized by outcome (attentional control, psychological well-being, and inflammatory processes).

References	Titles	Study type	Population	Intervention group	Comparison group	At-home practice	Dependent variables	Main findings
ATTENTIONAL CONTROL: BEHAVIORAL AND NEURAL FUNCTIONING								
Prakash et al., 2012b	Mindfulness disposition and default-mode network connectivity in older adults	Correlational	Older adults ($n = 25$, mean age = 66)	n/a	n/a	n/a	Resting-state default-mode network connectivity	Trait mindfulness is associated with greater connectivity in the dorsal posterior cingulate cortex and precuneus, regions of the default-mode network.
Fiocco and Mallya, 2015	The importance of cultivating mindfulness for cognitive and emotional well-being in late life	Correlational	Older adults ($n = 73$, mean age = 69)	n/a	none	n/a	Set-shifting (trail making test A & B), verbal fluency (controlled oral word association task), declarative memory (california verbal learning test).	Trait mindfulness is positively associated with set-shifting, but not verbal fluency or declarative memory.
Prakash et al., 2015	The role of emotion regulation and cognitive control in the association between mindfulness disposition and stress	Correlational	Older adults ($n = 48$, mean age = 65)	n/a	Young adults ($n = 50$, mean age = 24)	n/a	Inhibitory control (flanker task), working memory (N-back task), set-shifting (Task-switching paradigm)	Trait mindfulness is not significantly associated with inhibitory control, working memory, or set-shifting in older adults.
Pagnoni and Cekic, 2007	Age effects on gray matter volume and attentional performance in zen meditation	Cross-sectional comparison	Adult meditators ($n = 13$, mean age = 37, meditation experience = $\geq$3 years daily)	n/a	Older-adult non-meditators ($n = 13$ mean age = 36)	n/a	Sustained attention (rapid visual information processing task)	Meditators did not show a significant negative correlation between gray matter volume and attentional performance with age, as observed in controls.
van Leeuwen et al., 2009	Age effects on attentional blink performance in meditation	Cross-sectional comparison	Older-adult meditators ($n = 17$, mean age = 50, meditation experience = 1-20 years)	n/a	Older-adult non-meditators ($n = 17$, mean age = 50), young-adult non-meditators ($n = 17$, mean age = 24)	n/a	Temporal capacity of attention (attentional blink task)	Older-adult meditators showed a smaller attentional blink than age-matched and young-adult non-meditators.
Prakash et al., 2012a	Long-term concentrative meditation and cognitive performance among older adults	Cross-sectional comparison	Older-adult meditators ($n = 20$, mean age = 59, meditation experience = $\geq$10 years)	n/a	Older-adult non-meditators ($n = 20$, mean age = 60)	n/a	Working memory (digit span), response inhibition (stroop color word task), processing speed (letter cancelation, digit symbol substitution), set-shifting Ttrail making test, rule shift card test	Older-adult meditators performed better than age-matched non-meditators on all tests of attention except the digit span backwards test.
Lenze et al., 2014	Mindfulness-based stress reduction for older adults with worry symptoms and co-occuring cognitive dysfunction	Feasbility	Older adults with clinically significnat anxiety and cognitive dysfunction ($n = 34$, mean age = 71)	8-week MBSR: 2.5-h weekly meetings and a 1-day retreat ($n = 16$, mean age = 71)	12-week MBSR: 2.5-h weekly meetings and a 2.5-h retreat day ($n = 18$, mean age = 71)	Not explicitly stated, but followed the MBSR protocol that presumably included at-home practices	Verbal fluency, response inhibition (stroop task), short-term working memory (digit span forward), list learning (immediate and delayed), paragraph learning (immediate and delayed),	Significant pre to post changes were observed for list learning (delayed recall), paragraph learning (immediate and delayed), verbal fluency, and response inhibition.
O'Connor et al., 2014	The effects of mindfulness-based cognitive therapy on depressive symptoms in elderly bereaved people with loss-related distress: a controlled pilot study	Feasibility	Distressed older adults ($n = 65$, mean age = 78)	MBCT: 2-h weekly meetings for 8 weeks ($n = 32$, mean age = 78)	Wait-list group ($n = 33$, mean age = 77)	40 min of daily practice	Working memory (letter-number sequencing from WAIS-III administered via telephone)	Mindfulness group showed improvements in working memoyt at post-training compared to wait-list control participants.

(Continued)

TABLE 1 | Continued

References	Titles	Study type	Population	Intervention group	Comparison group	At-home practice	Dependent variables	Main findings
McHugh et al., 2010	Mindfulness as a potential intervention for stimulus over-selectivity in older adults	Experimental induction	Older adults ($n = 24$, mean age = 79)	10-min mindfulness induction	10-min unfocused attention" induction	n/a	stimulus over-selectivity	Brief mindfulness induction significantly reduced stimulus over-selectivity
Mallya and Fiocco, 2016	Effects of mindfulness training on cognitive and well-being in older adults	Quasi-RCT	Older adults ($n = 97$, mean age = 69)	MBSR: 2.5-h weekly meetings for 8 weeks ($n = 57$)	Reading and Relaxation group: 2.5-h weekly meetings for 8 weeks ($n = 40$)	30 min. of daily practice	Simple attention and switching (trail making tests A and B), processing speed (controlled oral word association test), episodic memory (CVLT)	No significant differences between groups on any of the measures following the intervention.
Alexander et al., 1989	Transcendental meditation, mindfulness, and longevity: an experimental study with the elderly	RCT	Older adults ($n = 62$, mean age = 81 years)	30 min. once/week sessions for 8 weeks: 1) Transcendental Meditation ($n = 20$); 2) Langer method of mindfulness meditation ($n = 21$)	Relaxation group ($n = 21$); no treatment ($n = 11$)	20 min of twice daily practice for the active groups	Paired associate learning (DST subtest), cognitive flexibility (overlearned verbal task, Stroop color word test [RT interference]), perceived control, verbal fluency (DST subtest)	TM and mindfulness groups improved more than both control groups on paired associate learning and one measure of cognitive flexibility. TM outperformed mindfulness meditation on both of these measures.
Moynihan et al., 2013	Mindfulness-based stress reduction in older adults: effects on executive function, frontal alpha asymmetry and immune function.	RCT	Older adults ($n = 201$, mean age = 73.4)	MBSR: 2.5-h weekly meetings for 8 weeks and a 7-h intensive retreat ($n = 101$; mean age = 73),	Wait-list group ($n = 100$, mean age = 74)	none	Processing speed (trail making test A) and set-shifting (trail making B/A ratio); left frontal alpha asymmetry	There were improvements in set-shifting and a reduced shift to rightward frontal alpha activation immediately following mindfulness training compared to wait-list, but these effects were not maintained at follow-up.
PSYCHOLOGICAL WELL-BEING								
Fiocco and Mallya, 2015	The importance of cultivating mindfulness for cognitive and emotional well-being in late life	Correlational	Older adults ($n = 73$, mean age = 69)	n/a	none	n/a	Psychological well-being (depressive symptoms, quality of life, stress)	Trait mindfulness is associated with greater psychological well-being on all measures.
Prakash et al., 2015	The role of emotion regulation and cognitive control in the association between mindfulness disposition and stress	Correlational	Older adults ($n = 48$, mean age = 65)	n/a	Young adults ($n = 50$, mean age = 24)	n/a	Perceived stress, emotion dysregulation	Trait mindfulness is negatively associated with perceived stress and emotion dysregulation mediates this relationship.
Prakash et al., 2017	Mindfulness and emotion regulation in older and young adults	Correlational	Older adults ($n = 48$, mean age = 65)	n/a	Young adults ($n = 49$, mean age = 24)	n/a	Emotion dysregulation, emotion regulation strategy use	Thought avoidance mediates the association between trait mindfulness and emotion dysregulation across both age groups. Age moderated this effect such that less mindfulness in young adults is associated with greater use of thought avoidance and greater emotion dysregulation.

(Continued)

TABLE 1 | Continued

References	Titles	Study type	Population	Intervention group	Comparison group	At-home practice	Dependent variables	Main findings
Morone et al., 2008	"I felt like a new person." The effects of mindfulness meditation on older adults with chronic pain: qualitative narrative analysis of diary entries	Feasability (qualitative)	Older adults with chronic pain ($n = 27$, mean age = 74)	8-week mindfulness meditation program modeled on MBSR: 1.5-h weekly meetings	none	50 min of daily practice	Diary contents	Diary themes reflected beneficial effects on pain, attention, sleep (latency and quality), achieving well-being (mood elevation, global quality of life).
Splevins et al., 2009	Do improvements in emotional distress correlate with becoming more mindful? A study of older adults	Feasibility	Older adults with significant stress or symptoms of depression or anxiety ($n = 22$, mean age = 65 years)	MBCT: 2-h weekly meetings for 8 weeks	none	none	Emotional wellbeing (depression, anxiety, stress levels)	Signfiicant improvements in emotional well-being post-MBCT. Increased mindfulness associated with improved emotional wellbeing; act with awareness and accept without judgmenet associated with reduced depression.
Szanton et al., 2011	Examining mindfulness-based stress reduction: perceptions from minority older adults residing in a low-income housing facility	Feasibility (qualitative focus groups)	Older-adult, African American, low-income women ($n =$ age range = 60-90)	Mindfulness meditation program modeled on MBSR: meeting duration not specified	none	none	Focus group discussion content	Primary themes: stress management, applying mindfulness, social support of group meditation; Used MBSR for stressors: growing older with physical pain, medical tests, financial strain, having grandchildren with significant mental, physical, financial, or legal hardships; used MBSR for coping with medical procedures and managing depression and anger.
Foulk et al., 2014	Mindfulness-based cognitive therapy with older adults: an exploratory study	Feasibility	Older adults with depression and/or anxiety ($n = 50$, mean age = 73)	MBCT: weekly meetings for 8 weeks and one 6-h retreat	none	30-40 min of daily practice	Anxiety (hospital anxiety and depression scale), rumination (ruminative responses scale), depressive symptoms (geriatric depression scale- short form), insomnia (sleep problems scale)	Participation in MBCT resulted in significant improvements in reported anxiety, ruminative thoughts, and sleep problems; reduced depressive symptoms.
Morone et al., 2009	A mind–body program for older adults with chronic low back pain: results of a pilot study	RCT	Older adults with lower back pain ($n = 40$, mean age = 78)	8-week mindfulness meditation program modeled on MBSR: 1.5-h weekly meetings	Education group ($n = 20$, mean age = 73)	50 min of daily practice	Disability, psychological function, pain severity	Both groups improved on measures of disability, pain, and psychological function at post-intervention and 4-month follow-up. No between group differences.
Young and Baime, 2010	Mindfulness-based stress reduction: effect on emotional distress in older adults	Feasibility	Older adults with clinically significant depression and anxiety ($n = 141$, mean age = 65)	MBSR: weekly meetings for 8 weeks	none	45 min of daily practice	Change in mood states (profile of mood states, short form)	Overall emotional distress and all subscales improved signfiicantly, >50% reduction in number of older adults with clinically significant depression and anxiety

(Continued)

TABLE 1 | Continued

References	Titles	Study type	Population	Intervention group	Comparison group	At-home practice	Dependent variables	Main findings
Creswell et al., 2012	Mindfulness-based stress reduction training reduces loneliness and pro-inflammatory gene expression in older adults: a small randomized Controlled Trial	RCT	Older adults ($n = 40$, mean age = 65 years)	MBSR: 2-h weekly meetings for 8 weeks and one 7-h retreat ($n = 20$, mean age = 64)	Wait-list group ($n = 20$, mean age = 65)	30 min of daily practice	Loneliness	Mindfulness training produced greater reductions in loneliness than the wait-list group.
Lenze et al., 2014	Mindfulness-based stress reduction for older adults with worry symptoms and co-occuring cognitive dysfunction	Feasbility	Older adults with clinically significnat anxiety and cognitive dysfunction ($n = 34$, mean age = 71)	8-week MBSR: 2.5-h weekly meetings and a 1-day retreat ($n = 16$, mean age = 71)	12-week MBSR: 2.5-h weekly meetings and a 2.5-h retreat day ($n = 18$, mean age = 71)	Not explicitly stated, but MBSR protocol includes at-home practices	Worry (Penn State worry questionaire)	Participants exhibited improvements in worry severity, with no additional benefit of the 12-week intervention over the 8-week intervention.
INFLAMMATORY PROCESSES								
Creswell et al., 2012	Mindfulness-based stress reduction training reduces loneliness and pro-inflammatory gene expression in older adults: a small randomized controlled trial	RCT	Older adults ($n = 40$, mean age = 65 years)	MBSR: 2-h weekly meetings for 8 weeks and one 7-h retreat ($n = 20$, mean age = 64)	Wait-list group ($n = 20$, mean age = 65)	30 min of daily practice	Pro-inflammatory gene expression (NF-κB leukocytes, C reactive protein)	Baseline loneliness was associated with and NF-κB gene expression. Compared to the wait-list group, MBSR participants exhibited down-regulation of NF-κB expression and reduced C-reactive protein levels, but no difference in IL-6 levels.
Gallegos et al., 2013	Toward identifying the effects of the specific components of mindfulness-based stress reduction on biologic and emotional outcomes among older adults	RCT	Older adults ($n = 200$)	MBSR ($n = 100$, mean age = 72)	Wait-list group ($n = 100$) not included in analysis	Participants engaged in at-home activities, but requirement not specified	Immune function (IL-6), circulating insulin-like growth factor (IGF)-1 concentrations, positive affect	More yoga practice associated with higher post-treatment IGF-1 and greater improvement in positive affect across intervention; sitting meditation associated with post-treatment IGF-1; greater use of body scanning associated with reduced antigen-specific IgM and IgG 3 weeks postintervention (but not 24 weeks); no associations between MBSR activities and IL-6 levels.
Moynihan et al., 2013	Mindfulness-based stress reduction in older adults: effects on executive function, frontal alpha asymmetry and immune function.	RCT	Older adults ($n = 201$, mean age = 73.4)	MBSR: 2.5-h weekly meetings for 8 weeks and a 7-h intensive retreat ($n = 101$; mean age = 73),	Wait-list group ($n = 100$, mean age = 74)	none	Antibody response (immunoglobulin G response to protein antigen).	There were higher baseline antibody levels after MBSR, but lower antibody responses 24 weeks after antigen challenge.
Black et al., 2015	Mindfulness meditation and improvement in sleep quality and daytime impairment among older adults with sleep disturbances	RCT	Older adults with moderate sleep disturbance ($n = 49$, mean age = 66)	Mindful awareness practices intervention: 2-h weekly meetings ($n = 24$, mean age = 67)	Sleep hygeine education ($n = 25$, mean age = 66)	Graduated daily practice (5-20 min)	Sleep disturbance (pittsburgh sleep quality index); insomnia, depression, anxiety, stress, and fatigue; inflammatory signaling NF-κB	Mindfulness group improved more on PSQI, insomnia symptoms, depression symptoms, fatigue interference, fatigue severity. No between group differences for anxiety, stress, or NF-κB (but these levels declines significantly over time in both groups).

(Fiocco and Mallya, 2015) and non-significant (Prakash et al., 2015) associations between this trait and set-shifting. Notably, despite Fiocco and Mallya's finding of a positive association with set shifting, neither study found a significant association with cost of shifting. One important methodological difference that could be contributing to the discrepant findings between these two studies is that the study by Fiocco and Mallya (2015) employed a paper and pencil measure (Trail Making Task B) that yields a total time to complete a 25-item task, whereas the study by Prakash et al. (2015) employed a computerized paradigm that allows for an examination of both accuracy and reaction time. Future investigations should continue to employ theoretically-informed measures and might benefit from the use of computerized paradigms that provide more detailed indices of performance.

A cross-sectional comparison of older adults with at least 10 years of meditation experience to age-matched individuals with no experience found that meditators exhibited better inhibitory control, processing speed, set-shifting, and working memory (Prakash et al., 2012a). Another study comparing older-adult meditators with a much broader range of meditation experience (1–29 years) to age-matched naïve controls and young-adult naïve controls revealed a smaller attentional blink in meditators (van Leeuwen et al., 2009). This finding suggests that older-adult meditators exhibited attentional blink benefits not only compared to their age-group peers but to younger individuals who have not experienced age-related attentional decline. Although these comparison studies provide information about the benefits associated with long-term practice, they are inherently limited by their cross-sectional nature. Instead, the use of randomized controlled trials (RCTs) of mindfulness training provides the most concrete evidence for benefits that may be directly attributed to mindfulness training.

One of the seminal studies to examine the causal role of mindfulness training in improving cognitive functioning of older adults compared transcendental meditation, involving the use of a mantra as a tool for turning attention inward to subtler levels of thought with: (1) the Langer mindfulness training method, in which the emphasis is placed on creative ways of problem solving; (2) a mental relaxation group; and (3) a no treatment condition. Participants were assessed on measures of paired associate learning, cognitive flexibility, and word fluency (Alexander et al., 1989). They found that the transcendental meditation group improved more than the mindfulness group, but that both were superior to relaxation and no treatment, on paired associate learning and cognitive flexibility, and mindfulness and TM improved similarly on word fluency. These results provided preliminary evidence for cognitive benefits following transcendental meditation, which has direct parallels with the current mindfulness training approaches.

More recently, three RCTs have evaluated the effects of the more standardized and widely used 8-week Mindfulness Based Stress Reduction program (MBSR; Kabat-Zinn, 1990) on cognitive outcomes in older adults. One study collected data on Trial Making Tests A and B, calculating a Trails B/A ratio as an index of executive function adjusted for processing speed (Moynihan et al., 2013). This study found that participation in the MBSR program significantly reduced the Trails B/A ratio immediately following the intervention compared to a waitlist condition; however, this difference was not maintained when assessed 3 and 24 weeks post-intervention (Moynihan et al., 2013). Another study found no differences in Trail Making Tests A and B, or a verbal fluency task that also indexes executive function, in MBSR compared to a reading and relaxation comparison group (Mallya and Fiocco, 2016). Thus, it is possible that the benefits observed by Moynihan et al. (2013) were not attributable solely to mindfulness training, but instead resulted from nonspecific factors as they did not include an active comparison condition. These might include interacting with others in a group setting and engaging in at-home practice of any sort, demand characteristics or expectancy effects arising from participation in an intervention study targeting attentional abilities, and practice effects resulting from repeated assessment. The third study evaluated the effect of an 8-week MBSR program, as well as the feasibility of a 12-week extended program, on immediate and delayed verbal memory, verbal fluency, inhibitory control, and working memory in older adults with clinically significant anxiety and worry symptoms (Lenze et al., 2014). This study did not employ a control group. Following the 8-week MBSR program, participants exhibited improved performance on all cognitive measures with the exception of immediate list learning, with no significantly superior outcomes for the 12-week program. Of note, one additional study evaluated Mindfulness Based Cognitive Therapy (MBCT), a clinical group intervention that involves elements of both cognitive-behavioral therapy and mindfulness meditation training (Segal et al., 2002), for bereaved older adults. This study found no significant improvements in attentional control, measured via working memory, compared to a waitlist comparison group (O'Connor et al., 2014). This lack of observed effects might be attributable to the clinical nature of the sample as depressive symptoms are associated with cognitive deficits (see Austin et al., 2001 for review). Additionally, it is again the case that the attentional improvements observed by Lenze et al. (2014) may have been due to nonspecific factors as these effects disappeared when a control group was included in the study by O'Connor et al. (2014).

Given the relative dearth of RCT studies in the literature, there is a clear need for further rigorous investigation of the attentional benefits following mindfulness training in older adults (See Future Directions box in **Figure 1**). Considering the many facets of attentional control and the various measures that can be employed to assess such abilities, it will be important for the field to take a systematic approach to the evaluation of the benefits of mindfulness. Future studies should adopt a framework through which they can base their conceptualization and measurement of attentional control in order to conduct hypothesis-driven experiments. First, adopting a framework based on the work of Dr. Raja Parasuraman and his colleagues would provide researchers with well-defined attention variables that exhibit well-characterized age differences. The use of such theoretically informed dependent variables would allow for an examination the degree to which mindfulness training alters (1) attentional processes that are driven by internally-mediated task-sets through the use of vigilance tasks to examine sustained attention

and inhibitory control and (2) attention to externally based stimulus properties through the use of cued-visual search tasks to examine the shifting and scaling of perceptual attention. Second, mind-wandering, or the direction of attention away from the task at hand and toward task-irrelevant information (Smallwood and Schooler, 2006), represents a potential mechanism through which mindfulness might impact attention. Interestingly, although mind-wandering decreases markedly with age (Giambra, 1989; Jackson and Balota, 2012), there is preliminary evidence that older adults who are higher in trait mindfulness exhibit the least amount of task-unrelated mind-wandering (Fountain-Zaragoza et al., 2016). Further, we have found that older adults who participated in 4 weeks of mindfulness training exhibited significantly decreased task-unrelated mind-wandering during a cognitive task compared to an active control group (Whitmoyer et al., under review). Thus, future studies might examine the degree to which mindfulness training further accentuates the decrease in mind-wandering observed across age, and whether this provides compensatory benefits for attentional performance.

By building from a systematic, basic science foundation, researchers can best choose and measure meaningful outcome variables for intervention studies. It will also be important for studies to evaluate specific mindfulness training programs in order to provide aggregate evidence for a particular program's benefits. This will necessitate the creation and use of standardized manuals for the implementation of such training programs. Studies should have randomized designs and include active comparison groups, in which control participants engage in training that is devoid of the component of interest (i.e., mindfulness) but that is matched for key nonspecific factors (e.g., duration, group size, instructor expertise, etc.), in addition to waitlist control groups that receive no training. Such practices will allow us to characterize the benefits that are specific to mindfulness training, rather than group interventions in general, and bolster our ability to make causal claims. And finally, much is still unknown regarding the dose-response relationship between mindfulness training and attentional improvements, the longitudinal impacts of training, and the degree of transfer of benefits to other domains of cognitive functioning in older adults. Future studies incorporating more ecologically valid measures of cognitive and affective functioning can allow for a systematic examination of the benefits of mindfulness training for older adults.

MINDFULNESS AND NEURAL CORRELATES OF ATTENTIONAL CONTROL

Age-Related Alterations in Neural Activity and Connectivity

Much work has focused on characterizing the neural changes that occur across development and elucidating the contribution of such changes to cognitive decline. In comparison to the more selective recruitment of the right prefrontal cortex observed in young adults during tasks of attentional control, older adults showed decreased prefrontal lateralization (Cabeza, 2002), over-recruitment of attentional control regions (Cabeza et al., 2004; Langenecker et al., 2004; Colcombe et al., 2005), and a decreased ability to modulate recruitment of attentional control regions in response to increasing demand (Prakash et al., 2009, 2012c). Although some studies have provided evidence for a positive association between activation of attentional control regions and behavioral performance in older adults (Reuter-Lorenz et al., 2000; Cabeza et al., 2004), more recent longitudinal data suggested that increases in frontal activation were associated with declines in performance for tasks of abstraction, chunking, inhibition, discrimination, switching, and manipulation (Goh et al., 2012). In addition, there is evidence of an age-related decrease in suppression of the default-mode network (DMN) which is activated during rest and internal, self-referential thought (Raichle et al., 2001; Raichle and Snyder, 2007; Buckner et al., 2008). The DMN is anticorrelated with executive control network activity during attentional control tasks (Fox et al., 2005) and the degree of this anticorrelation is associated with cognitive performance (Kelly et al., 2008). The importance of the DMN in cognitive aging is further highlighted by evidence that functional connectivity within the DMN (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Koch et al., 2010; Voss et al., 2010), as well as the cingulo-opercular and frontoparietal control networks (Geerligs et al., 2015), decreases with age. During cognitive tasks, older adults exhibited less suppression of DMN regions compared to younger adults (Lustig et al., 2003), particularly in response to increasing task demands (Prakash et al., 2009; Sambataro et al., 2010), which was associated with poorer performance (Prakash et al., 2012c).

Mindfulness and Neural Functioning

Theoretical accounts of mindfulness posit that its salutary effects on attentional and emotional regulation occur through increased top-down modulation of limbic and brainstem systems by the prefrontal cortex (Chiesa et al., 2013; Prakash et al., 2014). This model has been substantiated by evidence of improved resource allocation during early processing (Malinowski, 2013) and increased recruitment of attentional control regions, such as the prefrontal cortex and anterior cingulate cortex, in those who have received meditation training (see Chiesa and Serretti, 2009; Hölzel et al., 2011; Tang et al., 2015 for review). Notably, these are some of the same regions that have been identified as showing alterations in function with age that are implicated in age-related changes in cognitive performance.

Given that mindfulness involves the active allocation of attention, either to internal or external stimuli, trait levels of mindfulness are hypothesized to be associated with preserved integrity of the DMN with advanced age. A cross-sectional investigation testing this hypothesis found that mindfulness disposition in older adults was in fact associated with greater integrity of the DMN, particularly in the dorsal posterior cingulate cortex and precuneus (Prakash et al., 2012b). These regions are considered to be important hubs within the functional connectome that are highly implicated in integrating and processing information (Buckner et al., 2009). Specifically, the dorsal posterior cingulate serves as an interface between the DMN and the task-positive attentional control network (Leech

et al., 2011), a role that is critical for efficient cognitive functioning. Another cross-sectional study, comparing adult expert meditators (mean age = 37) to individuals with no prior meditation experience (mean age = 36), found that naïve controls exhibited the expected negative correlations between age and total gray matter volume as well as age and attentional performance, whereas these associations were not observed in expert meditators (Pagnoni and Cekic, 2007). However, it is unclear what maximum age was included in this study, potentially limiting its applicability to elderly individuals. Together, these preliminary data suggest a potential role of mindfulness in preserving brain integrity with age, but they are limited by their cross-sectional nature.

The examination of neural outcomes as a function of mindfulness training in older adults is currently limited to one study. This RCT examined the effects of an 8-week MBSR program on neural activation in older adults (Moynihan et al., 2013). Following mindfulness training, improvements in executive control, indexed as the Trails B/A ratio, were found to be accompanied by a reduced shift toward rightward frontal alpha activation, which is associated with avoidance or withdrawal, but rather sustained left frontal alpha activation, which is associated with appetitive approach behaviors. These findings were similar to an RCT conducted in young to middle-aged adults (23–56 years) that found increases in left-sided anterior activation following 8-week MBSR, a neural pattern that has been associated with positive affect (Davidson et al., 2003b).

The reviewed studies provide preliminary evidence that mindfulness training might have implications for preventing and/or ameliorating age-related declines in brain structure and function and associated cognitive functions. However, much work is needed to more fully characterize the benefits of mindfulness training for neural functioning. One unique challenge presented by the study of older adults is the large variability in structural and functional changes in the brain with age (e.g., Raz et al., 2010). This heterogeneity is not accounted for by commonly used group-based statistical approaches, thus obscuring our understanding of age-related differences in attention as well as group-based changes following mindfulness training interventions. Longitudinal studies examining within-individual changes in neural variables provide detailed information regarding the trajectories of change across age (e.g., Goh et al., 2012, 2013). However, researchers will need to be innovative in their study design and use of neuroimaging techniques to account for both individual and group-based differences when examining the effects of mindfulness interventions. Initial investigations in this field should attempt to recruit relatively homogenous samples of healthy older-adults in an effort to control for comorbid conditions (e.g., psychiatric, autoimmune, neurodegenerative, etc.) and lifestyle factors that might impact neural integrity and associated attentional functions. Further, implementation of randomized, pre-post study designs with comparison to both active and waitlist control groups will provide the most accurate depictions of neural change resulting from mindfulness training.

MINDFULNESS AND PSYCHOLOGICAL WELL-BEING

Successful aging is not limited to preserved cognitive function, but is conceptualized as multi-dimensional, including the preservation of both physical and cognitive functions, the maintenance of social interactions, and continued engagement in meaningful activities (Rowe and Kahn, 1997). Critically, attentional control is implicated in many of these aspects of older adults' daily functioning. For example, executive function is associated with functional status, as measured using the instrumental activities of daily living scale (Cahn-Weiner et al., 2000; Royall et al., 2004), as well as medical comprehension, decision-making, and adherence (Park, 1999; Insel et al., 2006). Such outcomes are important given that the percentage of adults with multimorbidity, or multiple chronic health conditions, increases significantly with age, and these conditions are associated with greater risks of disability, poor functional status, and poor quality of life (Salive, 2013).

Quality of life and well-being are integrally important to the holistic health of older adults, particularly as isolation increases due to decreases in the number and frequency of social contacts (Steptoe et al., 2013). Social isolation is associated with heightened inflammatory responses and greater risk for morbidity, which is associated with greater risks of poor functional status and poor quality of life (Salive, 2013). Mindfulness training is uniquely relevant to older adults who are at increased risk of experiencing chronic disease and pain in that internal sensations, both cognitive and physical, are often a central focus of training programs. Further, we have argued that mindfulness training is especially pertinent to older adults given its emphasis on emotion regulation, an ability that is highly preserved across age (Prakash et al., 2014). Central to socioemotional selectivity theory (Carstensen, 1993, 2006; Carstensen et al., 1999; Reed and Carstensen, 2012) is the finding that older adults exhibit increased prioritization of emotional goals and improvements in emotion regulation abilities with age. We have proposed that mindfulness training capitalizes upon this shift in motivation away from future-oriented goals toward present-focused optimization of emotional experience observed in older adults (Prakash et al., 2014). Given the interdependence of emotional and attentional control processes, mindfulness training simultaneously optimizes the use of attentional control abilities and the enactment of useful emotion regulation strategies.

Preliminary cross-sectional evidence suggested that trait levels of mindfulness were associated with enhanced psychological well-being, measured as self-reported depressive symptoms, quality of life, and stress, in older adults (Fiocco and Mallya, 2015) and that emotion regulation mediated the relationship between trait mindfulness and reduced perceived stress in both older and younger adults (Prakash et al., 2015). A detailed examination of emotion regulation strategy use during idiographic situations revealed that older adults reported greater use of acceptance-based strategies and less use of maladaptive strategies than young adults in moderate-intensity situations and situations evoking anxiety and sadness as well as less use of

maladaptive strategies in high-intensity situations (Schirda et al., 2016). Additionally, reported use of thought avoidance mediated the association between mindfulness and emotion dysregulation and this effect was dependent on age such that less mindfulness in young, but not older, adults was associated with greater use of thought avoidance and greater emotion dysregulation (Prakash et al., 2017). Further, both qualitative and experimental research provide encouraging evidence of emotional benefits following mindfulness training.

Qualitative studies have used focus groups and content analysis of group discussions and diaries to explore the central themes reported by individuals who have participated in mindfulness training. One such study in older adults suffering from chronic pain found that participants reported beneficial effects of mindfulness training on pain, sleep, and achieving well-being (Morone et al., 2008). Participants reported that enhanced well-being was reflected in both elevated mood and increased global quality of life. Similarly, older adults with clinically significant depression or anxiety who participated in MBCT reported improvements in anxiety, depression, ruminative thoughts, and decreases in sleep-related problems (Foulk et al., 2014). Key topics discussed by a group of older-adult, low-income, African American women who participated in an MBSR program included the social support they received during group meditation, the use of mindfulness for stress management, and the application of mindfulness in their daily lives (Szanton et al., 2011). These participants reported using mindfulness skills to cope with a variety of stressors including managing depression and anger; growing older and having physical pain; medical tests; financial strain; as well as having grandchildren with significant mental, physical, financial, or legal hardships. These highlight the positive experiences and many perceived benefits participants freely reported following various forms of mindfulness training. Although this information is useful in determining the acceptability and feasibility of such programs, the lack of quantitative results limits the interpretation of statistical and clinical significance of mindfulness training's effects.

Expanding upon these qualitative data, other investigations of mindfulness training have provided experimental evidence for mindfulness training's ability to ameliorate emotional distress and promote well-being. For example, an 8-week MBSR program produced significant reductions in loneliness compared to a waitlist group (Creswell et al., 2012). In a sample of older adults reporting stress or symptoms of depression or anxiety, MBCT had a moderate to large effect on increasing trait mindfulness levels and improving emotional well-being, which were positively associated with one another (Splevins et al., 2009). However, participants in this study were not randomly assigned to MBCT and there was no control group with which to compare the effects. When comparing mindfulness training to an education control group for older adults with lower back pain, no between-group differences were observed on several outcomes (Morone et al., 2009). Instead, both groups exhibited significant improvements on measures of quality of life, self-efficacy, disability, and pain at post-intervention, which were maintained at 4-month follow-up. As was discussed in the previous sections of this review, these findings again suggest that factors not specific to mindfulness may have affected outcomes. Particularly, the qualitative studies described above point to the potential benefit of receiving social support for improving multiple domains of well-being, which is not a mindfulness-specific component of training. These effects are undetectable when mindfulness training is not tested against an active comparison condition. Thus, rigorous experimental investigation must be pursued in order to replicate previous findings and further characterize the benefits of mindfulness training.

The use of mindfulness training in clinical settings is of great interest, and there is accumulating evidence that such interventions can be useful in reducing symptoms of psychopathology. MBSR has been found to produce a >50% reduction in the number of older-adult participants with clinically significant depression and anxiety (Young and Baime, 2010). In older adults reporting worry symptoms with co-occurring cognitive dysfunction, there was a large effect size for increased mindfulness and reduced worry severity following MBSR, although no control group was used for comparison in this study (Lenze et al., 2014). These findings have been corroborated by meta-analytic evidence in young to middle aged adults with chronic medical diseases. This meta-analysis found that MBSR produces small, significant effects on psychological distress as well as psychopathology symptoms, including depression and anxiety (Bohlmeijer et al., 2010). Interestingly, the study by Splevins et al. (2009) suggests that specific components of mindfulness might confer greater psychological benefits than others. They found that the "act with awareness" and "accept without judgment" facets were associated with greater reductions in depression symptoms, whereas the other facets (observe and describe) were not.

Together, the results of studies evaluating the emotional benefits of mindfulness are promising. Mindfulness training appears to yield benefits for older adults with both clinical and sub-clinical symptoms of emotional distress, highlighting the potential for flexible application of mindfulness in many contexts. Moreover, the effects of mindfulness are not limited to reducing negative symptoms, such as depression and anxiety, but extend into increasing social support and promoting well-being. Nonetheless, there is still much to be learned regarding the effect of mindfulness-specific components on psychological health for both community-dwelling and clinical populations of older adults.

MINDFULNESS AND INFLAMMATORY PROCESSES

Symptoms of emotional distress and/or psychopathology can be accompanied by changes in inflammatory processes, which are further linked to a myriad of health sequelae. Although much is still unknown regarding the full spectrum of mindfulness training's health benefits, there is a great deal of interest in using mindfulness training programs to improve health both in clinical and community-dwelling settings. There are several mechanisms through which mindfulness training may alter

inflammatory processes: alteration of hypothalamic-pituitary-adrenal axis or sympathetic nervous system functioning. These two systems are implicated in the transduction of the brain's perception of socio-environmental conditions into genomic responses through their production of stress-related hormones such as cortisol, epinephrine, and norepinephrine that directly alter expression of pro-inflammatory genes (Cole, 2009).

In a study of community-dwelling older adults, baseline levels of loneliness were associated with expression of the pro-inflammatory gene NF-κB in leukocytes and those who participated in an 8-week MBSR course exhibited significant down-regulation of NF-κB expression compared to a waitlist group (Creswell et al., 2012). However, the impact of mindfulness training on protein indicators of activated inflammatory responses was mixed. Although it was hypothesized that the MBSR group would exhibit reductions in all protein indicators, there was a significant reduction in serum C-reactive protein levels, but no significant change in IL-6 protein levels. A subsequent study attempted to parcel out the differential effects of specific components of MBSR on inflammatory processes in comparison to a waitlist group (Gallegos et al., 2013). This study likewise found no effects on IL-6 levels across groups. However, yoga practice and sitting meditation were associated with higher post-treatment insulin-like growth factor (IGF-1) concentrations, a protein that is implicated in neurogenesis and preserved cognitive function but that decreases with age (Anderson et al., 2002), and yoga practice was associated with greater improvement in positive affect across the intervention. However, body scanning practice, in which focused attention is directed to the sensations of successive areas of the body, was found to have negative effects as it was associated with reduced antibody responses (IgM and IgG) at 3 weeks post-intervention; although this effect did not remain at 24 weeks. In contrast, another study found the expected increase in IgG response following 8-week MBSR compared to waitlist, but this effect disappeared at 24 weeks post-intervention. It is important to note that these studies are all limited by the lack of active comparison groups with which to compare these changes.

The last study evaluating inflammatory processes in older adults recruited participants with moderate sleep disturbance who were randomized to a 6-week mindful awareness practices intervention or sleep hygiene education group (Black et al., 2015). Although those who participated in mindfulness training improved more on insomnia symptoms, depression symptoms, fatigue interference, and fatigue severity, there were no between-group differences for anxiety, stress, or NF-κB expression. Instead, NF-κB expression was significantly down-regulated over time in both groups. This finding highlights the sizable influences that can result from non-specific factors arising from participation in group-based interventions. It is critical that future RCTs utilize active control conditions to clarify the impact of mindfulness training on inflammatory processes above and beyond the benefits of social engagement that participants might garner from any type of training. In addition to elucidating mindfulness-specific effects on inflammatory processes, future studies must evaluate the degree to which these effects persist over time and have broader systemic benefits.

CONCLUSIONS AND FUTURE DIRECTIONS

There is great interest, both from the public and from healthcare providers, in the application of mindfulness techniques. This review article discussed what is currently known about the effect of mindfulness training on key areas of interest within geropsychology: attentional control performance (behavioral and neural correlates), psychological well-being, and inflammatory processes. Although the majority of the reviewed studies provide positive results for mindfulness training in each of these domains, the field is currently limited in its scope and much more work is needed in order to establish the causal impact of mindfulness practice on these outcomes. Moreover, the conclusions that might be drawn from the existing studies are obscured by the heterogeneity of samples and limitations of the methods being employed. Whereas some studies focused on older adults with chronic health conditions, others recruited participants with specific psychological symptoms or diagnoses, and many aimed to examine relatively healthy older adults. There are also inconsistencies in the training programs being tested and a myriad of outcomes being evaluated within each domain. The creation and dissemination of standardized training protocols and identification of theoretically informed dependent variables will allow for the systematic evaluation of mindfulness training's effects. Further, given the relative dearth of RCTs, future studies will need to replicate existing findings and employ rigorous experimental tests in order to lay the foundation for the continued growth of this field.

Given that mindfulness is often broadly defined, and often considered to be multifaceted, future research should focus on identifying which components of mindfulness training confer which benefits. Developing and testing a mechanistic account of mindfulness training's effects will allow for the optimal application of training to promote healthy aging. Researchers might then begin to address the gaps in what is known about the degree to which these benefits are maintained longitudinally across continually advancing age. Another important target of future research is to examine to what extent these benefits transfer to broader functions that are critically implicated in the everyday lives of older adults. These might include comprehension of medical information, health behaviors, social engagement, and functional status, all of which have a foundation in intact attentional control processes.

The reviewed evidence suggests that mindfulness may be advantageous for promoting cognitive, emotional, and physical health within the context of advanced aging. Moreover, these beneficial effects are conferred to those with little to no psychological symptoms as well as those with diagnosed psychological or medical conditions. This suggests that mindfulness training might be easily integrated into a variety of contexts, such as senior centers and group homes, and that it would be valuable and appropriate for such heterogeneous

audiences. We previously described an ideal training program for older adults as one that is pragmatic; that capitalizes on older adults' increased motivation toward emotional well-being; and that exhibits transfer effects to multiple domains ranging from specific cognitive processes to broad, everyday function (Prakash et al., 2014). In line with these criteria, we assert that mindfulness represents a potential intervention for not only reducing emotional distress in older adults, but for allowing them to flourish.

AUTHOR CONTRIBUTIONS

SF and RP contributed significantly to the conception of the work. SF completed the initial drafting the work and RP provided critical revisions for important intellectual content. RP provided final approval of the version to be published. SF and RP agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 08 February 2017
doi: 10.3389/fnagi.2017.00021

Transcranial Doppler Sonography Reveals Reductions in Hemispheric Asymmetry in Healthy Older Adults during Vigilance

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Given that older adults are remaining longer in the workforce, their ability to perform demanding cognitive tasks such as vigilance assignments needs to be thoroughly examined, especially since many vigilance assignments affect public safety (e.g., aviation, medicine and long distance driving). Previous research exploring the relation between aging and vigilance is conflicted, with some studies finding decreased vigilance performance in older adults but others finding no effect of age. We sought a better understanding of effects of age on vigilance by assessing neurophysiological change over the course of a vigil in young (aged 18–24) and healthy older (aged 66–77) adults. To measure temporal changes in cerebral blood flow, participants underwent functional transcranial doppler (fTCD) recording during a 1 h vigilance task. Based on research showing a compensatory effect of increased left hemisphere activation during vigilance in young adults and the "hemispheric asymmetry reduction in older adults" (HAROLD) model, we predicted that during vigilance our older adults would show greater left hemisphere activation but perform at a similar level compared to young adults. While cerebral blood flow velocity (CBFV) declined over time in both groups, only young adults showed the typical right-lateralized CBFV pattern. Older adults showed greater left hemisphere activation consistent with the HAROLD model. However, the increased left hemisphere activation did not appear to be compensatory as the older adults performed at a significantly lower level compared to young adults over the vigil. Findings are discussed in terms of the HAROLD model of healthy aging and the resource theory of vigilance.

Keywords: transcranial doppler, vigilance, cognitive aging, cognitive resources, compensatory effort

OPEN ACCESS

Edited by:
Aurel Popa-Wagner, University of Rostock, Germany

Reviewed by:
Brittney Yegla, University of Florida, USA
Raluca Sandu Vintilescu, University of Medicine and Pharmacy of Craiova, Romania

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Received: *29 October 2016*
Accepted: *26 January 2017*
Published: *08 February 2017*

Citation:
Harwood AE, Greenwood PM and Shaw TH (2017) Transcranial Doppler Sonography Reveals Reductions in Hemispheric Asymmetry in Healthy Older Adults during Vigilance. Front. Aging Neurosci. 9:21. doi: 10.3389/fnagi.2017.00021

INTRODUCTION

Older people are now remaining longer in the workforce than has been the case historically. It is projected that over 30% of people aged 65–74 will still be working in 2022, up from 20% in 2002 (Toossi, 2012). In light of well-documented age-related declines in fluid cognitive ability (Park et al., 2002), this change raises questions about risks to public safety. This may be particularly relevant for jobs with high cognitive demand, such as jobs requiring vigilance or sustained attention. Many real-life vigilance assignments affect public safety such as aviation (i.e., air traffic control, aircraft cockpit monitoring, TSA baggage inspection), military (i.e., intelligence gathering, cyber-security,

seaboard navigation, unmanned vehicle flight), homeland security, medicine and long distance driving (Parasuraman, 1979; Warm et al., 2008; Shaw et al., 2009; Helton et al., 2010). Vigilance performance is known to decline over time, a phenomenon known as the vigilance decrement. The decrement is evident as early as 5 min into the vigil (Teichner, 1974; Warm et al., 2008) though more typically within the first 15–30 min (e.g., Mackworth, 1948). Despite this rapid decrement, many real-life vigilance assignments last for several hours with few rest breaks. While some professions requiring vigilance specifically exclude workers over a certain age (e.g., air traffic control), other professions do not (e.g., anesthesiology). Therefore, it is important to assess vigilance performance in retirement-aged people that are now in the workforce in increasing numbers. Our approach to a better understanding of effects of aging on vigilance was to measure the neurophysiology underlying vigilance performance in older and younger adults using functional transcranial doppler sonography (fTCD).

Despite considerable research, there is no consensus concerning the effects of healthy aging on the vigilance decrement (e.g., Davies and Parasuraman, 1982; McAvinue et al., 2012). Some studies find that older adults show poorer vigilance performance than young adults (Filley and Cullum, 1994; Mouloua and Parasuraman, 1995; Berardi et al., 2001; McAvinue et al., 2012), while others find no age-related difference (Parasuraman and Davies, 1977; Davies and Parasuraman, 1982; Parasuraman et al., 1989; Parasuraman and Giambra, 1991; Deaton and Parasuraman, 1998). For example, in a large longitudinal study with multiple age cohorts from 18 to 80+, Giambra and Quilter (1988) found no effect of age on vigilance performance. In another large study, McAvinue et al. (2012) did find effects of age on vigilance performance on the Sustained Attention to Response Task (SART; Robertson et al., 1997). They found that younger adults outperformed their older counterparts. An examination of the underlying neurophysiology of aging during vigilance may shed light on the underlying performance processes involved, which could help to resolve some of the inconsistency in the literature.

Although there have been several theories of the vigilance decrement, there are currently two predominant theories: mindlessness theory and resource theory (Wickens, 2002; Warm et al., 2008; Helton et al., 2010). Mindlessness theory suggests that poor performance on vigilance arises when participants withdraw attention from the task due to the monotonous—yet easy—nature of the task (Robertson et al., 1997; Helton et al., 2005). In contrast, resource theory suggests that the vigilance decrement can be better attributed to the participant expending attentional resources from a limited pool that is depleted with continuous task performance (Wickens, 2002; Warm et al., 2008; Helton et al., 2010). While there is evidence to support both theories, the resource theory of vigilance is more comprehensively supported by studies using various methods of measuring workload including self-report measures—such as NASA-TLX (Hart and Staveland, 1988) or the Multiple Resource Questionnaire (MRQ; Boles and Adair, 2001). By understanding the perceived workload of a task through such self-report workload measures, decrements in performance can be attributed to work and effort during a vigil rather than task disengagement (Hitchcock et al., 2003; Warm and Parasuraman, 2009; Shaw et al., 2010, 2013a; Finomore et al., 2013).

Perhaps the strongest evidence for resource theory comes from neurophysiological studies of vigilance (Parasuraman et al., 1998; Lim et al., 2010; Langner et al., 2012; Shaw et al., 2013b). While several neurophysiological tools have been used to study brain activity during vigilance, fTCD has shown a notably consistent pattern of results. fTCD is an ultrasound procedure that allows for continuous monitoring of cerebral blood flow velocity (CBFV) in the main-stem intracranial arteries. The logic underlying fTCD is that when a particular area of the brain becomes metabolically active, such as during the performance of mental tasks, there is an increase in by-products of metabolic activity such as carbon dioxide (CO_2). The increase in CO_2 leads to an increase in oxygenated blood flow velocity to that region to remove the waste products (Aaslid, 1986). The middle cerebral artery (MCA) is commonly used to measure CBFV for complex cognitive tasks as it supplies 80% of the blood to each respective cerebral hemisphere's frontal lobe (Stroobant and Vingerhoets, 2000; Warm et al., 2008).

Resource theory is also supported by findings that the absolute level of blood flow velocity in the brain varies directly with task difficulty (Hitchcock et al., 2003; Warm and Parasuraman, 2009; Shaw et al., 2010, 2012, 2013a), and the vigilance decrement is paralleled by a temporal decline in cerebral hemovelocity (Shaw et al., 2009; Warm and Parasuraman, 2009). Importantly, these CBFV effects are not present in control observers who are exposed to an identical vigilance task with no work imperative (Hitchcock et al., 2003; Shaw et al., 2009, 2012). In addition, the CBFV effects are lateralized to the right cerebral hemisphere, consistent with PET and fMRI studies that point to a right-hemispheric system in the functional control of vigilance performance (Parasuraman et al., 1998; Langner and Eickhoff, 2013). However, much of the recent research has revealed that vigilance tasks imposing a strong demand on observers require resource recruitment from both the left and right cerebral hemispheres (Helton et al., 2010; Shaw et al., 2012, 2016). Thus, bilateral increases in CBFV may be indicative of higher effort.

In light of evidence that bilateral hemispheric activation may help to maintain vigilance performance in young people (Shaw et al., 2016), the motivating question for the current work was whether bilateral activation would also benefit vigilance performance in older people. Previous research has shown that for tasks during which young people show largely unilateral Blood Oxygen Level Dependent (BOLD) signals, healthy older people show bilateral activation. This has been seen in tasks of episodic memory, semantic memory, working memory, perception and inhibitory control (Grady et al., 1994, 2005) and confirmed in meta-analyses (Spreng et al., 2010; Maillet and Rajah, 2014). Cabeza (2002) synthesized

this research into the Hemispheric Asymmetry Reduction in Older Adults (HAROLD) hypothesis of functional brain organization. Cabeza (2002) speculated that older adults use bilateral activation in the prefrontal cortex either to compensate for cognitive decline or as a result of what Baltes and Lindenberger (1997) termed dedifferentiation indicating age-related reductions in brain specialization. Monitoring CBFV during a vigilance task may provide insight into this question by determining whether older adults show an increase in overall CBFV or whether the fTCD measure reveals reduced hemispheric asymmetry during vigilance.

The current investigation used fTCD to examine the neurophysiological correlates in healthy old age during the performance of a vigilance task. While previous research on this subject is mixed, we predicted that young adults would outperform older adults on measures of vigilance (i.e., higher hit rate, lower false alarm rate and faster reaction time). However, we predicted that this performance difference would be reduced if older adults showed more bilateral activation as revealed by CBFV. Thus, under the HAROLD model and the resource model of vigilance, we predicted greater bilateral activation in older compared to young adults during vigilance.

MATERIALS AND METHODS

Participants

Thirty participants were recruited into the study (**Table 1**). Young adults consisted of 15 participants (age range 18–24, M = 20 years) and were recruited from a large university in the Mid-Atlantic region of the United States. These participants were given course credit for their participation. Older adults consisted of 15 participants (age range 66–77, M = 69) and were recruited from local "lifelong learning" organizations as well as from fliers posted in the area surrounding the university. Older participants were given travel compensation of up to 10 dollars. Participants in both groups were all right-handed as indicated by self-report. Exclusion criteria included current use of psychoactive medications, recent (<6 months) concussion, and/or cardiovascular disorders (i.e., history of stroke). All participants underwent a brief cognitive assessment at the end of the experiment. **Table 1** shows average demographic information and the mean scores on the cognitive assessment tests. It should be noted that the lowest individual Mini-Mental State Examination (MMSE) score was 26, above the cutoff used by the Alzheimer's Disease Neuroimaging Initiative (ADNI). The study was approved by the Universities' Institutional Review Board.

Materials and Measures

Mini-Mental State Examination

Older participants were administered the MMSE (Folstein et al., 1975), a standard screening tool to eliminate volunteers who may be suffering from a dementing disease. The cut-off criterion was set at 26 out of a possible 30 points; no volunteers were excluded from participation based on the MMSE.

Vigilance Task

Participants participated in a continuous vigilance task during which they viewed the repetitive presentation of an array of five open circles (14 mm diameter) outlined by a 1 mm black line that appeared on a white background on a 17-inch computer screen. The circles were positioned 75 mm from the center of the screen at the 3, 5, 7, 9 and 12 o'clock locations. The critical signal for detection was the absence of a vertical 1 mm black line intersecting the 6 o'clock position within *one* of the five circles in the display. This display was chosen because of previous research that has shown that it exhibits appropriate psychometric properties and is of sufficient difficulty to influence performance (Finomore et al., 2006; Shaw et al., 2016). An example of the stimulus array is presented in the center panel in **Figure 1**. Prior to engaging in the actual vigilance testing session, all participants were given a brief practice session. The practice consisted of 75 trials, five critical (one for each position) and 70 neutral with auditory performance feedback (i.e., "hit", "miss", or "false"). The experimental test session consisted of six blocks of 150 trials, 10 critical (2 per position) and 140 neutral, without auditory feedback. Each trial consisted of a blank screen (2250 ms), followed by the stimulus (250 ms, with neutral or critical), a blank response screen (1500 ms) for a total of 4 s per trial. The entire vigilance task lasted for 60 min.

Events were presented serially, and the display was updated once every 4 s, resulting in an event rate of 15 events/min. All stimuli were exposed for 0.25 s. For each observer, critical signals came into view on an average of once per minute during each period of watch (signal probability = 0.067) and the signals appeared equally often on each of the five circles comprising the vigilance display. Participants signified their detection of critical signals by pressing the space bar on a

TABLE 1 | Group demographic and cognitive assessment information.

Group	*n*	Gender	Age	MMSE	WMSi	WMSd	Flanker Inc-Cong$_1$	CVS slope$_2$
Young adults	15	4 Males	20	N/A	8.75$_3$	6.25$_3$	−64.40	5.528
Older adults	15	7 Males	69	29	11.75	10.00	−94.41	6.133

[1]Eriksen flanker variables were analyzed using the compatibility effect—the average reaction time of the incongruent trials (Inc) minus the average reaction time of the congruent trials (Cong). [2]Cued visual search (CVS) slope refers to the slope of the Cue Size/RT function. [3]One young adult (non-native English speaker) was excluded from the WMSi and WMSd calculation due to low performance on those tests only.

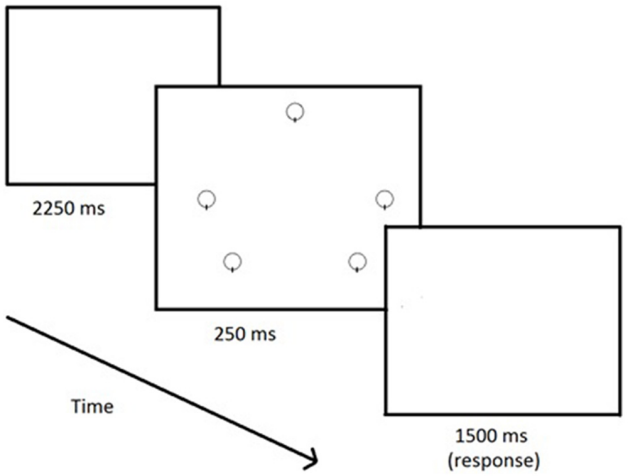

FIGURE 1 | Graphical depiction of a neutral trial.

computer keyboard. Responses occurring within 1.5 s after the appearance of critical signals were recorded as correct detections; responses to non-signal events were classified as false alarms.

Wechsler Memory Scale

The Wechsler Memory Scale (WMS Form 1, Wechsler, 1997) is a standard neuropsychological assessment of immediate and delayed episodic memory. The WMS, Logical Memory subtest, was administered by having the researcher first read the standard instructions for the test, and then read a paragraph aloud to the participant. Participants were asked to immediately recall the story aloud (WMS-Immediate score). After 30 min of another task and without being told in advance that they would be asked again to recall, the participants were asked again to recall as much of the story as they could (WMS-Delayed score). The researcher followed standardized instructions to score the test.

Eriksen Flanker

In the Eriksen Flanker task (EF; Eriksen and Eriksen, 1974) the participants were presented with a set of five arrows "<<<<<". Participants were required to indicate if the center arrow is facing right ">" or left ">" using the keyboard ("A" for left, "L" for right). There were two types of trials: congruent and incongruent. For the congruent trials, all the arrows pointed the same direction as the target arrow "<<<<<" or ">>>>>". In the incongruent trials, the other four arrows pointed the opposite directions as the target arrow "<<><<" or '>><>>". The participants were instructed to respond as quickly and as accurately as possible throughout the 15-min task. Data were pre-processed as compatibility effect reaction times (calculated using: [average incongruent trial reaction time] − [average congruent trial reaction time]; Lavie and Cox, 1997).

Cued Visual Search

For the cued visual search (CVS) task, participants monitored the computer screen for the presence of a pink "T" in a three by five array of letters. In most trials, the array of letters was preceded by a cue, which was a box drawn around one letter, one column, three adjacent columns, or the entire array. The participants were instructed to make a speeded response by pressing the spacebar to indicate when they saw the target. The target was present during 50% of the 1-min practice and 83.33% of the experimental trials. The entire task lasted 15 min. Data were calculated using the slope of the Cue Size/RT function (Greenwood and Parasuraman, 1999).

Procedure

Participants were greeted and shown to a windowless laboratory. After a short verbal description of the experiment, participants read and signed the consent form, and filled out a biographical questionnaire. Older participants were then administered the MMSE. Participants were then fitted with the fTCD sensors.

Prior to the vigilance practice session, participants were linked to a fTCD unit (Spencer Technologies model PMD150). The unit is equipped with two 2 MHz pulsed transducers embedded in a plastic bracket that is secured around the head with an adjustable Velcro strap. Both the left and right transducers were placed along the temporal bone dorsal and immediately proximal to the zygomatic arch. Ultrasound transmission gel was placed between each TCD transducer and the participant's skin to obtain a clear ultrasound signal. CBFV was measured from the mainstream MCA for the left and right cerebral hemispheres and provided a reading in cm/s. The MCA was monitored at approximate depths of 50–55 mm. The MCA is the artery most often measured in vigilance studies, as it supplies about 80% of the blood to the brain (Stroobant and Vingerhoets, 2000). A baseline was acquired by having the participant stare at a blank screen for 5 min. Blood flow data for the last 60 s of the baseline period was used as the baseline index, consistent with previous research (Aaslid, 1986; Shaw et al., 2009). Subjects wore the TCD headset for the duration of the experiment.

Next, the participant completed a short practice of the main vigilance task. In order to be retained in the vigilance experiment, the participant was required to have scored 80% or higher on hits and commit no more than 10% false alarms. If necessary, participants completed a second practice. Two participants required a second practice, while five participants were unable to meet this inclusion criterion and were therefore excluded from the experiment. Participants that did meet the practice criterion went on to complete the test trials of the vigilance task which lasted 60 min. After completion, the fTCD sensors were removed and the participant was given a 5-min break prior to the cognitive assessment.

For the cognitive assessment, the participant was first administered the WMSi (∼3 min). Next, they completed the EF task (∼ 15 min) and the CVS task (∼15 min), in counterbalanced order. The participant was then read the recall directions of the delayed WMS (WMSd). Finally, the participant was thanked for

his or her participation and the researcher provided a synopsis of the goals of the study and answered any questions. The younger participants were provided course credit and the older participants were offered ten dollars for travel compensation. The entire duration of the experiment was approximately 120 min. Data for the vigilance task and CBFV were examined using mixed-model analysis of variance (ANOVAs). Data for the Cognitive Assessment were analyzed using a MANOVA.

RESULTS

Cognitive Assessment

Table 1 shows that older adults on average scored 29 out of 30 on the MMSE (the lowest score was 26). A MANOVA conducted on the EF, CVS, WMSi and WMSd revealed a significant difference (Wilks lambda; $F_{(3,25)} = 4.666$, $p < 0.01$, $\eta^2 = 0.427$). Follow-up univariate analyses revealed that older adults had higher rates of immediate and delayed recall in the WMSi ($F_{(1,28)} = 6.288$, $p < 0.05$, $\eta^2 = 0.183$) and WMSd ($F_{(1,28)} = 7.570$, $p = 0.01$, $\eta^2 = 0.183$) memory tests. However, older adults had more interference due to incongruent stimuli as seen in the reaction time (when subtracting out the individual difference of reaction time for congruent stimuli) on the EF test ($F_{(1,28)} = 5.375$, $p < 0.05$, $\eta^2 = 0.161$). While not significant, older adults had slightly higher slopes on the CVS cue size/reaction time function. Although the older adults were slightly slower to respond, they were not cognitive impaired.

Vigilance Performance

In all repeated measures analyses, violations of sphericity were corrected using the Greenhouse-Geisser correction. Performance on the vigilance task was examined using the A prime statistic (Pollack and Norman, 1964), a nonparametric signal detection measure that is used to look at perceptual sensitivity (a ratio of correct detections to false alarms). **Figure 2** shows A prime means for each period plotted for both older and younger adults. A mixed-model two (age group) by six (period of watch) ANOVA revealed a significant main effect for group ($F_{(1,28)} = 5.508$, $p < 0.05$, $\eta^2 = 0.164$), such that younger adults had higher perceptual sensitivity than older adults. Neither the main effect of period or the interaction of group by period were significant.

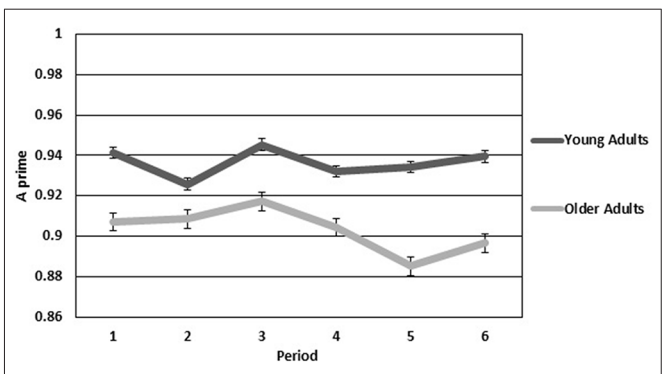

FIGURE 2 | Sensitivity for older and younger adults over the six continuous 10-min periods of the vigil. Error bars are standard error.

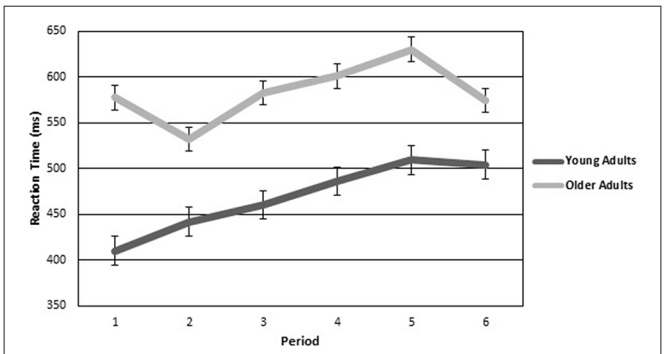

FIGURE 3 | Reaction Time for older and younger adults over the six continuous 10-min periods of the vigil. Error bars are standard error.

Reaction time to the target was also investigated with a two (age group) by six (period of watch) ANOVA. The analysis revealed a significant main effect of period ($F_{(5,98.692)} = 3.472$, $p < 0.05$, $\eta^2 = 0.126$), such that reaction time increased with time. **Figure 3** is a graphical representation of reaction time for each period plotted for both older and younger adults. There was a marginal main effect of group ($F_{(1,24)} = 3.948$, $p = 0.058$) such that older adults were slower to respond than young adults. There was no significant interaction.

Cerebral Blood Flow Velocity

CBFV scores for all participants were expressed as a proportion of the last minute of their 5-min baseline, consistent with previous work (Warm and Parasuraman, 2007; Shaw et al., 2016). **Figure 4** plots CBFV over time for left and right hemispheres for each age group. Importantly, there was no significant difference in baseline scores between groups ($p > 0.05$) on neither the left (young $M = 57.86$, SEM = 2.13; old $M = 55.62$, SEM = 1.93) or right (young $M = 58.13$, SEM = 2.10; old $M = 56.27$, SEM = 1.94) hemispheres. Thus, differences in hemovelocity during the vigil cannot be attributed to differences at baseline. A two (hemisphere) by two (age group) by six (periods of watch) ANOVA was conducted on the CBFV scores. There was a significant main effect of hemisphere ($F_{(1,28)} = 7.205$, $p < 0.05$, $\eta^2 = 0.206$), such that CBFV was higher in the right hemisphere than the left. There was also a significant main effect of period ($F_{(1,84.661)} = 7.205$, $p < 0.01$, $\eta^2 = 0.292$), such that CBFV declined over time. There was not a significant main effect of group. There was a significant hemisphere by group interaction ($F_{(1,27)} = 7.205$, $p < 0.05$, $\eta^2 = 0.211$). There were no other significant main effects or interactions.

The hemisphere by group interaction for CBFV was followed up with a simple effects analysis comparing hemisphere

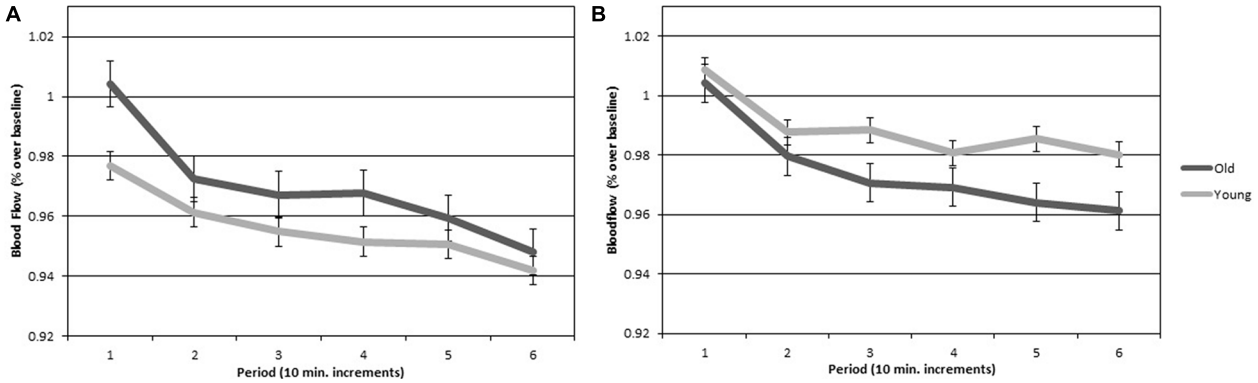

FIGURE 4 | (A) Cerebral hemovelocity relative to baseline (percent) plotted for older and younger adults for the left cerebral hemisphere over the six continuous 10-min periods of the vigil. **(B)** Cerebral hemovelocity relative to baseline (percent) plotted for older and younger adults for the right cerebral hemisphere over the six continuous 10-min periods of the vigil. Error bars are standard error.

for each group. There was a significant difference between the left and right hemispheres in young adults with higher CBFV in the right hemisphere ($F_{(1,27)} = 7.205$, $p < 0.05$, $\eta^2 = 0.228$). There was not a significant difference between the left and right hemispheres in older adults. **Figure 5** is a visual representation of CBFV for left and right cerebral hemispheres plotted for both older and younger adults. It can be seen in the figure that hemispheric asymmetry is reduced in older adults. To test the hypotheses that increased bilateral activation would have a compensatory effect on vigilance performance in older adults, a Pearson correlation analyses was conducted on the mean A prime scores and mean difference score between right and left hemisphere CBFV. The correlation was not significant ($p > 0.05$).

DISCUSSION

To test our hypothesis that having more resources committed to a vigilance task heightens performance regardless of age, we used CBFV to measure resources during vigilance in young and older people. Previous work has shown that task-related brain activation is more bilateral in healthy older people compared to young people. This bilateral activation has been linked to a compensatory mechanism for poorer cognitive performance (reviewed in Greenwood, 2007). Based on evidence that: (a) in young people vigilance performance is improved in groups who activate CBFV bilaterally (Shaw et al., 2016); and (b) high- but not low-functioning older people showed a bilateral activation pattern (Cabeza et al., 2002), we predicted that healthy older people would experience a benefit in vigilance performance from bilateral activation. Consistent with previous findings (Rogers, 2000; Warm et al., 2008), we found the young group showed stronger right than left hemisphere activation during vigilance. Although the healthy, cognitively normal (**Table 1**) older group showed bilateral activation, they also showed poorer vigilance performance than the young adults. These findings are relevant to several questions.

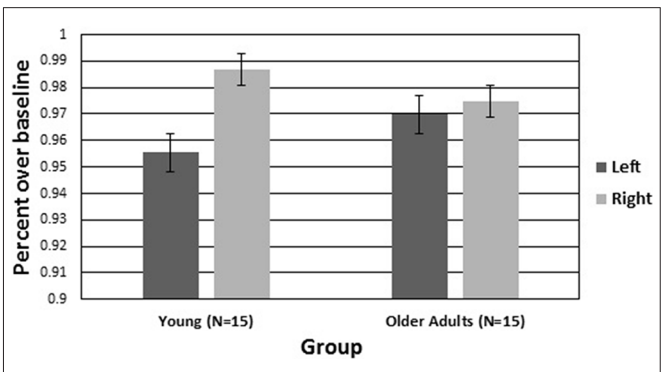

FIGURE 5 | Average cerebral hemovelocity relative to baseline (percent) plotted for older and younger adults for left and right cerebral hemispheres over the 60-min vigil. Error bars are standard error.

First, we found that older people did not perform as well as young on vigilance tasks. While the literature does not consistently show that vigilance is age sensitive (reviewed in Giambra, 1997), our study is consistent with such a conclusion. This is an important matter in light of the growing presence of retirement-aged people in the workforce, including in vigilance assignments relevant to public safety.

Second, our findings are relevant to the debate on whether increased regional activation in older people is related to a compensatory process. Beginning with the work of Grady et al. (1994, 2005), it has been found that tasks that induce unilateral hemispheric activation in young people instead induce bilateral activation in older people. Such evidence is the basis for the HAROLD hypothesis which argues that the decreased lateralization seen in older adults reflects either compensation or dedifferentiation (Cabeza, 2002). Greenwood (2007) hypothesized that in aging, functional plasticity leads to changed processing strategy which increases activation of atrophic regions (prefrontal and parietal) and thereby improves performance. Consistent with that, there

is recent evidence of "compensation by recruitment" in older people in memory processes (Lighthall et al., 2014; Kennedy et al., 2015; Fernández-Cabello et al., 2016), with confirmation by meta-analyses (Spreng et al., 2010; Maillet and Rajah, 2014). Although we did observe increased activation of frontal regions among the older people, that bilateral activation occurred together with poorer vigilance performance. Therefore, if the increased activation of the left hemisphere was compensatory, that compensation was not sufficient to raise the performance of the healthy old to the level of the young. Thus, our results from a vigilance task do not support the idea of "compensation by recruitment" in aging. However, there is previous evidence that compensation by recruitment occurs in young extraverts during vigilance performance (Shaw et al., 2016). Our findings that the older group showed more bilateral activation but poorer performance relative to the young group is consistent with dedifferentiation theory (Baltes and Lindenberger, 1997). That view predicts that age-related loss of regional brain specificity reflected in bilateral processing is accompanied by poorer performance. The hypothesis of dedifferentiation does not predict compensation. However, more recent hypotheses of brain aging have predicted it. First, Greenwood (2007) argued from the paradoxically increased activation of brain regions known to shrink with age that age-related reductions in regional brain integrity drives both changes in processing strategy and functional cortical reorganization. Subsequently, Park and Reuter-Lorenz (2009) advanced a very similar view, termed "scaffolding theory." The present study did not find evidence that the observed bilateral activation in the older group had compensatory effects. Considering the existing evidence together, it appears that compensation by recruitment can occur in both young and older people. Nevertheless, our results showed that for vigilance tasks, bilateral recruitment may be relatively ineffective in ameliorating the performance of older people.

Third, our findings add to the literature reporting variability in the strength of the vigilance decrement. We did not see a traditional vigilance decrement in performance sensitivity. One explanation could have been the relatively slow event rate (15 events/min). Event rate has been found to be a primary determinant of the vigilance decrement, such that slow event rates (e.g., 5 events/min) are not as resource demanding as faster event rates (30 events/min; Parasuraman and Davies, 1977). Indeed, the performance difference between older and younger adults was restricted to an overall difference in perceptual sensitivity. It is worth noting, though, that a significant slowing of reaction time was observed in the study, and there was a marginally significant main effect that points to more slowing in the older group. So, while both groups were able to maintain their detection performance over time, both older and younger adults slowed in their response over the course of the vigil, which could be evidence of the decrement function.

Our findings raise the question of whether, in light of public safety concerns, age alone is a sufficient predictor of vigilance performance in the real world. In a study that compared high- and low-cognitive functioning older adults, only the high-functioning group showed bilateral activation pattern (Cabeza et al., 2002). This suggests the importance of understanding the effect of overall cognitive functioning on the ability to compensate by recruitment. It will be important for future research to compare higher- and lower-functioning older adults for the ability to compensate for cognitive decline. A study of this sort is especially relevant given the relatively recent findings relating to increased "brain reserve" among older adults, in which older adults that engage in demanding cognitive and motor activities seem to show strengthened brain machinery (Freret et al., 2015).

It will also be important for future research to consider other sources of individual differences in vigilance performance and neurophysiological response. Shaw and colleagues (Shaw et al., 2010; Matthews et al., 2011, 2014) have shown the importance of linking operator characteristics to neurophysiological measures to gain insight into how individual differences affect resource allocation strategies. Recent research in this vein has considered a wide variety of operator characteristics such as extraversion (Shaw et al., 2010, 2016), neuroticism (Mandell et al., 2015), impulsivity (Shaw et al., 2010) and experience (Shaw et al., 2013b). This work reveals individual differences in both vigilance performance and hemispheric activation patterns. Although this suggests there may be some ability to compensate to maintain vigilance, the effect may be fragile or dependent upon a combination of multiple factors that were not considered in this study.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Human Subjects SOPs, Office of Research Integrity and Assurance's Institutional Review Board with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Office of Research Integrity and Assurance's Institutional Review Board.

AUTHOR CONTRIBUTIONS

The study was conceived and designed by THS, PMG and AEH. Data collection and analyses were conducted by AEH. The article was written and revised by AEH, THS and PMG.

FUNDING

Supported by Air Force Office of Scientific Research (AFOSR/AFRL) Grant FA9550-10-1-0385 and the Center of Excellence in Neuroergonomics, Technology and Cognition (CENTEC). Publication of this article was funded in part by the George Mason University Libraries Open Access Publishing Fund.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 14 February 2017
doi: 10.3389/fnagi.2017.00028

Age-Related Changes in the Ability to Switch between Temporal and Spatial Attention

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Background: Identifying age-related changes in cognition that contribute towards reduced driving performance is important for the development of interventions to improve older adults' driving and prolong the time that they can continue to drive. While driving, one is often required to switch from attending to events changing in time, to distribute attention spatially. Although there is extensive research into both spatial attention and temporal attention and how these change with age, the literature on switching between these modalities of attention is limited within any age group.

Methods: Age groups (21–30, 40–49, 50–59, 60–69 and 70+ years) were compared on their ability to switch between detecting a target in a rapid serial visual presentation (RSVP) stream and detecting a target in a visual search display. To manipulate the cost of switching, the target in the RSVP stream was either the first item in the stream (Target 1st), towards the end of the stream (Target Mid), or absent from the stream (Distractor Only). Visual search response times and accuracy were recorded. Target 1st trials behaved as no-switch trials, as attending to the remaining stream was not necessary. Target Mid and Distractor Only trials behaved as switch trials, as attending to the stream to the end was required.

Results: Visual search response times (RTs) were longer on "Target Mid" and "Distractor Only" trials in comparison to "Target 1st" trials, reflecting switch-costs. Larger switch-costs were found in both the 40–49 and 60–69 years group in comparison to the 21–30 years group when switching from the Target Mid condition.

Discussion: Findings warrant further exploration as to whether there are age-related changes in the ability to switch between these modalities of attention while driving. If older adults display poor performance when switching between temporal and spatial attention while driving, then the development of an intervention to preserve and improve this ability would be beneficial.

Keywords: spatial attention, temporal attention, aging, switching, cognitive flexibility

OPEN ACCESS

Edited by:
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Received: *14 September 2016*
Accepted: *30 January 2017*
Published: *14 February 2017*

Citation:
Callaghan E, Holland C and Kessler K (2017) Age-Related Changes in the Ability to Switch between Temporal and Spatial Attention. Front. Aging Neurosci. 9:28. doi: 10.3389/fnagi.2017.00028

BACKGROUND

Driving cessation can be detrimental to older adults' independence and has been shown to be a risk factor in developing depression (Marottoli et al., 1997; Ragland et al., 2005; Windsor et al., 2007). Identifying age-related changes in cognition that contribute towards reduced driving performance is the first step in a trajectory of research towards developing an

intervention to improve older adults' driving. This could lead to long-term advantages such as prolonging the time that people can continue to drive and help to preserve their independence.

At-fault collision statistics show that, while older adults have an overall reduced crash risk in comparison to young drivers, they present a disproportionate risk of at-fault collisions at intersections and collisions caused by a failure to give way, or to notice other objects, stop signs or signals (Hakamies-Blomqvist, 1993; McGwin and Brown, 1999; Guo et al., 2010; Arai and Arai, 2015). Consistent with higher risks at intersections (Hakamies-Blomqvist, 1993), in their seminal work Parasuraman and Nestor (1991) concluded that older drivers' accidents were often due to failures in attention, particularly selective attention and switching. These findings are consistent with older drivers' own self-perceptions, who have reported an increased difficulty to read and process signs in time (Musselwhite and Haddad, 2010). It is therefore a viable hypothesis that changes in spatial attention and attention switching are having an impact on driving skills later in life.

Spatial Attention

There is extensive research demonstrating the relationship between spatial attention and driving performance and exploring how this changes with age (Hennessy, 1995; Richardson and Marottoli, 2003; Hoffman et al., 2005; Ball et al., 2006; Leversen et al., 2013; Cuenen et al., 2015). However, poor spatial attention does not result in poor driving in all older individuals (Vaucher et al., 2014). These findings highlight the need to further investigate attentional deficits in older drivers and identify the factors that determine whether deficits in attention affect driving performance.

There is a consensus that there is no specific decline in visual search performance with healthy aging when the target is distinct from the distractors and "pops out" of the display—i.e., a pop-out search (Plude and Doussardroosevelt, 1989; Foster et al., 1995; Humphrey and Kramer, 1997; Bennett et al., 2012; Li et al., 2013). Although older adults show increased response times (RTs) to detect targets in pop-out searches in comparison to young adults, age group differences in RTs remain constant with increasing numbers of distractors (Plude and Doussardroosevelt, 1989) and have therefore been attributed to general slowing (Foster et al., 1995). In contrast, visual search performance is thought to decline with age when the target is visually indistinct from distractors (i.e., in so-called "conjunction search", where targets are defined as a combination of features shared with the distractors) and a serial search is required (Plude and Doussardroosevelt, 1989; Foster et al., 1995; Humphrey and Kramer, 1997; Bennett et al., 2012; Li et al., 2013). The increase in RTs with increasing numbers of distractors gets steeper with age, suggesting a specific deficit in serial visual search rather than a general slowing of RTs.

It is often argued that older adults have deficits in inhibiting irrelevant visual information (Hasher and Zacks, 1988; Greenwood and Parasuraman, 1994; Adamo et al., 2003; Maciokas and Crognale, 2003; Lustig et al., 2007; Gazzaley et al., 2008). It may be that poor selective attention is caused by deficits in inhibitory mechanisms. Competition models of visual selective attention (Treisman, 1988; Desimone, 1998; Bundesen et al., 2005; Beck and Kastner, 2009; Scalf et al., 2013) and evidence from single cell recordings (Reynolds et al., 1999) suggest that multiple stimuli are processed in parallel but in separate cell groups (Luck et al., 1997). Visual stimuli compete for processing resources and attention is implemented to bias excitation in favor of salient and task relevant stimuli. The Neural Theory of Visual Attention (NTVA; Bundesen et al., 2005) proposes that attention works to increase or decrease the number of cells involved in processing each object and alters the firing rate of neurons coding for certain features. Impairments in these excitatory-inhibitory attentional mechanisms may lead to difficulties in inhibiting irrelevant visual information and exciting target stimuli in older adults. This hypothesis would explain older participants' disproportionately increased number and duration of saccadic eye movements on serial visual searches (Porter et al., 2010). In contrast, Lien et al. (2011) demonstrated that older and younger participants were equally able to attend to task-relevant stimuli and inhibit salient but irrelevant stimuli. However, it may be that the salience of the distractors aided inhibition due to the distinct visual features prompting a strong inhibitory response. Thus, deficits in excitatory-inhibitory mechanisms could lead to difficulties in selective attention.

There is evidence to suggest that older adults compensate for excitatory-inhibitory deficits with top-down control of attention. Neider and Kramer (2011) found that older participants not only benefited more than younger participants from using contextual information in a visual search within a realistic scene, but also displayed greater costs to their performance when the location of the visual search target was incongruent with its contextual information. Furthermore, McLaughlin and Murtha (2010) found that older adults utilized cues more than younger people in a visual search task. Similarly, Watson and Maylor (2002) demonstrated that the benefits of visual marking were preserved in adults aged 65–80 years. Visual marking is where a proportion of distractors within a visual search task is shown before the onset of the remaining distractor stimuli and the target stimulus, enabling top-down driven inhibition of the distractors that were presented first. However, the benefits of visual marking were not preserved in older adults when visual search items were moving. Previous research has demonstrated that older participants have lower motion detection thresholds (Conlon and Herkes, 2008) and find it more difficult to judge the speed of moving stimuli and vehicles (Scialfa et al., 1991; Schiff et al., 1992; Norman et al., 2003; Snowden and Kavanagh, 2006). The absence of visual marking of moving stimuli in older adults could therefore be due to difficulties in processing moving stimuli. Together findings suggest that older participants may rely more on top-down processes to compensate for declines in excitatory-inhibitory mechanisms in attention.

Temporal Attention

In addition to the importance of spatial attention in driving, the allocation of attention to events changing in time, i.e., temporal attention, is important to be able to attend, process and respond to rapidly changing visual stimuli in a dynamic environment

such as driving. It is well established that older adults require longer to process visual stimuli—i.e., have slower processing speeds (Ball et al., 2006; Rubin et al., 2007) and display an increased magnitude of the so-called "attentional blink" (Lahar et al., 2001; Maciokas and Crognale, 2003; Lee and Hsieh, 2009; Shih, 2009; van Leeuwen et al., 2009). The attentional blink is the reduced ability to detect a second target (T2) in a rapidly changing stream of stimuli—i.e., a rapid serial visual presentation (RSVP) stream—up to 500 ms after detecting a first target (T1) in the stream (Raymond et al., 1992). This effect is inflated and lasts for an increasing length of time with increased age. There is evidence to suggest that, whereas individuals in their 60s have no difficulties in temporal attention (Lee and Hsieh, 2009; Quigley et al., 2012), difficulties may begin to develop between the ages of 70–80 years (Conlon and Herkes, 2008; Shih, 2009). Conlon and Herkes (2008) concluded that impairments were due to slowed processing speed. However, age-related deficits observed in other temporal attention tasks have been demonstrated not to be due to general slowing (Maciokas and Crognale, 2003; Lee and Hsieh, 2009). Difficulties in temporal attention in those aged over 70 years could therefore be due to a specific decline in selective attentional mechanisms and could share the same underlying cause as difficulties in spatial selective attention, i.e., in excitatory-inhibitory selective attention processes, where excitatory mechanisms fail to respond to the target and inhibitory mechanisms fail to mitigate interference from the distractors in the RSVP stream.

Switching Attention between Time and Space

Equally vital to safe driving, particularly at intersections, is the ability to switch between temporal and spatial attention. For example, when driving, one must switch from attending to fast moving and changing cars on the road ahead, to distributing attention across space to attend to road signs and surrounding hazards. Although there is extensive research displaying inflated switch-costs with increased age in task switching paradigms (Cepeda et al., 2001; Gamboz et al., 2009; Gold et al., 2010) there has been very little research on switching between different modalities of attention in any age group.

Overlapping networks across occipital, frontal, parietal and motor regions have been implicated in both directing attention in time and space (Coull and Nobre, 1998; Shapiro et al., 2002; Gross et al., 2004; Fu et al., 2005; Madden et al., 2007; Li et al., 2013). Although Coull and Nobre (1998) found overlapping activation for both temporal and spatial attention in a functional magnetic resonance imaging (fMRI) study, they found that patterns of activation for the two types of attention were distinct. In an extension of the NTVA, it has been proposed that as temporal expectation increases temporal attention works to increase the firing rate of neurons that represent certain features. In contrast, one would expect spatial attention to alter the number of cells allocated to processing objects in the visual field (Bundesen et al., 2005; Vangkilde et al., 2012, 2013). Thus, it may be expected that switching between temporal and spatial attention requires the efficient re-allocation of cells to receptive fields, as well as changes to the perceptual bias towards features which in turn influences the firing rate of neurons.

There is limited research into age-related changes in the ability to switch between temporal and spatial attention. Jefferies et al. (2015) demonstrated that younger adults require less time than older adults to narrow their focus of attention from two RSVP streams to one, indicating that there may be an age-related decline in the redistribution of attention spatially from a single location. However, both RSVP streams remained on the screen. Rather than a deficit in switching to distribute attention spatially, increased times taken to divert attention may be due to an age-related impairment in disengaging from task irrelevant stimuli (Greenwood and Parasuraman, 1994). In Lee and Hsieh (2009) study, participants switched from attending to an RSVP stream to identify a target, to allocating their attention in space to identify and point to a masked peripheral target in varying locations. Although the older age group displayed lower performance when the peripheral target was presented at 100, 300 and 700 ms after the RSVP target onset, lower performance was exaggerated at 100 and 300 ms. These findings show that older participants had greater difficulties in switching from temporal to spatial attention when there was 300 ms or less between target onsets. Russell et al. (2013) has since replicated these findings, further demonstrating that the impairment lasted for 450 ms. However, Lee and Hsieh (2009) aim was to investigate the attentional blink in older adults, resulting in a failure to distinguish between impaired task performance resulting from an increased attentional blink after processing the RSVP target, or due to increased switch-costs between temporal and spatial attention. Poorer performance at 100 and 300 ms, but not 700 ms, could equally be due to requiring longer to switch between temporal and spatial attention, or an extended attentional blink. A comparison of the relevant attentional blink and attention switching literature is presented in **Table 1**. The table compares the duration of the attentional blink in older age groups in addition to the duration of impairment from attention switching.

The Current Study

The aim of the current study was to explore whether there are age-related changes in the ability to switch between temporal and spatial attention and to explore the cognitive mechanisms that might underpin these changes. Age groups were compared on their ability to switch from allocating attention in time, in order to identify a single target in an RSVP stream, to allocating attention spatially, in order to identify a visual search target. To manipulate the cost of switching, the position of the target in the RSVP stream was either the first item in the stream, towards the end of the stream, or absent from the stream. When the target was the first item in the stream (Target 1st condition), participants were no longer required to attend to the stream, and thus no cost of switching was expected. On the contrary, when the target was near the end of the stream (Target Mid condition) or the stream consisted of only distractor items (Distractor Only condition), participants needed to attend to the stream until towards the end of the stream, inducing a cost of switching. Longer visual search RTs were therefore expected

TABLE 1 | Comparison of results from previous studies.

Author	Mean age (years)	Method	Duration of impairment
Attentional blink			
Lahar et al. (2001)	68.70	Attentional blink	520 ms
Lee and Hsieh (2009)	59.30	Attentional blink	300 ms. No impairment at 700 ms
Maciokas and Crognale (2003)	64–79	Attentional blink	824 ms
Switching			
Jefferies et al. (2015)	66.40	Time taken to narrow focus from 2 to 1 RSVP stream	266 ms
Lee and Hsieh (2009)	55–62	Attention switch from temporal to spatial attention	300 ms. No impairment at 700 ms
Russell et al. (2013)	66.00	Attention switch from temporal to spatial attention	450 ms

when switching from the single target RSVP task to the visual search in both the Target Mid and Distractor Only conditions, which each behaved as switch conditions, in comparison to the Target 1st condition, which behaved as a no-switch condition. It was hypothesized that there would be an age-related increase in the cost of switching from the RSVP task to initiate the visual search task, which would be reflected in greater increases in RTs from the no-switch condition to the two switch conditions in the older groups in comparison to the younger groups. In contrast to Lee and Hsieh (2009) study, the inclusion of the Distractor Only condition enabled the investigation of whether any observed differences were due to difficulties in switching between attentional mechanisms or an increased attentional blink. If there is a deficit in switching between attentional mechanisms, then age-related inflated switch-costs would be present in both the Distractor Only and Target Mid conditions. Conversely, if age-related increases in switch-costs result from an extended attentional blink after processing the RSVP target, then age differences in switch-costs would only be observable in the Target Mid and not the Distractor Only condition.

Based on previous evidence that suggests that visual selective attention to temporal events is more difficult in those over the age of 70 years (Conlon and Herkes, 2008; Shih, 2009) but not in those aged 60–70 years (Lee and Hsieh, 2009; Quigley et al., 2012), it was expected that participants in the 70+ years age group would detect and identify fewer targets in the RSVP stream in comparison to younger adults, but that the 60–69 years age group would not be impaired.

It is well established that there is a decline in working memory capacity with increased age (Richardson and Vecchi, 2002; Toepper et al., 2014). It could be argued that the increased working memory load from retaining the target digit in the current task could impair older participants' performance in switching. However, it is unlikely that retaining a single target would place enough demand on working memory to affect task performance. Furthermore, Akyürek and Hommel (2005) demonstrated that working memory load does not interact with the duration of the attentional blink, implying that working memory load should not affect visual search target processing. Although working memory capacity is unlikely to affect task performance in the current task, performance is likely to be affected by age-related declines to the central executive (Baddeley, 1992). Baddeley's (1992) working memory model proposed that the central executive controls the allocation of attentional resources. It may therefore be expected that a decline in executive function could affect the ability to switch from allocating attention to events changing in time (i.e., the RSVP stream) to distribute attention spatially (i.e., to visual search stimuli). We therefore implemented the Random Number Generation task (RNG) to measure executive functions of updating and inhibition (Miyake et al., 2000) in order to examine the effect of executive function on task performance. Performance on random generation tasks has previously been found to decline with age (van der Linden et al., 1998).

Consistent with age-related declines in serial but not pop-out search performance (Plude and Doussardroosevelt, 1989; Foster et al., 1995; Humphrey and Kramer, 1997; Bennett et al., 2012; Li et al., 2013) and general slowing of RTs (Salthouse, 2000; Verhaeghen and Cerella, 2002), it was predicted that there would be an age-related increase in visual search RTs that would be greater for serial than pop-out searches.

To establish an understanding of the mechanisms that underpin switching between modalities of attention, additional cognitive measures were recorded. The useful field of view (UFOV) task was implemented to measure visual processing speed, divided attention and selective attention. Performance on the UFOV (Ball et al., 2006; Rubin et al., 2007; Edwards et al., 2009) tasks have been found to decline with age.

MATERIALS AND METHODS

Participants

One hundred and five participants in five age groups (21–30, 40–49, 50–59, 60–69, and 70+ years) participated. The 21–30 years group were used as a comparison group for age-related cognitive changes for all other groups and the 40–49 and 50–59 years groups were used as middle-aged comparison groups for the 60–69 and 70+ years groups. Due to the study being advertized as research related to driving, many of the participants were regular drivers. The percentage of participants in each group who could drive are displayed next to participant demographics in **Table 2**. Participants with photosensitive epilepsy were excluded from participation, in addition to those who scored less than the 87 cut off for possible cognitive impairment on the Addenbrookes Cognitive Examination 3 (ACE-3; Noone, 2015). The ACE-3 consists of a series of short tasks which provide measures of language, memory, attention, fluency and visuospatial abilities.

TABLE 2 | Participant demographics.

		Age group (years)				
		21–30 (*n* = 20)	**40–49 (*n* = 20)**	**50–59 (*n* = 20)**	**60–69 (*n* = 21)**	**70+ (*n* = 21)**
Age (years)	Mean	25.00	44.15	55.80	66.00	74.86
	SD	2.62	3.31	2.28	2.32	5.72
Gender	Male	10	9	8	10	8
	Female	10	11	12	11	13
Handedness	Right	19	18	17	21	19
	Left	1	2	2	0	2
	Ambidextrous	0	0	1	0	0
Level of education	A-Level	1	4	8	5	3
	Degree	4	7	8	10	9
	Post degree qualification	15	9	4	6	8
ACE-3	Mean	96.50	95.42	95.9	94.95	95.33
	SD	3.20	2.61	2.49	2.54	2.06
Drivers	Regular drivers	17	19	20	20	21

The number of participants who are left and right handed, and the number of participants who are male and female are presented for each age group, in addition to the mean age of each age group. One participant from the 40–49 years group was excluded from the ACE-3 analysis as their performance was impaired on vocabulary dependent sections of the task due to English being their second language.

Participants in the 21–30 and 40–49 years groups were recruited from Aston University staff and students and the community. Participants aged over 60 years were recruited from the Aston Research Centre for Healthy Ageing participation panel and University of the Third Age groups around the West Midlands. Participants received £7.50 towards their travel expenses. All participants provided written informed consent before participating. The research was approved by Aston University Research Ethics Committee. Vulnerable populations were not involved.

One participant from the 60–69 years group and two from the 70+ years group scored equal to or lower than the 87 cut-off on the ACE-3 (Noone, 2015) and were therefore excluded from further analyses. One participant in the 40–49 years group scored lower than 87 on the ACE-3, however, this was due to English being their second language and so they were not excluded from the study. Their ACE-3 score was excluded from the analysis. All other participants scored over 87. After excluding participants with low ACE-3 scores, the mean age of the 60–69 years group was 66.00 years (SD = 2.32), and the mean age for the 70+ years groups was 74.86 years (SD = 5.72).

Fisher's Exact test comparing group differences in level of education (A-level equivalent or lower/degree equivalent/post degree qualification) revealed a significant difference in the level of education between groups (p = 0.049). The number of participants in the 21–30 years group with post degree qualifications was greater than expected (z = 2.1). A one-way ANOVA comparing group differences in general cognitive function measured with the ACE-3 revealed no significant group differences in ACE-3 scores ($p > 0.05$).

Materials and Procedures

Attention Switching Task

In the attention switching task, participants alternated between attending to an RSVP stream and attending to a visual search display. Each trial consisted of a fixation cross, presented for 2000 ms, followed by the RSVP stream, which was immediately followed by the visual search display. Stimuli were presented on stimulus presentation software E-Prime 2.0 Professional (Psychology Software Tool. Inc., Sharsburg, PA, USA) on a windows computer, on a 22″ monitor (1280 × 1050 resolution) which was approximately 55 cm in front of the participant. All stimuli were presented in black (RGB 0-0-0) on a gray background (RGB 192-192-192).

The RSVP stream consisted of a rapidly changing stream of letters in the center of the display. There were ten items in each RSVP stream, each presented for 100 ms with no inter-stimulus interval. Stimuli were presented in font size 30 pt (0.75 × 0.75 cm, 0.78°). On two thirds of the trials, one of the items in the stream was a target digit ranging from 1 to 9. The participant's task was to remember the digit. The remaining one third of the trials contained no target. Based on their visual similarity to certain numbers, letters I, O and S were excluded from the stream, as well as visual search targets K and Z. It should be noted that the current RSVP task differs from the attentional blink paradigm as the RSVP stream contains only a single target.

The visual search display consisted of eight letters presented in a circle around a fixation cross in the center of the screen, including seven distractors and one target. The target letter was always either a "K" or a "Z". Stimuli were presented in font size 20 pt (0.50 × 0.50 cm, 0.52°) and the center of each stimulus was 2.3 cm (2.40°) from the center of the fixation cross. Participants pressed the "space-bar" once they identified the target. Participants' RTs to press the space-bar were recorded. An initial space-bar response was implemented instead of a choice RT to minimize variability in RTs that result from the additional process of deciding which key to press. In a pilot study we found that while the overall pattern of means was the same, there was increased variability in RTs when participants responded by pressing either a "K" or "Z" key, depending on which letter the visual search target was, in comparison to using a single space-bar response. Higher variability from a choice RT may have affected older more than younger participants' performance. Older participants are

thought to show increased variability in RTs (Hultsch et al., 2002) and so it is important to minimize this variability. Participants were instructed to keep their eyes fixed on the cross while they completed the visual search and to respond as quickly as possible. Participants then indicated by typing on the keyboard whether it was a "K" or a "Z" in the display, followed by whether they had seen a target digit in the RSVP stream by typing "Y" if they had, and "N" if they had not. If a digit was correctly detected in the RSVP stream, participants then typed on the keyboard which number they saw. Accuracy throughout the task was recorded. Participants wore headphones through which a "ding" sound was played after a correct response and a chord sound was played after an incorrect response.

On 50% of the trials the visual search display was a "pop-out" visual search, in which the distractors were all the letter "P", allowing the target to "pop-out" to the participant. On 50% of the trials the visual search display was a "serial" visual search, in which all distractor letters were unique prompting a serial search. To manipulate the cost of switching, the position of the target in the RSVP stream that preceded the visual search was either the first item in the stream (Target 1st), which behaved as a no-switch condition, or the target was either the seventh, eighth or ninth item in the stream (Target Mid) or absent from the stream (Distractor Only), which both behaved as switch conditions. Illustrations of the RSVP stream and of the visual search display are presented in **Figure 1**.

There were 30 trials of each of the six conditions (Pop-out search: Target 1st/Target Mid/Distractor Only; Serial search: Target 1st/Target Mid/Distractor Only), with a total of 180 trials. To provide the opportunity for breaks, trials were divided into 10 blocks. Trials were randomized within blocks. Participants completed 10 practice trials before starting the experimental trials. One participant from the 40–49 years group, one from the 50–59 years group, five from the 60–69 years group and 11 from the 70+ years group required an additional 10 practice trials.

Useful Field of View Task

The Useful Field of View task (UFOV; Ball et al., 1988) was administered to measure processing speed, selective attention and divided attention. The UFOV consists of three sub-tasks on the computer, where the stimulus presentation duration begins at 500 ms and reduces to 16.7 ms until the participant achieves less than 75% accuracy. The shortest presentation duration at which the participant achieves 75% accuracy is recorded as the participant's processing speed threshold in each of the tasks.

On the processing speed task, either a picture of a car or a picture of a truck was presented in the center of the screen. Participants then indicated whether the image presented to them was a car or a truck. The divided attention task was the same as the processing speed task with the addition of the simultaneous presentation of a peripheral stimulus, which was also either a car or a truck. Participants both identified the item presented in the center of the screen and the location of the peripheral stimulus. The selective attention task was the same as the divided attention task with the addition of distractor stimuli simultaneously presented surrounding the two target stimuli. A full description of the UFOV has been described previously by Ball et al. (1993).

Random Number Generation task

The RNG (Towes and Neil, 1998) was administered to measure executive functions. For 2 min, participants were played a

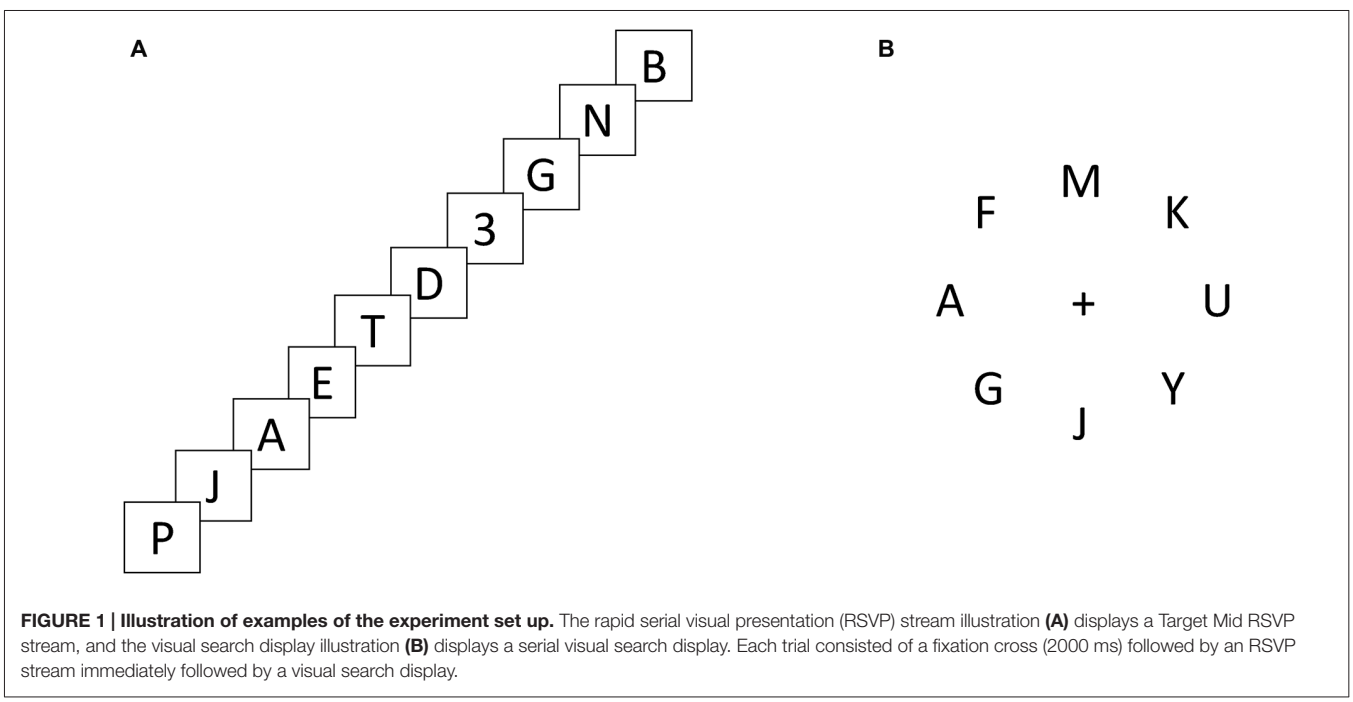

FIGURE 1 | Illustration of examples of the experiment set up. The rapid serial visual presentation (RSVP) stream illustration **(A)** displays a Target Mid RSVP stream, and the visual search display illustration **(B)** displays a serial visual search display. Each trial consisted of a fixation cross (2000 ms) followed by an RSVP stream immediately followed by a visual search display.

metronome beat at 60 beats per minute and called aloud random numbers from 1 to 9 in time with the beat. Random was defined using Horne et al.'s (1982) hat analogy.

Towes and Neil (1998) software, Rgcalc, was used to calculate measures of randomness. In accordance with Miyake et al. (2000) Principal Components Analysis, Evans' (1978) *RNG score*, a measure of how frequently number pairs/triplets occurred, was selected to measure inhibition, and *Redundancy* (R), a measure of how frequently each number occurred, was selected to measure updating. Lower scores on each measure indicates poorer randomization.

Data Analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS 21).

Attention Switching Task

Participants' median visual search RTs (ms) on trials where responses were correct on both the visual search and RSVP tasks were extracted using E-Prime data viewing application E-DataAid. Participants' proportions of correct visual search target identifications, RSVP target detections, RSVP target identifications and correct responses on the RSVP task on the Distractor Only condition were also extracted.

Older adults display higher proportions of false positive responses than younger individuals (Kenemans et al., 1995; Bolton and Staines, 2012). D prime (D′) was used as an unbiased measure of RSVP target detection sensitivity, as has been done in previous work on visual attention in the aging population (Parasuraman et al., 1989; Mouloua and Parasuraman, 1995; Berardi et al., 2001). Differences between age groups and RSVP conditions in both RSVP target detection and target identification were analyzed in two 2 × 5 mixed ANOVA, with RSVP condition (Target Mid/Target 1st) as a within subjects factor, and age group (21–30/40–49/50–59/60–69/70+ years) as a between subjects factor.

Differences in median visual search RTs between age groups, visual search conditions and RSVP conditions were analyzed in a 2 × 3 × 5 mixed ANOVA, where within subject factors were visual search condition (serial/pop-out) and RSVP condition (Distractor Only/Target Mid/Target 1st), and age group (21–30, 40–49, 50–59, 60–69, 70+ years) was a between subjects factor. Multiple comparisons were corrected for with Bonferroni correction.

The data were expected to violate assumptions of equality of variance due to increases in inter-individual variability with age (Hale et al., 1988; Morse, 1993). There is evidence to support that the ANOVA is robust to violations to homogeneity of variance (Budescu and Appelbaum, 1981; Budescu, 1982). Levene's test for equality of variance is therefore not reported.

To further explore the interactions between independent variables that were identified from the ANOVA on RSVP accuracy, independent *t*-tests were implemented to compare age groups on target identification separately for Target Mid and Target 1st RSVP conditions.

To further explore the interactions between independent variables that were identified in the RT ANOVAs, percentage differences between conditions were calculated for each individual and independent *t*-tests were implemented to compare age groups' percentage differences in RTs. It is important to note that *t*-tests were exploratory rather than hypothesis driven, and hence Restricted Fisher's Least Significant Difference test was applied and corrections for multiple comparisons were not conducted (Snedecor and Cochran, 1967). Where Levene's test for equality in variance was significant ($p < 0.05$) when computing *t*-tests, "Equality of variance not assumed" statistics were reported.

Cognitive Measures

The relationship between switch-costs and each cognitive measure, including UFOV subtasks processing speed, divided attention and selective attention and RNG indices for updating (R) and inhibition (RNG), and the relationship between each UFOV subtask and pop-out search RTs on the Target 1st condition, were explored with Spearman's correlation analyses. It should be noted that correlations were exploratory and corrections for multiple comparisons were not conducted.

RESULTS

Attention Switching Task

One participant in the 60–69 years group was excluded from the attention switching task analyses due to achieving chance level visual search accuracy in several conditions, including the Distractor Only pop-out search condition (mean = 0.40), the Target Mid pop-out search condition (mean = 0.53), and the Target Mid serial search condition (mean = 0.57). The participant's low proportion of correct visual search responses indicates that they may not have understood the task. One participant from the 70+ years group was excluded from RT analyses due to poor visual search and RSVP target identification, resulting in less than one third of serial search trials remaining in the Target 1st condition. Nineteen participants remained in the 70+ years group in the RT analysis and there were 20 participants in 60–69 years group in the remaining analysis.

RSVP Accuracy

Both the ability to detect targets in the RSVP stream and the proportion of correctly identified targets, where the participant correctly reported the target digit, were examined. Poor target detection would suggest that participants have a deficit in temporal selective attention. Group differences in target identification and not target detection may indicate a deficit in consolidation or recall of the target. Thus, distinguishing between correctly detected and identified targets could reveal specific age-related deficits in different cognitive processes.

Target Detection

A 2 × 5 (RSVP condition × age group) ANOVA was conducted on measures of D′, an index of target detection sensitivity. D′ provides a measure of detection sensitivity while controlling for false positive response rates, which has been shown to be inflated in older participants (Kenemans et al., 1995; Bolton and

Staines, 2012). D′ has previously been used as a measure of target sensitivity in work on visual attention in the ageing population (Parasuraman et al., 1989; Mouloua and Parasuraman, 1995; Berardi et al., 2001). D′ for each RSVP condition are presented for each age group in **Figure 2**.

There were significant main effects of age ($F_{(4,95)}$ = 9.04, $p < 0.001$, η_p^2 = 0.28) and RSVP condition ($F_{(4,95)}$ = 43.55, $p < 0.001$, η_p^2 = 0.31) on D′. There was no significant interaction between age and RSVP condition ($p > 0.10$).

Main effect of age

Post hoc comparisons revealed that the main effect of age on detection sensitivity resulted from greater detection sensitivity in the 21–30 years group in comparison to the 50–59 (p = 0.036), 60–69 ($p < 0.001$) and 70+ years ($p < 0.001$) groups. The 40–49 years group displayed a significantly higher detection sensitivity than the 60–69 (p = 0.005) and 70+ years groups (p = 0.001). There were no other significant group differences in detection sensitivity ($p > 0.10$).

No further analysis was carried out on D′. Age differences in target detection suggest that difficulties derive from declines in selective attention that will similarly affect RSVP target identification, as is evident in **Figure 2**. Instead, target identifications were examined in more depth.

Target Identification

Figure 2 illustrates a decrease in target identification with increased age. A 2 × 5 (RSVP condition × age group) mixed ANOVA was conducted on the proportion of correctly identified RSVP targets.

There was a significant main effect of age ($F_{(4,95)}$ = 9.06, $p < 0.001$, η_p^2 = 0.28) and RSVP condition ($F_{(1,95)}$ = 43.40, $p < 0.001$, η_p^2 = 0.31) on RSVP target identification, as well as a significant age × RSVP condition interaction ($F_{(4,95)}$ = 3.15, p = 0.018, η_p^2 = 0.12).

Main effect of age

It was hypothesized that the 70+ years age group would identify fewer targets in comparison to younger groups but that there would be no difference in the proportion of targets identified in the 60–69 years age group. *Post hoc* comparisons showed that the main effect of age resulted from the 21–30 years group identifying significantly more RSVP targets than the 50–59 (p = 0.017), 60–69 (p = 0.001) and 70+ years ($p < 0.001$) groups. The 40–49 years group identified significantly more targets than the 70+ years group (p = 0.002). The higher target identification in the 40–49 years group in comparison to the 60–69 years group did not reach significance (p = 0.078). There were no other significant group differences in target identification ($p > 0.10$).

Main Effect of RSVP Condition

The main effect of RSVP condition resulted from participants identifying more targets in the Target 1st than the Target Mid condition.

Interaction between age and RSVP Conditions

To further explore the interaction between age group and RSVP condition on target identification independent t-tests were implemented to compare age groups on RSVP target identification on each RSVP condition separately.

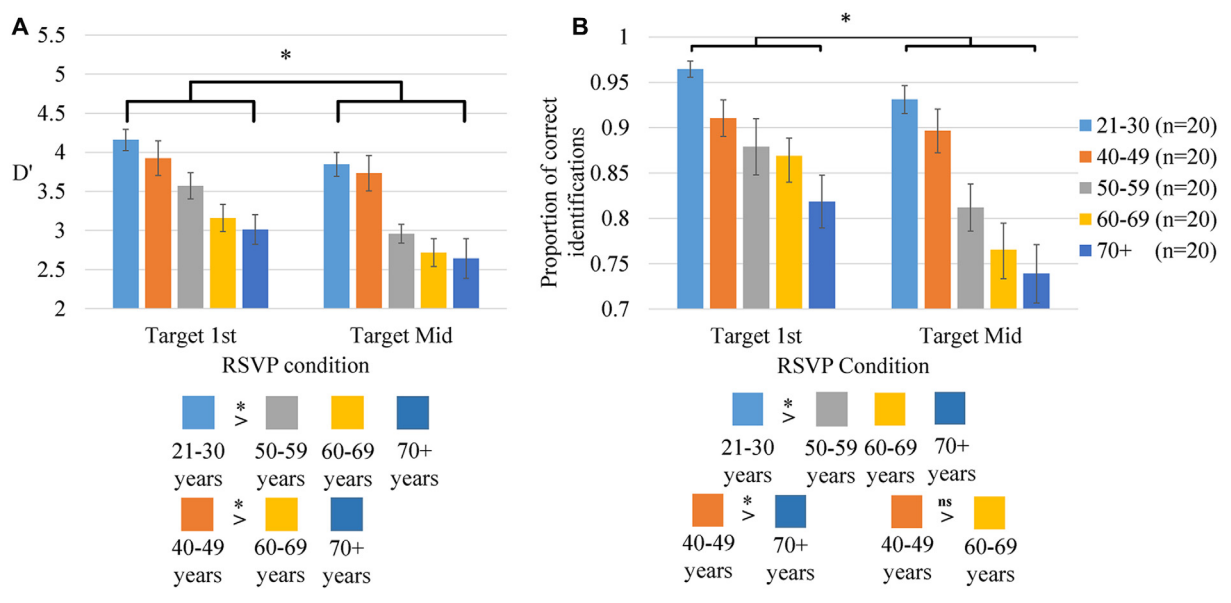

FIGURE 2 | RSVP Accuracy. An index of RSVP target detection sensitivity, D′ **(A)** and the proportion of correctly identified RSVP targets **(B)** in each RSVP condition for each age group. The asterisk above each graph represents significant differences between RSVP conditions, collapsed across age groups. The color coded boxes below each graph illustrate significant age group differences collapsed across RSVP conditions. Vertical bars represent the standard error of the mean.

In the Target 1st condition, the 21–30 years group identified significantly more targets than the 40–49 ($t_{(26.24)}$ = 2.46, p = 0.021), 50–59 ($t_{(22.14)}$ = 2.65, p = 0.015), 60–69 ($t_{(26.77)}$ = 4.49, $p < 0.001$) and 70+ ($t_{(22.54)}$ = 4.79, $p < 0.001$) years groups, and the 40–49 years group identified more targets than the 70+ years group ($t_{(38)}$ = 2.60, p = 0.013).

In the Target Mid condition, the 21–30 years group identified significantly more targets than the 50–59 ($t_{(38)}$ = 3.93, $p < 0.001$), 60–69 ($t_{(28.76)}$ = 5.00, $p < 0.001$) and 70+ ($t_{(27.31)}$ = 5.39, $p < 0.001$) years groups, the 40–49 years group identified significantly more targets than the 50–59 ($t_{(38)}$ = 2.38, p = 0.022), 60–69 ($t_{(38)}$ = 3.45, p = 0.001) and 70+ ($t_{(38)}$ = 3.92, $p < 0.001$) years groups, and there was a non-significant trend for the 50–59 years group to identify more targets than the 70+ years group ($t_{(38)}$ = 1.77, p = 0.086).

Visual Search

All groups correctly identified over 94% of visual search targets in all six conditions. Thus, no further analysis was carried out on visual search accuracy.

A 2 × 3 × 5 (visual search condition × RSVP condition × age group) mixed ANOVA was conducted with participants' median RTs. Mauchly's Test of Sphericity was significant for RSVP condition ($\chi^2_{(2)}$ = 8.56, p = 0.014) indicating that the assumption of sphericity has been violated. Greenhouse-Geisser corrected statistics were therefore reported. Mean visual search RTs for each age group for serial and pop-out searches are presented in **Figure 3**.

Significant main effects of age ($F_{(4,94)}$ = 13.39, $p < 0.001$, η^2_p = 0.36), visual search condition ($F_{(1,94)}$ = 335.17, $p < 0.001$, η^2_p = 0.78), and RSVP condition ($F_{(1.84,172.80)}$ = 133.57, $p < 0.001$, η^2_p = 0.59) on visual search RTs were revealed, in addition to a significant age × visual search condition interaction ($F_{(4,94)}$ = 4.98, p = 0.001, η^2_p = 0.18), a significant age × RSVP condition interaction ($F_{(7.35,172.80)}$ = 2.72, p = 0.009, η^2_p = 0.10), and a significant visual search condition × RSVP condition interaction ($F_{(1.99,187.19)}$ = 5.37, p = 0.005, η^2_p = 0.05). There was no significant age × visual search condition × RSVP condition interaction ($p > 0.10$).

Main effects of age

Based on widely acknowledged age-related slowing of RTs, RTs were expected to increase with increased age (Salthouse, 1985, 2000; Foster et al., 1995). *Post hoc* comparisons illustrated that the 21–30 years group was significantly faster than the 50–59 (p = 0.024), 60–69 ($p < 0.001$) and 70+ ($p < 0.001$) years groups, but not the 40–49 years group ($p > 0.10$). The 70+ years group was slower than both the 40–49 (p = 0.001) and 50–59 years groups (p = 0.004). There were no other significant group differences in RT ($p > 0.10$).

Main effects of visual search condition

Participants were significantly faster on the pop-out in comparison to serial visual search.

Main effects of RSVP condition

We hypothesized that RTs would be faster on the no-switch (Target 1st) condition, when participants no longer need to attend to the RSVP stream after identifying the target digit, in comparison to when they are required to attend to the RSVP stream to the end of the stream in the two switch conditions (Target Mid/Distractor only). The main effect of RSVP condition on visual search RTs resulted from significantly faster RTs on the Target 1st condition in comparison to both the Distractor Only ($p < 0.001$) and Target Mid ($p < 0.001$) conditions. There was no significant difference between the Distractor Only and Target Mid conditions ($p > 0.10$).

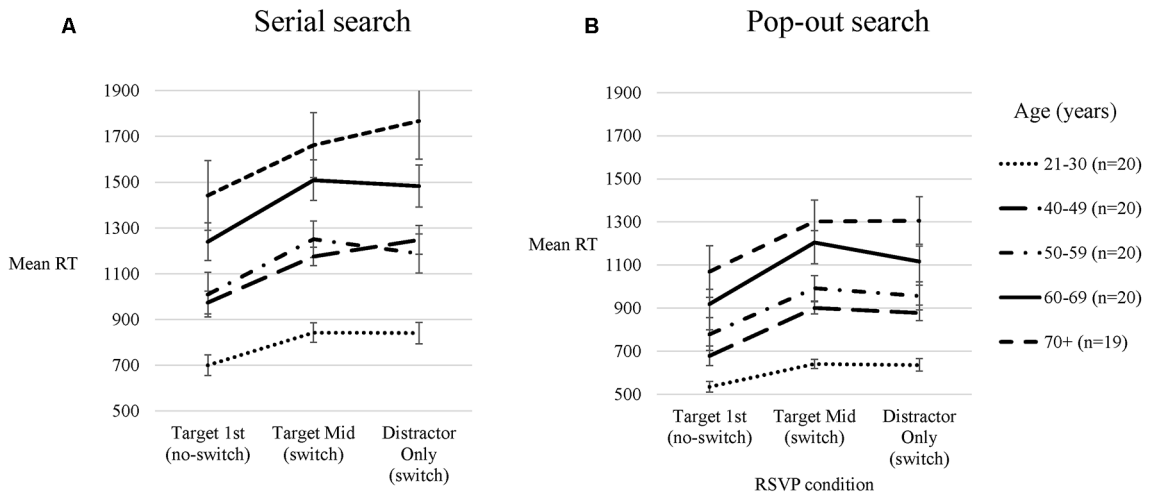

FIGURE 3 | Visual search response times (RTs). Means of participants' median visual search RTs for each RSVP condition for each age group on serial **(A)** and pop-out **(B)** visual searches. Vertical bars represent the standard error of the mean.

Interaction between age and visual search conditions

It is well established that older participants display deficits in serial but not in pop-out visual searches (Plude and Doussardroosevelt, 1989; Foster et al., 1995; Humphrey and Kramer, 1997; Bennett et al., 2012; Li et al., 2013). It was hypothesized that the increase in RTs on serial in comparison to pop-out search would be greater in older than younger groups. In support of this hypothesis, there was a significant age × visual search condition interaction. To investigate this hypothesis further, the percentage increase in RTs from the pop-out to serial search, collapsed across RSVP conditions, was calculated and entered into independent *t*-tests to compare groups. To collapse visual search RTs across RSVP conditions separately for serial and pop-out search RTs, each participant's median RTs was averaged across RSVP conditions separately for the pop-out search RTs and the serial search RTs. The mean percentage increase in RTs from pop-out to serial search is presented in **Table 3**.

Independent *t*-tests revealed that there was a significantly larger difference between serial and pop-out search RTs in the 40–49 years than the 50–59 ($t_{(38)} = 2.89$, $p = 0.007$). The larger difference between pop-out and serial search RTs in the 40–49 years group in comparison to the 21–30 ($t_{(38)} = -1.85$, $p = 0.072$), 60–69 ($t_{(38)} = 1.80$, $p = 0.080$) and 70+ ($p > 0.10$) years groups did not reach significance. There were no further significant group differences in the percentage increase in RT from pop-out to serial search ($p > 0.10$).

Interaction between age and RSVP conditions

It was hypothesized that there would be greater difficulties in switching between the temporal and spatial attention tasks with increased age. To investigate the hypothesis that switch-costs would be greater with increased age, the interaction between age and RSVP condition was further explored. Each participant's percentage increases in RTs from the no-switch (Target 1st) condition to each of the switch conditions (Target Mid/Distractor Only) were calculated as measures of switch-costs. Collapsing visual search conditions to calculate switch-costs lead to finding no significant age group differences in switch-costs ($p > 0.10$). Thus, although there was no three-way interaction between age, visual search condition and RSVP condition ($p > 0.10$), switch-costs were calculated separately for serial and pop-out search RTs to gain a detailed understanding of the interaction between age and RSVP conditions. The resulting measures of switch-costs were entered into independent *t*-tests to compare groups. It is important to note that *t*-tests were exploratory, however, remain in the scope of current hypotheses. The means and standard deviations of each group's switch-costs on serial search and pop-out search RTs are presented in **Table 4**.

The percentage increase in pop-out search RTs from the Target 1st to Target Mid condition were significantly greater for both the 40–49 ($t_{(38)} = -2.39$, $p = 0.022$) and 60–69 years groups in comparison to the 21–30 years group ($t_{(38)} = -2.28$, $p = 0.028$). The greater switch-costs in the 50–59 years group in comparison to the 21–30 years groups did not reach significance ($t_{(38)} = -1.73$, $p = 0.091$). There were no significant differences in switch-costs between any other age groups for either visual search condition ($p > 0.10$).

Interaction between visual search conditions and RSVP conditions

No further analysis was carried out on the interaction between RSVP condition and visual search condition, as it is unrelated to the current hypotheses.

Cognitive Function

The cognitive mechanisms that underpin switching between modalities of attention were explored. Mean scores on UFOV processing speed, divided attention and selective attention, and the RNG index (inhibition) and R (updating) scores (Miyake et al., 2000) can be found in **Table 5**.

The Relationship between Switch-Costs and Cognition

To identify cognitive functions that may affect switching ability, the relationships between switch-costs and cognitive measures were examined separately for each age group. Relationships were examined only for switch-costs in the target-switch pop-out search condition, as it was in this condition only that age group differences were found. Shapiro Wilks test of normality demonstrated that the distribution of scores from all cognitive measures except the RNG index violated the assumption of normality for one or more age groups ($p < 0.05$). Spearman's rho correlation coefficients are therefore reported, which can be found in **Table 6**. Correlation strengths are interpreted based on Cohen (1992, 1988). It should be noted that correlations were exploratory and corrections for multiple comparisons were not conducted.

UFOV Processing Speed

There was a significant negative moderate correlation between switch-costs and UFOV processing speed in the 60–69 years group ($p = 0.033$). Those with greater switch-costs displayed faster processing speeds. The correlation between switch-costs

TABLE 3 | Means and standard deviations of the percentage difference from Pop-out to Serial search RTs for each group.

		Age Group (years)				
		21–30 (*n* = 20)	40–49 (*n* = 20)	50–59 (*n* = 19)	60–69 (*n* = 20)	70+ (*n* = 20)
Percentage Difference	Mean	21.68	27.21	19.21	22.65	23.17
	SD	11.01	7.61	9.95	8.41	8.58

Percentage difference indicates the percentage increase in serial search RTs in comparison to pop-out search RTs.

TABLE 4 | Means and standard deviations of switch-costs for each age group.

			Age group (years)				
			21–30 (*n* = 20)	40–49 (*n* = 20)	50–59 (*n* = 19)	60–69 (*n* = 20)	70+ (*n* = 19)
Serial	Target mid	Mean	16.46	16.21	17.41	18.48	13.22
		SD	11.36	12.68	12.48	12.39	14.63
	Distractor	Mean	15.94	20.65	12.78	16.30	18.15
	Only	SD	13.26	10.85	21.23	14.33	12.68
Pop-out	Target mid	Mean	15.39	23.89	21.51	23.33	18.44
		SD	11.57	10.87	10.75	10.41	9.71
	Distractor	Mean	16.78	21.44	16.78	16.75	17.61
	Only	SD	8.48	10.01	15.03	13.28	11.84

Switch-costs were calculated as the percentage increase in RT from the no-switch (Target 1st) condition to each of the switch conditions (Target Mid/Distractor Only) separately and separately for each visual search condition.

and processing speed did not reach significance in the 50–59 years group ($p = 0.083$). There were no other significant correlations between switch-costs and processing speed ($p > 0.10$).

UFOV Divided Attention

In the 50–59 years group there was a significant negative moderate correlation between switch-costs and UFOV divided attention ($p = 0.027$). Those with greater switch-costs performed better on the UFOV divided attention task (i.e., had faster processing thresholds). There were no other significant correlations between UFOV divided attention and switch-costs in any other age group ($p > 0.10$).

UFOV Selective Attention

There was a significant negative strong correlation between switch-costs and UFOV selective attention in the 50–59 years group ($p < 0.001$) and a non-significant negative moderate correlation between switch-costs and selective attention in the 60–69 years groups ($p = 0.061$). Participants with greater switch-costs had faster processing thresholds in the selective attention task. There were no other significant correlations between UFOV selective attention and switch-costs in any other age group ($p > 0.10$).

The direction of the relationship between switch-costs and performance on processing speed, divided attention and selective attention UFOV tasks was unexpected, as poor performance on the UFOV tasks was related to smaller switch-costs. These findings may be explained by a significant positive correlation between visual search RTs in the Target 1st condition and UFOV on processing speed ($r = 0.445$, $p < 0.001$, $n = 99$), divided attention ($r = 0.592$, $p < 0.001$, $n = 99$) and selective attention ($r = 0.577$, $p < 0.001$, $n = 99$). Those who perform poorly on the UFOV tasks have slower visual search RTs on the Target 1st condition. Slow RTs on the Target 1st condition result in smaller switch-costs, as the difference between switch and no-switch conditions becomes smaller.

RNG Task

There were no significant correlations between switch-costs and RNG measures R or RNG in any age group ($p > 0.10$).

DISCUSSION

The aim of the current study was to investigate whether there is an age-related decline in the ability to switch between temporal and spatial attention and to explore the cognitive mechanisms that might underpin these changes. Identifying age-related cognitive changes that affect driving behavior is an important first step in working towards developing a cognitive intervention to improve driving performance and prolong the length of time that people are able to continue to drive.

There were decreases in both RSVP target detection sensitivity and target identification with increased age. Deficits in target identification but not target detection would suggest that group differences are related to memory and not temporal attention. Results therefore indicate that older participants' impaired performance derives from temporal attention mechanisms and results are not due to memory difficulties. It was hypothesized that there would be age-related difficulties in target identification in the 70+ years age group but not the 60–69 years age group. On the contrary, the 21–30 years group identified more targets than all other age groups in both the Target 1st condition and the Target Mid condition. Age group differences were more extensive in the Target Mid condition in comparison to the Target 1st condition, and significantly fewer targets were identified in the Target Mid condition in comparison to the Target 1st condition overall. Poorer target identification in the Target Mid condition likely results from the presence of distractor stimuli both forward and backward masking Target Mid targets, whereas Target 1st targets were only backward masked. It is likely that the effect of distractors masking the target was further exacerbated by older adults' inhibitory deficits (Adamo et al., 2003; Maciokas and Crognale, 2003).

Consistent with previous research and with expectations, RTs were slower on serial than pop-out searches (Wolfe, 1998). These findings are due to attention being immediately drawn to the distinct target in pop-out searches, in contrast to when needing to complete a serial search (Treisman, 1985). Consistent with age-related slowing of RTs (Salthouse, 2000; Verhaeghen and Cerella, 2002), and supporting current hypotheses, there was an age-related increase in visual search RTs.

TABLE 5 | Means and standard deviations for cognitive measures.

		Age group (years)				
		21–30 (*n* = 20)	**40–49 (*n* = 20)**	**50–59 (*n* = 20)**	**60–69 (*n* = 21)**	**70+ (*n* = 21)**
Updating (R)	Mean	1.41	1.45	1.06	1.22	1.08
	SD	1.78	1.07	0.81	0.52	0.71
Inhibition (RNG)	Mean	0.33	0.34	0.32	0.34	0.36
	SD	0.03	0.50	0.05	0.03	0.04
Processing speed	Mean	16.72	16.70	21.54	25.44	22.54
	SD	0.07	0.00	9.53	23.38	13.37
Divided attention	Mean	24.22	39.05	58.20	49.26	79.04
	SD	31.30	53.87	63.24	51.25	76.34
Selective attention	Mean	54.39	101.36	127.08	151.50	186.06
	SD	28.97	59.55	58.57	87.36	87.37

One participant in the 70+ years group did not complete the UFOV, resulting in 20 participants in this group for the processing speed, divided attention and selective attention measures.

A greater increase in RTs from pop-out to serial search in the 40–49 years group in comparison to both younger and older groups was unexpected and contrasts with previous findings. Age-related deficits in serial but not pop-out search are well established (Plude and Doussardroosevelt, 1989; Foster et al., 1995; Humphrey and Kramer, 1997; Bennett et al., 2012; Li et al., 2013). The absence of greater differences between visual search conditions in the older groups may be due to ceiling effects, with slow RTs in both visual search conditions. In contrast, RTs on the pop-out search in the 40–49 years group remain fast and result in a larger percentage increase in RT from the pop-out to serial search.

Consistent with predictions, RTs were faster when switching from the RSVP task when the target was the first item in the stream in comparison to when the target was absent or in the middle of the stream. This can be attributed to larger switch-costs when attending to the RSVP stream to near the end of the stream than when able to disengage from the stream. These finding show that costs in switching from the temporal attentional task cause a delay to initiating a visual search.

Larger switch-costs in the 40–49 and 60–69 years groups in comparison to the youngest group for the Target Mid condition only partially supports the hypothesis that there would be increased switch-costs with age. Greater age-related switch-costs in only the 40–49 and 60–69 years age groups raises the question of why the 70+ years groups did not also display greater switch-costs in comparison to the youngest group and why the larger switch-costs in the 50–59 years group in comparison to the youngest group did not reach significance. RTs in the 40–49 years group were not significantly slower than RTs in the youngest group. It may be that fast RTs in the Target 1st condition are inflating the switch-costs in the 40–49 years group, as the percentage increase in RTs when they have to switch is greater. In contrast, switch-costs in the 50–59 years group are partially masked by their slow RTs in the Target 1st condition.

The question remains as to why greater switch-costs are seen in the 60–69 years and not in the 70+ years group. One explanation may be that the oldest group have developed efficient compensation strategies that are not yet present in the 60–69 years group. It may become necessary to adapt new strategies and recruit wider neural networks with older age due to increasingly impaired attentional and switching mechanisms combined with slowed RTs, whereas faster RTs in younger participants are sufficient to compensate for impaired switching. The recruitment of broader neural circuits with increased age is widely supported (Toepper et al., 2014), including in frontoparietal regions during attentional tasks (Madden et al., 2007), although it is unclear whether wider activation is due to compensation (Madden, 2007; Madden et al., 2007) or increased noise due to deficits in inhibitory mechanisms (Fabiani et al., 2006; Gazzaley et al., 2008). This raises the possibility that greater switch-costs were not seen in the 70+ years group due to increased variability in RTs masking switch-costs. Increased variability masking greater switch-costs in the 70+ years age group is supported by the increased variability observed with age in the current data.

TABLE 6 | Spearman's rho correlation coefficients, correlating cognitive measures with switch-costs.

	Age group (years)				
	20–39 (*n* = 20)	**40–49 (*n* = 20)**	**50–59 (*n* = 20)**	**60–69 (*n* = 20)**	**70+ (*n* = 19)**
R	−0.03	−0.23	−0.03	0.13	−0.01
RNG	−0.16	−0.32	0.29	0.21	−0.14
Processing speed	−0.06	–	**−0.40**	**−0.49***	0.14
Divided attention	0.22	0.04	**−0.50***	0.07	−0.12
Selective attention	−0.17	0.12	**−0.73*****	**−0.43**	0.02

*$p < 0.05$, ***$p < 0.001$; Updating (R), inhibition (RNG).*

A common limitation in aging research is self-selection bias. Older volunteers tend to be healthy, highly educated people who seek to stay active in later life. Both a physically, socially and cognitively active lifestyle, and higher levels of education and occupation have been shown to be protective factors against cognitive decline (Anstey and Christensen, 2000; Fratiglioni et al., 2004; López et al., 2014) and aspects of lifestyle such as level of education, video gaming habits and employment status have been shown to predict performance in visual attention tasks (Wilms and Nielsen, 2014). Thus, sample attributes may result in switch-costs in the 60–69 but not 70+ years, where there is less of a bias towards healthy, highly motivated people. However, the 70+ years group did not display a significantly higher level of education and did not perform better on the ACE-3, which is a basic measure of cognitive function.

As a third alternative, the difference between switch and no-switch conditions may have been reduced in the 70+ years group due to participants taking longer to process the Target 1st target and/or taking longer to disengage attention from the RSVP stream in the no-switch condition due to difficulties in inhibiting distractor stimuli. In both scenarios, visual search RTs in the no-switch condition would be inflated, reducing the difference between switch and no-switch conditions. These explanations would be consistent with increased visual processing speeds with increased age (Ball et al., 2006; Rubin et al., 2007) and with evidence that suggests that temporal attention is impaired only in those over the age of 70 years and not in those aged 60–69 years (Lee and Hsieh, 2009; Shih, 2009), explaining why increases in switch-costs are seen in the 60–69 years group and not the 70+ years group. This explanation would also account for the surprising findings of increased switch-costs with faster processing speed thresholds in the UFOV processing speed and selective attention tasks that were seen in both the 50–59 and 60–69 years groups. This relationship was in the opposite direction to expectations. To perform well on the UFOV selective attention task, one is required to inhibit irrelevant distractors across the screen to selectively attend to the target. Thus, inhibitory deficits seem to be resulting in both a smaller difference between no-switch and switch conditions, due to difficulties in disengaging from the RSVP stream, and longer processing speeds in the UFOV selective attention task. However, it is important to note that correlation analyses were exploratory and corrections for multiple comparisons were not conducted. Further research with larger sample sizes is needed to corroborate these findings.

However, switch-costs did not correlate with the RNG index, which is a measure of inhibition. This may be because inhibitory mechanisms implemented in the RNG task to inhibit repetition and number sequences are separate from those involved in inhibiting visual distractors. Excitatory-inhibitory competition in the visual cortex is involved in selectively attending visual information (Beck and Kastner, 2009; Reynolds et al., 1999), whereas inhibition during the RNG task is likely to involve the inhibition of response in working memory localized to the prefrontal cortex (Daniels et al., 2003). This conclusion is supported by Madden et al. (2007) who, in a serial visual search task, found that whereas young adults' performance was associated with occipital lobe activation, older adults' performance was more strongly related to frontal and parietal activity. These findings are consistent with a specific decline in serial search performance with age caused by deficits in excitatory-inhibitory mechanisms during visual processing.

Age differences in switch-costs in the Target Mid condition and not in the Distractor Only condition are likely due to the requirement to consolidate the RSVP target. It could be that increased switch-costs in this condition are due to slow processing speeds resulting in participants taking longer to process the target, which delays the switch to allocate attention spatially. On the contrary, fast processing speeds were related to increased switch-costs. Current findings therefore suggest that deficits in switching between temporal and spatial attention were not due to general slowing.

The current results support Lee and Hsieh (2009) findings of an age-related increase in difficulties in switching from attending to an RSVP stream to identify a target, to allocating attention in space to identify and point to a masked peripheral target. However, Lee and Hsieh (2009) aim was to investigate the attentional blink in older adults, and thus does not distinguish between impaired task performance resulting from an increased attentional blink, or due to deficits in switching between temporal and spatial attention. The inclusion of the Distractor Only condition in the current task enabled the investigation of whether age-related deficits in switching were due to increases in the time taken to switch between attentional mechanisms or an increased attentional blink. If there was a deficit in switching between attentional mechanisms, then older adults should be impaired in switching in both the Distractor Only and Target Mid conditions when compared with younger adults. Conversely, the current findings of increased switch-costs in the Target Mid condition only indicate that higher switch-costs may result from an increased attentional blink after processing the RSVP target. However, **Figure 3** could also indicate that increased variability in the Distractor Only condition may have prevented group differences from emerging (e.g., 70+ group). Despite attempts to minimize variability in RTs by using an initial space-bar response, high variability masking differences in statistical power is corroborated by generally increased variability in RTs with increased age in the current dataset. The absence of a significant difference in RTs between the Distractor Only condition and the Target Mid condition further supports that group differences in switch-costs in the Distractor Only condition were not seen due to variability in RTs masking differences in statistical power.

Further work is required to explore how age-related declines in switching translate to driving behavior. It may be that difficulties in switching between temporal and spatial attention cause difficulties in switching from attending to traffic on the road ahead to attend to road signs and other surrounding objects. The current authors are presently

exploring how attention switching predicts simulated driving performance. Previous work has shown that age-related difficulties in selective attention affect driving ability in some older drivers but not others (Vaucher et al., 2014). It may be that similarly, difficulties in switching between modalities of attention negatively affect the performance of some drivers but not others. If difficulties in switching are found to affect driving performance, then it will be important to develop an intervention to improve switching between modalities of attention to help improve driver performance and safety. Long-term, this will prolong the time that older drivers can continue to drive and help to preserve their independence.

Limitations

In contrast to previous visual search paradigms (Humphrey and Kramer, 1997; Li et al., 2013), participants were required to make an initial space-bar response to indicate that they had identified the target and then report which letter they had seen. A limitation of this approach is that participants may modify their decision after they have made a response with the aid of visual memory. It is not known whether the ability to adopt this strategy is greater in young adults than older adults. However, the opportunity to implement this strategy was present in both switch and no-switch trials and therefore should not have affected our main findings.

A further limitation of the current paradigm is that we did not explore how switching affects the ongoing visual search processes, as the number of distractor stimuli in the visual search display was not manipulated. In the current paradigm we were interested in the efficiency of switching to initiate a search. Further research is required to investigate how switching influences ongoing search processes. It may be that switching has a large effect on search speed at the beginning of a search but the effect on search speed plateaus with increasing numbers of distractors, as time since the switch increases. Furthermore, it may be that this switch-cost is not specific to switching between types of attention, but would also affect performance in other cognitive functions. Although it is switching between temporal and spatial attention that is important to driving, where declines in efficiency may have a negative impact on a person's life, this difficulty may generalize to other tasks. This is an important question to ask when developing an intervention.

The 40–49 and 50–59 years age groups were intended as middle-age comparison groups for the two oldest age groups and the 21–30 years group was intended as a comparison group for all other age groups. The finding of higher switch-costs in the 40–49 years group was unexpected, particularly as no differences in RTs were found between the 21–30 and 40–49 years groups. Future research would benefit from also including a 30–39 years age group in order to obtain a view of how the ability to switch between attentional mechanisms changes throughout the adult lifespan.

It is well established that working memory capacity declines with healthy aging, including both verbal (Hultsch et al., 1992; Zacks et al., 2000) and visual (Faubert, 2002; Brockmole and Logie, 2013) short term memory. A limitation of the current study is that no measure of verbal or visual working memory capacity was taken to look at the influence of memory on switching. However, the strain on working memory is very low, as the participant is only required to hold a single item in memory (i.e., the RSVP target digit). It is therefore unlikely that difficulties in working memory would affect switching performance. Furthermore, Akyürek and Hommel (2005) found that working memory load did not interact with the duration of the attentional blink. Additionally, working memory load remains constant across both the no-switch and Target Mid switch conditions and so memory deficits should not have influenced our main findings.

Although age-related declines in working memory capacity are unlikely to have affected switching performance in the current task, it is possible that declines in executive function affected switching performance. In relation to Baddeley's (1992) working memory model, the current task would require the top-down control of attention from the central executive. It was therefore expected that measures of executive function would predict switching performance. However, measures of executive function obtained from the RNG did not correlate with task performance. It was found that there were no age group differences in RNG measures, despite age-related declines in executive function being widely acknowledged in the literature (Cepeda et al., 2001; Gamboz et al., 2009; Gold et al., 2010). It may be that RNG performance is too susceptible to interference from the use of alternative strategies, such as visualization techniques. Further research is needed to explore the relationship between executive function and switching between temporal and spatial attention to come to more sound conclusions.

A further limitation of the methodology is that eye tracking data were not recorded and participants' actual fixation was not controlled for to ensure that participants were focusing on the visual search fixation cross. Participants' failure to focus on the fixation cross could result in error in the measurements of RTs to complete the visual search. However, participants were instructed to keep their eyes fixed on the fixation cross, a protocol that is commonly used across cognitive paradigms (Humphrey and Kramer, 1997; Watson and Maylor, 2002; Li et al., 2013). Furthermore, participants' attention to the RSVP stream before the onset of the visual search display ensured that participants were focusing on the center of the screen at the beginning of each trial. Trials in which participants failed to correctly identify the target digit in the RSVP stream were excluded from RT analyses, which ensured that only trials in which participants were attending to the task were included in analyses.

Gender differences in the decline of certain attentional mechanisms have previously been found (Conlon and Herkes, 2008). The current study did not look at gender differences in age-related changes in switching ability as it was beyond the scope of the study. Future work could investigate whether there are any gender differences in the ability to switch between temporal and spatial attention in older age.

Conclusions and Future Directions

The hypothesis that there would be greater switch-costs in older than younger groups was partially supported, as people aged 40–49 and 60–69 years displayed greater switch-costs than those aged 20–29 years. There was also a non-significant trend for greater switch-costs in the 50–59 years group. Increased switch-costs in the 40–49 and 60–69 years groups but not the 70+ years groups was surprising. However, switching difficulties in the oldest group may have been masked by slow RTs on the Target 1st condition due to a failure to inhibit and disengage from the RSVP stream. This conclusion would explain the surprising findings of decreased switch-costs with slower selective attention processing speeds. Poor selective attention could mask switch-costs due to difficulties with inhibiting the remainder of the RSVP stream in the Target 1st condition resulting in slow RTs. Future studies investigating switching between temporal and spatial attention would benefit from including a condition that contains a target with no distractor stimuli.

Increased switch-costs in the Target Mid condition but not the Distractor Only condition indicates that increased switch-costs could result from either an increased attentional blink following RSVP target identification, which delays the allocation of attentional resources to the visual search, or increased variability in RTs in the Distractor Only condition.

The current authors are presently investigating whether age-related difficulties in switching affect driving performance. If difficulties in switching affect driving performance, then this cognitive process should be targeted in the development of interventions that aim to improve driver performance and safety. Long-term, this will prolong the time that older drivers can continue to drive.

AUTHOR CONTRIBUTIONS

EC contributed towards the design of the research, played a key role in data collection, data analysis and interpretation of the analysis, in addition to drafting and revising the written article and approving the final version to be published. CH contributed towards the conception and design of the work, to the data analysis and interpretation, in addition to contributing towards the critical revision of the article and approving the final version to be published. KK made a substantial contribution to the conception and design of the work, to the data analysis and interpretation, in addition to contributing towards the critical revision of the article and approving the final version to be published.

ACKNOWLEDGMENTS

This research was supported by funding from The Rees Jeffreys Road Fund and by the School of Life and Health Sciences at Aston University.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer DW declared a collaboration with one of the authors CH to the handling Editor, who ensured that the process met the standards of a fair and objective review.

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frontiers in Aging Neuroscience

REVIEW
published: 23 February 2017
doi: 10.3389/fnagi.2017.00033

Activating Developmental Reserve Capacity Via Cognitive Training or Non-invasive Brain Stimulation: Potentials for Promoting Fronto-Parietal and Hippocampal-Striatal Network Functions in Old Age

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OPEN ACCESS

Edited by:
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Received: *23 September 2016*
Accepted: *08 February 2017*
Published: *23 February 2017*

Citation:
Passow S, Thurm F and Li S-C (2017) Activating Developmental Reserve Capacity Via Cognitive Training or Non-invasive Brain Stimulation: Potentials for Promoting Fronto-Parietal and Hippocampal-Striatal Network Functions in Old Age. Front. Aging Neurosci. 9:33. doi: 10.3389/fnagi.2017.00033

Existing neurocomputational and empirical data link deficient neuromodulation of the fronto-parietal and hippocampal-striatal circuitries with aging-related increase in processing noise and declines in various cognitive functions. Specifically, the theory of aging neuronal gain control postulates that aging-related suboptimal neuromodulation may attenuate neuronal gain control, which yields computational consequences on reducing the signal-to-noise-ratio of synaptic signal transmission and hampering information processing within and between cortical networks. Intervention methods such as cognitive training and non-invasive brain stimulation, e.g., transcranial direct current stimulation (tDCS), have been considered as means to buffer cognitive functions or delay cognitive decline in old age. However, to date the reported effect sizes of immediate training gains and maintenance effects of a variety of cognitive trainings are small to moderate at best; moreover, training-related transfer effects to non-trained but closely related (i.e., near-transfer) or other (i.e., far-transfer) cognitive functions are inconsistent or lacking. Similarly, although applying different tDCS protocols to reduce aging-related cognitive impairments by inducing temporary changes in cortical excitability seem somewhat promising, evidence of effects on short- and long-term plasticity is still equivocal. In this article, we will review and critically discuss existing findings of cognitive training- and stimulation-related behavioral and neural plasticity effects in the context of cognitive aging, focusing specifically on working memory and episodic memory functions, which are subserved by the fronto-parietal and hippocampal-striatal networks, respectively. Furthermore, in line with the theory of aging neuronal gain control we will highlight that developing age-specific brain stimulation protocols and the concurrent applications of tDCS during cognitive training may potentially facilitate short- and long-term cognitive and brain plasticity in old age.

Keywords: aging, neuronal gain control, dopamine, fronto-parietal network, hippocampal-striatal network, cognitive training, transcranial electrical stimulation

INTRODUCTION

Normal aging is accompanied by alterations in multiple cognitive functions with negative consequences on various daily activities. Facing the historically unprecedented global challenge of demographic change, with larger populations of individuals older than 65 years than the populations of youths younger than 20 years (Harper, 2014), a crucial agenda of geronto-psychology and geronto-neuroscience is to develop interventions that could activate the reduced but still available cognitive and brain resources in old age to buffer and delay cognitive declines. Indeed, early investigations of cognitive plasticity in the elderly provided evidence for the concept of developmental reserve capacity, which illustrates the malleability of older adults' cognitive performance been enhanced by environmental supports (Baltes et al., 1986; Baltes, 1987). Results from neurocomputational studies and empirical research provide compelling support for a close link between neuromodulation and cognitive functions. For instance, neurocomputational studies have contributed to the current understandings of cholinergic (Sarter et al., 2014), serotoninergic (Dayan and Huys, 2009) and dopaminergic (Servan-Schreiber et al., 1990; Li et al., 2001; Montague et al., 2004) systems in regulating neuronal information transmissions and their computational consequences on cognition and behavior. Of particular relevance in the context of aging, the efficacy of the cholinergic (Ellis et al., 2009; Mitsis et al., 2009; Richter et al., 2014), serotoninergic (Wong et al., 1984; Yamamoto et al., 2002; Nord et al., 2014), and dopaminergic (see Bäckman et al., 2010; Li and Rieckmann, 2014 for reviews) modulations decline substantially during the course of normal aging. The computational theory of aging neuronal gain control (Li et al., 2001) explicates a sequence of computational mechanisms that associate aging-related deficient dopaminergic neuromodulation with a variety of cognitive aging deficits. Specifically, in the simulated "old networks" deficient dopamine (DA) modulation is modeled by reducing the gain control (modeled with a lower slope) of the information transfer function that relates pre-synaptic signal input and post-synaptic response activities (**Figure 1A**). Consequently, the signal-to-noise ratio (SNR) of information processing is decreased in the simulated "old" network with a lower gain control, resulting in increased random processing fluctuations (**Figure 1B**), and consequently attenuated rate (drift rate, v) of evidence accumulation (**Figure 1C**). Generalizing from these mechanisms, other simulation studies showed that the thus simulated "old network" exhibited less distinctive representations of activation patterns and less selective recruitment of specific processing modules that accounted for aging-related declines in working memory (Li and Sikström, 2002). Furthermore, associative memory deficit (Li et al., 2005) as well as a range of other cognitive impairments commonly observed in old age could also be accounted for by the aging neuronal gain control theory (see Li and Rieckmann, 2014, for a recent review).

Notwithstanding declines in neurocognitive resources, considerable "latent reserve capacity" at the cognitive and brain levels are still preserved in old age (cf. Baltes et al., 1986), which, given appropriate environmental supports or interventions, could potentially be activated to promote successful aging (Rowe and Kahn, 1987). In particular, the concept of "developmental reserve capacity" was introduced to denote the extent that an individual's maximum cognitive performance level could be enhanced through structured environmental supports i.e., interventions (Baltes, 1987). In this context, "baseline reserve capacity" reflects the amount of available neurocognitive resources at a given moment for certain cognitive operations, whereas "developmental reserve capacity" more specifically highlights the extent of older adults' potential to benefit from interventions in raising the levels of their cognitive functions. Couched in the terms of a more recent conceptual framework of adult cognitive plasticity (Lövdén et al., 2010), activating "developmental reserve capacity" in this context denotes the potential of raising the level of organismic supplies of functional resources in older adults through interventions.

In this article, we review existing findings of cognitive training and non-invasive brain stimulation interventions i.e., transcranial direct current stimulation (tDCS) and discuss their promises and constraints in activating the reduced but still available neurocognitive resources to buffer or ameliorate older adults' cognitive functions. Furthermore, we also consider and review first promising evidence from concurrent applications of tDCS during cognitive training as means to further promote short- and long-term training effects on cognitive and brain plasticity in old age. We will discuss the potential underlying mechanisms of these positive effects within the theoretical framework of neuronal gain control, namely how cognitive training and/or brain stimulation intervention may enhance dopaminergic neurotransmission and consequently modulate the SNR of information processing with performance enhancing effects in older adults. We will focus specifically on working memory and episodic memory functions, which are supported by the fronto-parietal and hippocampal-striatal circuitries, respectively.

AGING-RELATED DECLINES IN FRONTO-PARIETAL AND HIPPOCAMPAL-STRIATAL MEMORY FUNCTIONS

Aging-Related Declines in Working Memory

Cognitive control functions are described as the ability to flexibly adapt behavior by facilitating relevant over competing irrelevant information processing in order to achieve specific goals. Hence, the ability to manipulate and maintain goal-relevant information over a short period of time i.e., working memory, is essential (e.g., Engle, 2002; Cowan et al., 2005; Miller and Wallis, 2009; Fukuda et al., 2010). For instance, the content and information provided by task instructions must be actively represented and kept in mind to bias attentional allocation and response selection toward task-related goals, particularly when an inappropriate response is dominant and needs to be suppressed. Neurocognitive models of working memory suggest a dynamic interplay between prefrontal and parietal brain

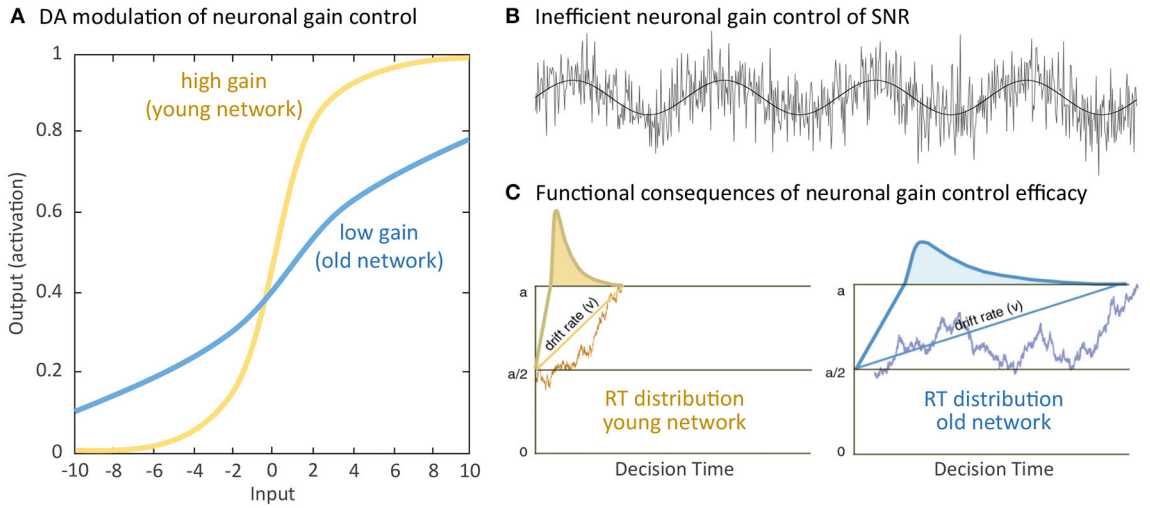

FIGURE 1 | Simulating computational effects of aging neuronal gain control: (A) Aging-related deficiency of dopamine (DA) modulation attenuates the gain parameter of the sigmoidal transfer function relating pre-synaptic input and post-synaptic output and thus reduces the slope of the neuronal response function. **(B)** Attenuated gain control increases random processing fluctuations, which functionally reduce the signal-to-noise ratio (SNR) of information processing. **(C)** For instance, in a simple decision process between criterion a or 0, increased SNR of information processing limits the rate (drift rate, v) of evidence accumulation for either decision and precision of information processing with broader reaction time (RT) distribution, indicated by the curves, in the old compared to the young network. Further negative impacts on a wide range of cognitive functions have been discussed (Li et al., 2001; see Li and Rieckmann, 2014 for commonly observed neurocognitive aging deficits accounted for by the simulated effects of aging neuronal gain control).

areas (D'Esposito, 2007; Linden, 2007; Darki and Klingberg, 2015). Posterior brain regions seem to play important roles in forming and maintaining representations, whereas prefrontal regions contribute to the selection of relevant information and the stabilization of representations during maintenance (Postle, 2006). Moreover, the fronto-striatal circuitry also implicates working memory (e.g., Cools et al., 2008; McNab and Klingberg, 2008; Darki and Klingberg, 2015). Critically, frontal and basal ganglia activity precede the filtering of irrelevant information during working memory encoding and predict storage-related parietal activity as well as inter-individual differences in working memory capacity (McNab and Klingberg, 2008).

On the neurochemical level, it has been shown that different neurotransmitters, such as serotonin (Luciana et al., 1998; Cano-Colino et al., 2014), norepinephrine (Zhang et al., 2013), and acetylcholine (Hasselmo and Stern, 2006) are involved in working memory processes (see Ellis and Nathan, 2001 for review). We focus on the role of DA here as its roles for working memory processes is best established (e.g., Sawaguchi and Goldman-Rakic, 1991; Goldman-Rakic, 1996; Arnsten, 1998; Braver and Cohen, 2000; Durstewitz et al., 2000a,b; Frank et al., 2001; Cools et al., 2008; D'Ardenne et al., 2012). Evidence from animal and human studies show that maintenance processes are supported by prefrontal DA signaling (e.g., Williams and Goldman-Rakic, 1995; Goldman-Rakic, 1996; Abi-Dargham et al., 2002). Accordingly, the dual-state theory of prefrontal DA function proposes the existence of two discrete, dynamic, and functionally different states. A D1-receptor dominated state that favors robust maintenance of information in working memory despite distractions and a D2-receptor dominated state contributing to the flexible integration of new information (Durstewitz and Seamans, 2008). Besides the role of prefrontal DA signaling in working memory processes, neurocomputational models (Braver and Cohen, 2000; Frank et al., 2001) and empirical work (D'Ardenne et al., 2012) suggest that DA signaling in the basal ganglia acts as a gating mechanism, which regulates the encoding of new information in the prefrontal cortex (PFC) and consequently the updating of context information in working memory. Selective lesions of prefrontal DA neurons in animals were associated with increased striatal DA release (Roberts et al., 1994), while enhancing DA activity in the PFC inhibited striatal DA release (Kolachana et al., 1995; Karreman and Moghaddam, 1996). Furthermore, an overexpression of D2 receptors in the striatum led to alterations in prefrontal D1 receptor activity and consequently functional impairments in working memory and behavioral flexibility tasks (Kellendonk et al., 2006). Taken together, being closely intertwined via the cortico-striato-cortical pathway the interactions between prefrontal and striatal DA systems are crucial for working memory processes and adaptive, goal-directed behavior.

There is a wealth of evidence that normal aging is accompanied by significant declines in working memory (e.g., Bopp and Verhaeghen, 2005; Borella et al., 2008; Li et al., 2008; see Lever et al., 2006; Sander et al., 2012 for reviews). At the brain functional level, aging-related changes in working memory are associated with altered task-related activations in prefrontal and posterior brain regions in older compared to younger adults (e.g., Grady et al., 1998; Cabeza et al., 2004; see Rajah and D'Esposito, 2005 for review; Rypma and D'Esposito, 2000; Schneider-Garces et al., 2010). Similarly, compared to younger

adults, older adults did not show significant striatal activation during a working memory task before training intervention (Dahlin et al., 2008a). At the neurochemical level, there is ample evidence that the density of pre-synaptic (DA transporter) and post-synaptic (D1 and D2 receptors) DA markers in striatal and extra-striatal regions decline markedly from early to late adulthood (see Bäckman et al., 2010 for review). Lesion and pharmacological animal studies provide direct evidence that DA depletion (Brozoski et al., 1979; Collins et al., 1998) but also excessive DA receptor stimulation (Murphy et al., 1996; Zahrt et al., 1997) in the PFC had negative consequences for working memory functions. For instance, depletion of DA in the dorsolateral prefrontal cortex (DLPFC) in rhesus monkeys resulted in impaired working memory performance, which could be pharmacologically reversed by the DA precursor levodopa and the DA agonist apomorphine (Brozoski et al., 1979). In humans, reduced frontal and striatal DA markers were associated with an under-recruitment of the fronto-parietal network during working memory (Landau et al., 2009; Bäckman et al., 2011a) as well as reduced fronto-striatal (Klostermann et al., 2012) and fronto-parietal (Rieckmann et al., 2011) functional connectivity. Interindividual differences in caudate D1 receptor density were related to interindividual differences in functional connectivity of the right DLPFC to the right parietal cortex and of the medial PFC to the right intraparietal sulcus and postcentral gyrus during working memory performance (Rieckmann et al., 2011). In a similar vein, Klostermann et al. (2012) could show that suboptimal levels of DA synthesis capacity in the caudate were correlated with reduced functional connectivity between the right inferior frontal gyrus and the caudate, which in turn was associated with decreased working memory performance. Thus, aging-related differences in functional activations and connectivity in the cortico-striato-cortical pathway seem to be linked to suboptimal DA signaling and may underlie aging-related changes in working memory performance.

Aging-Related Declines in Episodic Memory and Spatial Learning

The memory of experienced events i.e., episodic memory, encompasses multiple facets of information. For instance, the memory about a conversation includes the content of the conversation, the persons involved as well as the time and spatial location in which the conversation took place. Associative memory mechanisms are required to bind the different aspects of an experience into an integrated episode in long-term memory. The fronto-hippocampal circuitry implicates the strategic organization and elaboration of memory materials as well as the binding of different aspects of memory features during encoding, memory consolidation, and memory retrieval (Simons and Spiers, 2003), for instance pattern association which describes the function to link certain input and certain memory patterns to enable memory retrieval also with varying input patterns. Relative to semantic memory (i.e., memory for specific facts or knowledge), older adults are particularly impaired in episodic strategic organization and elaboration that are subserved by the frontal executive control processes as well as associative mechanisms that implicate the hippocampal regions (Chalfonte and Johnson, 1996; Old and Naveh-Benjamin, 2008; Shing et al., 2008). For instance, older adults' episodic memory deficit was particularly apparent in conditions requiring the memorization of associations between memory items (Naveh-Benjamin, 2000) relative to memory of single items. The aging neuronal gain control theory accounted for older adults' associative binding deficit through the less distinctive representations of the associations between items, which was the computational consequence of attenuated gain control in the memory network (Li et al., 2005). Moreover, ample evidence from functional magnetic resonance imaging (fMRI) and positron emissions tomography (PET) studies relates deficits in episodic memory encoding and retrieval in old age with alterations in functional episodic memory networks, especially with patterns of functional under-recruitment and non-selective additional bilateral recruitment of prefrontal regions, which is not observed in younger adults (see Reuter-Lorenz, 2002; Nyberg et al., 2012 for review). For instance, during episodic memory encoding older adults showed additional activation in right frontal regions while at the same time task-relevant left frontal regions were under-recruited, probably due to insufficient (i.e., non-selective) allocation of brain resources (e.g., Logan et al., 2002; Leshikar et al., 2010). Similarly, during episodic memory retrieval, older adults showed reduced selectivity of prefrontal activation during context (Cabeza et al., 2000) and recognition memory tasks (Madden et al., 1999) and reduced specificity of prefrontal and hippocampal activations during retrieval of item vs. relational memory information (Giovanello and Schacter, 2012). Simulation results from the aging neuronal gain control theory indicate that such aging-related increases of non-specific recruitments of presumably distinct processing pathways may, in part, be related to deficient DA modulation of the underlying task relevant networks (Li and Sikström, 2002).

One other specific aspect of episodic memory i.e., the spatial configuration of a memory episode, relies particularly on the hippocampal-striatal circuitry (see Moser et al., 2008 for review). Animal research showed that, whereas complex representations of spatial layouts and locations relative to environmental geometric features (e.g., spatial boundaries and shapes of the environment) are supported by the hippocampus (e.g., O'Keefe and Dostrovsky, 1971; O'Keefe and Burgess, 1996; Hartley et al., 2000), the computationally less demanding cue-based spatial learning (e.g., using fixed cue–location associations) is mainly subserved by the dorsal striatum (e.g., Packard et al., 1989; Packard and McGaugh, 1992; McDonald and White, 1994; Miyoshi et al., 2012). Applying desktop virtual reality-based fMRI spatial navigation tasks in humans, a similar dissociation was shown in healthy young adults with stronger hippocampal involvement during spatial exploration of new routes and during learning and remembering of object locations relative to a visible boundary; whereas, stronger striatal activation was shown during route following and during learning and remembering of object locations relative to an intra-environmental cue (e.g., Hartley et al., 2003; Iaria et al., 2003; Wolbers and Büchel, 2005; Doeller et al., 2008).

Younger adults further showed a prioritization of relying on hippocampal-dependent spatial over striatal-dependent cue-based navigation strategies (e.g., Bohbot et al., 2012; Wiener et al., 2013). Other aspects of spatial navigation such as path integration that strongly rely on self-motion without the need of visual input also involve hippocampal-based spatial processing. Path integration, however, implicates additional human motion complex activity together with working memory-related location updating and monitoring processes of the medial PFC (e.g., Wolbers et al., 2007; De Nigris et al., 2013) and performance differences in path integration across human adulthood are, so far, not entirely understood (e.g., Harris et al., 2012, but Skolimowska et al., 2011). The complexity of the brain network underlying spatial navigation notwithstanding, we will in the following primarily focus on spatial memory subserved by the hippocampal-striatal circuitry.

Of specific interest, the relative prioritization of hippocampal- and striatal-dependent processes of spatial learning is influenced by aging. With increasing age, spatial learning, and memory decline, with an overall bias toward relying on cue-based strategies and recruitments of striatal regions (e.g., Moffat and Resnick, 2002; Driscoll et al., 2005; Bohbot et al., 2012; Etchamendy et al., 2012; Harris et al., 2012; Rodgers et al., 2012; Konishi and Bohbot, 2013; Wiener et al., 2013; Schuck et al., 2015). Specifically, whereas younger adults' behavioral data and hippocampal activity was consistent with a computational model predicting object locations relative to the geometry of the virtual environment's boundary, older adults' navigation behavior was best predicted by a model interfering object locations relative to an intra-maze location cue and was associated with larger caudate than hippocampal activation. Behaviorally, aging-related deficits in spatial learning were more prominent in hippocampal-dependent boundary learning than in striatal-dependent cue-based learning (Schuck et al., 2015). Previous research indicated that aging-related structural and neurobiological alterations in the hippocampus (see Rosenzweig and Barnes, 2003 for review; Wilson et al., 2006) as well as neuromodulatory changes in the midbrain DA system (see Bäckman et al., 2010; Li and Rieckmann, 2014 for reviews) might contribute to deficits in spatial learning and memory in old age. During normal aging, hippocampal volume progressively declines by 1–2% per year (Raz et al., 2005), which presumably affects spatial memory performance in old age (Erickson et al., 2011). Based on evidence from animal studies, the aging hippocampus, especially the perforant path receiving input from the entorhinal cortex, is further characterized by a multitude of subtle alterations in synaptic plasticity, including loss and shrinkage of synapses (Geinisman et al., 1992; Smith et al., 2000; Nicholson et al., 2004), reduced excitability leading to increasing stimulation thresholds (Barnes et al., 1994, 2000) and faster decay of long-term potentiation (Landfield et al., 1978; Barnes and McNaughton, 1985). Atrophy of the perforant path was also observed in healthy older compared to younger adults using diffusion tensor imaging (Kalus et al., 2006) and was even more pronounced in postmortem brain tissue of older adults with mild cognitive impairment (MCI) despite otherwise comparable volumes in the unimpaired and MCI groups (Scheff et al., 2006). Moreover, the extent of synaptic loss in the perforant path was negatively correlated with pre-mortem memory status. Taken together, aging-related changes in structure and function of the hippocampus may at least in part underlie older adults' increased reliance on striatal-dependent cue-based navigation strategies.

Evidence from animal research indicates that midbrain DA modulation of the hippocampus plays an important role in stabilizing transient memory traces and maintaining encoded memory associations in long-term memory (Bethus et al., 2010; see Lisman and Grace, 2005 for review; Rossato et al., 2009). In the context of spatial learning, Kentros et al. (2004) showed that DA D1/D5 agonist enhances the stability of hippocampal place fields in rats. In humans, a recent pharmacological imaging study showed that a DA agonist and DA precursor levodopa enhanced episodic memory and brain activation in older adults (Chowdhury et al., 2012). Relatedly, recent behavioral genetic evidence showed that genetic predispositions of DA transporter (*DAT1*) and receptor (*DRD2*) genes are associated with individual differences in serial memory (Li et al., 2013) and long-term episodic memory forgetting, particularly in older adults (Papenberg et al., 2013). In terms of spatial learning, a recent study with Parkinson's (PD) patients showed that, after the patients had some prior experiences with a given spatial environment, the prioritization of hippocampal-dependent boundary learning was increased relative to striatal-dependent cue-based learning when they were on dopaminergic medication (Thurm et al., 2016).

Taken together, in the two sections above we have reviewed findings indicating that normal aging is associated with prominent declines in working memory and episodic memory, with negative consequences for older adults' daily activities. Structural and functional changes as well as aging-related suboptimal dopaminergic neuromodulation in the fronto-striatal-parietal and fronto-hippocampal-striatal brain network, respectively, may contribute to these aging-related working memory and episodic memory impairments. According to the framework of the aging neuronal gain control theory (Li et al., 2001), reduced working memory and episodic memory capacity may stem from suboptimal DA modulation of the relevant networks, which may impair the SNR of information transfer within and between the respective brain circuitries, thus causing reduced specificity of information processing and less distinctive brain activation patterns. Facing increasing population aging, developing interventions that could activate the developmental reserve capacity in older adults and augment the aging brain's attenuated neuronal gain control to maintain or promote working memory and episodic memory functions (see **Figure 2** for a schematic diagram) is of high societal relevance. In the following sections, evidence for why cognitive training and non-invasive brain stimulation can be seen as potential candidate interventions for promoting the aging brain's neuronal gain control will be reviewed, alongside with critical discussions about the short- and long-term effects of these interventions.

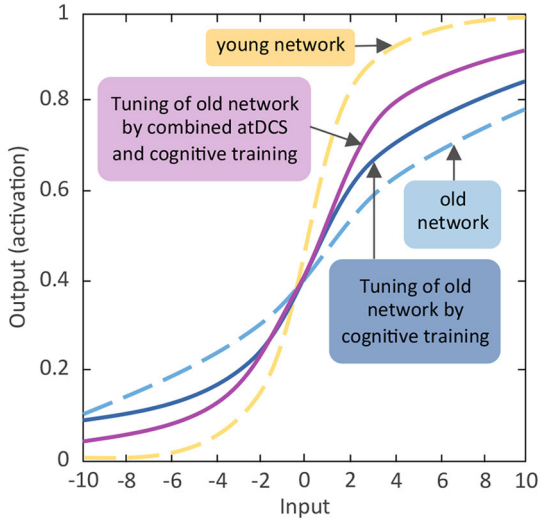

FIGURE 2 | Schematic diagram of expected effects of activating aging neuronal gain control through cognitive training and non-invasive brain stimulation. Comparable to **Figure 1A** the y-axis indicates the activation value of units of the artificial neural network. The activation value as bounded by the sigmoidal activation function is between 0 and 1. The x-axis denotes incoming excitatory or inhibitory inputs, which ranged from −10 to +10. The s-shaped logistic activation function transforms the net inputs into the strength of an output signal. The responsivity of a unit to inhibitory or excitatory inputs is modulated by the slope of the function, which is regulated by the gain parameter (see Li et al., 2001). Reducing the slope flattens the activation function and the unit becomes less responsive, whereas steepening the slope of the function enhances the responsivity.

INTERVENTION METHODS ENHANCING NEURONAL GAIN CONTROL

Behavioral Training Interventions Enhancing Neuronal Gain Control

Ameliorating older adults' cognitive decline through behavioral interventions has received a lot of attention during the last couple of years. Thus, a plethora of heterogeneous intervention methods has been developed and evaluated. For instance, cognitive, physical or combined cognitive and physical interventions (see Bamidis et al., 2014 for review) as well as action video game training (see Bavelier et al., 2012 for review) have been shown to induce behavioral and/ or brain plasticity effects. In the following we will primarily focus on cognitive training interventions in the working memory and episodic memory domain and refer readers interested in other interventions methods to the cited reviews.

Cognitive training promotes structural changes in the brain's gray and white matter. According to the animal literature, candidate cellular mechanisms underlying gray matter plasticity encompass axon sprouting, dendritic branching and synaptogenesis, neurogenesis and glial changes (see Zatorre et al., 2012 for review). Beyond these structural changes, of specific relevance in the context of this review is the evidence for training-induced changes in neurotransmitter systems. For instance, animal studies showed that motor training in rats seems to increase the expression of muscarinic acetylcholine (Ibarra et al., 1995) and DA (MacRae et al., 1987; Soiza-Reilly et al., 2004) receptors in the striatum. Spatial working memory training in monkeys has been shown to induce a reduction in the variability of firing rates across trials and a decline in cross-trial correlations of neuronal discharges, suggesting that training could lower random processing fluctuation which functionally increases the SNR of information processing and the precision of stimulus representations in PFC neurons (Qi and Constantinidis, 2012a,b). Of note, human studies using PET imaging in younger adults provide evidence for training-induced changes in striatal (Bäckman et al., 2011b) and cortical dopaminergic neuromodulation that were associated with larger working memory training gains (McNab et al., 2009). Taken these findings together, training interventions seem to be promising candidates to enhance neuronal gain control in older adults and thus promote cognitive and brain plasticity, with potential transfer effects to other functions than the trained domains. In the following, we will review in more details adult age differences in working memory and episodic memory plasticity. Other than focusing on training gains of the trained tasks, improvements in non-trained tasks closely related to working memory or episodic memory (so-called near-transfer effects), performance gains in other functional domains (so-called far-transfer effects), and stability of training- and transfer-effects (maintenance effect) will be highlighted.

Age Differences in Working Memory Training-Induced Behavioral and Brain Plasticity

Lifespan age differences in cognitive plasticity following training seems to vary across cognitive domains, with comparable effect sizes of immediate working memory training gains across younger and older adults (Schmiedek et al., 2010; Karbach and Verhaeghen, 2014). In contrast, near- and far-transfer effects were shown to be present in younger adults (e.g., Jaeggi et al., 2008; Chein and Morrison, 2010) but reduced or absent in older adults (e.g., Buschkuehl et al., 2008; Dahlin et al., 2008b; Li et al., 2008; Schmiedek et al., 2010; Richmond et al., 2011; Brehmer et al., 2012). With regard to maintenance effects in older adults there is evidence that training and transfer-effects of working memory training remain stable over a period of months (Dahlin et al., 2008b; Li et al., 2008; Borella et al., 2010; Richmond et al., 2011; Zinke et al., 2014).

Working memory training studies in humans have revealed quantitative changes in functional activation (see Constantinidis and Klingberg, 2016 for review; Olesen et al., 2004; Dahlin et al., 2008a; Jolles et al., 2013; Kühn et al., 2013; Thompson et al., 2016) and DA signaling (McNab et al., 2009; Bäckman et al., 2011b) of the fronto-striatal-parietal network (see **Figure 3** for an overview diagram). For instance, compared to pre-training fronto-parietal functional connectivity increased in younger adults (Jolles et al., 2013; Thompson et al., 2016). Furthermore, changes in striatal brain activity have also been observed and associated with working memory training-induced improvements (Dahlin et al., 2008a; Kühn et al., 2013). Of note, using PET imaging in humans, McNab and colleagues provide evidence for a training-induced enhancement in cortical

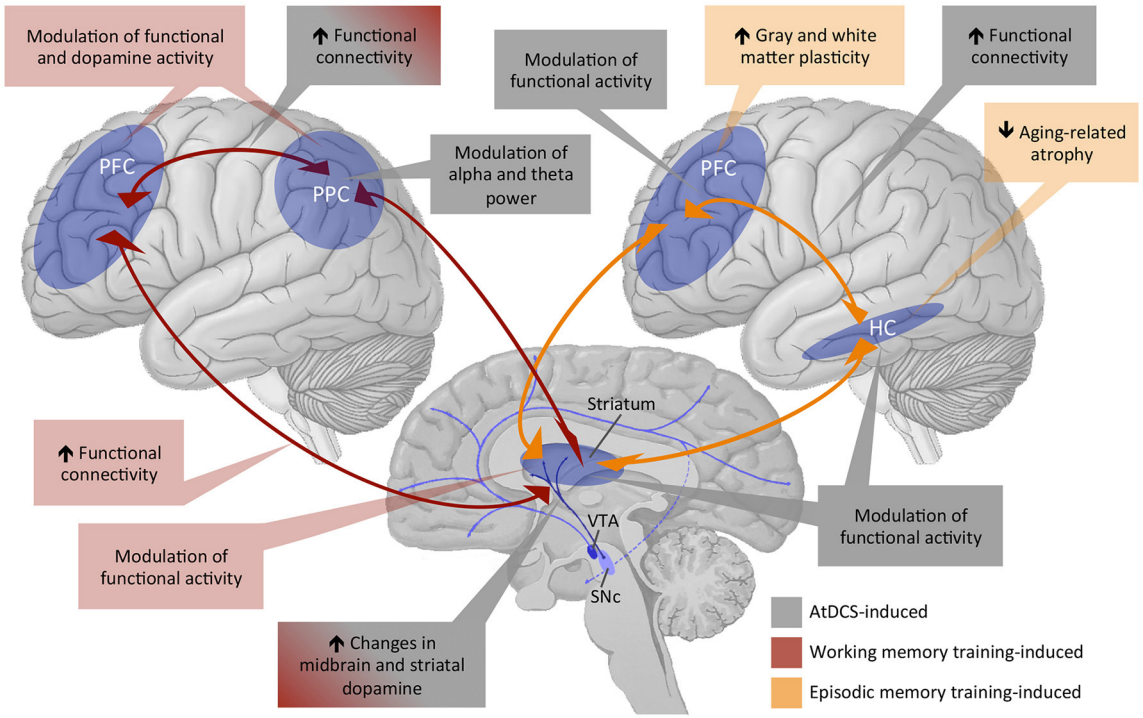

FIGURE 3 | Overview of existing evidence of training and tDCS effects on working memory and episodic memory functions subserved by the fronto-striatal-parietal and fronto-hippocampal-striatal circuitries. PFC, prefrontal cortex; PPC, posterior parietal cortex; HC, hippocampus; VTA, ventral tegmental area; SNc, subthalamic nucleus; AtDCS, anodal transcranial direct current stimulation.

DA neuromodulation that is reflected by reduced D1-receptor binding potential, which could reflect enhanced DA release after training in task-relevant brain areas. Individuals who showed greater training-induced changes in D1 receptor binding potential also showed greater training-related improvements in working memory performance (McNab et al., 2009). A further PET imaging study could show that working memory training results in enhanced striatal DA release in younger adults (Bäckman et al., 2011b).

So far, studies investigating the neural correlates of working memory training in older adults are rather scarce. There is evidence for training-induced decreases in cortical brain activations (frontal, parietal, temporal, occipital), pointing to an increase in neural efficiency, and training-induced increases in subcortical (thalamus and caudate) brain activations. Critically, the degree of the striatal changes was associated with training gains (Brehmer et al., 2011). Regarding transfer effects of working memory training, Dahlin and colleagues indicated that younger adults' transfer effects were based on training-induced increases in striatal activity in the trained and transfer task whereas this was not the case in older adults (Dahlin et al., 2008a). Thus, based on these results and given the working memory training-induced effects on striatal DA release (Bäckman et al., 2011b), aging-related reduction in transfer effects in older adults may be driven by their deficient striatal DA functioning.

Age Differences in Episodic Memory Training-Induced Behavioral and Brain Plasticity

Episodic memory plasticity has been shown to be more limited in old age compared to young adulthood or childhood (see Brehmer et al., 2007; Shing et al., 2010 for review; Shing et al., 2008). These age differences in training-induced plasticity are more pronounced for episodic compared to working memory (see Lindenberger, 2014 for review; Schmiedek et al., 2010). Notwithstanding the more limited episodic memory plasticity in old age, cognitive interventions might be able to reduce aging-related performance disadvantages by providing sufficient environmental support (cf. Lindenberger, 2014). For instance, aging-related under-recruitment in prefrontal regions can be reversed when encoding strategies are externally provided rather than self-initiated by the participants (Logan et al., 2002).

Early episodic memory training interventions mainly focused on instructing mnemonic (e.g., method of loci) and other memory strategies in order to facilitate task-specific encoding or retrieval in younger and older adults (see Brehmer et al., 2014 for review). For instance, Brehmer and colleagues compared the effects of a multisession mnemonic training in a lifespan sample, from childhood to old age. As a function of mnemonic instruction and adaptive training, all age groups showed improvements in the trained memory task but with older adults clearly showing the smallest training gains (Brehmer et al., 2007). Other studies showed equivocal or less promising results of

various memory trainings (e.g., Jennings et al., 2005; Craik et al., 2007; Lustig and Flegal, 2008). In the very old (i.e., older adults aged 75–100 years or older), memory plasticity seems to be further reduced resulting in observable but very small negligible gains from instruction and adaptive practice compared to old adults below the age of 75 years (Singer et al., 2003). Training gains in very old age might be increased when memory training is combined with other training modules (Oswald et al., 2006) or intervention techniques.

In the COGITO study (Schmiedek et al., 2010), 100 days of memory training with verbal, numerical, and spatial material was associated with reliable near-transfer effects in both younger and older adults. However, the effect sizes for performed episodic memory tasks and latent cognitive variables were rather small in older adults (latent effect size of .09 compared to .52 in younger adults). Similarly, the ACTIVE study investigated potential far-transfer effects to functions of everyday life in older adults by comparing a verbal memory, a speed of processing, and a reasoning training with a passive control group. Cognitive training involved 10 sessions of 60–75 min over 5–6 weeks, followed by four additional training sessions two and 5 years after the initial training intervention was completed. The memory training group showed significant practice gains in the trained cognitive domain, which were stable up to 5 years after the intervention, but no further gains following additional training and no far-transfer effects of the memory training or the additional memory training on measures of everyday life functioning could be observed (Ball et al., 2002; Willis et al., 2006). Overall, the literature indicates that older adults can benefit from episodic memory training but direct training gains, so far, are much smaller compared to younger age groups and other cognitive domains. Furthermore, evident (far)-transfer effects are limited at best or lacking (cf. Noack et al., 2009, 2014).

The small behavioral effects with regard to transfer and generalizability notwithstanding, episodic memory training-induced alterations in brain structure and function have been reported (see **Figure 3** for an overview diagram). For instance, at the structural level, memory training was associated with increases in cortical thickness and gray matter volume in younger, middle-aged and older adults (Engvig et al., 2010, 2012, 2014). Training-induced improvements in memory performance were further positively correlated with the extent of cortical thickness increase in the lateral orbitofrontal cortex and the right fusiform gyrus (Engvig et al., 2010) and with the extent of volume increase in the left hippocampus (Engvig et al., 2014). A further study investigated effects of a spatial memory training i.e., episodic memory training with spatial context, on cognitive and structural brain plasticity in younger and older adults. Four months of spatial memory training in a virtual zoo not only facilitated task performance but also counteracted aging-related hippocampus shrinkage up to 4 months after training in both age groups (Lövdén et al., 2012). However, training-related cortical thickening in the left paracentral lobule and precuneus were only evident in younger but not in older participants (Wenger et al., 2012), indicating that aging-related differences in training-induced structural plasticity are region-specific. Additionally, hippocampal volume prior to cognitive interventions might be one predictor of memory training outcomes in old age (Engvig et al., 2012). At the functional level, effects of episodic memory training have, so far, mainly been observed in the fronto-parietal network (Nyberg et al., 2003). After being instructed to use the method of loci as a mnemonic strategy, increased brain activities in frontal as well as occipito-parietal regions were observed in younger adults. In contrast, accompanying their reduced episodic memory plasticity as indicated by the reduced training gain, older adults did not show training-related increase in frontal activity, and only those older adults who benefited from the memory training showed increased occipito-parietal activity. Moreover, animal literature indicates that DA plays a crucial role for long-term maintenance of episodic memory training-induced effects (Rossato et al., 2009; Bethus et al., 2010), although direct evidence of enhanced DA modulation after episodic memory training is still lacking. Brain-derived neurotrophic factor (BDNF) might be one further factor modulating DA effects on episodic memory consolidation following training in rodents (Rossato et al., 2009) and spatial memory training-induced effects on cognitive and brain plasticity in adult humans (Lövdén et al., 2011).

In summary, both working memory and episodic memory training research reveal that cognitive plasticity following interventions is more limited in older adults and this is particularly so in the domain of episodic memory. So far, evidence for the transfer of training-effects to related or other cognitive processes (i.e., near- and far-transfer effects) in older adults is rare. This may reflect that solely relying on cognitive training interventions could be limited in their effects in promoting behavioral and brain plasticity in older adults (see **Figure 2** for a schematic diagram). Thus, other interventions or the combination of training with other intervention methods need to be explored. Since the last 15 years transcranial electrical stimulation methods (tES) are receiving increasing attention in the field of behavioral and brain plasticity. In the following, we will briefly highlight in what ways tES, particularly anodal transcranial direct current stimulation (atDCS), may be suitable for the enhancement of neuronal gain control and thus cognitive performance in older adults. Afterwards, we will review current existing findings about the behavioral and brain plasticity effects of atDCS applications in the field of working memory and episodic memory.

Transcranial Direct Current Stimulation (tDCS) as a Means for Enhancing Neuronal Gain Control

Transcranial direct current stimulation (tDCS) in which a constant, low intensity current (1–2 mA) is passed through two electrodes is one commonly applied stimulation mode in the field of tES techniques. Besides tDCS, tES techniques also encompass transcranial alternating current stimulation (tACS) in which a sinusoidal current is applied to modulate brain oscillatory activity and transcranial random noise stimulation (tRNS) in which current intensity and frequency vary in a random manner (see Antal and Herrmann, 2016 for review). During the last couple of years the number of published articles on tES-induced effects on cognition has increased tremendously. The endeavor of

reviewing findings of all three tES methods on working memory and episodic memory functions would be beyond the scope of this article. As tDCS is the most systematically studied tES method, we limited our review on tDCS studies only.

During tDCS subthreshold changes of neuronal resting membrane potentials are induced, which alter cortical excitability and activity, dependent on the direction of the current flow. Studies of stimulating the human motor cortex have shown that anodal tDCS (atDCS) facilitates, while cathodal tDCS (ctDCS) reduces excitability. Stimulations lasting for a few seconds seems to induce solely changes in membrane potentials, while longer-lasting stimulation for a few minutes induce changes in cortical excitability, which remain stable for about 1 h or longer (see Kuo and Nitsche, 2015 for review; Nitsche and Paulus, 2000, 2001). Studies applying atDCS have shown beneficial effects on cognitive functions in young (e.g., see Brunoni and Vanderhasselt for review; Parasuraman et al., 2014; Scheldrup et al., 2014), and old age (e.g., Berryhill and Jones, 2012; see Hsu et al., 2015 for review; Flöel et al., 2012), presumably by enhancing excitability (Nitsche and Paulus, 2000, 2001), facilitating synaptic (Stagg et al., 2009; Stagg and Nitsche, 2011), neural (Islam et al., 1995) and cognitive plasticity (see Filmer et al., 2014 for review; Liebetanz et al., 2002; Flöel and Cohen, 2010), and by changing brain network connectivity (e.g., Meinzer et al., 2012; Sehm et al., 2012).

Non-invasive brain stimulation techniques seem to have a modulatory effect on dopaminergic neurotransmission (Strafella et al., 2001; Keck et al., 2002; Cho and Strafella, 2009; Tanaka et al., 2013). For instance, repetitive transcranial magnetic stimulation (rTMS) over prefrontal brain regions has been shown to induce increased extracellular DA levels in striatal (Strafella et al., 2001; Keck et al., 2002) and extra-striatal brain regions i.e., anterior cingulate and orbitofrontal cortex (Cho and Strafella, 2009). With regard to tDCS an animal study provides direct evidence for a modulatory effect of tDCS on dopaminergic neurotransmission. More specifically, extracellular DA levels in the striatum of rats increased for more than 400 min following the application of 10 min cortical ctDCS but not atDCS (Tanaka et al., 2013). Combined tDCS and drug-intervention studies further support a link between DA and tDCS-induced excitability and neuroplastic after-effects (Nitsche et al., 2006; Kuo et al., 2008; Monte-Silva et al., 2010; Fresnoza et al., 2014a,b). For instance, levodopa significantly prolongs the after-effects of tDCS applied over the motor cortex (Kuo et al., 2008), but in a non-linear, dose-dependent manner (Monte-Silva et al., 2010). More specifically, low and high dosage of levodopa abolished excitatory as well as inhibitory modulatory effects of tDCS, whereas a medium dosage turned excitatory into inhibitory plasticity and prolonged inhibitory plasticity effects. Taken together, although the exact underlying mechanisms are yet not completely understood, tDCS-induced plasticity effects seem to be partly driven by changes in the dopaminergic system. Evidence of neurocomputational, receptor imaging, and behavioral genetic studies suggests that deficient dopaminergic neurotransmission contribute to aging-related declines in working memory and episodic memory (see Li and Rieckmann for review) and older adults' reduced plasticity (Kishore et al., 2014). Consequently, tDCS interventions may be a promising tool for enhancing behavioral and neural plasticity via modulating dopaminergic signaling. Within the theoretical framework of neuronal gain control tDCS-induced improvements in dopaminergic neurotransmission are likely to enhance the gain control of the information transfer function and consequently improve the SNR of information processing in older adults resulting in higher representational distinctiveness and more selective recruitment of relevant processing modules. In terms of functional consequences this more efficient processing is likely to lead to behavioral and neural benefits in working memory and episodic memory functions. In the following two sections, we will review findings on the effects of tDCS on behavioral and brain plasticity in the domains of working memory and episodic memory (for an overview of tDCS-study characteristics see **Table 1**).

Effects of tDCS on Working Memory Plasticity

As aforementioned, working memory processes rely on a broad network encompassing frontal, parietal and striatal brain regions. During the last couple of years a plethora of studies assessing tDCS effects on working memory performance in humans targeting frontal and parietal stimulation sites have been published, for instance, 10 min of ctDCS with a current intensity of 1.5 mA over the right posterior parietal cortex (PPC; P4 electrode site of the International 10–20 system) impaired working memory performance dependent on the specific working memory process that was probed. Recognition performance was impaired, whereas verbal recall of the encoded objects remained unchanged. Interestingly, atDCS did not show any effect (Berryhill et al., 2010). Inconsistent with these findings, Tseng et al. (2012) could show that 15 min of 1.5 mA atDCS but not ctDCS over the right PPC had a performance enhancing effect in a visual change-detection paradigm. There is also evidence that effects of tDCS over the right PPC were only apparent for a more challenging task and that younger adults with high working memory capacity benefited from either atDCS or ctDCS application, whereas those with low working memory capacity did not (Jones and Berryhill, 2012). In contrast, applying atDCS over the right PPC revealed that participants with low compared to those with high working memory capacity performed better in a difficult change detection task during atDCS (Tseng et al., 2012). Thus, tDCS over the posterior parietal cortex seems to modulate working memory performance, but the type and the consequences of stimulation are inconsistent. The resulting heterogeneity across studies may be due to differences in task paradigms, corresponding task difficulty and interindividual differences in baseline working memory capacity. Studies investigating the effects of atDCS over the left PFC on working memory performance (e.g., Ohn et al., 2008; Andrews et al., 2011; Zaehle et al., 2011) reported more consistent performance enhancing effects. In order to reduce heterogeneity across studies a recent meta-analysis included only non-invasive brain stimulation (NIBS) studies assessing the effects of atDCS and rTMS effects over the right, left or bilateral DLPFC on performance in n-back tasks. Critically

TABLE 1 | Overview of characteristics of working memory and episodic memory tDCS studies.

Authors	Design	Conditions (excluding sham)	tDCS set-up				Task sample		
			Anode–Cathode	Density (mA/cm^2)	Duration (min)		*N*	Age	Female%
WORKING MEMORY									
Berryhill et al., 2010	Cross-over	1	left cheek–P4	0.043	10	WM	11	25.0	45
		2	P4–left cheek	0.043	10	WM	11	25.0	45
Tseng et al., 2012	Cross-over	1	P4–left cheek	0.094	15	WM	20	22.0	65
Jones and Berryhill, 2012	Cross-over	1	left cheek–P4	0.043	10	WM	20	23.25	60
		2	P4–left cheek	0.043	10	WM	20	23.25	60
Zaehle et al., 2011	Cross-over	1	left mastoid–F3	0.029	15	WM	16	23.0–27.0	62.5
		2	F3–left mastoid	0.029	15	WM	16	23.0–27.0	62.5
Berryhill and Jones, 2012	Cross-over	1	F3–right cheek	0.043	10	WM	25	63. 7	57
		2	F4–left cheek	0.043	10	WM	25	63. 7	57
Nilsson et al., 2015	Cross-over	1	F3–right SO	0.029	25	WM	30	69.0 ± 7.0	46.7
		2	F3–right SO	0.057	25	WM	30	69.0 ± 7.0	46.7
EPISODIC MEMORY									
Manenti et al., 2013	Cross-over/ between	1	left/right DLPFC/PARC–cSO	0.043		LTM	32	23.7 ± 3.2	71.9
		2	left/right DLPFC/PARC–cSO	0.043		LTM	32	67.9 ± 4.7	53.1
Sandrini et al., 2014	Between	1 (reminder)	F3–right SO	0.043	15	LTM	12	67.5 ± 2.7	66.7
		2 (no reminder)	F3–right SO	0.043	15	LTM	12	67.6 ± 4.3	66.7
Sandrini et al., 2016	Between	1	F3–right SO	0.043	15	LTM	14	68.6 ± 4.2	64.3
Smirni et al., 2015	Cross-over/ between	1	shoulder–F3/F4	0.029	20	LTM	20	23.6 ± 2.3	88.9
		2	F3/F4–shoulder	0.029	20	LTM	16	24.7 ± 2.2	88.9
Zwissler et al., 2014	Between	1	F3–right shoulder	0.029	15	LTM	24	24.8 ± 2.9	62.5
		2	right shoulder–F3	0.029	15	LTM	24	24.8 ± 2.9	62.5
Jones et al., 2014 (tDCS-encoding)	Cross-over	1	P3–right cheek	0.043	15	LTM	20	23.4 ± 3.3	75
Jones et al., 2014 (tDCS-maintenance)	Cross-over	1	P3–right cheek	0.043	15	LTM	20	22.2 ± 2.5	70
Pisoni et al., 2015	Between	1	P3–P4	0.043	15	LTM	15	23.5 ± 2.6	
		2	T3–T4	0.043	15	LTM	15	23.1 ± 3.5	
Boggio et al., 2009	Cross-over	1	F3–right SO	0.057	30	LTM	10	79.1 ± 8.8	60
		2	T7–right SO	0.057	30	LTM	10	79.1 ± 8.8	60
Ferrucci et al., 2008	Cross-over	1	P3/T5-P6/T4–shoulder	0.057	15	LTM	10	75.2 ± 7.3	70
		2	shoulder–P3/T5-P6/T4	0.057	15	LTM	10	75.2 ± 7.3	70
Brunyé et al., 2014	Cross-over/ between	1	T8–CP6, FC6, FT10, TP10	HDtDCS	up to 20	SM	16	20.1	0
		2	T7–CPS, FC5, FT9, TP9	HDtDCS	up to 20	SM	16	20.1	
Hampstead et al., 2014	Between	1	Pz–AF4	0.057	20	SM	8	24.6 ± 2.4	50
		2	AF4–Pz	0.057	20	SM		24.4 ± 5.1	37.5
Krishnamurthy et al., 2015	Between	1	Pz–AF4	0.057	20	rs-fMRI		19–27	33.3
		2	AF4–Pz	0.057	20	rs–fMRI		19–27	33.3
Flöel et al., 2012	Cross-over	1	P6–left SO	0.029	2	SM	20	62.1 ± 9.2	50

cSO, contralateral supraorbital cortex; SO, supraorbital cortex; HD-tDCS, high-definition tDCS; WM, working memory; LTM, long-term memory; SM, spatial memory; rs-fMRI-resting-state functional magnetic resonance imaging; N, number of participants; PARC, parietal cortex.

for the current review, atDCS was shown to improve n-back performance, which was reflected by shorter reaction times, when compared to sham tDCS. This pattern of results was present across different stimulus intensities, stimulus durations, and in healthy and clinical samples (see Brunoni and Vanderhasselt, 2014 for review). Unfortunately, effect sizes in dependence of stimulation site i.e., right, left, or bilateral DLPFC, were not further discussed.

Studies investigating the underlying neuronal mechanisms of tDCS-induced effects on working memory performance are scarce (for an overview see **Figure 3**). Zaehle et al. (2011) studied working memory performance after a single application of 15 min 1 mA atDCS or ctDCS over the left DLPFC and the corresponding changes in oscillatory activity by using electroencephalography (EEG). The results revealed that tDCS altered working memory performance and changed the underlying neural oscillations at posterior electrode sites in a polarity-specific way (Zaehle et al., 2011). Specifically, atDCS amplified, whereas ctDCS attenuated oscillatory power in the theta and alpha bands, which are both critical for working memory processes. Local increases in alpha amplitude are related with preventing uptake of irrelevant information during working memory retention, whereas theta oscillations are thought to play an important role in the integration and organization of the different cognitive processes involved in working memory (see Sauseng et al., 2010 for review). Investigating the effects of atDCS over the left DLPFC on brain network connectivity using resting-state fMRI indicated a significant increase in functional connectivity in the default-mode and left and right fronto-parietal resting-state network (Keeser et al., 2011). The relevance of fronto-parietal functional connectivty for working memory is well established (e.g., Hampson et al., 2010; Rieckmann et al., 2011), but a direct link between tDCS-induced alterations in resting-state functional connectitvity and changes in working memory performance remains to be determined.

Evidence for enhancing effects of atDCS on cognitive functions in older adults is much more limited than in younger adults but slowly accumulating. Recent meta-analyses lend support for enhancing effects of NIBS methods on cognitive performance in older adults (Hsu et al., 2015; Summers et al., 2016). Hsu et al. (2015), for instance, considered studies examining tDCS and also TMS effects on performance across a broad variety of tasks targeting different cognitive processes (e.g., working memory, episodic memory, inhibition, error awareness). The meta-analysis revealed an overall moderate effect size (0.42). However, a systematic review and meta-analysis comparable to Brunoni and Vanderhasselt (2014) including only studies applying stimulation over the same brain area, the same working memory paradigm, and analyzing the same outcome measures in older adults is unfortunately still missing. Overall there are mixed results for atDCS-effects on working memory performance in older adults. For instance, Berryhill and Jones (2012) conducted a sham-controlled experiment with atDCS over the DLPFC before a visuo-spatial and verbal working memory task. The anode was placed either over the F3 or F4 electrode site of the 10–20 International system and 1.5 mA direct current was applied for 10 min. The results indicated that atDCS improved working memory performance independently of stimulation site. Critically, only older adults with high education levels showed the stimulation effect, which may reflect that highly educated older adults employ a different working memory strategy that can be boosted by atDCS compared to older adults with lower levels of education (Berryhill and Jones, 2012). More recently, Nilsson et al. (2015) systematically investigated the influence of atDCS over the left DLPFC on performance in an n-back task in older adults. The authors compared different current intensities (1 vs. 2 mA) and investigated the temporal development of the atDCS effect i.e., n-back performance was assessed before, three times during, 5 and 30 min after the 25 min-stimulation period. The results revealed no significant effects of atDCS. Compared to sham stimulation atDCS did not modulate working memory performance at any point during or after stimulation (Nilsson et al., 2015). These results should be interpreted with caution, as possible practice effects due to multiple testing in sham and atDCS stimulation conditions may have masked the stimulation effects. However, the lack of a robust effect after a singular application of tDCS is consistent with a meta-analysis, indicating that multi-session stimulations are more effective than single-session stimulations in older adults (Hsu et al., 2015).

Effects of tDCS on Episodic Memory Plasticity

Most studies investigating potential facilitating effects of atDCS on episodic memory functions focused on verbal and visual memory, which are memory functions subserved by a broader fronto-hippocampal-parietal circuitry. As direct stimulation of critical subcortical structures such as the hippocampus or striatum is not applicable in healthy human subjects, network activations via the stimulation of cortical areas as the frontal and parietal cortex are commonly applied. There is evidence indicating that, relative to sham or control site conditions, atDCS stimulation of the left DLPFC with a current of 1–2 mA for up to 20 min during or immediately after encoding of the stimulus material improved immediate recognition and retrieval or reduced long-term forgetting of verbal and visual episodic memories in younger (e.g., Javadi and Walsh, 2012; Manenti et al., 2013; Gray et al., 2015) and older adults (e.g., Manenti et al., 2013; Sandrini et al., 2014, 2016). Stimulation effects were independent of stimulation hemisphere in young adulthood but memory improvements in older adults were only observed following left hemisphere stimulation (Manenti et al., 2013). Nevertheless, beneficial stimulation effects have also been observed 48 h later (Sandrini et al., 2014, 2016) or up to 1 month after applying atDCS (Sandrini et al., 2014) in older adults. However, there are also other studies that failed to replicate these results in younger adults (Smirni et al., 2015) or even reported an increase of false alarm rates in episodic memory (Zwissler et al., 2014).

Fewer studies involving younger adults investigated potential effects of atDCS over the temporal or parietal cortices. For instance, Jones and colleagues showed facilitations in verbal long-term memory in younger adults when atDCS was administered during encoding but not during maintenance over the left PPC with a current of 1.5 mA for 15 min (Jones et al., 2014). Bilateral atDCS (i.e., the anode over the left and the cathode over the right temporal cortex or the PPC) during the recognition phase of a word list learning task showed differential effects in younger adults: recognition performance of old (hit) but not new items (correct rejection) was improved in the temporal cortex stimulation group whereas recognition performance of new but not old items was improved in the PPC stimulation group (Pisoni et al., 2015). Such findings indicate that potential effects of facilitation vs. inhibition of new afferent information

depend on the stimulation site and, hence, on the underlying brain circuitry of the respective cognitive domain. Evidence from healthy aging studies is, so far, missing, but improvements in recognition memory up to 4 weeks after stimulation (over the left DLPFC or bilateral over temporoparietal areas with 1.5–2 mA for 15–30 min) had been observed in Alzheimer's disease patients (Ferrucci et al., 2008; Boggio et al., 2009).

Thus, far, there are even fewer studies, which investigated effects of tDCS on spatial learning and memory. Nevertheless, the available results offer some optimism regarding tDCS-induced spatial memory plasticity in the adult lifespan. In younger adults, applying atDCS at 2 mA for 20 min over the right centrotemporal cortex during spatial navigation in a virtual environment facilitated later performance in a sketch map drawing test that required the participants to re-draw the layout of the virtual environment from memory. Interindividual differences in the sense of direction predicted atDCS-induced spatial navigation benefits, with low-performing individuals benefitting more (Brunyé et al., 2014).

Regarding the underlying neural correlates, animal literature, so far, provides only tentative evidence that BDNF and neurogenesis in the dentate gyrus might play a role in atDCS-induced improvements in episodic and spatial memory performance (see Bennabi et al., 2014 for review). Recent studies combining tDCS with fMRI investigated the effects of tDCS on activation and functional connectivity within the fronto-hippocampal-striatal network in humans (Hampstead et al., 2014; Krishnamurthy et al., 2015; see **Figure 3** for an overview diagram). Network-modulatory effects of tDCS were investigated by applying 20 min of 2 mA tDCS offline before the participants performed a spatial navigation task assessing hippocampal- vs. striatal-based spatial memory in the MR scanner. The anode and cathode were placed over midline parietal and frontal regions, respectively. The parietal-anode/frontal-cathode montage had no effect on hippocampal activity in both hippocampal- and striatal-dependent spatial navigation conditions but was associated with increased right caudate activation during sequential stimulus-response-based spatial navigation and greater connectivity between the left prefrontal and the parietal cortex. In contrast, the frontal-anode/parietal-cathode montage was associated with increased right hippocampal and bilateral activity in prefrontal regions during hippocampus-dependent navigation and with greater connectivity between prefrontal regions and the right hippocampus (Hampstead et al., 2014). The parietal-anode/frontal-cathode montage was further associated with increased fMRI resting-state functional connectivity between the superior parietal lobule and other brain regions of the spatial learning and memory network 10 min after the stimulation (Krishnamurthy et al., 2015). To our knowledge, only one study has, so far, investigated effects of atDCS on spatial memory in healthy older adults (Flöel et al., 2012). In a 2-sessions within-subject cross-over design, atDCS with a current of 1 mA for 20 min over the right temporoparietal cortex was applied during the learning phase of an object-location learning paradigm. Despite lacking tDCS-induced effects during learning, healthy older adults showed tDCS-induced benefits of memory recall 1 week after stimulation, indicating that tDCS can have medium- to long-term effects on spatial memory even in old age.

Taken together, only a small number of studies have investigated the effects of atDCS on episodic and spatial memory in older adults and existing findings indicate further needs of systematic investigations. Of note, in the domain of working memory the results are rather mixed. Two possible factors may explain the, for now, inconsistent results. Given that interindividual variability in widespread changes in brain physiology and brain plasticity increase with old age, optimal tDCS parameters (i.e., current intensity, stimulation duration, and frequency, electrode montage) for applications in older adults can be expected to differ from those for younger adults (Zimerman and Hummel, 2010; Fertonani et al., 2014). Thus, developing age-appropriate stimulation protocols require more systematic investigations. Furthermore, across various cognitive functions multi-session tDCS applications seem to be more efficient compared to single-session application in older adults (Hsu et al., 2015). Thus, tDCS applied in combination with cognitive training over multiple sessions may provide the added neural boost for enhancing and prolonging transfer effects that are known to be reduced or lacking in older adults (see **Figure 2** for a schematic diagram).

COMBINING COGNITIVE TRAINING AND tDCS

Very recently, a few studies have started to explore the effects of combining motor learning (Reis et al., 2009) or cognitive training with atDCS interventions in younger (Meinzer et al., 2014; Richmond et al., 2014; Au et al., 2016; Looi et al., 2016; Mancuso et al., 2016) and older adults (Jones et al., 2015b; Stephens and Berryhill, 2016). In younger adults, first evidence for atDCS-enhancing effects on training gains have been shown across various cognitive functions, e.g., arithmetic operations (Looi et al., 2016), language (Meinzer et al., 2014), and working memory (Richmond et al., 2014; Au et al., 2016). For episodic memory though, there is yet no study investigating synergistic effects of atDCS and episodic memory training neither in healthy young nor older populations. There is, to the best of our knowledge, only one study that applied 2 mA atDCS for 25 min over the left DLPFC during 10 sessions of memory training in Alzheimer's disease patients without being able to show ameliorating effects of atDCS on the training-related memory improvements (Cotelli et al., 2014).

With respect to working memory, Richmond et al. (2014) let their participants take part in an adaptive training over 10 sessions concurrent with either 15 min of 1.5 mA atDCS or sham stimulation over the left DLPFC. The results showed that compared to sham stimulation atDCS enhanced learning and near-transfer to other non-trained working memory tasks. Far-transfer or maintenance effects were not investigated. Enhanced training performance due to additional atDCS could also be reported by Au et al. (2016). In seven sessions participants

received 25 min of 2 mA atDCS over the right or left DLPFC concurrent with a visual-spatial working memory training. Near-transfer to non-trained visual or spatial working memory tasks could also be observed but only in the right DLPFC stimulation group which is in line with the right-hemispheric dominance of the DLPFC for spatial working memory functions (Wager and Smith, 2003). Critically, the authors also assessed maintenance effects and could show that the atDCS- enhanced training effects remained stable up to 8 months after training completion (Au et al., 2016). Thus, there is promising evidence for prefrontal atDCS-enhancing effects on immediate training gains and near-transfer effects. The effects on far-transfer effects still need to be explored. Taken together, the currently existing empirical findings in younger adults lend support to the idea that concurrent atDCS-training applications might bolster older adults' limited working memory training and transfer gains.

There is already some preliminary but promising evidence suggesting that older adults can benefit from combined atDCS and training interventions. For instance, older participants who received 30 min of 2 mA atDCS over the DLPFC during 10 sessions of computer-based cognitive training showed greater improvements in verbal working memory compared to a sham stimulation group. This effect maintained up to 28 days (Park et al., 2014). Near- and far-transfer effects were not assessed. Jones et al. (2015b) could provide evidence for maintenance effects of atDCS on training-related improvements and transfer effects in older adults. In their study older adults received sham or atDCS over the right DLPFC, parietal, or alternating prefrontal/parietal cortices (stimulation site was varied across training sessions). The participants were randomly assigned to one of the four groups and were matched according to age, education and cognitive status. In 10 sessions, after 10 min of 1.5 mA tDCS participants performed a working memory task. All groups benefited from working memory training and showed significant improvements in the trained and near-transfer tasks. Critically, after 1 month of no contact, only the participants in the atDCS group maintained the significant improvement for the trained and near-transfer tasks. Interestingly, the magnitude of this improvement did not vary as a function of stimulation site condition indicating that all stimulation sites equally well targeted the fronto-parietal network, which could also be confirmed by current modeling (Jones et al., 2015b). In a more recent study of the same group, standard far-transfer effects (i.e., processing speed, cognitive flexibility, arithmetic) and ecologically valid far-transfer effects were assessed to investigate translation to other cognitive abilities and daily activities as e.g., scheduling appointments, driving, safety awareness, and route planning. In this study older adults took part in a 5-day working memory training combined with 15 min of either sham, 1, or 2 mA atDCS over the right DLPFC. Comparable to their first study, the authors replicated the general improvement in the trained task across all groups. Critically, 2 mA atDCS induced significantly greater far-transfer gains after 1 month of no contact (Stephens and Berryhill, 2016). Taken together, working memory training when combined with atDCS seems to offer promise in enhancing and maintaining older adults's working memory training as well as near- and far-transfer gains. Whether the effect sizes of atDCS-enhancing training gains in older adults are comparable to those of younger adults needs to be determined.

LIMITATIONS AND OUTLOOK

Notwithstanding the promising effects of combined atDCS and cognitive training interventions, there are several open questions and limitations that should be addressed in future studies. As there was no comparison group in all the combined atDCS and cognitive training studies that underwent only tDCS, no firm conclusions about the synergistic effects of brain stimulation and cognitive training intervention can yet be drawn. Thus, future work should include a tDCS-only control group to clarify whether tDCS, cognitive training and the combination of tDCS and cognitive training contribute differently to short- and long-term benefits. The response to tDCS has been shown to be state-dependent and critically vary as a function of interindividual differences in educational level (Berryhill and Jones, 2012) or baseline task performance (Jones and Berryhill, 2012; Tseng et al., 2012). It is likely that tDCS interacts with individual endogenous activity levels within the region of targeted neurons, rather than exerting a homogeneous effect across individuals (Learmonth et al., 2015). Further, the results of a previous study could show that tDCS effects were boosted after supplying a task strategy or financial motivation (Jones et al., 2015a). Thus, considerable attention should be paid to the thorough assessment of baseline task ability and the influences of motivational factors when designing future tDCS and combined tDCS and training interventions. Given the existence of an inverted-U relationship between DA level and cognition (Li and Sikström, 2002; Cools and D'Esposito, 2011) and non-linear, dose-dependent effects of levodopa on tDCS-induced plasticity (Monte-Silva et al., 2010), atDCS could also shift performance beyond the optimal range. Thus, interindividual differences in baseline DA-level should be kept in mind when interpreting interindividual differences in tDCS-induced effects. Furthermore, so far, we can only infer that the effects of combined tDCS and training interventions on working memory may be mediated through the strengthening of functional connectivity in the fronto-striatal-parietal as well as dopaminergic modulation of this circuitry (Jones et al., 2015b). Future fMRI and PET studies should, therefore, investigate the underlying neuronal mechanisms of combined tDCS and training effects in order to explore whether these effects go beyond the known training-induced changes in brain activation and functional connectivity in the fronto-striatal-parietal network (e.g., Dahlin et al., 2008a; Jolles et al., 2013; Kühn et al., 2013; Thompson et al., 2016) as well as cortical and striatal DA signaling (McNab et al., 2009; Bäckman et al., 2011b). Given that older adults' reduced cognitive plasticity following cognitive training interventions is particularly limited in the domain of episodic memory, future studies should investigate whether similarly promising results can be shown for episodic memory and maybe other cognitive domains. Furthermore, as older adults are particularly limited in

transfer effects of cognitive training interventions, future work should by default include both, near- and far-transfer tasks and invest more effort in developing protocols that enable the investigation of transfer particularly to daily activities. Related to this, future work should also focus on the home-based applicability of combined tDCS and training interventions to pave ways for more ecologically valid interventions that may promote the maintenance of autonomy and quality of life in old age.

AUTHOR CONTRIBUTIONS

SP, FT, and SL did substantial contributions to the conception and design of the review article. SP, FT, and SL drafted the work and revised it critically for important intellectual content. SP, FT, and SL did the final approval of the version, to be published. Finally SP, FT, and SL agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ACKNOWLEDGMENTS

The work was supported by the Deutsche Forschungsgemeinschaft (DFG) through the Collaborative Research Center (SFB 940/2 "Volition and Cognitive Control: Mechanisms, Modulators, and Dysfunction") Project B3 (PIs: SL, FT, Michael Smolka) as well as a grant to SL (LI 879/18-1) and SP (PA 2972/1-1). Further support was provided by a grant to SL (FZK 01GQ1424D) of the Bundesministerium für Bildung und Forschung (BMBF). In addition, we acknowledge support by the Open Access Publication Funds of the TU Dresden.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer YS declared a shared secondary affiliation, though no other existing collaboration, with one of the authors SL to the handling Editor, who ensured that the process nevertheless met the standards of a fair and objective review.

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 28 February 2017
doi: 10.3389/fnagi.2017.00041

Evidence for Narrow Transfer after Short-Term Cognitive Training in Older Adults

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The degree to which "brain training" can improve general cognition, resulting in improved performance on tasks dissimilar from the trained tasks (transfer of training), is a controversial topic. Here, we tested the degree to which cognitive training, in the form of gamified training activities that have demonstrated some degree of success in the past, might result in broad transfer. Sixty older adults were randomly assigned to a gamified cognitive training intervention or to an active control condition that involved playing word and number puzzle games. Participants were provided with tablet computers and asked to engage in their assigned training for 30 45-min training sessions over the course of 1 month. Although intervention adherence was acceptable, little evidence for transfer was observed except for the performance of one task that most resembled the gamified cognitive training: There was a trend for greater improvement on a version of the corsi block tapping task for the cognitive training group relative to the control group. This task was very similar to one of the training games. Results suggest that participants were learning specific skills and strategies from game training that influenced their performance on a similar task. However, even this near-transfer effect was weak. Although the results were not positive with respect to broad transfer of training, longer duration studies with larger samples and the addition of a retention period are necessary before the benefit of this specific intervention can be ruled out.

Keywords: cognitive training intervention, reasoning ability, video games, transfer of training, cognitive aging

OPEN ACCESS

Edited by:
Pamela M. Greenwood, George Mason University, USA

Reviewed by:
Cyrus Foroughi, United States Naval Research Laboratory, USA
Jacky Au, University of California, Irvine, USA

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Received: *30 October 2016*
Accepted: *15 February 2017*
Published: *28 February 2017*

Citation:
Souders DJ, Boot WR, Blocker K, Vitale T, Roque NA and Charness N (2017) Evidence for Narrow Transfer after Short-Term Cognitive Training in Older Adults. Front. Aging Neurosci. 9:41. doi: 10.3389/fnagi.2017.00041

INTRODUCTION

Increases in life expectancy, along with decreasing fertility rates, have led to older adults making up a larger proportion of the global population than ever before (i.e., Population Aging; United Nations, 2015). This trend is significant because age-related changes in cognition can threaten the ability of older adults to live independently, and the societal cost of supporting an increasing number of older adults may be quite large. Considering this demographic trend and its implications, exploring methods to stave-off age-related cognitive decline is important, and has been of increasing interest to the scientific community (e.g., Hertzog et al., 2008).

Greenwood and Parasuraman (2010) hypothesized that successful cognitive aging involves the interaction between neuronal plasticity (i.e., structural brain changes on the cellular level stimulated by experience) and cognitive plasticity (i.e., changes in cognitive strategy). This would be the case if (1) the normal mechanisms of neuronal plasticity are sustained into old age, (2) exposure to novelty in terms of new experiences continues to drive changes in neuronal plasticity, and (3) neural

integrity is upheld by beneficial diet, exercise, and other factors. There are a number of studies that support the idea that older adults' brains retain plasticity (i.e., the ability to adapt or benefit from experiences), which suggests that by making healthy lifestyle choices (e.g., balanced diet, regular exercise) and/or engaging in cognitively demanding activities, older adults can maintain a high level of cognitive functioning (reviewed in detail in Greenwood and Parasuraman, 2012). In other words, new learning can result in cognitive plasticity, which encourages neuroplasticity, which then supports additional learning. This theoretical account is consistent with claims made by the proponents of brain training programs.

The potential benefits of cognitive training interventions aimed at averting or reducing cognitive decline in old age have led to the emergence of commercial programs with the aim of improving cognition through game-like tasks. Brain training is currently a billion dollar industry (Commercialising Neuroscience: Brain Sells, 2013; Sharp Brains, 2013). However, the degree to which brain training (especially commercially available brain training programs) is effective, remains controversial. Currently available data have spawned dissenting "consensus" statements, one arguing against the efficacy of brain training with respect to meaningfully improving cognition (A consensus on the brain training industry from the scientific community, 2014) and one arguing for it (Cognitive Training Data, 2014). These opposing statements with hundreds of academic signatories highlight that the effectiveness of commercial cognitive training for older adults remains unclear. Many of the promised benefits of brain training are vague and the evidence that brain training companies point to in support of their products' effectiveness is often flawed (Simons et al., 2016).

Cognitive training as a means of combatting age-related cognitive decline hinges on the notion that training specific cognitive functions that support the performance of a variety of tasks (e.g., working memory) can lead to improvements on many tasks beyond the trained one (i.e., far transfer). Jonides (2004) has argued that transfer from a trained to an untrained task occurs when the two tasks share processing components and activate overlapping brain regions. Many efforts to induce far transfer have focused on training working memory, due to its integral and ubiquitous role in many other cognitive and everyday tasks, with pre- to post-training increases sometimes observed in younger adults' executive functions and reasoning or memory (e.g., Jaeggi et al., 2008; Au et al., 2015). However, these findings are far from uncontroversial (e.g., Morrison and Chein, 2011; Shipstead et al., 2012; Melby-Lervåg and Hulme, 2013; Melby-Lervåg et al., 2016).

In some cases, transfer to untrained cognitive tasks that recruit working memory in older adults seems more limited relative to younger adults, so it is important to examine the effect of training in both populations. Dahlin et al. (2008) randomly assigned older and younger adults to a group that received memory-updating training or to a control group that received no training. Transfer to tasks involving perceptual speed, working memory, episodic memory, verbal fluency, and reasoning was assessed after 5 weeks of training and in an 18-month follow-up post-training. Results showed that both younger and older adults that received the training improved on the trained tasks, and these benefits were still evident at the 18-month follow-up. Younger participants also showed transfer to a 3-back task, which required updating similar to the trained task but was not trained. However, older participants in this study did not show similar transfer. Further, in younger adults, no other transfer was observed to tasks of fluency or reasoning, lending support to the notion that transfer is only possible when untrained tasks utilize similar processing components (in this case, the striatum) as the trained tasks.

It is reasonable to expect improvement on trained cognitive tasks after undergoing training, and studies with older adults are consistent with this expectation (e.g., Ball et al., 2002; Willis et al., 2006). However, examples of successful far transfer from cognitive training to everyday functioning are rare. Follow-up studies from the ACTIVE trial and other studies using speed of processing training are some of the most widely cited examples in the literature of far transfer to everyday functioning, attributed to older adults' participation in cognitive training. Participants that had taken part in either the speed of processing or reasoning training in the ACTIVE trial were reported to have lower rates of at-fault collision involvement in the 6 years following their involvement in the study (Ball et al., 2010), though higher rates of not-at-fault collisions with no overall collision benefit observed. Other studies that have used this speed of processing training in older adults have found that participants receiving training have reported less driving difficulty, more driving time, and longer driving distances than controls (Edwards et al., 2009b), as well as fewer driving cessations after a 3-year follow-up period (Edwards et al., 2009a). Still, overall, the literature is mixed, and the ACTIVE trial and various follow up studies, when examined closely, seem to provide only limited evidence for the benefits of training (Simons et al., 2016).

Due to the precarious support for cognitive training's benefit for older adults, it is important to compare observed cognitive benefits to those of a strong, active control group with surface plausibility. Mentally stimulating activities, such as word or number puzzles, have long been commonly thought to stave off cognitive decline, though evidence for their benefit is lacking. The current study investigated the cognitive effects in older adults using a gamified cognitive training suite (Mind Frontiers) compared to those in an active control group that played similarly-delivered word and number puzzles (crossword, word search, and Sudoku) that were believed by participants to be cognitively beneficial (Boot et al., 2016).

METHODS

Participants

Our goal was to obtain a sample 60 older adults (age 65+) to be randomly and evenly distributed between two conditions (intervention and control; $N = 30$ per group). Due to the attrition of 18 participants, 78 older adults were recruited from the Tallahassee, Florida region, the majority of whom were recruited via the lab's participant database. Six participants dropped out of the study from the control group, eight from the intervention group, and four before random assignment. All participants were prescreened to assess basic demographic information as well as to ensure that they met the criteria necessary to qualify

for the study (e.g., English fluency, no limiting physical and/or sensory conditions). To ensure that potential participants were cognitively intact, the short portable mental status questionnaire (Pfeiffer, 1975) was used, as well as the logical memory subscale of the Wechsler Memory Scale (age-adjusted; Wechsler, 1997). Descriptive information concerning the sample is available in **Table 1**. This study was carried out in accordance with the recommendations of the Belmont Report with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by Florida State University's Human Subjects Committee. Participants were compensated $20 for the initial lab visit, $60 for completing the at-home training, and $20 after returning the training materials and finishing the post-training cognitive assessment, totaling $100.

Study Design

Once eligibility was confirmed, participants were randomly assigned to either the intervention or control conditions and completed a battery of cognitive tests to assess baseline cognitive functioning. Participants then attended a 2-h training session, which involved a tutorial on how to use the provided tablet (10 inch Acer Iconia A700), as well as how to play the games they were assigned per their condition. Over the course of 1 month, participants in both groups were asked to play three games per day (including weekends) for 15 min each, totaling 45 min of playtime each session. Journals were given to participants to record their playtime.

Participants in the intervention condition were provided tablets with the Mind Frontiers application preinstalled on their system. Mind Frontiers is a Western-themed game hub comprised of seven gamified cognitive tasks modified to improve the tasks' aesthetics, as well as to include motivating feedback to encourage participants to continue playing the games (see Baniqued et al., 2015 for more details). These gamified tasks were designed to exercise inductive reasoning, planning, spatial reasoning ability, speed of processing, task switching, and working memory updating. For an overview of the games included in Mind Frontiers, see **Table 2**. Participants played a subset of the seven games that varied each day to ensure that the same games were not played in consecutive sessions. In comparison, participants assigned to the control condition were tasked with playing three common puzzle games each day (crossword, Sudoku, and word search). In both conditions, tablets were locked-down so that participants could not use the tablet for any other purpose. After 1 month of playtime, participants returned to the laboratory with the tablets and journals and completed the post-training cognitive battery.

TABLE 1 | Descriptive information regarding the sample of older adults that participated in the study.

Variable	Overall $N = 60$	Mind frontiers $n = 30$	Control $n = 30$
AGE IN YEARS MEAN (*SD*)			
	72.35 (5.20)	72.27 (4.88)	72.43 (5.58)
GENDER *N* (%)			
Female	34 (56.7%)	17 (56.7%)	17 (56.7%)
Male	26 (43.3%)	13 (43.3%)	13 (43.3%)
ETHNICITY *N* (%)			
African-American	3 (5%)	1 (3.3%)	2 (6.7%)
Caucasian	55 (91.7%)	29 (96.7%)	26 (86.7%)
Hispanic	2 (3.3%)	0 (0%)	2 (6.7%)
EDUCATION *N* (%)			
High school/some college	20 (33.3%)	12 (40.0%)	8 (26.7%)
College degree	40 (66.7%)	18 (60.0%)	22 (73.3%)

Measures

Cognitive Battery

A cognitive battery was administered before and after the at-home training to establish a baseline performance level and to measure change in performance as a function of training. The battery was comprised of nine computer and paper and pencil-based cognitive and perceptual assessments[1].

Reasoning Ability

Four computerized tests were used to assess reasoning ability: form boards, letter sets, paper folding, and Raven's Advanced Progressive Matrices.

Form boards

For each problem, participants were shown a target shape and had to select which of the presented shapes would fill the target shape exactly (Ekstrom et al., 1976). This task primary tapped visuospatial reasoning. Two alternative forms were presented to participants before and after training (counterbalanced). Participants were allotted 8 min to complete as many problems correctly as possible out of a total of 24 problems (primary measure).

Letter sets

For each problem, participants were presented with a set of five strings of letters (Ekstrom et al., 1976). Participants identified the one letter set that did not conform to the same rule as the others. This task served as a measure of inductive reasoning. Participants were allowed 10 min to complete as many problems as possible out of 15. Two alternative forms were presented to participants before and after training (counterbalanced). The primary measure of performance was the number of correctly solved problems.

Paper folding

For each problem, participants were shown a folded piece of paper with a hole punched through it (Ekstrom et al., 1976). The task of the participant was to identify the pattern that would result when the paper was unfolded. This represented a measure of spatial reasoning ability. Participants were given 10 min to solve a maximum of 12 problems. Two alternative forms were counterbalanced across pre- and post-testing. The primary

[1]The battery originally contained 10 measures, but due to a programming error data from an n-back working memory test could not be analyzed.

TABLE 2 | A brief description of each of the seven games included in the Mind Frontiers application.

Mind Frontiers Game	Description
Ante Up	Players are shown cards organized in a certain pattern and must replicate this pattern over the course of a specified number of moves with the cards they are provided. This game exercises planning ability and is based on the Tower of London test (Shallice, 1982).
Irrigator	Players are tasked with building a water pipeline from a well to various targets before time runs out using provided pipe pieces that change with each turn. As players progress, various obstacles must be avoided to reach the target. This game challenges visuospatial processing and is similar to a training task previously used by Mackey et al. (2011).
Pen 'Em Up	Players must sort objects dropped from a UFO into two pens by swiping either left or right based on specific criteria provided at the start. The sorting criteria varies based upon the objects' characteristics (e.g., trees, farm animals) or style (e.g., plain, striped). This task-switching game is based on the training developed by Karbach and Kray (2009).
Riding Shotgun	Players are riding in a horse drawn wagon, and the scene in front of the wagon contains a grid of tiles that could light up one at a time. The player must remember the sequence in which tiles of the grid are illuminated. They must then replicate the pattern in the correct order. This task taps visuospatial memory and is similar to the training provided by Klingberg et al. (2002).
Safe Cracker	Players are tasked with cracking codes to open various safes and collect the money inside before the time runs out. Stimuli are series of letters, numbers, months, etc., and the player must determine the next item in the sequence. This game is intended to exercise inductive reasoning skills and is similar to the training described by Willis and Schaie (1986).
Sentry Duty	Players are tasked with remembering the sequence in which sentries outside of a fort wall lift a lantern and say a word. They must decide whether the location and word of the current sentry matches that of the sentry *N* turns prior. This dual n-back game challenges working memory and is similar to the training task developed by Jaeggi et al. (2008).
Supply Run	Players adopt the role of a merchant traveling through a town. Townspeople request items along the way. The player must remember the last item requested from each of the provided categories so they may be purchased at a town store at the end of the trip. This working memory game is similar to the training used by Dahlin et al. (2008).

measure of performance was the number of correctly solved problems.

Ravens matrices

Each problem presented participants with a complex pattern (in the form of a 3 × 3 matrix; Raven, 1962). The task of the participant was to identify the option that would complete the missing piece from the pattern. This was a measure of fluid intelligence. Participants were given up to 10 min to solve a maximum of 18 problems. Two alternative forms were counterbalanced across pre- and post-testing. The number of correctly solved problems served as the primary measure of performance.

Processing Speed

Two measures of processing speed were administered: pattern comparison (paper and pencil) and simple/complex response time (computer test).

Pattern comparison

Participants viewed several pairs of line figures on each page and had to write "S" or "D" (for "same" or "different") between them depending on whether the figures were identical or not (Salthouse and Babcock, 1991). Participants completed two pages each assessment, with 30 s allowed for each page. Two parallel forms were administered before and after training, and form order was counterbalanced. Total number of correct responses within the allotted time was used as the primary measure of performance.

Simple/choice reaction time

This task was similar to the one administered previously by Boot et al. (2013). In two blocks of trials, participants saw a green square appear at the center of the screen and had to push a key as quickly as possible when it appeared (30 trials each block). In another block of trials, the box appeared to the right or left side of the screen and participants pushed one of two buttons to indicate its location (60 trials). Average speed of accurate trials was used as the primary measure of performance.

Memory

One computerized test was used to assess memory.

Corsi block tapping

This task (similar to Corsi, 1972) was run using PEBL (Mueller and Piper, 2014). Participants viewed a spatial array of nine blue squares on the screen. These squares changed one at a time from blue to yellow, then back to blue, in a randomized sequence. Participants were asked to replicate the observed sequence using the mouse and then click the done button at the bottom of the screen. Each participant completed three unrecorded practice trials and was given feedback in order to become familiar with the task. The recorded task's sequence started with two squares and each participant completed two trials of each sequence length before the length increased by one. The sequence increased by one whenever the participant correctly demonstrated at least one of the two sequences at that sequence length, and the task ended if the participant failed both of the sequences at a given length. The primary measure of this task was a span measure based on the length of the sequence when the task ended.

Executive Control

A task-switching paradigm (computerized) and Trails B (paper and pencil) were used to assess executive control.

Task-Switching

This task was similar to the one used by Boot et al. (2013). Participants viewed digits that appeared one at a time at the

center of the screen for 2.5 s each and had to judge whether each digit was high or low (above or below 5), or whether it was odd or even depending on the color of the square surrounding the digit (blue or pink). A blue square indicated participants had to judge whether the number was high or low, while a pink square indicated that participants had to judge whether the digit was odd or even. The digits 1 through 9 were randomly presented, with the exception that the digit 5 was never used. The "z" key was used to indicate either low or odd while the "/" key was used to indicate high or even. Participants completed four blocks of 15 trials each in which they only had to perform one task or the other. Then they completed a version of the task in which the color of the background was randomized, meaning they often had to switch from one task to the other. After 15 practice dual-task trials, participants completed 160 real trials. Switch cost, or the decrement involved in having to switch from one task to another, was used as the primary measure of task-switching. This was calculated by comparing the average performance (accurate response time) of single task blocks of trials to the dual-task block.

Trails B (controlling for Trails A)

In this task, participants were presented with a sheet of paper containing numbers and letters (Reitan, 1955). Participants were asked to connect the numbers and letters in sequential order, alternating between numbers and letters (1, A, 2, B, etc.). Completion time was the primary measure of performance. Completion time of Trails A, in which participants performed the same task but did not have to switch between numbers and letters, was subtracted from Trails B completion time to provide a measure of switch cost.

RESULTS

Intervention adherence was acceptable in that participants engaged in, on average, more than 70% of their assigned training sessions according to their journals ($M = 22$ sessions, $SD = 9.0$ vs. $M = 23$ sessions, $SD = 7.7$ for the control and intervention groups, respectively). To help interpret results in light of potential placebo effects, participants' expectations for improvement were assessed after training. These data are reported elsewhere, so will not be discussed in detail, but in general participants in each group either expected a similar amount of improvement as a result of training, or expected the control condition to improve cognition more (Boot et al., 2016). Any differential improvement by the intervention group is thus unlikely due to a placebo effect. Next we turn to potential changes in performance on tasks in the cognitive battery. Our general analysis approach was to explore whether groups differed on their post-training performance controlling for pre-training scores. Scores for all measures are reported in **Table 3** and standardized (*z*-score) improvement scores are represented in **Figure 1**. Note that the degrees of freedom fluctuate slightly in the reported analyses due to occasional missing data.

Reasoning Ability

Form Boards

Time 2 (post-training) scores were entered into an ANCOVA with Time 1 (baseline) scores as a covariate and group (Mind Frontiers vs. Control) as a between-participant variable. This analysis revealed a significant effect of the Time 1 covariate [$F_{(1, 57)} = 21.65$, $p < 0.001$, $\eta_p^2 = 0.28$], but no effect of group [$F_{(1, 57)} = 3.04$, $p = 0.09$, $\eta_p^2 = 0.05$]. Adjusted marginal means revealed numerically better post-training performance for the control group relative to the intervention group ($M_{adj} = 6.25$, $SE = 0.53$ vs. $M_{adj} = 4.95$, $SE = 0.53$ for the control and intervention groups, respectively).

Letter sets

Time 2 (post-training) scores were entered into an ANCOVA with Time 1 (baseline) scores as a covariate and group (Mind Frontiers vs. Control) as a between-participant variable. This analysis revealed a significant effect of the Time 1 covariate [$F_{(1, 55)} = 29.55$, $p < 0.001$, $\eta_p^2 = 0.35$], but no effect of group [$F_{(1, 55)} = 1.73$, $p = 0.19$, $\eta_p^2 = 0.03$]. Adjusted marginal means were similar for the control group and the intervention group ($M_{adj} = 9.17$, $SE = 0.37$ vs. $M_{adj} = 9.86$, $SE = 0.37$ for the control and intervention groups, respectively).

Paper folding

Time 2 (post-training) scores were entered into an ANCOVA with Time 1 (baseline) scores as a covariate and group (Mind Frontiers vs. Control) as a between-participant variable. This analysis revealed a significant effect of the Time 1 covariate [$F_{(1, 56)} = 11.02$, $p < 0.01$, $\eta_p^2 = 0.16$], but no effect of group [$F_{(1, 56)} = 0.30$, $p = 0.59$, $\eta_p^2 = 0.005$]. Adjusted marginal means were similar for the control group and the intervention group ($M_{adj} = 4.76$, $SE = 0.40$ vs. $M_{adj} = 4.45$, $SE = 0.41$ for the control and intervention groups, respectively).

Ravens

Time 2 (post-training) scores were entered into an ANCOVA with Time 1 (baseline) scores as a covariate and group (Mind Frontiers vs. Control) as a between-participant variable. This analysis revealed a significant effect of the Time 1 covariate [$F_{(1, 56)} = 21.89$, $p < 0.001$, $\eta_p^2 = 0.28$], but no effect of group [$F_{(1, 56)} = 0.002$, $p = 0.96$, $\eta_p^2 < 0.001$]. Adjusted marginal means were similar for the control group and the intervention group ($M_{adj} = 3.58$, $SE = 0.32$ vs. $M_{adj} = 3.60$, $SE = 0.32$ for the control and intervention groups, respectively).

Processing Speed

Simple/Choice Reaction Time

An aggregate speed measure was created by averaging simple and choice reaction time conditions. Time 2 (post-training) scores were entered into an ANCOVA with Time 1 (baseline) scores as a covariate and group (Mind Frontiers vs. Control) as a between-participant variable. This analysis revealed a significant effect of the Time 1 covariate [$F_{(1, 57)} = 49.52$, $p < 0.001$, $\eta_p^2 = 0.47$], but no effect of group [$F_{(1, 57)} = 0.55$, $p = 0.46$, $\eta_p^2 < 0.01$]. Adjusted marginal means were similar for the control group and the intervention group ($M_{adj} = 376$ ms, $SE = 6.58$ vs. M_{adj}

TABLE 3 | Means and 95% CIs for all measures.

Test	Measure	Group	n	Pretest	Posttest	Difference	ANCOVA Group Effect
Form Boards	#Correct	Control	30	5.20 [4.07, 6.33]	6.20 [4.88, 7.52]	1.00 [−0.38, 2.38]	$p = 0.09$, $\eta_p^2 = 0.05$
		MF	30	5.40 [3.93, 6.87]	5.00 [3.82, 6.18]	−0.40 [−1.51, 0.71]	
Letter Sets	#Correct	Control	29	9.17 [8.37, 9.98]	9.17 [8.18, 10.17]	0.00 [−0.87, 0.87]	$p = 0.19$, $\eta_p^2 = 0.03$
		MF	29	9.17 [7.91, 10.43]	9.86 [9.00, 10.73]	0.69 [−0.25, 1.63]	
Paper Folding	#Correct	Control	30	4.40 [3.46, 5.34]	4.77 [3.92, 5.61]	0.37 [−0.56, 1.38]	$p = .59$, $\eta_p^2 = 0.005$
		MF	29	4.37 [3.54, 5.22]	4.45 [3.50, 5.39]	0.07 [−0.86, 1.00]	
Ravens	#Correct	Control	29	3.62 [2.69, 4.55]	3.59 [2.89, 4.29]	−0.03 [−0.72, 0.65]	$p = 0.96$, $\eta_p^2 < 0.001$
		MF	30	3.60 [2.62, 4.58]	3.60 [2.78, 4.41]	0.00 [−0.98, 0.98]	
Reaction Time	RT (ms)	Control	30	396 [378, 413]	385 [366, 403]	10 [−3, 23]	$p = 0.46$, $\eta_p^2 < 0.01$
		MF	30	373 [357, 388]	361 [345, 378]	11 [−3, 26]	
Pattern Comparison	#Correct	Control	30	24.40 [21.82, 26.98]	24.17 [21.45, 26.88]	−0.23 [−3.81, 3.34]	$p = 0.57$, $\eta_p^2 < 0.01$
		MF	30	26.07 [23.84, 28.30]	25.37 [23.45, 27.28]	−0.70 [−3.17, 1.76]	
Task Switch	Switch Cost (ms)	Control	30	248 [135, 362]	237 [177, 297]	12 [−100, 123]	$p = 0.22$, $\eta_p^2 = 0.03$
		MF	30	321 [221, 422]	314 [232, 397]	7 [−86, 100]	
Trails B (Minus A)	Switch Cost (s)	Control	29	41 [32, 50]	48 [37, 60]	−7 [−16, 2]	$p = 0.07$, $\eta_p^2 = 0.06$
		MF	30	50 [41, 59]	43 [36, 49]	7 [−2, 16]	
Corsi Block	Span	Control	29	4.50 [4.20, 4.80]	4.59 [4.29, 4.88]	0.09 [−0.15, 0.32]	$p = 0.009$, $\eta_p^2 = 0.16$
		MF	30	4.38 [4.13, 4.64]	4.90 [4.64, 5.16]	0.52 [0.29, 0.74]	

P-values and effect sizes represent the effect of group on posttest performance controlling for pretest performance. Difference scores were computed for all measures such that higher scores represent greater improvement. Effect sizes are reported as partial eta-squared (η_p^2). Cohen (1969) recommendation for interpretation are ~0.01 for small, 0.06 for medium, and 0.14 for large effects.

= 370 ms, $SE = 6.58$ for the control and intervention groups, respectively).

Pattern Comparison

Number of correct responses per allocated time served as the primary measure of performance. Time 2 (post-training) scores were entered into an ANCOVA with Time 1 (baseline) scores as a covariate and group (Mind Frontiers vs. Control) as a between-participant variable. This analysis revealed no significant effect of the Time 1 covariate [$F_{(1, 57)} = 1.66$, $p = 0.20$, $\eta_p{}^2 = 0.02$] and no effect of group [$F_{(1, 57)} = 0.32$, $p = 0.57$, $\eta_p{}^2 < 0.01$]. Adjusted marginal means were similar for the control group and the intervention group ($M_{adj} = 24$, $SE = 1.15$ vs. $M_{adj} = 25$, $SE = 1.15$ for the control and intervention groups, respectively).

Executive Control

Task-Switching

Switch cost in terms of response speed was chosen as the primary measure of performance for this task. Time 2 (post-training) scores were entered into an ANCOVA with Time 1 (baseline) scores as a covariate and group (Mind Frontiers vs. Control) as a between-participant variable. This analysis revealed a significant effect of the Time 1 covariate [$F_{(1, 57)} = 10.42$, $p < 0.01$, $\eta_p{}^2 = 0.16$], but no effect of group [$F_{(1,57)} = 1.56$, $p = 0.22$, $\eta_p{}^2 = 0.03$]. Adjusted marginal means were similar for the control group and the intervention group ($M_{adj} = 246$ ms, $SE = 32.81$ vs. $M_{adj} = 305$ ms, $SE = 32.81$ for the control and intervention groups, respectively).

Trails B (Minus Trails A)

Trails B completion time minus Trails A time served as a measure of executive control. Time 2 (post-training) scores were entered into an ANCOVA with Time 1 (baseline) scores as a covariate and group (Mind Frontiers vs. Control) as a between-participant variable. This analysis revealed a significant effect of the Time 1 covariate [$F_{(1, 56)} = 20.81$, $p < 0.001$, $\eta_p{}^2 = 0.27$], but no effect of group [$F_{(1, 56)} = 3.42$, $p = 0.07$, $\eta_p{}^2 = 0.06$]. Adjusted marginal means revealed numerically better post-training performance (smaller cost for Trails B relative to A) for the intervention group relative to the intervention group ($M_{adj} = 51$ s, $SE = 3.97$ vs. $M_{adj} = 40$ s, $SE = 3.91$ for the control and intervention groups, respectively).

Memory

Corsi Block Tapping

Memory span served as the primary measure of performance. Time 2 (post-training) scores were entered into an ANCOVA with Time 1 (baseline) scores as a covariate and group (Mind Frontiers vs. Control) as a between-participant variable. This analysis revealed a significant effect of the Time 1 covariate

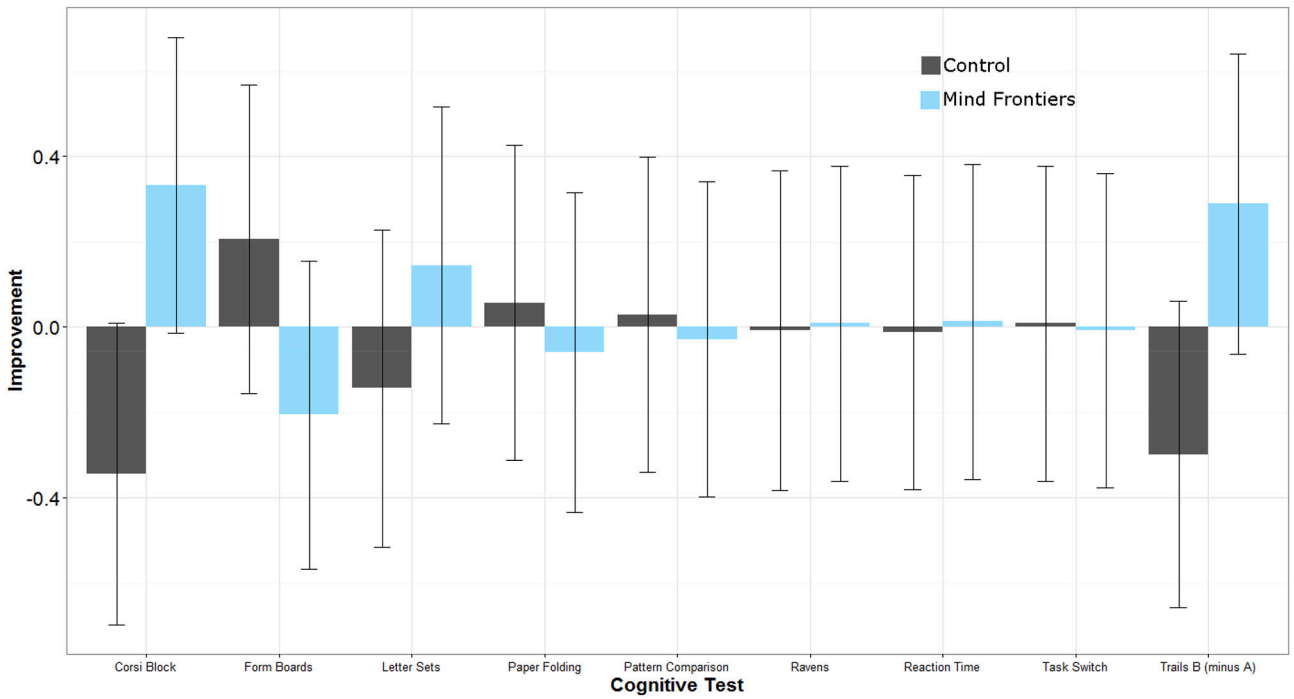

FIGURE 1 | Standardized improvement scores (larger scores represent greater improvement) for all cognitive measures as a function of condition. Error bars represent 95% Confidence Intervals.

$[F_{(1, 56)} = 44.48, p < 0.001, \eta_p{}^2 = 0.44]$, and a trend for an effect of group $[F_{(1, 56)} = 7.31, p = 0.009, \eta_p{}^2 = 0.16]$, with better performance for the intervention group compared to the control group ($M_{adj} = 4.55$, $SE = 0.103$ vs. $M_{adj} = 4.94$, $SE = 0.101$ for the control and intervention groups, respectively). While these data are consistent with a benefit, they should be considered in light of the number of analyses conducted. This effect would not be significant under a conservative Bonferroni correction (alpha 0.05/9 tests = 0.0056).

Game Improvement

The difficulty of each game was adjusted over time depending on participants' performance. Transfer effects are unlikely if participants did not improve their game performance. An algorithm within each game dynamically adjusted difficulty based on successful game performance each time a game was played. For example, for *Riding Shotgun*, correctly remembering a sequence increased the difficulty level and added one more item to the sequence to be remembered. Incorrectly recalling a sequence decreased the difficulty level and removed one item from the sequence to be remembered. We were able to extract game performance data for 25 participants in the Mind Frontiers condition. **Figure 2** depicts the average increase in game difficulty level over the course of training for each game. What was observed was a mixed pattern of improvement. Little improvement was observed for *Sentry Duty*, the game closest to n-back training which has been argued to improve fluid intelligence. However, improvement was observed for the *Riding Shotgun* game which is similar to the corsi block tapping task. A trend for improvement was observed for this outcome measure, though improvement was not significant after correcting for the number of outcome measures tested. Baniqued et al. (2015) similarly found that participants only improved to a small degree on *Sentry Duty* and *Supply Run* compared to other games in a study involving a younger adult sample. Across games, it is unclear whether differences in improvement relate to the

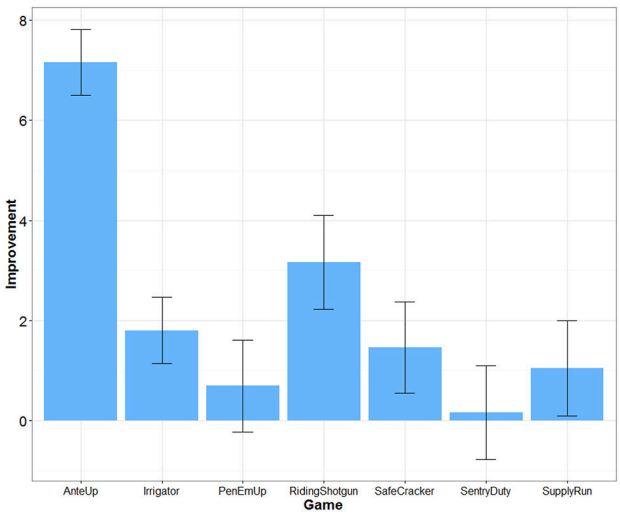

FIGURE 2 | Improvement in game difficulty level as a function of game. Error bars represent 95% Confidence Intervals.

demands of the game or scoring algorithm used by the Mind Frontiers software package.

DISCUSSION

In general, little evidence of transfer was observed in the current study. The only measure that hinted at a benefit for the intervention group relative to the control group was the corsi block tapping task. Within the Mind Frontiers game suite, the *Riding Shotgun* game was essentially a gamified version of this outcome task. Even though a dual n-back training component was part of the current intervention, and previous studies have linked this type of intervention to improved reasoning ability (especially with respect to matrix reasoning tasks, e.g., Jaeggi et al., 2008), no benefits were observed as a result of the intervention. Evidence was largely consistent with a recent review of the literature in that the strongest evidence was for near rather than far transfer of training (Simons et al., 2016). Even this effect, though, was ambiguous given the number of measures collected and the possibility of Type I error.

All studies examining brain training effects need to be considered in light of potential methodological and statistical shortcomings (Simons et al., 2016). Some of these shortcomings may overestimate the potential of brain training and others may underestimate it. Next we present a discussion of these issues.

To guard against the effect of experimenter degrees of freedom (flexibility in the way analyses can be conducted that increase the likelihood of false-positive results; Simmons et al., 2011), it is now generally recommended that studies be preregistered. The current study was not preregistered, but our lab has made a commitment to preregister future cognitive intervention studies based on current recommendations. When study design and analysis approaches are not preregistered, positive findings here and elsewhere provide less convincing evidence in favor of brain training effects. In the absence of preregistration it is unclear whether Type I error was appropriately controlled for. Despite the absence of preregistration, little evidence of transfer was observed. Thus, Type I error control was unlikely to be a large problem here with respect to overestimating the degree of transfer.

To guard against placebo effects that may overestimate transfer effects, studies should include a strong active control condition. The current study had an active control condition featuring games that were not expected to tap the same perceptual and cognitive abilities exercised by the Mind Frontiers game. Further, expectation checks should be implemented to ensure that differential improvement of the intervention group isn't linked to greater expectations for improvement (with differential effort exerted post training for the task with greater expectations). Expectation checks were included in the current study, and it was found that any differential improvement of the intervention group (even though little evidence of transfer was observed) would be unlikely due to a placebo effect (Boot et al., 2016). However, this analysis indicated that the intervention and control groups were not perfectly matched; participants in the Mind Frontiers group actually expected *less* improvement with respect to changes in vision and response time. It is conceivable that the greater expectations of the control group may have masked transfer produced by the intervention (see Foroughi et al., 2016; for evidence that expectations can influence cognitive task performance).

Statistical power should always be considered as well when evaluating the effect of cognitive training interventions. With approximately 30 participants in each group for reported analyses and using an ANCOVA approach, the current study was powered only to detect large effects ($f = 0.40$) with a probability of about 0.80 using an alpha level of 0.05. This means that subtle effects may have gone undetected.

Dosage, retention, and training gains are important issues as well. Had participants adhered perfectly, they would have completed 22.5 h of training. While this is a reasonable dosage in comparison to many studies (e.g., the ACTIVE trial), cognitive intervention effects may require similar engagement over many months or years to provide protection against cognitive decline. Almost no studies to date have examined the effect of long-term engagement in cognitive training (see Requena et al., 2016; for an exception). Studies such as ours, typical of the field, test whether or not there may be a "quick fix" provided by cognitive training. In addition to overall dosage, it may be important to consider dosage of each game within the Mind Frontiers suite. With seven total games, participants were asked to play about 3 h of each game over the course of 1 month. If some of these games are more effective than others at producing near and far transfer, the training schedule of our study may underestimate transfer. Of particular note is the lack of improvement for some games (**Figure 2**). Although game timing parameters were adjusted to be more appropriate for older adult participants, participants appeared to struggle with making progress within some games, especially *Sentry Duty* and *Pen 'Em Up*. Given the difficulty and complexity of these two game in particular, it is possible that improved game instructions and training might help participants make more progress.

Finally, our study examined transfer immediately after training. While it is reasonable to assume effects would be largest immediately after training, others have suggested that cognitive protection provided by cognitive training may not be observed until cognition begins to show steeper declines. Our study did not assess performance at later time points (as the ACTIVE trial has nicely done), so we cannot rule out such "sleeper effects" of cognitive training.

Which particular mechanisms are responsible for the benefits of cognitive training, and the question of whether broad transfer from cognitive training is even possible, are currently controversial topics. No one study provides a definitive answer and evidence needs to be evaluated with respect to the strength of a study's design and analysis approach. The current study contributes to the idea that there are no short-term, easy methods to boost cognitive performance in older adults. Whether other cognitive training interventions or longer-term interventions can produce broad transfer and improve the performance of everyday tasks important for

independence (e.g., driving, financial management) remains to be seen.

AUTHOR CONTRIBUTIONS

WB, DS, and NC designed the study. KB, TV, and DS supervised data collection and data management. NR assisted with data processing and analysis. DS and WB completed the first draft of the manuscript, and all authors were involved in the editing process.

ACKNOWLEDGMENTS

We gratefully acknowledge support from the National Institute on Aging, Projects CREATE III & IV—Center for Research and Education on Aging and Technology Enhancement (www.create-center.org, NIA PO1 AG017211 and NIA P01 AG017211-16A1). We are also grateful to Aptima Inc., especially Charles Dickens, for technical support during this project. We thank Sarah Ahmed for her assistance with manuscript editing.

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Conflict of Interest Statement: Aptima, Inc., designer of the Mind Frontiers software package, provided technical support for the reported project at no cost. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 01 March 2017
doi: 10.3389/fnagi.2017.00042

Maintaining Cognitive Functioning in Healthy Seniors with a Technology-Based Foreign Language Program: A Pilot Feasibility Study

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Researchers have hypothesized that learning a foreign language could be beneficial for seniors, as language learning requires the use of extensive neural networks. We developed and qualitatively evaluated an English training program for older French adults; our principal objective was to determine whether a program integrating technology is feasible for this population. We conducted a 4-month pilot study (16, 2-h sessions) with 14 French participants, (nine women, five men, average age 75). Questionnaires were administered pre- and post-intervention to measure cognitive level and subjective feelings of loneliness or social isolation; however, these scores did not improve significantly. Post-intervention, semi-directive interviews were carried out with participants, and a content/theme analysis was performed. Five main themes were identified from the interviews: Associations with school, attitudes toward English, motivation for learning English, attitudes toward the program's organization, and social ties. The program was found to be feasible for this age group, yet perceived as quite difficult for participants who lacked experience with English. Nonetheless, most participants found the program to be stimulating and enjoyable. We discuss different suggestions for future programs and future directions for foreign-language learning as a therapeutic and cognitive intervention.

Keywords: older adults, foreign language learning, technology, cognitive plasticity, cognitive reserve

OPEN ACCESS

Edited by:
Xiong Jiang,
Georgetown University, USA

Reviewed by:
Neha Sehgal,
Children's Hospital of Philadelphia, USA
Mark Antoniou,
Western Sydney University, Australia

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Received: *15 September 2016*
Accepted: *16 February 2017*
Published: *01 March 2017*

Citation:
Ware C, Damnee S, Djabelkhir L, Cristancho V, Wu Y-H, Benovici J, Pino M and Rigaud A-S (2017) Maintaining Cognitive Functioning in Healthy Seniors with a Technology-Based Foreign Language Program: A Pilot Feasibility Study. Front. Aging Neurosci. 9:42. doi: 10.3389/fnagi.2017.00042

INTRODUCTION

As the population ages, more older adults will be at risk of developing neurodegenerative syndromes such as Alzheimer's disease and other age-related dementias, yet no pharmaceutical treatment has been found to successfully prevent or delay the development of these neurological conditions (Gauthier et al., 2012; Selkoe, 2012). In the absence of pharmacological solutions, alternative interventions demand exploration (Hughes, 2010; Dresler et al., 2013; Law et al., 2014). Thus, there is significant interest in prevention studies that explore the effects of cognitive stimulation and/or physical exercise on the cognitive functioning of older adults. Along with age, genetics, level of physical activity, and subjective cognitive complaints, formal education level has been identified as an influential factor in the development of dementia (Kivipelto et al., 2006). In addition, both depression and loneliness have been shown to negatively affect global cognitive

functioning (Tzang et al., 2015; Zhong et al., 2016), and involvement in social and leisure activities has been associated with a decreased risk of dementia in the elderly (Wang et al., 2002). Due to these findings, educational and social programs geared toward older adults, like *Senior Odyssey*, have been developed with the goal of maintaining healthy cognitive functioning in this population (Stine-Morrow et al., 2007). We propose focusing on a specific type of educational intervention involving second-language learning. To the authors' knowledge, no foreign language-oriented program has been developed for cognitively healthy older adults with the goal of maintaining cognitive functioning.

In gerontology research, language is a significant field of study as the development of cognitive impairment or dementia can greatly affect its use (Forbes-McKay and Venneri, 2005). Furthermore, linguistic ability may contribute to cognitive reserve, the brain's cognitive capacities that allow it to compensate for age or disease-related brain pathology (Gold et al., 2013), also defined as 'functional resistance to structural brain damage' (SantaCruz et al., 2011). Bilingualism has been shown to affect the brain's anatomy, with lifelong bilinguals possessing greater white matter in the frontal lobes than their monolingual counterparts (Olsen et al., 2015). Bilingualism seems to play an important role in cognitive reserve, and thus may help to delay the onset of Alzheimer's (Bialystok et al., 2007). Additionally, novelty and learning have been associated with the maintenence of cognitive plasticity in older adults (Greenwood and Parasuraman, 2010). In this vein, Antoniou et al. (2013) put forth the hypothesis that learning a foreign language could increase cognitive reserve in older adults. They suggest that learning a foreign language could improve cognitive plasticity as learning languages requires the utilization of extensive neural networks, soliciting working memory, inductive reasoning, sound discrimination, speech segmentation, task switching, rule learning, and semantic memory. Moreover, they posit that learning a foreign language could have important social implications, as gaining access to a second language could facilitate communication with foreigners and increase both travel and job opportunities. The development of foreign-language learning programs is needed to test these hypotheses.

Despite the common belief that seniors cannot learn foreign languages as successfully as younger adults or children, it has been shown that older adults do indeed have the capacity to learn a second language (Gómez, 2016). Moreover, seniors can relearn previously acquired words just as well as younger subjects (Van der Hoeven and de Bot, 2012), even years after the language was originally learned. Bahrick (1984) found that most second-language knowledge is retained for over 50 years, even without its use. However, learning a completely new language can be more challenging for older adults, as working memory is often impaired with age (De Bot and Makoni, 2006).

Naturally, seniors have special needs and interests concerning learning. In a study by Duay and Bryan (2008), the authors interviewed 36 older learners and identified three main determinants that facilitate effective learning: involvement, the instructor, and relevant, familiar topics. Seniors expressed a preference for taking an active role in learning through questions and discussion, and for flexible, organized instructors who taught with authority. Regarding setting, researchers have found that seniors prefer learning situations outside of the traditional classroom with classmates of similar age (Clough, 1992). Additionally, it has been shown that educational settings involving social activities and online programs increase older adults' motivation to learn (Chang and Lin, 2011).

Recent research on computer-assisted language learning (CALL) suggests that technology could be an effective tool in learning a foreign language. Golonka et al. (2014) affirm that 'technological innovations can increase learner interest and motivation; provide students with increased access to target language (TL) input, interaction opportunities, and feedback; and provide instructors with an efficient means for organizing course content and interacting with multiple students.' In addition, the use of technology in language learning has been associated with autonomous learning (Godwin, 2015).

Computer-assisted language learning programs are varied and can include videos, online dictionaries (Ranalli, 2013), and games. Certain programs can be found online and accessed free of charge such as 'Duolingo,' 'BBC Learning English,' and 'News in Levels.' Youtube videos can also be utilized for foreign language learning (Terantino, 2011). Moreover, foreign-language vocabulary can be learned through viewing television series in the TL. In a study by Kuppens (2010), scores on English aptitude tests were higher for Belgian students who watched captioned English-language movies and television than for those who did not.

However, research has shown that older individuals do not use contemporary technologies as frequently as their younger counterparts, and that they are fairly resistant to embracing them (Purdie and Boulton-Lewis, 2003; Wu et al., 2015). Nevertheless, being computer savvy is not essential for participants to obtain positive results from technologically assisted learning (Kueider et al., 2012). The act of learning how to use a computer can add to a sense of mastery for aging subjects (Lee et al., 2013), and affect older adults' well-being, sense of independence, and social relations (Shapira et al., 2007). Moreover, with the Internet as a resource for learning, individuals can find material that is of specific interest to them.

Inspired by Antoniou et al.'s (2013) article on the potential cognitive and social benefits of teaching a foreign language to older persons, we developed a foreign-language learning program geared toward French seniors that incorporated tablet computers. Our main objective was to examine the participants' subjective experience of learning a foreign language in order to explore the feasibility of the program.

MATERIALS AND METHODS

Participants

Participants were recruited from a panel of volunteers who had previously agreed to participate in research studies led at Broca Hospital, a Paris-based geriatric hospital. In total

TABLE 1 | Participant demographics.

Characteristics	Participants ($n = 14$)
Age	75.42 (±8.93)
Mini/Maxi	63/90
Male/Female	5/9
Education	5.1 (±1.4)
Beginner English level	5
Intermediate English level	5
Advanced English level	4
MOCA	26 (±2.67)

TABLE 2 | Themes of the sessions.

Lesson 1: Meeting for the first time	Lesson 9: Blind date
Lesson 2: Making breakfast	Lesson 10: Getting ready to go out
Lesson 3: Gardening	Lesson 11: Antiques and bargaining
Lesson 4: Dinner with colleagues	Lesson 12: Sleeping and waking up
Lesson 5: Shopping for clothes	Lesson 13: Getting hurt
Lesson 6: Taking care of pets	Lesson 14: Expressing nostalgia
Lesson 7: Expressing love	Lesson 15: Leaving for a trip
Lesson 8: Jealousy and trust	Lesson 16: Newspaper and learning websites

14 (five men and nine women) mean age 75, community-dwelling, cognitively healthy older adults without auditory or visual impairment were recruited. Baseline cognitive level was determined with Nasreddine et al.'s (2005) French version of the Montreal Cognitive Assessment (MoCA). Most participants had completed over 12 years of formal education, and thus had some exposure to the English language. Level of English proficiency was determined by the instructor during the first meeting through informal conversation and questions concerning the participants' previous experience with English. Five participants were identified as beginner, five as intermediate, and four as advanced. **Table 1** presents participant characteristics. All participants signed consent forms to participate in this experiment, and the study was approved by the local Committee of Ethical Evaluation for Research in Health.

This qualitative and exploratory study was structured into two phases: The development and design of the program with an interdisciplinary team of professionals involved in geriatric care, and program implementation and assessment with participants. The research was conducted at LUSAGE Laboratory at Broca Hospital, between April and July of 2014.

Measures

In addition to semi-structured qualitative interviews, two quantitative measures were included. The MoCA is a brief cognitive test designed to efficiently evaluate global cognitive functioning in older adults. Russell's (1996) University of California Loneliness Assessment (UCLA) scale is designed to measure subjective feelings of loneliness or social isolation in youth, adults, and older adults. In our study, we used Grâce et al.'s (1993) French version of the UCLA.

Development and Design of the Program

While we initially envisaged an onsite learning program in a group setting with an instructor, we then considered using technology to facilitate offsite learning in order to increase the program's intensity. We therefore decided to develop a program with a multimedia approach using online videos and dictionaries on tablets or PCs. Participants who owned a laptop or tablet would be encouraged to train at home by connecting to the websites shown in class in addition to attending the group lessons.

With the intention of catering to participants' interests and reviving memories from their youth, we selected content from public-domain television series that aired in the 1950s and 1960s, as well as popular music by artists of the era available online. Not only have songs been proven to be an effective way of teaching a foreign language (Ludke et al., 2014), we hypothesized that using this material might be a more enjoyable and stimulating approach than traditional lessons involving written texts or grammar textbooks. Moreover, familiar topics have been shown to be better understood in a foreign language than unfamiliar topics (Schmidt-Rinehart, 1994). Using series that may be familiar to participants might increase their interest and motivation to understand the content. Based on the contents of each scene or song, we structured each lesson around a specific theme, as shown in **Table 2**.

Implementation of the Program

The program encompassed sixteen 2-h group sessions with 16 topics, held once a week over a 4-month period.

For each session, tablets and a transcription of a scene in English were distributed to the participants. Each line was enumerated, and the participants were asked one at a time to read a line out loud and to attempt to translate that line. The participants were encouraged to use their tablets to look up any unknown words on an online dictionary. Afterward each of these words' translations were written on the board by the instructor. The participants wrote the translation of each line on their copy of the transcription. Once the scene was translated, each participant was asked again to individually read a line out loud. The scene was then shown again, this time with the subtitles in French. After each line, the scene was paused in order for the group to repeat the line out loud in unison. After the scene, a time for questions was allowed. Finally, English-learning websites, as well as Youtube music videos were shown to the participants in order to familiarize them with learning methods that could be continued at home.

All sessions were conducted by a native English-speaking psychologist with experience teaching English to adults and children. Two other French-speaking psychologists attended the sessions to facilitate use of the tablets and laptops.

Assessment of the Program

At pre- and post-intervention, the French versions of the MoCA and the UCLA were administered. Following the end of the 4-month training period, the participants met individually with one of the psychologists for an interview

concerning his or her experience in the group. The semi-structured interview included, but was not limited to, these five questions:

(1) What was your experience in the group?
(2) What are your suggestions?
(3) What did you think of the group dynamic?
(4) What did you think of learning English with the tablets?
(5) Do you have anything else to add?

Quantitative Analysis

Pre- and post-intervention scores of the UCLA and the MoCA were analyzed with a paired sample *T*-test.

Qualitative Analysis

The interviews were recorded and transcribed. A content/theme analysis using the method proposed by Braun and Clarke (2006) was performed. After careful word-by-word transcription, the interviews were read separately multiple times by three researchers. Each researcher coded every transcript separately, and the ideas expressed in the interviews were regrouped into themes. The themes were then analyzed by the psychologist team. Afterward, the interviews were read again to check the accuracy of the themes. The quotes selected from the participants' interviews were translated from French to English by the first author.

RESULTS

Ten participants attended the sessions regularly and were interviewed at the end of the program. Four participants attended the sessions sporadically and were not available for the final interviews, three of whom were beginners in English.

Paired sample *T*-test of pre- and post-intervention data for the UCLA and the MoCA showed no significant change in scores. These results are shown in **Table 3**.

Five main themes were identified in the qualitative analysis of the interviews: associations with school, attitudes toward learning English, motivation for learning English, attitudes toward the program's organization, and social ties. These themes are detailed in **Table 4**.

TABLE 3 | Pre–post intervention results.

Scale	Pre	Post	*P*
MOCA	26.46	26.77	0.67
UCLA	39.15	40.83	0.15

TABLE 4 | Main themes and subthemes.

Main themes	Subthemes and number of participants concerned
Associations with school	- School memories (10) - Comparing the program with school (3)
Attitudes toward English	- Learning English is fun (7) - English is difficult to understand (6) - Learning English is beneficial (4) - Learning English is essential (3)
Motivation for learning English	- Connecting with family (3) - Desire for more (3) - Getting out of the house (5)
Attitudes toward the program's organization	- Different English levels are challenging (9) - Technology and English learning are linked (5) - Immersion is needed (3) - It went too quickly, feeling left behind (3) - Focus on spoken English (2) - Scenes from the series (3)
Social ties	- Absence of bonding (10) - Convivial atmosphere (9) - 'Our generation' (4)

Theme 1: Associations with School

All of the participants mentioned school during the interviews, whether it was in comparison to the program or in reminiscing about their first experiences with English. In particular, one participant spoke about how learning English brought back memories: 'There's an advantage to re-sourcing, to coming back to one's sources [. . .] coming back to former memories is very good' (P1, male 70). Another participant said that the experience made him feel younger. 'I really liked it, it made me, well, it made me feel a bit younger' (P2, male 73).

Some participants mentioned that the group was beneficial specifically because it differed from their school experience:

Doing common, current English, I found that to be very positive, because it completes official education. I felt the benefits because, as I told you, she familiarized us with usual daily expressions or journalistic expressions that we don't learn (usually) (P4, male 87).

However, sometimes the association with school seemed to activate feelings of inadequate education, 'I only completed middle school, and when I passed the last year I only had two over 20 in English, so I was never able to catch up' (P5, female 67).

Theme 2: Attitudes toward Learning English

'English Is Difficult'

Most of the participants expressed that English was difficult to understand, and that new words were hard to remember: 'I remember words that I learned 40 years ago, but I must repeat and repeat the words that I learn nowadays and it's annoying' (P7 female 74).

Three participants expressed how English was overwhelming to them, and that they felt left behind in the program. However, they also mentioned that their comprehension improved as they continued.

'I was a little overwhelmed by the events, you see? Especially concerning English. I said to myself that I was behind. And then I wasn't traumatized because we were all pretty much the same level and in the same category' (P7 female 74).

Stimulating and Fun

Most participants said that the sessions were amusing, playful, and fun. The group seemed to enjoy the sessions; many said they were a pleasure to attend. Other participants mentioned the stimulating and mind-opening quality of the group: 'it's very good for memory, to speak it effectively, it obliges certain brain zones to work,' (P8, male 66) and 'it opens up your mind, it's better than staying home and doing nothing . . . I like to participate so it's pretty interesting to discover something else actually' (P5 female 67).

English Is Essential

Some emphasized the importance of the English language. One participant commented, 'First of all, English has become *indispensable*, we are integrated into the English language' (P1, male 70). Another expressed, 'English is the most common, the most necessary in daily life, the most current' (P3, female 90). Similarly, one participant noted that speaking a second language is profitable: 'It's an advantage in the work world to be able to master a second language, it's a *richness*' (P9 female 68).

Theme 3: Motivations for Learning English

Desire for More

Participants expressed a desire for a more expansive English-language program. In particular, participants mentioned wanting a wider range of subjects to learn, more locations for the groups to gather, and more volunteer educators: 'The question would be to spread out this type of activity. There will be more and more elderly, it would be good to have more and more activities like this' (P4, male 87). 'I would like to do the same thing in German, and even in Spanish. . .' (P3, female 90).

Some expressed a desire to continue the English group, asking when the sessions would recommence. One participant expressed that, although she did not have time to pursue English, she would remember the English-learning websites for the future. She insisted:

I'll remember, I'll remember, I'll remember, and I'm keeping it handy, and I won't forget, and I think that when I have more personal time, I'll put myself to it (P9, female 68).

Family

Three participants specifically mentioned family living abroad when discussing English. In particular, when asked if she would continue learning English in the future, one participant said that she is now less motivated because her daughter has moved back to France: 'I would like to, but I'm less motivated, you know why, my daughter is here, and she will not go back to the United States. It motivated me, you understand' (P7 female 74).

'Getting Out of the House'

Finally, it seems that the idea of getting out of the house was an important motivating factor for participation in this study. One participant expressed thusly, 'first of all, it got me out of my place because I had a goal, and it brought me a lot, I found that it was very nice' (P7, female 74).

Theme 4: Attitudes toward the Program's Organization

Different Levels in English

The participants' different levels in English proficiency were mentioned consistently: 'I found that there were people who knew too much, I found that they didn't really belong in the group' (P5, female 67). Another participant shared his feelings of inadequacy in comparison to the other participants, saying that he felt uncomfortable because he didn't know as much as the others did, and that his English level was quite poor in comparison (P2, male 73). Alternatively, one of the participants emphasized the fact that the different proficiency levels in English and technology facilitated contact with others as she had to ask others for help (P10, female 63).

Technology

Another prevalent topic the participants addressed was the use of technology. Opinions were divided between those who found that it was helpful to use the tablets in learning English, and those that considered it to be useless or overly time-consuming. One participant said that learning English helped her to learn how to use the tablets, 'firstly it allowed me to learn about the tablets by looking up words even though it made the translation take longer' (P7, female 74). For some, the use of the tablets seemed to stimulate motivation to learn English. One participant expressed; 'It's really very amusing, it's stimulating, it motivates you to make progress, to look up alphabets, dictionaries, I found it very good' (P3, female 90). Another participant mentioned a link between learning English and technology: 'There's a connection, and it allowed me to discover your dictionary with many meanings' (P7, female 74).

Scenes of the Series

Three participants mentioned the videos viewed during the sessions. One beginner participant commented that she was not always able to understand everything just by watching the video. Another participant remembered watching one of the series in French as a child, and therefore said she very much enjoyed rediscovering it in English. One of the participants purchased a DVD of one of the series used during the lessons for his spouse who has Alzheimer's.

Rhythm

The rhythm of the class was an issue for some participants. Three participants said that they felt lost at times during the sessions:

It was a bit fast, to see, and to write, and to understand . . . to translate lots of new words, expressions and everything, it was a bit dense . . . there were so many things that I became as if I was little bit of a beginner again (P10, female 63).

Immersion

Some participants emphasized the importance of immersion. Three participants said that if they had been immersed in the language they would have learned more. In this vein, one participant suggested that linguistic trips could be organized for the elderly, just as they are often organized for youth (P8, male 66).

Use of Spoken English

The oral use of English was seen as beneficial. One beginner-level participant mentioned that saying things out loud made her learning experience more enjoyable: "After I felt much more comfortable, the fact that you had us first say things out loud, even if I didn't understand anything, it wasn't a big deal (P5, female 67). Another participant mentioned how learning to speak English was more important than learning to read it, as most of them had already learned to read English at school (P8, male 66).

Theme 5: Social Ties

When asked about the group dynamic, all of the participants expressed that they did not establish strong social ties with one another. This did not seem to concern everyone, but two participants in particular regretted this lack of bonding: 'What I regret is that we weren't able to establish a connection, I mean in order to keep in touch, even through the internet, I didn't find it. . .everyone has their own life' (P7 female 74). Another participant commented: 'I would have really liked to spend a little time on the phone with my colleagues . . . I regret it a little, because we could have had more of a relationship' (P2 male 73).

Nonetheless, almost all the participants remarked on the convivial atmosphere of the group, calling it 'sympathique,' a common word in French that can be translated as 'nice, pleasant, or enjoyable.' Four participants used the phrase 'our generation' during the interviews. In particular, one participant mentioned that people of their generation do not make friends easily, that although they can make acquaintances, building friendship is much more difficult at a later age (P8, male, 66).

DISCUSSION

The objectives of this study were to develop a technology-based, foreign-language intervention geared toward seniors and to evaluate its feasibility. The qualitative data suggest that this intervention, although perceived as difficult by some, is feasible for older adults. The main themes expressed in the interviews with participants were organized into five categories: associations with school, attitudes toward English, motivation for learning English, attitudes toward the program's organization, and social ties. Although cognitive and loneliness perception scores did not significantly improve in our study, we discuss the potential social and cognitive benefits of foreign-language learning interventions for older adults.

School Memories

During the interviews about their experiences in the program, all of the participants mentioned school, either reminiscing about their education and youth or comparing the current intervention to their past experience with English. For some, this association was positive: 'Learning English brings back old memories, it's good to go back to one's sources.' This could be compared to reminiscence therapy, in which reactivating past memories could improve self-acceptance, resolve past conflicts, and provide perspective (Gaggioli et al., 2014).

English Is Difficult, Fun, and Essential

As shown in the qualitative results, English was perceived to be difficult, fun, and essential. Participants who had limited prior experience with English seemed to be the most challenged, saying that English was difficult to understand. Even some of those who had experience with English expressed difficulty retaining new vocabulary, which seemed to cause frustration. Undoubtedly, short-term memory deficits constitute an added roadblock for older learners (De Bot and Makoni, 2006).

Nonetheless, the difficulty of language learning could determine its cognitive impact. Schroeder and Marian (2016) claim that improvements in cognitive processing occur with repetitive and challenging activities due to the 'supply demand mismatch' hypothesis. The authors explain that when cognitive resources do not meet cognitive demands, cognitive supply is increased. The challenge of foreign-language learning could therefore determine the extent of its cognitive benefits. With repetitive practice, cognitive capacities expand to meet cognitive demands. Indeed, participants who had expressed difficulty learning English at the start of the program said that it eventually became easier. In addition, some participants said that learning English was 'fun,' 'stimulating,' and 'mind-opening.' This coincides with the finding that cognitive training has been shown to affect older adults' openness to experience (Jackson et al., 2012). Learning a new language could similarly affect an individual's open-mindedness. Other participants described English as 'essential,' 'indispensable,' or 'profitable.' These perceptions could have contributed to participants' motivation for learning English.

Motivations for Learning English

Learner motivation plays an important role in language acquisition. It can compensate for deficiencies in foreign-language learning aptitude and even weaknesses in the course's methodology (Marinova-Todd et al., 2000; Dörnyei, 2005). Kim and Kim (2015) found that 'self-actualization,' defined as 'the feelings of satisfaction and delight . . . from knowing English' to be the most powerful motivating factor among Korean learners of English.

With sufficient personal motivation, learning a foreign language is feasible for older adults. Participants in our study expressed their motivations for learning English in terms of their desire to continue the program, family connections, and opportunity to 'get out of the house.' Variations of this last theme have been observed in other studies on older adult learning. According to Duay and Bryan (2008), 66% of seniors interviewed said that their engagement in educational activities allowed them to stay involved with the outer world. In turn, it seems that learning activities could help older adults maintain a connection with society and their peers, while remaining mentally, physically, and socially active (Purdie and Boulton-Lewis, 2003).

English Level Heterogeneity and Technology

Participants commented most on the heterogeneity of English proficiency levels, the rhythm of the sessions, and the use of technology.

The participants' different proficiency levels in English proved to be an issue for some. A few participants compared their English comprehension and performance with others and said they felt they were falling behind. The rhythm of the sessions was also mentioned, with some participants saying that the classes went too quickly. Future research should thus take into account participants' proficiency in the TL and adapt the course's pace accordingly. Moreover, three of the five participants who did not attend final sessions were beginners in English. Participants' limited experience with English could have been a demotivating factor for those with lower proficiency in English.

In contrast, participants who had already studied English seemed more comfortable with the intervention's pace and organization. Indeed, adults with second-language experience show a learning advantage over those who are learning a language for the first time (Hansen et al., 2002). Future studies should thus give special attention to beginners, providing them with individual attention and a slow, steady pace.

The use of audiovisual tools was not mentioned by all of the participants, but three participants specifically mentioned the materials. The lack of comments on the program's audiovisual content was perhaps due to the fact that during the interviews the psychologists did not directly inquire about the videos. However, much was said about the use of tablets.

This study used a method that integrated technology with traditional one-on-one instruction. This proved an extra challenge for some, while facilitating learning for others. The multimedia approach seemed to be quite useful for teaching and stimulating participants. In addition, having the participants use the tablets to look up words encouraged their involvement by providing them with the tools to translate on their own. However, only two participants mentioned using online English programs at home. Although some language-learning websites were introduced, the participants were not fully trained to use them. More computer training might have encouraged participants to study at home and provide continuity beyond the end of the program.

Language Learning as a Social Activity

All of the participants mentioned an absence of social bonding with fellow participants, and some regretted not being able to form stronger social ties with one another. This could also be observed in the lack of significant improvement in the results from the UCLA questionnaire. Differences in English proficiency among participants may have hindered the creation of social bonds. One participant remarked that she thought some people did not belong in the group because of their advanced English skills. On the other hand, another participant mentioned that differences in English fluency could have encouraged participants to ask one another for help and thus foster social interaction. Perhaps the issue of generation also contributed to the lack of social ties, as one participant noted that those belonging to their generation did not make friends easily.

The Significance of Language Learning

Nonetheless, learning activities have been shown to help older adults develop coping strategies and self-confidence (Boulton-Lewis, 2010). The study of language is a unique discipline, notably in regards to its social and subjective implications. Dörnyei (2005) writes that language concerns one's social identity; therefore, learning a foreign language could change one's self-image, facilitate the use of new behaviors and customs, and greatly impact the learner's social being. Foreign-language learning could also affect psychological mechanisms, as language has been said to structure the unconscious itself (Lacan, 1966).

Language Learning as Cognitive Stimulation

Pre- and post-intervention scores of the MoCA did not significantly differ. This is probably due to our study's small sample size, as well as participants' generally high cognitive level. These results could also imply that our intervention played a role in the maintenance of participants' cognitive level. Although research has focused on early bilingualism's contribution to cognitive reserve, it has been shown that even those who acquire a language after childhood have a cognitive advantage over monolinguals (Vega-Mendoza et al., 2015). For instance, compared to their monolingual peers, late bilinguals have demonstrated higher scores in tests of auditory attention span (Bak et al., 2014). In addition, differences in executive functioning can be attributed to second-language proficiency, and brain anatomy has been shown to change as language skills advance, even during the earliest stages of second-language acquisition (Mechelli et al., 2004; Osterhout et al., 2008).

Foreign-language acquisition has been shown to demonstrate structural neuroplasticity in children, adults, and older adults, even after short-term language training (Hosoda et al., 2013; Li et al., 2014; Pliatsikas et al., 2015). Learning a foreign language later in life could thus strengthen cognitive functioning in older adults.

Furthermore, with conversation training, recovery of a second language has been demonstrated in patients who have Alzheimer's (Nold, 2005). With an adapted program and sufficient participant motivation, could this type of second-language learning program be appropriate for those with cognitive impairment? Further studies are needed to test the feasibility of such a program for those with MCI and dementia.

Limitations

Although the current findings present a useful starting point for the development of cognitively stimulating, language-learning programs for older adults, this exploratory qualitative study cannot be generalized to the rest of the population due to its small size. The older adults were recruited from a panel of individuals who may have been particularly open to research and technology, as some of them had been involved in other studies at Broca Hospital in the past. Therefore, their opinions

may not be representative of the general older French population. Additionally, not all of the participants were available for interviews at the end of the intervention, which could have biased the results. As for the structure of the interviews, the questions may have been too narrow in scope, and perhaps did not allow for participants to fully express their thoughts on the program. As this study is primarily qualitative, quantitative measures were used only for cognitive level and perceptions of loneliness. Furthermore, different proficiency levels in English were not controlled for, as beginner, intermediate, and advanced participants were included in the same group. English acquisition measures were also absent, and therefore it is unclear how much was genuinely learned by participants. In future studies, more thorough cognitive and psychological testing should be carried out, including executive functioning measures at pre- and post-intervention, as well as language acquisition tests.

CONCLUSION

In our study we developed a technology-integrated, foreign-language program for seniors. We found that this program was feasible for a cognitively normal French senior group. In the future, it would be beneficial to have different groups for different language levels and adapt the program according to participants' interests and basic needs. Further research should explore the quantitative cognitive effects of learning a second language in later life.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the 'Commission Nationale de l'Informatique et des Libertés' with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the 'Commission Nationale de l'Informatique et des Libertés.'

AUTHOR CONTRIBUTIONS

A-SR supervised the project from the start, led focus groups throughout the study, read and analyzed the qualitative data, and greatly contributed to the writing and proofing of the manuscript. LD and SD were present during all of the sessions of the study in helping facilitate the use of tablets by participants. They were key to the development and execution of the study, conducting initial and post-evaluation interviews with participants, as well as analyzing the results and proofreading the manuscript. JB read and analyzed all the transcribed interviews. MP was present from the beginning of the project's inception, attended important focus group meetings and contributed to the writing and proof-reading of the article. Y-HW contributed to focus group meetings, discussing the development and results of the program, and aided in the writing and proof-reading of the manuscript. VC guided CW in the project design with her expertise in qualitative research, she also helped to write and proofread the manuscript. CW came up with the idea of the program, and with the contribution of all the authors, developed and executed the program. She carried out post-intervention interviews, transcribed and analyzed them, and is the main author of the manuscript.

FUNDING

This study was supported by the University of Paris VII Diderot in the form of a doctoral scholarship awarded to Caitlin Ware.

ACKNOWLEDGMENT

The authors would like to thank David Mullins for editing the article.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

MINI REVIEW
published: 13 March 2017
doi: 10.3389/fnagi.2017.00052

Tuning Up the Old Brain with New Tricks: Attention Training via Neurofeedback

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Neurofeedback (NF) is a form of biofeedback that uses real-time (RT) modulation of brain activity to enhance brain function and behavioral performance. Recent advances in Brain-Computer Interfaces (BCI) and cognitive training (CT) have provided new tools and evidence that NF improves cognitive functions, such as attention and working memory (WM), beyond what is provided by traditional CT. More published studies have demonstrated the efficacy of NF, particularly for treating attention deficit hyperactivity disorder (ADHD) in children. In contrast, there have been fewer studies done in older adults with or without cognitive impairment, with some notable exceptions. The focus of this review is to summarize current success in RT NF training of older brains aiming to match those of younger brains during attention/WM tasks. We also outline potential future advances in RT brainwave-based NF for improving attention training in older populations. The rapid growth in wireless recording of brain activity, machine learning classification and brain network analysis provides new tools for combating cognitive decline and brain aging in older adults. We optimistically conclude that NF, combined with new neuro-markers (event-related potentials and connectivity) and traditional features, promises to provide new hope for brain and CT in the growing older population.

Keywords: EEG, ERP, biofeedback, brain modulation, SVM, cognitive aging, BCI

OPEN ACCESS

Edited by:
Pamela M. Greenwood, George Mason University, USA

Reviewed by:
Shulan Hsieh, National Cheng Kung University, Taiwan
Tomas Ros, University of Geneva, Switzerland

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Received: *01 November 2016*
Accepted: *22 February 2017*
Published: *13 March 2017*

Citation:
Jiang Y, Abiri R and Zhao X (2017) Tuning Up the Old Brain with New Tricks: Attention Training via Neurofeedback. Front. Aging Neurosci. 9:52. doi: 10.3389/fnagi.2017.00052

The ability to focus attention, encode and maintain information are among the brain's most important cognitive functions. Attention is a central component of cognitive ability. Measurements of neural activity have become strong predictors of cognitive impairments in persons afflicted with various kinds of cognitive deficits. Lapses in attention can impair memory and behavioral performance.

Complaints about declined attention and memory are common in healthy and cognitively intact older adults during brain aging. Deficits in attention and memory are also the most common symptoms in older adults with dementia such as Alzheimer's disease (AD), Parkinson's, or vascular dementia (VD). Old-age dementia affects patients' daily lives with memory loss and cognitive impairments. The most common early symptoms of AD are problems with short-term memory (Reiman et al., 2011). Since there is no effective drug treatment thus far to stop cognitive decline, attention training has become an increasingly attractive option. The effectiveness

of cognitive rehabilitation including attention training has been under debate for decades. A recent review has shown evidence that attention training enhances attention and memory with moderate success (Cicerone et al., 2011). Since attention is a core function for multitude of cognitive processes (e.g., memory and perception), most cognitive training (CT) programs seek to increase the existing attentional capacity.

BRAIN-COMPUTER INTERFACE (BCI)

Research on Brain-Computer Interface (BCI), also known as brain-machine interface (BMI), dates back to the 1960s (Miranda et al., 2015). BCIs and BMIs are systems that utilize recorded brain activity to communicate between the brain and computers in order to control the environment in a manner that is compatible with the intentions of humans and to receive feedback from environment. In BCI, the brain activity is recorded through various neuroimaging methods, which can be categorized in two groups: invasive and noninvasive. Electrocorticography (ECoG) and Electroencephalography (EEG) are known as the most common invasive and noninvasive methods, respectively (Nicolas-Alonso and Gomez-Gil, 2012). A closed-loop BCI system with real-time (RT) modulation and communication can not only be employed in directly controlling external devices, but can also be utilized as a biofeedback platform to improve and enhance the cognitive abilities of individuals (Chaudhary et al., 2016).

NEUROFEEDBACK (NF)

Neurofeedback (NF) is a form of EEG biofeedback used to successfully improve cognitive and physical performance of humans (Daly and Wolpaw, 2008; Pfurtscheller et al., 2008; Machado et al., 2013; Broccard et al., 2014; Chaudhary et al., 2016). Cognitive enhancement training after mild traumatic brain injury (mTBI) has been shown to increase focused attention and memory, thus improving the patient's performance in daily life (Cicerone et al., 2011). More convincing evidence of effectiveness of working memory (WM) and executive-control training in older adults comes from a meta-analysis by Karbach and Verhaeghen (2014). They examined 61 independent samples in adults over the age of 60. Cognitive interventions resulted in significant improvement in performance on the trained task and untrained similar tasks. There was even a small but significant training-induced improvement in untrained tasks in a different domain, demonstrating that training has transferred far into learning.

The presently popular CT method is attention process training (APT; Sohlberg et al., 2000), which also includes WM components. While efficacy of these methods differs, all have been reported to enhance performance in focused attention tasks, cognitive function and WM tasks. Some attention training showed a learning transferable effect, i.e., improved performance in untrained tasks (Sinotte and Coelho, 2007; Westerberg et al., 2007; Cicerone et al., 2011; Kuo et al., 2014). However, evidence for improvement in everyday life utilizing cognition has been limited thus far, which provides impetus for developing better and time-efficient methods to directly train neural processes underlying attention. Cicerone et al. (2011) concluded that attention seems to train better than other domains of cognition. For treatment of children with attention deficit/hyperactivity disorder (ADHD), NF has been shown to be a better intervention than traditional attention (Hurt et al., 2014; Steiner et al., 2014) or WM training (YuLeung To et al., 2016). Notice though, evidence from meta-analyses of randomized controlled trials fails to support NF as an effective treatment for ADHD in children and adolescents. The significant treatment results only occur in the outcome measures that are not properly blinded (Cortese et al., 2016). In a comprehensive review on EEG-based BCI NF, Ordikhani-Seyedlar et al. (2016) pointed out that, despite amazing progress, a major challenge for attentional training via NF is improving signal processing algorithms that dissociate brainwaves of attended from those of unattended items.

WHAT'S SPECIAL ABOUT COGNITIVE AND BRAIN AGING?

Challenges of Training Older Adults

The challenge of attentional training in older adults is that measurement of CT is often confounded with multiple factors, such as individual differences that tend to increase with age. These factors include individual differences in brain aging associated with visual attention (Monge et al., 2016), attention capture to rewarding objects (e.g., a parieto-occipital electrophysiological responses; Donohue et al., 2016), WM and performance (Parasuraman and Jiang, 2012), learning transfer beyond trained tasks (Greenwood and Parasuraman, 2016), and placebo effects where performance of older adults is simply improved by participating in CT (Foroughi et al., 2016).

Unlike ADHD in children, prominent cognitive deficits in aging brain occur in the switching and division of attention, whereas phasic arousal and focused attention to stimulus features are only minimally affected in the early stages of AD. For instance, selective attention deficit is one of the first cognitive indicators of neocortical dysfunction in early AD (Parasuraman and Haxby, 1993). Despite many challenges, comprehensive treatment in patients with mild cognitive impairments (MCI), including NF training, diet and fitness programs, has shown great promise in cognitive improvement (Bredesen et al., 2016; Fotuhi et al., 2016). Importantly, efficacy of all NF training schemes will need to be rigorously tested by comparing independent measures and sensitive indicators of attention and WM before and after attention training.

Training Attention and Working Memory to Prevent AD Risk

Besides attention, neural mechanisms underlying short-term memory (e.g., WM) undergo a significant early change in

aging (Lawson et al., 2007) and in AD dementia patients (Grady et al., 2001). The memory decline also includes neural mechanisms underlying repetition learning, a form of implicit memory (Jiang et al., 1999, 2009). Early AD/MCI manifests itself in loss of short-term memory but retention of intact long-term memory. Since WM and attention shared common neural mechanisms (e.g., Gazzaley and Nobre, 2012), enhancement of attention improves encoding, maintenance and retrieval of items held in WM for online usage.

It is critical that future attention training via NF in older adults targets specific neuro-markers underlying attention/WM and related performance. For instance, a short-term memory paradigm based on well-established single-cell electrophysiological experiments in primates (Miller and Desimone, 1994) was developed for human neuroimaging using functional magnetic resonance imaging (fMRI; Jiang et al., 2000, 2016), and EEG (Lawson et al., 2007; Guo et al., 2008). Using the short-term memory paradigm, the same patterns of brain responses in older adults and MCI have been validated in a Chinese cohort of older adults (Yu et al., 2016). Testing a cohort of cognitively normal older adults in the U.S., Jiang et al. (2016) reported that increased bilateral parietal connectivity during the short-term memory task is correlated with higher Tau levels in Cerebrospinal fluid (CSF) biomarker, indicating increased risk of AD. CSF Tau AD biomarker did not show such a link to brain connectivity during resting state, but only when the brain was challenged with a cognitive task. In contrast to CSF AD biomarkers, which showed no associations with cognitive status in normal these adults, functional brain connectivity between left temporal and parietal gyri during the memory task strongly correlated with overall cognitive status. Furthermore, modulating cognitive neuro-markers validated by AD biomarkers (e.g., CSF) should be even more effective approach in cognitive improvement specifically targeting aging brain.

ADVANCEMENT IN BRAIN TRAINING METHODOLOGY

The effectiveness of CT has been subject to doubt for decades. Recently, brain training has experienced a renaissance due to new advances in brain imaging, BCI and advanced analytical tools. Applying state-of-the-art RT classification tools, a recent study used fMRI to provide NF during attention training and successfully improved visual attention and behavioral performance (deBettencourt et al., 2015). This study also aimed to increase the efficiency of attention so that a person may sustain high attention to a task for a longer period of time to improve memory, which is the key element for improvement in cognitive aging.

EEG Based Neurofeedback Training

EEG has been in use since 1930s (Adrian and Matthews, 1934). What are the new tricks for improving brain training? For decades, scalp EEG studies of AD mainly focused on characterizing clinically-evident disease stages rather than preclinical AD. The important EEG components in human adults are the delta (<4 Hz), theta (4–7 Hz), alpha (8–13 Hz), and beta waves (>13 Hz). Theta and delta waves are known as slow waves. Alpha waves, sourced in frontal sites including anterior cingulate cortex, are related to attention, WM, and related performance in humans. It has been shown to be sensitive to suppression of unattended stimuli (Händel et al., 2011). EEG theta oscillations are also related to hippocampal activity during WM (Tesche and Karhu, 2000). Spatial attention is a constant theta-rhythmic sampling process implemented through gamma-band synchrony (Landau et al., 2015).

NF using traditional EEG and new EEG neuro-markers has demonstrated success in recent times, especially in children with ADHD in the 6–12 age range (Holtmann et al., 2014). Relative power of theta, alpha, beta, theta/alpha and theta/beta ratios were applied during successful training in children with ADHD (Hillard et al., 2013), and by using Theta/Alpha Ratio (Steiner et al., 2014). Similar success has been shown in NF training using theta/Alpha ratio in children age 6–12 with a learning disorder (Fernández et al., 2016). However, in slightly older children with ADHD, failure of improvement was reported in a double-blind placebo-controlled study (Vollebregt et al., 2014), which theta/beta ratio and theta/alpha ratio were utilized. The outcome measures of neurocognitive performance before and after treatment failed to show improvement, possibly due to sensitivity of the outcome measures and other study limitations.

As for NF training in the older brains, the seminal work by Angelakis et al. (2007) applied EEG NF in the older population and showed improved processing speed and executive functions (EFs). Additional success has been reported using EEG-based NF for attention training and WM in young adults (Egner and Gruzelier, 2001; Zoefel et al., 2011; Ros et al., 2013, 2014), in post-traumatic stress disorder (Ros et al., 2016), and in older dementia patients (e.g., Surmeli et al., 2016). We summarize some of the recent studies on attention or WM training in older and younger adults in **Table 1**.

NOVEL NEURO-MARKERS FOR COGNITIVE CHANGE IN OLD AGE

Recent work has identified neurosynaptic changes as one of the earliest biomarkers of preclinical AD, appearing before onset of tau-mediated neuronal injury or brain structure changes (Jack et al., 2011; Sperling et al., 2011). EEG recordings directly measure post-synaptic potentials and are able to detect these early changes. It has been shown that measured synchronized electrophysiological signals during sleep and rest can be used as neurophysiological biomarkers for the early detection and classification of dementias (Al-Qazzaz et al., 2014).

Cognitive ERP Markers

The averaged EEG signals, i.e., ERPs during cognitive events known as cognitive ERP, provides a promising neuro-markers for indexing changes of neural mechanisms underlying cognition and memory (Olichney et al., 2011). Altered amplitude or

TABLE 1 | Selective studies on attention or working memory training using neurofeedback (NF) in older and younger adults.

Publications	Age group	Mean age (Range in years)	Tasks (number of participants)	Neuro-markers	Improvement?
Angelakis et al. (2007)	Older adult (H)	74 (70–78)	Memory, Processing speed; NFT and SNFT (n = 3 each group/condition)	Alpha Frequency	Y (Speed and EF)
Lecomte and Juhel (2011)	Older adult (H)	75.25 (65–85)	Working Memory; NFT and SNFT	Alpha, Theta	Mixed (Memory)
Becerra et al. (2012)	Older adult (H)	65.8 (60–84)	Executive Function + Memory Tasks; NFT and SNFT (n = 7 each)	Theta	Y (WM)
Wang and Hsieh (2013)	Young + Older (H)	21.8 (21–25); 64.6 (61–67)	Attentional Network + Recognition Task; NFT and SNFT (n = 8 each)	Fronto-midline Theta	Y (Attention and WM)
Staufenbiel et al. (2014)	Older adult (H)	67.8	Intelligence + Memory Task; Beta and Gamma Groups (n = 10 each)	Gamma, Beta	Y (WM)
Luijmes et al. (2016)	Older adult (AD)	64–78	Cognitive Examination; NFT (n = 10)	Delta, Theta, Alpha, Beta	Y (WM)
Reis et al. (2016)	Older adult (H)	65.97 (59.3–72.6)	Working Memory Task; NFT (n = 9), NFCT (n = 8), CT (n = 7), SNFT (n = 6)	Theta, Alpha	Y (WM)
Surmeli et al. (2016)	Older adult (AD + VD)	68.9 (58–79)	EEG-guided NFT (n = 20); within subjects' design	Inhibit Theta, Alpha, Beta (21–32 Hz)	Y* (MMSE)
Egner and Gruzelier (2001)	Young adult (H)	22.1	Oddball Task; NFT (n = 22)	P300 ERP, beta1, SMR learning	Y (Attention)
Zoefel et al. (2011)	Young adult (H)	23 (21–26)	Mental Rotation Task; NFT (n = 14), SNF (n = 10)	Upper Alpha Frequency	Y (Mental rotation)
Ros et al. (2013)	Adult (H)	32.6 (22–42)	Attentional and Oddball Tasks; NFT and SNFT (n = 17 each)	fMRI, Alpha frequency	Y (Attention)
deBettencourt et al. (2015)	Adult (H)	20.3	Selective attention task (superimposed images **Figure 1**; n = 16 each condition)	Real-time fMRI	Y (Attention)

H, Healthy participants; LD, Leaning disorder; ADHD, attention deficit hyperactivity disorder; AD, Alzheimer's disease; VD, vascular dementia; mTBI, mild traumatic brain injury; NFT, neurofeedback training group; SNFT, sham neurofeedback group; CT, cognitive training; NFCT, neurofeedback and cognitive training group; RT, real-time; EF, executive function; WM, working memory; Y, some of the participants; MMSE, Mini Mental State Exams.*

latency of ERP signals in patients with AD have been reported (Jackson and Snyder, 2008). In addition, abnormal cognitive ERP P600 during a word memory task in a small sample of older adults with preclinical AD has been reported (Olichney et al., 2008, 2011, 2013). Similar to EEG, cognitive ERP biomarkers are a noninvasive and more cost-effective method than CSF, PET biomarkers for early diagnosis of AD. Cognitive ERP biomarkers are sensitive to WM and attention deficits before conventional biomarkers of AD can be detected by behavioral performance changes (Li et al., 2017).

Brain Network-Based Neuromarkers

Recent evidence in animal models and neuroimaging also points to brain connectivity networks as novel neuro-markers for indexing early deficits in AD risk. Aß peptides disrupt neural activity at the synaptic level and induce aberrant activity patterns in neural network circuits within and between brain regions in animal models (Palop and Mucke, 2010). Resting-state network based technology using EEG has demonstrated abnormalities in cognitive ability (Babiloni et al., 2006a,b, 2009, 2010; Prichep et al., 2006; Prichep, 2007). Patterns of functional brain connectivity in humans are highly predictive of cognitive performance (Hachinski et al., 2006; Finn et al., 2015). Recent fMRI work shows that brain connectivity correlates differentially with CSF AD biomarkers both during resting state and cognitive tasks (Jiang et al., 2016).

ADVANCED REAL-TIME EEG ANALYSIS

Advanced Network Causality Analysis in Old Brains

As brain ages, Aβ plaques form within distinct regions of the brain's default-mode network (Buckner and Vincent, 2007). Other factors such as age, genes and cognitive reserve in older individuals also add to the complexity of predicting AD risk in an individual. While fMRI connectivity is a good indicator for network of brain circuits, EEG offers superior temporal resolution, simpler and more affordable application in clinical settings. For instance, the network EEG neuro-marker can be a predictive neuro-marker for AD risk (Stam, 2014). Growing evidence has shown that brain functional connectivity changes in dementia can be identified in EEG recordings (McBride et al., 2013, 2014, 2015; Sargolzaei et al., 2015). Engels et al. (2015) reported decreasing functional connectivity in the posterior regions, together with a shifted hub location from posterior to central regions with increasing AD severity. In addition, causality analysis is taking the

center stage. For instance, causality analysis based on the Granger method was used to infer synaptic transmission, which was reflected in EEG measurement and information flow in the neural network (Trongnetrpunya et al., 2016). The Granger causality algorithm was also used to assess brain connectivity in scalp EEG with success (e.g., Barrett et al., 2012). They identified significant increases in bidirectional Granger causality during loss-of-consciousness, especially in the beta and gamma frequency ranges. In contrast to Granger causality analysis (Bressler and Seth, 2011), Sugihara et al. (2012) proposed the dynamic causation concept (Deyle and Sugihara, 2011). A novel brain functional connectivity marker based on Sugihara's causality definition (McBride et al., 2015) has been developed to allow characterization of brain network changes beyond traditional features at localized brain sites. **Figure 1** illustrates the consistent connectivity changes in older brain using measures of network EEG (**Figure 1A**), fMRI connectivity (**Figure 1B**), and white matter integrity (**Figure 1C**) in the aging cohort followed by Sanders-Brown Center on Aging at Bluegrass Region in Central Kentucky. These findings open up new ways in training older brainwaves during tasks toward those seen in younger brains.

Real-Time EEG and fMRI Based NF Training

Brain training using frequency based EEG features (alpha, theta, or theta/beta power) is commonly used in the NF attentional training. Applying EEG-based NF for improving cognitive performance has been reviewed comprehensively by Gruzelier (2014). New studies using EEG neuro-markers beyond frequency neuromarkers have been showing new promise. The brain dynamics (EEG long-range temporal correlations) can be modulated with stimulation in an involuntary manner, which is an excitation-inhibition balance change achieved by the closed-loop neuro-regulation (Ros et al., 2014; Reis et al., 2016; Zhigalov et al., 2016). Using simultaneous EEG and fMRI, Zotev et al. (2014) demonstrated potential applications of novel NF paradigms for treating mental disorders including cognitive aging. Liu et al. (2015) proposed a fractal dimension (FD)-based NF training protocol with adaptive algorithm. The FD-based NF does not require before-training recording. The efficiency of the FD-based NF training in comparison with traditional individual theta/beta based NF training is assessed for focused attention and test of attentional vigilance. They reported that after NF training participants from FD-based training group have similar or better test performance than the one from the ratio-based group.

RT classification of complex brain activity has been an exciting development. A recent study demonstrated that NF using "RT" fMRI during attention training can be used to successfully improve visual attention (deBettencourt et al., 2015). Although fMRI-based NF has definite advantage of revealing where the modulation occurs in the brain, the use of MRI requires participants to remain motionless during training sessions. Additionally, fMRI technique indirectly measures neural activity by quantifying blood oxygen levels, and is costly as well. Thus, there is renewed interest in developing user-friendly advanced EEG-based NF. Aided by new EEG recording technologies such as wireless EEG headsets (e.g., Emotiv device featured in **Figure 1D**) and gaming devices, more investigations on NF via brain network that utilize faster RT classification analysis have emerged. The following example is how the combination of EEG frequency and advanced EEG features analysis (e.g., spectral entropy) are used to modulate brain activity for better attention training.

Feature Extraction and Close-Loop BCI Neurofeedback

The employed features from collected EEG data for focused target in initial testing and validation of the platform are oscillation activity of delta, theta, alpha, beta and gamma bands, as well as the spectral entropy. Additionally, spectral entropy is information entropy that is able to quantify the spectral complexity of an uncertain system. Modeled after successful fMRI paradigm of attention training (deBettencourt et al., 2015), a new noninvasive BCI system has been developed using scalp EEG to decode the sustained attention level of a human participant with an efficient NF based on his/her level of attention-related brain signals. **Figure 1D** shows a schematic of the attention-based NF system. During the test, scalp EEG signals of a subject are recorded via wireless EEG headset while the subject is focusing on a sequence of superimposed images. Each image is a mixture of two transparent pictures from two categories (Scene vs. Face). At a given time, an observer is instructed to pay attention to the task-relevant stimulus (e.g., scene) and ignore the irrelevant stimulus (e.g., face). The level of the attentional state of the subject towards the targeted task-relevant stimulus will be determined from a regression model of the EEG signals in RT. If the attentional level is high for the current image, then the subject is rewarded with improved sharpness of the target stimulus in the next composite image. Thus, the dynamics of changing superimposed images serves as rewarding positive NF, encouraging the subject to focus his/her attention on the target visual stimuli. Several EEG and EPR-based BCI platforms for prosthetic control (Abiri et al., 2015a, 2016a) and NF of attention training have been developed in adults (Abiri et al., 2015b, 2016b), which is promising as foundation for the next step of testing in older adults using well designed and controlled experiments.

CONCLUSION

This review has summarized the rapid growth in BCI technology, online machine learning classification, and advanced brain network analysis, which are some of the exciting new methods in combatting cognitive and brain training in older adults. BCI-based NF training provides new methods for instant reward of brainwave patterns associated with better cognitive functions or younger brains. We envision great progress

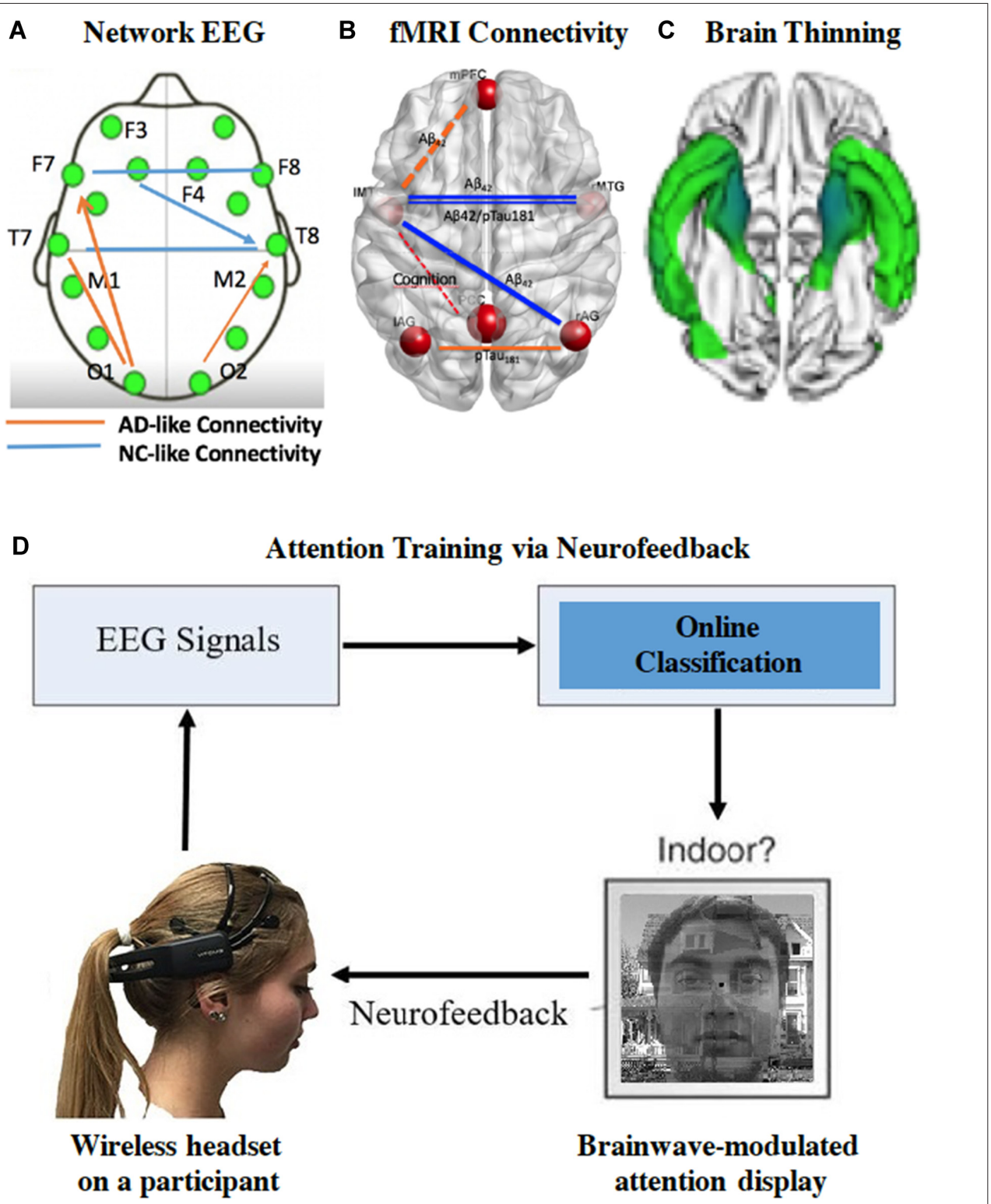

FIGURE 1 | The individual brainwaves are neuromarkers for cognitive states. (A) The network electroencephalography (EEG) causality analysis of brain connectivity differentiates healthy older adults (NC) from early Alzheimer's disease (AD) patients (Adaptation of McBride et al., 2015). **(B)** Functional magnetic resonance imaging (fMRI) brain network analysis from cognitive normal participants in the University of Kentucky cohort (bilateral anterior temporal connectivity correlates with early AD risk; Jiang et al., 2016). **(C)** Cortical thinning in temporal cortices (n = 24) was seen in older patients with very early stage of AD at the Unviersity of Kentucky. **(D)** The integrated platform for EEG/ERP closed-looped neurofeedback (NF) during attention training. Facial images are used with permission.

will occur in brain training of attention and short-term memory, core cognitive abilities, by modulating non-invasively recorded electrical brain activity via RT NF in older adults. This is an exciting time for developing CT in older adults. With the work reviewed here, we conclude that RT NF, combining traditional frequency and new neuro-markers, promises to provide new hope for brain and CT in older adults.

AUTHOR CONTRIBUTIONS

YJ wrote the first draft. RA and XZ made significant and original contribution.

FUNDING

Part of the work was supported by National Institute of Aging, Henry Jackson Foundation and NeuroNET.

ACKNOWLEDGMENTS

This work was greatly influenced by the late Professor Raja Parasuraman's contribution to the literature. We thank S. Abul-Khoudoud for assistance in the table and the figure, S. Strothkamp for proof-reading, Drs. W. High, G. Jicha, and S. McILwrath for helpful discussion, and two reviewers for their valuable suggestions.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 16 March 2017
doi: 10.3389/fnagi.2017.00059

White Matter Integrity Declined Over 6-Months, but Dance Intervention Improved Integrity of the Fornix of Older Adults

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Degeneration of cerebral white matter (WM), or structural disconnection, is one of the major neural mechanisms driving age-related decline in cognitive functions, such as processing speed. Past cross-sectional studies have demonstrated beneficial effects of greater cardiorespiratory fitness, physical activity, cognitive training, social engagement, and nutrition on cognitive functioning and brain health in aging. Here, we collected diffusion magnetic resonance (MRI) imaging data from 174 older (age 60–79) adults to study the effects of 6-months lifestyle interventions on WM integrity. Healthy but low-active participants were randomized into Dance, Walking, Walking + Nutrition, and Active Control (stretching and toning) intervention groups (NCT01472744 on ClinicalTrials.gov). Only in the fornix there was a time × intervention group interaction of change in WM integrity: integrity declined over 6 months in all groups but increased in the Dance group. Integrity in the fornix at baseline was associated with better processing speed, however, change in fornix integrity did not correlate with change in processing speed. Next, we observed a decline in WM integrity across the majority of brain regions in all participants, regardless of the intervention group. This suggests that the aging of the brain is detectable on the scale of 6-months, which highlights the urgency of finding effective interventions to slow down this process. Magnitude of WM decline increased with age and decline in prefrontal WM was of lesser magnitude in older adults spending less time sedentary and more engaging in moderate-to-vigorous physical activity. In addition, our findings support the anterior-to-posterior gradient of greater-to-lesser decline, but only in the in the corpus callosum. Together, our findings suggest that combining physical, cognitive, and social engagement (dance) may help maintain or improve WM health and more physically active lifestyle is associated with slower WM decline. This study emphasizes the importance of a physically active and socially engaging lifestyle among aging adults.

Keywords: DTI, diffusion, randomized clinical trial, fractional anisotropy, processing speed, physical activity, fitness, brain

OPEN ACCESS

Edited by:
Thomas Espeseth, University of Oslo, Norway

Reviewed by:
Jennifer Rusted, University of Sussex, UK
Eugen Bogdan Petcu, Griffith University School of Medicine, USA
Yunglin Gazes, Columbia University Medical Center, USA

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Received: *28 October 2016*
Accepted: *28 February 2017*
Published: *16 March 2017*

Citation:
Burzynska AZ, Jiao Y, Knecht AM, Fanning J, Awick EA, Chen T, Gothe N, Voss MW, McAuley E and Kramer AF (2017) White Matter Integrity Declined Over 6-Months, but Dance Intervention Improved Integrity of the Fornix of Older Adults. Front. Aging Neurosci. 9:59. doi: 10.3389/fnagi.2017.00059

INTRODUCTION

Disruption of (WM) microstructure—degeneration or loss of axons and myelin—is considered one of the primary mechanisms underlying age-related cognitive slowing and memory decline (Gunning-Dixon and Raz, 2000; Madden et al., 2012). Therefore, preventing age-related "structural disconnection" (Raz and Rodrigue, 2006) or improving WM integrity is key in preserving cognitive performance necessary for independent functioning in older individuals.

WM microstructure can be studied non-invasively with diffusion magnetic resonance imaging (MRI). Diffusion imaging provides voxel-wise estimation of magnitude and directionality of water diffusion in WM. Fractional anisotropy (FA), is a measure of the directional dependence of diffusion (Basser, 1995), and reflects fiber orientation, density and coherence within a voxel (Beaulieu, 2002). Lowered FA has been observed in various conditions in which loss of fiber integrity occurs (Beaulieu, 2002), such as Alzheimer's disease (Medina et al., 2006). Radial diffusivity (RD) represents diffusivity perpendicular to the main fiber direction (Basser, 1995; Song et al., 2002). Increases in RD have been linked to degeneration or loss of myelin (Song et al., 2003, 2005). Axial diffusivity (AD) represents diffusion parallel to the axon fibers and is related to axonal integrity (Basser, 1995; Song et al., 2002). Finally, mean diffusivity (MD) reflects the magnitude of total water diffusion within a voxel, which depends on the density of physical obstructions such as cellular membranes (Beaulieu, 2002; Sen and Basser, 2005). Increased MD, paralleled by increases in both RD and AD, was observed in conditions of WM degeneration (Beaulieu et al., 1996; Beaulieu, 2002; Concha et al., 2006).

To date, numerous neuroimaging studies described age-related differences in WM properties using cross-sectional comparisons (Burzynska et al., 2010; Madden et al., 2012). There are, however, two critical obstacles in understanding the age-related changes in WM and, subsequently, in slowing down or reversing these age-related changes in the human brain. First, there are still few studies describing age-related change in WM integrity in a longitudinal design. Specifically, there are only five studies that described changes in WM over time and across numerous WM regions or tracts[1]. Sexton et al. (2014) and Storsve et al. (2016) followed 203 adults between 20 and 84 years of age over on average 3.5 years. They found extensive and overlapping, significant annual decreases in FA, paralleled by increases in RD, AD, and MD. Rieckmann et al. (2016) followed up 108 older adults over on average 2.6 years and found significant declines in FA and increases in RD, AD, and MD. Bender et al. (2016b) found changes in FA and RD over periods of time of 1 to 7 years in healthy adults of age 50–84. Barrick et al. (2010) observed significant decline in FA in healthy adults 50–90 years old over 2 years.

Some of these studies reported acceleration of microstructural decline in older age (Sexton et al., 2014; Bender et al., 2016b; Storsve et al., 2016), but other did not (Barrick et al., 2010). Some argued the superior-to-inferior gradient of greater-to-lesser decline (Sexton et al., 2014; Storsve et al., 2016), while longitudinal data (Barrick et al., 2010) did not support "last-in-first-out" hypothesis of anterior-to-posterior decline suggested in cross-sectional studies (Bartzokis et al., 2010).

Together, these studies show consistent decline in WM integrity represented by increases in RD, AD, and MD, and decreases in FA. However, there is no consensus on the spatial gradient of decline and WM decline has not been observed over periods shorter than a year. Knowing short-term dynamics of WM decline would be useful in assessing the outcomes of typically short-term interventions (months) as well as in differentiating between normal and abnormal speed of decline in patients presenting first cognitive symptoms. Finally, there is little evidence for the ability to improve WM integrity in older adults. Cross-sectional studies suggest that lifestyle factors such as physical activity (PA) and cardiorespiratory fitness (CRF) are protective against cognitive and neural decline. For example, we have shown that greater PA and CRF are associated with greater WM integrity (Burzynska et al., 2014; Oberlin et al., 2016) and that older aerobically trained athletes have greater brain structural integrity and cognitive performance than their sedentary low-fit peers (Tseng et al., 2013; Burzynska et al., 2015; Young et al., 2016). However, a recent meta-analysis showed only modest cross-sectional effects of CRF and aerobic PA on WM in aging (Sexton et al., 2016). The longitudinal evidence for positive effect of exercise on WM is still very scarce. Voss et al. (2010) demonstrated in 70 adults (55–80 years old) that increases in CRF as a result of 1-year the aerobic walking intervention was associated with fronto-temporal increase in FA and enhanced short-term memory. However, there was no difference between the walking and the active control group (stretching and toning) in their changes of WM integrity over 1-year.

In the current study we address these two critical limitations of the existing studies: short-term dynamics in WM change in different diffusivity parameters, and the effects of lifestyle interventions to improve WM integrity in aging.

To this aim, we collected diffusion, cognitive, CRF and PA data from 174 healthy, non-demented (MMSE>26) adults 60–79 years old at baseline[2], and after a 6-months lifestyle intervention (randomized clinical trial, NCT01472744 on ClinicalTrials.gov). The interventions included aerobic exercise (Walking) and an Active Control group (stretching and toning, not aimed to increase CRF). In addition, we included a group that combined aerobic PA, cognitive, and social stimulation (Dance), and an aerobic Walking that also received a nutritional supplement (Walking + Nutrition).

We expected to observe a time × group interaction, with Walking and Dance groups showing maintenance or increase in WM integrity as compared to the decline in the Active Control group. We expected to observe this effect especially in the frontal

[1]Vik et al. (2015) found decline in fronto-striatal FA over a period of 3 years in 76 adults of 49–80 age at inclusion (only FA for selected tracts was analyzed). Similarly, Pfefferbaum et al. (2014) reported decline in FA across white matter in 56 older individuals over 1–8 years (control sample).

[2]The total sample included 247 participants, but only 174 had good quality pre-post DTI data (see Methods).

and temporal regions (Colcombe et al., 2006; Voss et al., 2010). Next, we expected to observe declines in FA and increases in MD, RD, and AD across the WM and that this decline will be accelerated in the oldest, more sedentary, less active, and less fit (lower CRF) adults. However, given the shorter time scale, we expected these changes to be of smaller magnitude and more spatially restricted than in the existing studies with time lags greater than a year. Finally, we expected that change in FA in the Walking or Dance groups would be behaviorally relevant, i.e., be related to change in cognitive performance, especially in the speed and memory domains (Lövdén et al., 2014; Wang et al., 2015; Bender et al., 2016a) as compared to crystallized and fluid abilities (Virginia Cognitive Aging Project Battery; Salthouse and Ferrer-Caja, 2003; Salthouse, 2004, 2005, 2010)[3].

METHODS

Participants

The University of Illinois institutional review board approved this study, written informed consent was obtained from all participants and the study was performed in accordance with the 1964 Declaration of Helsinki. The sample was recruited to participate in a randomized controlled exercise trial ("Influence of Fitness on Brain and Cognition II" at ClinicalTrials.gov, clinical study identifier NCT01472744). Healthy, low active older adults were recruited in the Champaign county area to participate in a series of neuroimaging, cognitive, and cardiorespiratory testing, before and after a 6-months aerobic exercise intervention program. Of the 1,119 participants recruited, 247 ($n = 169$ women) met inclusion criteria and agreed to enroll in the study (See Supplementary Material 1 for subject flow). Eligible participants met the following criteria: (1) were between the ages of 60 and 80 years old; (2) were free from psychiatric and neurological illness and had no history of stroke or transient ischemic attack; (3) scored <10 on the geriatric depression scale (GDS-15); (4) scored $\geq$75% right-handedness on the Edinburgh Handedness Questionnaire; (5) demonstrated normal or corrected-to-normal vision of at least 20/40 and no color blindness; (6) cleared for suitability in the MRI environment; that is, no metallic implants that could interfere with the magnetic field or cause injury, no claustrophobia, and no history of head trauma; (7) reported to have participated in no more than two moderate bouts of exercise per week within the past 6-months; (8) were not taking medication for cardiovascular disease (e.g., beta blocker, diuretics), neurological, or psychiatric conditions (e.g., antidepressant, neuroleptic, anxiolytic). The sample contained more females because fewer older males met the above inclusion criteria or showed willingness to participate in the study. After the baseline measurement, the participants were randomized using a computer data management system and baseline-adaptive randomization scheme (Begg and Iglewicz, 1980) into four intervention group (Walking $n = 54$, Walking + Nutrition $n = 54$, Dance $n = 69$, Active Control $n = 70$). Randomization was stratified by gender and age. Neither self-reported nor objectively measured PA was used as a randomization criterion.

The timeline for data collection was as follows: (1) Pre-Screening Interview and Mock MRI session; (2) Neuropsychological assessments (Virginia Cognitive Aging Battery but also spatial working memory task, task switching, not discussed here but described in the Supplementary Material 2); (3) Street crossing assessment (data presented elsewhere); (4) MRI session; (5) Treadmill test (CRF testing). We aimed to complete the above sessions within 3 weeks, but due to participant's availability it took longer for several subjects. All tests were completed at least 1 day before intervention onset. Sessions 2–5 were repeated after 6-months intervention.

Interventions

Following baseline cognitive and cardiorespiratory assessment, participants were randomized into one of the four intervention groups, taking into account equal distributions of age and gender: Dance, Walking, Walking + Nutrition, and Active Control. All participants attended supervised, 1-h sessions three times per week for 6-months. **Dance:** This intervention was designed to improve physical fitness as well as aspects of cognition necessary for learning complex social dance sequences in a socially engaging environment. Sessions were conducted in an appropriate dance space and were taught by experienced dance instructors. The choreographed dance combinations became progressively more challenging over the course of the 6-months program. Group social dance styles were selected (i.e., Contra and English Country dancing) to minimize lead-follow roles. Instead, these social dances required participants to move between partners during each dance. Each participant learned and alternated between two roles for each dance, increasing the cognitive challenge. **Walking:** This intervention was designed to increase CRF through brisk walking. Research staff supervised all walking sessions. Frequent assessment of heart rate, using either palpation or Polar Heart Rate Monitors, and rating of perceived exertion ensured that participants' exercise intensity was performed at the prescribed level. Exercise logs were completed after each exercise session to assess exercise frequency, intensity (RPE) and enjoyment levels. **Walking + Nutrition:** The Walking + Nutrition condition engaged in the same protocol as those in the walking condition. Additionally, they ingested a daily supplement supplied by Abbot Nutrition that contained beta-alanine. Beta alanine is thought to promote an increase in lean muscle mass (Zoeller et al., 2007), thereby enhancing the effect of increased CRF on brain health to boost the effect of increased CRF on brain health. Research staff supervised all walking sessions. Frequent assessment of heart rate, using either palpation or Polar Heart Rate Monitors, and rating of perceived exertion ensured that participants' exercise intensity was performed at the prescribed level. Exercise logs were completed after each exercise session. Participants were instructed to take the supplement drink daily, which was a liquid, milk-based formula supplied by Abbott Nutrition. **Active Control:** This intervention served as the active control group to account for the social engagement in the other interventions. A trained exercise specialist at a facility on the University of Illinois campus conducted all strength and balance

[3]The detailed results for time × group effects on cognitive measures will be covered in another publication. Here we use cognitive data only to show cognitive relevance of WM microstructure and its changes over 6-months.

sessions. This program focused on improving strength, stretching and stability for the whole body and was specifically designed for individuals 60 years of age and older. The program includes non-aerobic stretches, simple strength exercises, and basic balancing activities for all the large muscle groups. Each stretch was gently held to a point of slight tension but not pain for approximately 20–30 s. Each stretching and toning session included a 10–15 min warm-up and cool-down and 30–45 min of the above described stretching and toning exercises. Participants completed exercise logs on a weekly basis. The intervention was conducted in four waves from October 2011 to November 2014.

Diffusion Tensor Imaging (DTI)

Diffusion-weighted images were acquired on a 3T Siemens Trio Tim system with 45 mT/m gradients and 200 T/m/s slew rates (Siemens, Erlangen, Germany). All images were obtained parallel to the anterior-posterior commissure plane with no interslice gap. DTI images were acquired with a twice-refocused spin echo single-shot Echo Planar Imaging sequence (Reese et al., 2003) to minimize eddy current-induced image distortions. The protocol consisted of a set of 30 non-collinear diffusion-weighted acquisitions with b-value = 1,000 s/mm^2 and two T2-weighted b-value = 0 s/mm^2 acquisitions, repeated two times (TR/TE = 5,500/98 ms, 128 × 128 matrix, 1.7 × 1.7 mm^2 in-plane resolution, FA = 90, GRAPPA acceleration factor 2, and bandwidth of 1698 Hz/Px, comprising 40 3-mm-thick slices).

DTI Analysis

DTI allows inferences about WM microstructure *in vivo* by quantifying the magnitude and directionality of diffusion of water within a tissue (Beaulieu, 2002). Visual checks were performed on every volume of the raw data of every participant by AZB and TC. In case a diffusion scan contained more than two volumes with artifacts, these volumes as well as the corresponding b-vectors and b-values were removed before processing. If artifacts were found in more than two volumes, such datasets were excluded from analyses, resulting in 174 good quality pre-post datasets (Supplementary Material 1).

Next, DTI data were processed using the FSL Diffusion Toolbox v.3.0 (FDT: http://www.fmrib.ox.ac.uk/fsl) in a standard multistep procedure, including: (a) motion and eddy current correction of the images and corresponding b-vectors, (b) removal of the skull and non-brain tissue using the Brain Extraction Tool (Smith, 2002), and (c) voxel-by-voxel calculation of the diffusion tensors. Using the diffusion tensor information, FA maps were computed using DTIFit within the FDT. All motion- and eddy-current outputs, as well as FA images were visually inspected.

We used tract-based spatial statistics (TBSS, a toolbox within FSL v5.0.1), to create a representation of main WM tracts common to all subjects (also commonly known as the WM "skeleton") (Tract-Based Spatial Statistics, Smith et al., 2004, 2006, 2007). This included: (1) nonlinear alignment of each participant's FA volume to the 1 × 1 × 1 mm^3 standard Montreal Neurological Institute (MNI152) space via the FMRIB58_FA template using the FMRIB's Nonlinear Registration Tool (FNIRT, Rueckert et al., 1999), (2) calculation of the mean of all aligned FA images, (3) creation of the WM "skeleton" by perpendicular non-maximum-suppression of the mean FA image and setting the FA threshold to 0.25, and (4) perpendicular projection of the highest FA value (local center of the tract) onto the skeleton, separately for each subject. The same procedures were applied to baseline and post-intervention images.

Next, we selected regions of interest on the TBSS skeleton with the use of the DTI WM atlas to probe FA in the core parts of the selected tracts (Burzynska et al., 2013). The 20 WM tracts and their respective acronyms are specified in **Figure 3**. The prefrontal WM region was defined as $y > 12$ in MNI coordinate space and whole WM included the whole TBSS skeleton. Corpus callosum was segmented as in Hofer and Frahm (2006).

Virginia Cognitive Aging Battery

We administered a cognitive battery as described in the Virginia Cognitive Aging Project to measure latent constructs of fluid intelligence (Raven's Advanced Progressive Matrices test), perceptual speed (letter comparison, patter comparison, digit symbol substitution), and vocabulary (vocabulary, picture vocabulary, synonym vocabulary, and antonym vocabulary; Salthouse and Ferrer-Caja, 2003; Salthouse, 2004, 2005, 2010; Supplementary Material 2). The computer-based tasks were programmed in E-Prime version 1.1 (Psychology Software Tools, Pittsburgh, PA) and administered on computers with 17" cathode ray tube monitors. Several participants had missing or invalid data for single tasks 0.165 out of 174 had complete cognitive data.

To obtain components representing the four cognitive constructs and to confirm the validity of task structure as presented in Salthouse and Ferrer-Caja (2003), we performed principal component analysis (PCA) with varimax rotation. Individual scores on each of the 16 tasks were first screened for outliers and winsorized [maximum 5 cases out of 174 (<3%) were adjusted per variable]. The resulting constructs are presented in Supplementary Material 2. The component scores were saved as variables.

Cardiorespiratory Fitness (CRF)

Baseline CRF was used to predict the change in FA over 6-months of intervention. Participants received consent from their personal physician before cardiorespiratory fitness testing was conducted. CRF (VO_2 peak) was assessed by graded maximal exercise testing on a motor-driven treadmill. The protocol involves walking at a self-selected pace with incremental grades of 2–3% every 2 min. Measurements of oxygen uptake, heart rate and blood pressure were constantly monitored. Oxygen uptake (VO_2) was measured from expired air samples taken at 30-s intervals until a peak or maximum VO_2 (VO_2 peak or max) was attained; test termination was determined by symptom limitation, volitional exhaustion, and/or attainment of VO_2 peak as per ACSM guidelines (acsm.org). Due to technical problems CRF data was not collected from 2 participants, resulting in $n = 172$ for CRF.

Objective Physical Activity (PA) Assessment

Quantitative baseline PA was used to assess baseline lifestyle PA and predict the change in FA over 6-months of intervention.

PA was measured by accelerometer (Model GT1M or GT3X; Actigraph, Pensacola, FL). Each participant was instructed to wear the accelerometer on the non-dominant hip during waking hours for 7 consecutive days, and record the time that they wore the device each day on a log. When scored with an interruption period of 60 min, those with at least 10 h of wear time on at least 3 days were retained in analyses (Troiano et al., 2008; Peterson et al., 2010). These data were downloaded as activity counts, which represent raw accelerations that have been summed over a specific epoch length (e.g., 60 s), and these counts vary based on frequency and intensity of the recorded acceleration (Fanning et al., 2016). Next, these data were processed using cut points designed specifically for older adults (Copeland and Esliger, 2009) such that 50 or fewer counts per minute corresponded with sedentary behavior, 51–1,040 counts per minute corresponded to light PA, and 1,041 counts or greater represented moderate-to-vigorous PA (MVPA), related to increased heart rate and ventilation (Rejeski et al., 2016). Five participants did not have valid accelerometer data, resulting in final sample of 169 for PA.

Statistical Analyses

To investigate the effects of time and time x group interactions for the group of 174 participants we used repeated measures ANOVA in SPSS v.24 as our data were complete and the interval between baseline and post-intervention measurements was same for all participants (Liu et al., 2012).

RESULTS

Sample Characteristics at Baseline

First, we tested whether randomization based on age and gender resulted in same baseline characteristics among the four intervention groups. **Table 1** shows the demographics for the final sample of 174 people who had good quality of pre and post-intervention diffusion scans. One-way ANOVA revealed that the different intervention groups did not differ at baseline with respect to age, gender, education, BMI, VO_2 peak ($n = 172$), PA ($N = 169$), and cognitive status (MMSE).

Next, we investigated baseline characteristics in various diffusion measures. Regional values for FA, RD, MD, and AD for the whole sample and for each of the intervention groups are shown in the Supplementary Material 3. Using one-way ANOVA, we determined that FA, RD, AD and MD measures did not significantly differ among the four intervention groups at baseline in any of the region (for details see Supplementary Tables 3.1 to 3.4).

Changes in WM Diffusivity Characteristics over 6-Months

Next, we examined change in FA, RD, AD, and MD over 6-months of the intervention. We found that time had a significant effect on all diffusivity values in multiple regions. **Table 2** represents mean regional % change for the entire sample ($n = 174$, $p < 0.05$, uncorrected) and the Active Control group (no expected change in CRF or MVPA that would affect cognition or brain health). As we observed only one time x group interaction (fornix, see Section Change in diffusivity parameters: the effects of intervention), we consider the results of entire sample consistent with the Active Control.

In sum, out of 21 regions, FA consistently decreased in 11 regions as well as in the prefrontal WM and the entire skeleton. RD increased in 13 regions as well as in the prefrontal WM and the entire skeleton. AD increased in 10 regions as well as in whole WM. MD increased in 10 regions, as well as in the prefrontal WM and the entire skeleton. This regionally specific pattern of overlap of changes in FA, RD, and AD is summarized in **Figure 1** (MD is not included as highly redundant to RD and AD). Only in fMAJ RD, AD, and MD decreased.

Change in Diffusivity Parameters: The Effects of Intervention

We used repeated measures ANOVA with time as within-subject factor and the four intervention groups as between-subject factors to investigate differences in FA change between the three intervention groups and the Active Control group (Supplementary Material 4). Out of 21 regions, only the fornix

TABLE 1 | Sample characteristics at baseline.

	Total	Dance	Walking	Walking + nutrition	Active control	Group difference*(*p*-value)
N	174	49	40	42	43	–
Age	65.4 ± 4.46	65.88 ± 4.70	64.98 ± 4.00	64.95 ± 4.18	66.72 ± 4.65	0.272
Gender	120 F (69%)	37 F (76%)	27 F (68%)	27 F (64%)	29 F (67%)	0.688
Education (years)	15.92 ± 3.00	3.86 ± 1.26	3.90 ± 1.08	3.90 ± 1.19	4.12 ± 1.10	0.474
MMSE	28.52 ± 1.46	28.43 ± 1.59	28.6 ± 1.55	28.50 ± 1.33	28.56 ± 1.39	0.952
VO_2 peak [ml/min/kg]	19.77 ± 4.29	20.14 ± 4.34	20.67 ± 4.83	20.28 ± 4.31	19.76 ± 4.45	0.801
PA						
Light PA [hours daily]	4.53 ± 1.10	4.48 ± 1.09	4.50 ± 1.05	4.61 ± 1.34	4.56 ± 0.93	0.946
Sedentary [hours daily]	8.96 ± 1.41	9.24 ± 70.84	8.80 ± 1.64	8.88 ± 1.28	8.88 ± 1.57	0.480
MVPA [minutes daily]	45.14 ± 28.42	42.15 ± 23.02	51.73 ± 34.26	42.98 ± 29.12	44.84 ± 27.64	0.434
BMI [kg/m^2]	30.57 ± 5.49	30.58 ± 5.94	31.18 ± 4.93	29.81 ± 4.85	30.34 ± 6.04	0.720

*All results: M ± SD; F, female; * Result of one-way ANOVA with group as fixed factor; MMSE, Mini-mental State Examination; PA, physical activity; MVPA, moderate to vigorous PA.*

TABLE 2 | Percentage Δ in FA, RD, AD, and MD during 6-months for the entire sample and the active group.

WM region	*N*	FA %Δ ± SD	RD %Δ ± SD	AD %Δ ± SD	MD %Δ ± SD
ACC	174	**−0.69 ± 3.72**	**0.71 ± 3.57**	0.12 ± 3.61	0.39 ± 3.01
	43	**−01.40 ± 3.73**	**1.19 ± 3.49**	0.11 ± 3.39	0.62 ± 2.83
ALIC	174	**−0.53 ± 2.78**	**1.17 ± 4.05**	**0.46 ± 2.66**	**0.76 ± 2.90**
	43	**−0.91 ± 0.77**	**1.90 ± 4.53**	0.74 ± 2.98	**1.24 ± 3.34**
EC	174	**−1.38 ± 3.49**	**1.43 ± 3.23**	**0.61 ± 1.98**	**1.03 ± 2.47**
	43	**−2.04 ± 3.25**	**1.89 ± 2.96**	**0.68 ± 2.13**	**1.31 ± 2.39**
fMAJ	174	0.25 ± 2.27	**−0.78 ± 3.20**	**−0.38 ± 1.97**	**−0.55 ± 1.74**
	43	0.01 ± 2.34	−0.90 ± 3.80	**−0.66 ± 1.62**	**−0.75 ± 1.93**
fMIN	174	0.34 ± 3.43	0.08 ± 3.39	0.11 ± 2.10	0.09 ± 2.60
	43	−0.47 ± 3.56	0.48 ± 3.57	−0.01 ± 1.93	0.24 ± 2.63
FX	174	**−1.39 ± 8.00**	**2.11 ± 5.39**	**0.98 ± 3.75**	**1.61 ± 4.40**
	43	**−3.57 ± 7.04**	**4.08 ± 5.35**	**1.96 ± 3.38**	**3.12 ± 4.23**
gyrRect	174	−0.04 ± 4.02	0.34 ± 3.69	0.17 ± 2.97	0.25 ± 3.02
	43	−0.24 ± 4.33	−0.59 ± 4.01	−0.89 ± 3.06	−0.74 ± 3.22
HIPP	174	**−0.75 ± 5.53**	**2.05 ± 6.84**	**0.83 ± 4.30**	**1.31 ± 4.18**
	43	−0.41 ± 5.48	2.16 ± 7.74	**1.82 ± 4.71**	**1.91 ± 5.14**
ILF_temp	174	−0.39 ± 4.77	0.50 ± 3.58	0.22 ± 3.27	0.36 ± 3.21
	43	−0.87 ± 4.77	1.02 ± 3.53	0.89 ± 3.19	0.95 ± 3.15
IFOF_ILF_occ	174	**−0.57 ± 3.32**	**0.69 ± 3.56**	−0.14 ± 2.91	0.18 ± 2.20
	43	**−0.96 ± 3.05**	0.79 ± 3.27	−0.44 ± 2.58	0.06 ± 2.12
IFOF_UNC	174	**−0.55 ± 3.68**	**1.11 ± 3.48**	**0.57 ± 2.37**	**0.81 ± 2.42**
	43	−0.91 ± 4.44	**1.31 ± 3.46**	0.60 ± 2.34	**0.92 ± 2.28**
PCC	174	0.16 ± 10.96	1.38 ± 11.09	0.75 ± 8.21	0.93 ± 7.92
	43	0.10 ± 10.09	1.37 ± 11.47	0.88 ± 6.81	1.04 ± 7.72
PLIC	174	**−0.85 ± 2.63**	**3.30 ± 7.01**	**1.50 ± 2.87**	**2.10 ± 4.02**
	43	**−1.33 ± 2.58**	**4.08 ± 7.43**	**1.43 ± 3.01**	**2.32 ± 4.25**
cc1	174	**−0.45 ± 2.34**	**1.79 ± 5.06**	**0.71 ± 2.34**	**1.06 ± 2.60**
	43	−0.51 ± 2.40	**1.77 ± 5.15**	**0.88 ± 2.38**	**1.19 ± 2.60**
cc2	174	−0.38 ± 5.22	**1.72 ± 7.39**	**0.52 ± 2.87**	**0.92 ± 3.15**
	43	−0.56 ± 5.59	1.19 ± 7.58	0.07 ± 3.08	0.46 ± 3.24
cc3	174	0.19 ± 5.35	0.71 ± 7.71	0.44 ± 3.77	0.46 ± 3.55
	43	0.26 ± 5.54	−0.01 ± 7.24	−0.15 ± 4.13	−0.16 ± 3.21
cc4	174	0.52 ± 6.21	0.03 ± 8.73	0.52 ± 3.57	0.28 ± 4.49
	43	−0.28 ± 5.53	0.49 ± 8.71	0.08 ± 3.71	0.25 ± 4.31
cc5	174	0.18 ± 1.76	−0.50 ± 8.30	0.15 ± 2.12	−0.06 ± 2.92
	43	−0.08 ± 1.53	0.65 ± 7.40	0.38 ± 2.37	0.44 ± 3.02
SCR	174	**−0.41 ± 2.25**	**0.88 ± 3.15**	**0.31 ± 1.60**	**0.55 ± 2.09**
	43	**−0.81 ± 2.59**	**1.47 ± 3.62**	0.40 ± 1.81	**0.87 ± 2.42**
SLF	174	−0.26 ± 2.21	**0.66 ± 2.25**	**0.43 ± 1.61**	**0.53 ± 1.62**
	43	−0.26 ± 2.39	**0.91 ± 2.39**	**0.75 ± 1.63**	**0.83 ± 1.65**
UNC_pfc	174	**−1.01 ± 4.22**	**0.51 ± 2.80**	−0.21 ± 2.53	0.17 ± 2.36
	43	−1.06 ± 5.12	0.34 ± 2.33	−0.40 ± 2.42	−0.01 ± 1.88
Prefrontal	174	**−0.33 ± 2.03**	**0.46 ± 1.97**	0.15 ± 1.56	**0.30 ± 1.58**
	43	**−0.71 ± 2.24**	0.57 ± 2.05	0.02 ± 1.40	0.30 ± 1.50
Whole WM	174	**−0.38 ± 1.84**	**0.61 ± 1.86**	**0.27 ± 1.21**	**0.44 ± 1.34**
	43	**−0.68 ± 1.84**	**0.85 ± 1.86**	0.32 ± 1.13	**0.58 ± 1.29**

*Regions are listed in **Figure 1**. Significant effects of time ($p < 0.05$, uncorrected) are marked in bold.*

showed significant time x group interaction: $F_{(3, 170)} = 5.6$, $p = 0.001$ (significant after Bonferroni correction of the p-value from 0.05 to 0.002). *Post-hoc* pairwise comparisons showed that FA in the fornix decreased in both Walking and the Active Control group, but in the Dance group increased on average by 0.68×10^{-2} (**Figure 2**). We found that this time x group

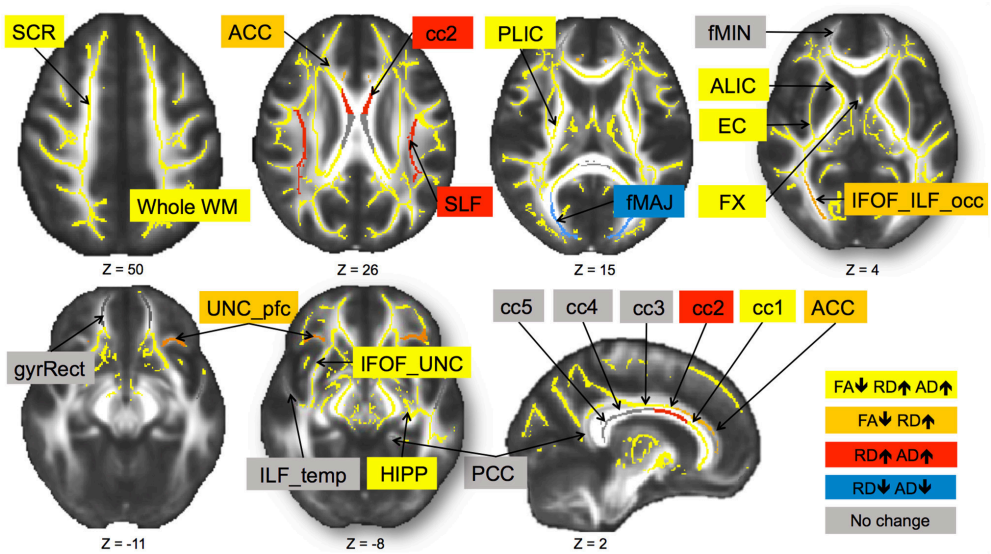

FIGURE 1 | Change in diffusivity measures over 6-months in healthy older adults 60–79 years old. Different patterns of overlap of change in diffusivity parameters are represented by different colors. Superior corona radiata (SCR), superior longitudinal fasciculus (SLF), anterior and posterior limb of the internal capsule (ALIC, PLIC), external capsule (EC), fornix (FX), five regions of the corpus callosum (cc1–5), forceps major (fMAJ), forceps minor (fMIN), anterior and posterior cingulum (ACC, PCC), WM containing occipital portion of inferior longitudinal fasciculi and inferior frontal-occipital fasciculi (IFOF_ILF_occ), WM of the straight gyrus (gyrRect), parahippocampal WM (HIPP), ventral prefrontal part of uncinate fasciculus (UNC_pfc), WM containing uncinate and the inferior frontal-occipital fasciculi (IFOF_UNC), and WM of the temporal pole related to inferior longitudinal fasciculus (ILF_temp). Regions are overlaid on the FMRIB58_FA template.

A

Group	FA Δ ± SD (x 10^{-2})	RD Δ ± SD (x 10^{-4})	MD Δ ± SD (x 10^{-4})
Active Control	-1.31 ± 2.38	0.53 ± 0.70	0.49 ± 0.66
Dance	0.68 ± 2.20	0.03 ± 0.63	0.06 ± 0.66
Walking	-0.87 ± 2.42	0.36 ± 0.66	0.32 ± 0.67
Walking + Nutrition	-0.77 ± 2.97	0.23 ± 0.83	0.15 ± 0.81
df	3	3	3
p-value Group x time	0.001	0.007	0.023

B

FIGURE 2 | (A) Time × group interaction in diffusivity parameters in the fornix in the four intervention groups. SD, standard deviation; Df, degrees of freedom. **(B)** Graphic representation of changes (delta) in FA, RD, and MD during 6-months presented in **(A)**. Error bars: standard deviation.

interaction in the fornix was driven by RD and MD: There was a significant effect for RD [$F_{(3, 170)} = 4.122$, $p = 0.007$] and MD [$F_{(3, 170)} = 3.250$, $p = 0.023$], where RD and MD increased to a significantly lesser extent in the Dance group compared to all other (**Figure 2**). The result on RD and MD was significant after Bonferroni correction of the *p*-value from 0.05 to 0.016. Pairwise *post-hoc* analyses are presented in Supplementary Material 5.

Relation of Change in Diffusivity to Cognitive Performance

We tested whether the increase in FA in the fornix in the Dance group had cognitive relevance. 165 out of 174 participants had complete cognitive data. Using one-way ANOVA, we found no significant group differences for any of the four cognitive constructs at the baseline (Supplementary Material 6). Next, correlation of baseline fornix FA with the four cognitive constructs yielded a positive association only for processing speed ($r = 0.19$, $p = 0.013$, $n = 165$, 2-tailed; significant after Bonferroni correction to $p = 0.013$ but not significant if controlled for age; **Figure 3**), but not for memory, vocabulary or reasoning ($p > 0.05$). Therefore, further analyses were restricted to the processing speed. First, we did *post-hoc* correlations between baseline fornix FA and the three tasks within the processing speed construct. They were all positively related to fornix FA: digit symbol ($r = 0.18$, $p = 0.021$, $n = 173$), pattern comparison ($r = 0.17$, $p = 0.029$, $n = 174$) and letter comparison ($r = 0.15$, $p = 0.047$, $n = 174$). These *post-hoc* analyses were not corrected for multiple comparisons. Repeated measures ANOVA on these three tasks revealed significant effect of time for the digit symbol [$F_{(1, 166)} = 3027.728$, $p = 0.000$] and pattern comparison [$F_{(1, 166)} = 19.165$, $p = 0.002$]: all groups showed increased performance over the 6-months of the trial (significant at corrected $p = 0.016$). Given lack of time x group interaction for processing speed, we correlated % change in the task performance with % change in fornix FA, but found no significant effects ($r = -0.05$, $p = 0.492$, $n = 172$).

Effect of Age, CRF, and PA on FA Decline over 6-Months

We investigated whether the decrease in FA accelerates in older age. To this aim, we correlated % change in FA with chronological age, controlling for the intervention group. The correlation was significant in fMAJ ($r = -0.26$, $p = 0.000$, $df = 171$), IFOF_ILF_occ ($r = -0.16$, $p = 0.033$, $df = 171$), SCR ($r = -0.17$ $p = 0.025$, $df = 171$), and whole WM ($r = -0.19$, $p = 013$, $df = 171$; **Figure 4**). Only fMAJ remained significant after Bonferroni correction.

Given the relationships between CRF and PA and WM integrity (Burzynska et al., 2014), we investigated whether greater CRF and levels of PA or sedentary time at baseline were associated with lesser decline in FA over 6-months. A correlation of baseline CRF or light PA and % change in FA, controlled for age, yielded no significant relationships[4]. Greater MVPA was related to more positive change in FA in the prefrontal WM, controlled for age ($r = 0.15$, $p = 0.048$, not corrected). More time spend on sedentary behavior at baseline was associated with more negative change in FA in cc2 section of the corpus callosum ($r = -0.18$, $p = 0.018$, $df = 166$) and in the prefrontal WM ($r = -0.16$, $p = 0.036$, $df = 166$, not corrected), controlled for age. Repeated measures ANOVA showed no significant interaction time × gender interaction, indicating no sex difference in FA decline over 6-months.

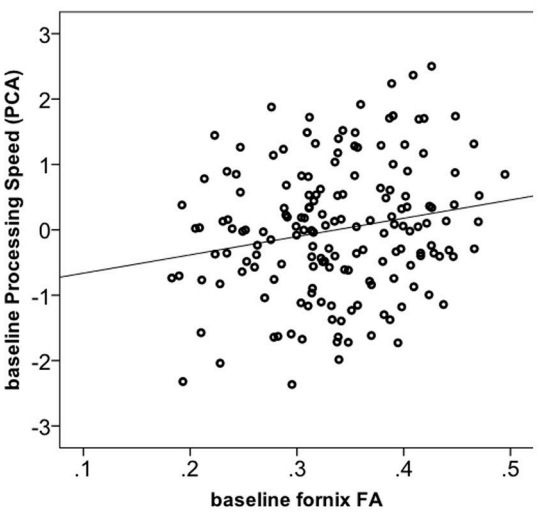

FIGURE 3 | Correlation between fornix FA and processing speed construct at baseline ($n = 165$).

DISCUSSION

We investigated changes in WM microstructure over 6-months in 174 healthy non-demented older adults that underwent four lifestyle interventions. Our main findings are: (1) Only the fornix showed a time x intervention group interaction, namely, FA declined in all groups but increased in the Dance group. Changes in FA were paralleled by changes in RD and MD; (2) FA in the fornix at baseline was related to processing speed, however, there was neither time x intervention group interaction for processing speed nor correlation between change in speed and change in FA; (3) FA decreased over 6-months in the majority of tracts, while RD, AD, and MD increased; (4) There was a spatially-variable pattern of overlap of changes in FA, RD, AD, and MD; (5) Older age was related to greater magnitude of FA decline, especially in fMAJ, IFOF_ILF_occ, SCR, and whole WM; (6) Less sedentariness and more MVPA was associated with less negative change in FA. We discuss these finding in relation to recent longitudinal and intervention studies, theories of neurocognitive aging, and outline future research directions.

Dance Intervention Improved FA in the Fornix

We found that while FA in the fornix declined over 6-months in most groups, it increased in the Dance group. Greater FA in the fornix at baseline was associated with faster processing speed, also at baseline. We discuss this observation in terms of the role of the fornix in cognition, mechanisms underlying increase in FA, and dance as a complex intervention.

[4]Partial correlations controlling for gender, or age and gender yielded the same results. Correlations between % change in FA and baseline CRF within each gender group were also not significant (gender was included as VO_2 max or peak differs between genders).

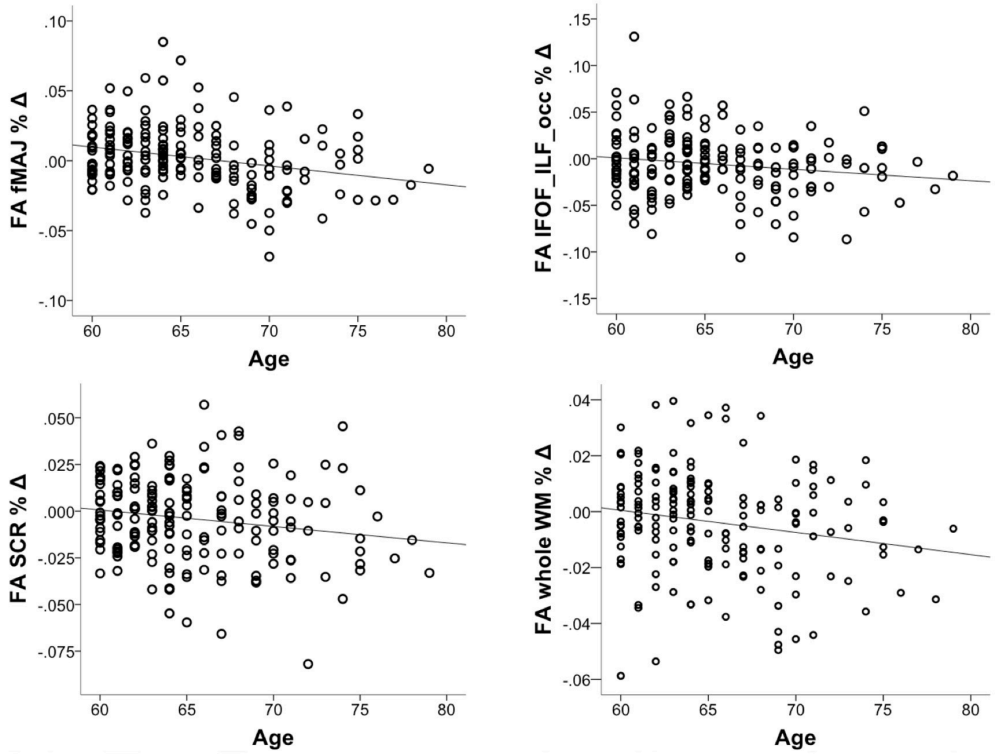

FIGURE 4 | Correlations between chronological age and % decline in FA over 6-months ($n = 174$).

Role of the Fornix in Cognition

The fornix acts as the major output tract of the hippocampus that connects the medial temporal lobes to the mammillary nuclei of the hypothalamus, septal area, and the basal forebrain (Thomas et al., 2011). The fornix is known to play an important role in the encoding, consolidation, and recall of declarative and episodic memory (Thomas et al., 2011). Damage to the fornix as a result of mechanical injury, tumor, or neurodegenerative diseases has been linked to anterograde amnesia and episodic memory impairments (Douet and Chang, 2015). In addition, microstructural and volume changes to the fornix and mammillary bodies have been linked to transition from mild cognitive impairment to clinical Alzheimer's disease (Copenhaver et al., 2006; Mielke et al., 2012; Fletcher et al., 2013; Rémy et al., 2015). In the current study, we observed no relationships between fornix FA and memory. Instead, we found associations with processing speed. We speculate that the relationships between WM microstructure and cognition may be different in clinical samples and in healthy age-related decline. For example, studies including lifespan or healthy older samples showed that fornix integrity correlates not only with episodic memory (Metzler-Baddeley et al., 2011), but also with working memory, motor performance and problem solving (Zahr et al., 2009). As most lifespan studies did not relate fornix integrity to a broader array of cognitive tasks, there is little evidence for the specific role of the fornix in other cognitive domains. Importantly, there is a study that reported specific relationships between fornix integrity and processing speed but not memory in temporal lobe epilepsy patients (Alexander et al., 2014). Together, our results confirm previous associations of WM microstructure and cognitive function in aging and suggest a role of the fornix in cognition beyond long-term memory (Madden et al., 2012).

Mechanisms of Increased FA

Increases in FA reflect increase in anisotropy of the tissue (Sen and Basser, 2005). This implies changes in the microstructure that would result in more directional diffusion if the water molecules. We showed that this interaction was driven by lack of decrease in RD and the related maintenance of MD. This points to restricted diffusion perpendicular to main fiber direction, which is related to presence and integrity of axonal membrane and myelin. In other words, at the cellular level, the suggested increase in FA is most likely related to stabilization or increase in myelin integrity (Burzynska et al., 2010). There is *in vitro* and animal evidence that repetitive stimulation of certain WM connections, such as in learning of complex motor skills in mice, results in increased myelination (McKenzie et al., 2014). In addition, there is *in vivo* evidence for increases in FA as a result of training in healthy adults (Bengtsson et al., 2005; Scholz et al., 2009; Sampaio-Baptista et al., 2013).

However, there may be an alternative explanation for increased FA, and reduced RD and MD, namely, macrostructural rather than microstructural changes. Fornix is a thin tract surrounded by lateral ventricles and therefore affected by partial

volume with cerebrospinal fluid. The Dance intervention might have increased the volume of the fornix, leading to decreased partial volume and decreased RD and MD. Local increases in WM volume and macrostructural integrity have been observed as a result of lifestyle interventions with physical activity (Colcombe et al., 2006; Bolandzadeh et al., 2015). In sum, we speculate that the observed increase in FA results from both macro- and micro-structural reorganization of the fornix.

Dance as a Complex Intervention

Dance is a pleasurable and captivating activity, which involves aerobic exercise, sensorimotor stimulation, and cognitive, visuospatial, social, and emotional engagement. Epidemiological studies found that ballroom dance has also been associated with a protective effective against dementia onset in older adults (Verghese et al., 2003) and reduced depression in community-dwelling older adults with depression (Haboush et al., 2006). Indeed, there is increasing interest in dance as a therapeutic intervention for various clinical groups (Dhami et al., 2015), such as in Parkinson's disease (McNeely et al., 2015) and dementia (Ballesteros et al., 2015; Adam et al., 2016). Our current data indicate that this broad, multimodal stimulation had greater benefit for WM integrity than aerobic exercise alone (i.e., Walking and Walking + Nutrition). This is in line with recent findings that combined exercise and cognitive interventions have more benefit for cognitive, physical, and mental health in older population than each intervention alone (Oswald et al., 2006; Law et al., 2014; Bamidis et al., 2015; Lauenroth et al., 2016). Combined cognitive and physical interventions may also have more long-lasting effects (Rahe et al., 2015). Interestingly, despite positive changes in the WM in the Dance group, we found no cognitive benefit for any of the intervention groups. This may be explained by the observation that changes in neuroimaging outcomes may precede changes in cognition by several years in older population (Jack and Holtzman, 2013). Therefore, improvements in cognition may not be detectable after 6-months of intervention, with most participants improving due to test-retest effect. Future interventions of longer duration are required to test this hypothesis of cognitive benefits following neural changes. Also, available evidence for correlations between decline in FA and cognitive change come from measurements acquired at least 2 years apart (Lövdén et al., 2014; Ritchie et al., 2015; Bender et al., 2016a). Together, although evaluation of decline or increase in WM integrity over 6-months gives insight into short-term neural dynamics in old age, it may not be sufficient to detect robust brain-cognition correlations and effects of intervention groups on cognition.

WM Microstructure Changes over 6-Months

We observed significant time effects on WM microstructure over a 6-months period in majority of tracts. Currently, this is the shortest period of time over which changes in WM microstructures in healthy older adults have been detected. We discuss our findings in terms of magnitude of annual % change, spatial overlap of changes in FA, RD, AD, and MD, and spatial gradient of change.

Magnitude of Change

We carefully compared the observed magnitudes of % change over 6-months with annual % changes reported in three previous longitudinal studies and one intervention. For this comparison we chose to focus on changes in diffusivity values for the whole WM as most comparable to global WM or averages across tracts reported in other studies.

We observed the greatest semi-annual change in RD (+0.61, +0.85%), followed by MD (+0.44, +0.58%), FA (–0.38, –0.68%) and AD (+0.27, +0.32%; for whole sample and the active control, respectively). These values are of the same order and a very similar magnitude as annual % change in 203 neurologically healthy (MMSE>25) adults over the span of 3.6 years (Sexton et al., 2014). Specifically, using same tools as in the current study (TBSS) to create representation of major WM tracts, the authors reported the following annual % change for the whole WM skeleton: RD +0.50%, MD +0.30%, FA −0.30%, and AD +0.20% (Sexton et al., 2014). A subsequent tract-based analysis of a subset of this dataset ($n = 118$) yielded the average annual changes of RD +0.60%, MD +0.43%, AD +0.29%, and FA −0.27% (Storsve et al., 2016). Similarly, in a sample of 108 cognitively normal (MMSE>26) adults aged 66–87 measured on average 2.6 years apart, mean annual change in FA over several tracts was −0.5% (Rieckmann et al., 2016). Finally, Voss et al. (2013b) compared changes in lobar diffusivity properties of 55 to 80 years old healthy adults (mMMSE>51) randomized into two intervention groups: aerobic walking group and stretching-tonic active control. We averaged diffusivity values of the 4 lobes to obtain annual % change for the whole WM (TBSS skeleton). The values were +0.43% for RD, −0.42% for FA, and +0.15% for AD for 35 adults in the stretching-toning group, consistent with the above reports.

Together, magnitudes of % annual change are consistent across the existing studies and exceed estimates from cross-sectional designs (Barrick et al., 2010; Lövdén et al., 2014; Rieckmann et al., 2016). The small deviations in magnitude of change seem to depend on analysis method of the diffusion data: skeleton-based used by Sexton et al. (2016), Voss et al. (2013b), and current study, tract-based used by Storsve et al. (2016) and Rieckmann et al. (2016). In addition, sample's age may influence the observed FA decline. Studies reporting greater magnitude of change (Voss et al., 2013b; Rieckmann et al., 2016) included older sample (55+) while Sexton et al. (2014) and Storsve et al. (2016) used adult lifespan sample (age 23–87) to estimate annual change. Thus, greater magnitude of change observed in our study may be due to acceleration of changes in WM diffusivity in the 5th decade and thereafter (Sexton et al., 2014). It remains to be determined whether studying change in center of tracts with maximal tract coherence is more or less sensitive to detecting change in WM microstructure as compared to studying the entire volume of the tracts.

Patterns of Overlap in FA, RD, AD, and MD Changes

We observed a pattern of spatial overlap of changes in different diffusivity parameters. The whole WM (i.e., the skeleton) showed significant decreases in FA overlapping with RD and AD increases (and the resulting increases in MD). This pattern was

also present in projection fibers (both limbs of the internal capsule, superior corona radiate), limbic system structures (WM near hippocampus, fornix), association fibers (inferior fronto-occipital fasciculus), and in the commissural fibers (genu corpus callosum). In our earlier cross-sectional work we referred to this pattern of diffusivity changes as "chronic WM degeneration" (Burzynska et al., 2010), as it has been observed in chronic or advanced stages of WM degeneration. This involves an increase in extracellular volume fraction resulting from losses in both axons and myelin (Thomalla et al., 2004; Cosottini et al., 2005; Sen and Basser, 2005; Concha et al., 2006; Lindquist et al., 2007; Sidaros et al., 2008; Sun et al., 2008). In line with our earlier cross-sectional work (Burzynska et al., 2010), we localized this "chronic" pattern of microstructural changes to the genu corpus callosum and association fibers. These structures are known to be most vulnerable to environmental and metabolic challenges due to thin myelin and low oligodendrocyte-to-axon ratio (Pfefferbaum and Sullivan, 2001; Bartzokis, 2004; Bartzokis et al., 2004). While in the cross-sectional study this "chronic" pattern accounted for 24% of WM volume showing age differences in FA (Burzynska et al., 2010), in the current longitudinal analyses the "chronic" pattern dominated the WM skeleton.

We observed decreases in FA in parallel with increases in RD in association fibers (anterior cingulum, occipital part of the inferior fronto-occipital fasciculus, and prefrontal part of the uncinate fasciculus). This pattern of increased diffusivity change perpendicular to the main fiber direction has been associated with myelin loss or degeneration (Song et al., 2002, 2005; Ciccarelli et al., 2006; Burzynska et al., 2010) suggesting that these tracts undergo predominantly short–term myelin changes.

We reported decrease increases in RD and AD, and MD without a net change in FA in the premotor section of the corpus callosum (cc2) and in the superior longitudinal fasciculus. We interpret this pattern as subtle changes in both axons and myelin, which are likely to progress to the "chronic" stage with significant FA decrease. We consider fiber reorganization less likely given increase in MD, indicating decrease in cellular barriers within these WM regions. In one region (fMAJ) we found decreases in both RD and AD. Decrease of diffusivity has been related to increase in tissue density such as in gliosis (Burzynska et al., 2010), or with increased partial volume with surrounding gray matter.

Finally, some regions showed no significant change in diffusivity during 6-months. These include forceps minor (anterior thalamic radiations), WM of the gyrus rectus (fibers of frontal pole and orbitofrontal cortex), inferior longitudinal fasciculus (temporal lobe), posterior cingulum, and the body and splenium of the corpus callosum (motor, sensory and parieto-occipital sections; cc3–cc5). These structures showed only weak age differences in FA or no age difference in our earlier cross-sectional work (Burzynska et al., 2010). Therefore, microstructure in these regions may be relatively stable throughout the adulthood, with subtle decline from early to late adulthood but no significant short-term changes during 7th and 8th decade of life.

In sum, longitudinal patterns of diffusivity changes confirm previous cross-sectional evidence for spatially variable increases in RD, AD, MD, and decreases in FA. In contrast to cross-sectional analyses, 6-months longitudinal data provided no evidence for decreases in MD, RD, and AD (except for fMAJ). Qualitative differences in diffusivity patterns across WM regions between cross-sectional and longitudinal samples suggest region-specific and non-linear time courses of adult age changes in WM microstructure.

Spatial Gradients of Change

There have been several attempts to organize the age-related changes using developmental or anatomical frameworks. Sexton et al. (2014) described an inferior-to superior gradient of lesser-to-greater age related changes. This framework builds on cross-sectional evidence that superior fibers may be more vulnerable to age-related changes (Sullivan et al., 2010a; Sullivan and Pfefferbaum, 2010b) and that WM maturation proceeds from inferior to superior regions (Colby et al., 2011). The related "last in, first out" developmental framework posits that tracts that myelinate last in ontogenic development are most vulnerable and first undergo age-related deterioration (Bartzokis et al., 2010). Prefrontal regions and related association fibers myelinate late as compared to motor and sensory regions. Based on this, the "last in, first out" framework can be refined to anterior-to-posterior gradient of greater to lesser decline (Raz et al., 2005). Clearly, within the corpus callosum, our findings support the anterior-to-posterior, "last in, first out" hypothesis, with the "chronic" pattern of diffusivity changes in the genu and no changes observed in the posterior to middle sections. A similar gradient can be seen within the cingulum bundle. However, the mixed pattern of changes in the remaining tracts does not equivocally support any other developmental or anatomical framework. Namely, over 6-months, we observed changes in both superior, inferior, as well as both anterior and posterior association and projection tracts.

Together, the reported WM changes over a 6-months period will have important implications for planning the timeline of future interventions and longitudinal studies, as well for diagnostic follow-ups. For example, knowing that change is robustly detectable over 6-months, the magnitude of decline in FA or other parameters could be used in identifying accelerated slopes and, therefore, individuals at risk of cognitive decline or conversion to MCI at early stages.

Effects of Age, CRF, and PA on FA Decline

We found that FA decline increased in magnitude with advancing age, especially in fMAJ, IFOF_ILF_occ, SCR, and whole WM. This is consistent with previous reports of accelerated WM decline after 5th decade of life (Storsve et al., 2016). We found no effects of gender and CRF on FA changes. Interestingly, we found that adults engaging in more MVPA and spending less time on sedentary behaviors showed less negative change in FA, especially in the prefrontal WM. Prefrontal regions have been shown previously to benefit from exercise interventions (Colcombe et al., 2006; Voss et al., 2013b). There are a number of not mutually exclusive mechanisms of action of active lifestyle on the brain: increased levels of neurotrophic and insulin-like

growth factors (Carro et al., 2000; Zoladz et al., 2008; Rasmussen et al., 2009; Voss et al., 2013a), better brain perfusion and cerebrovascular health (Black et al., 1990; Bullitt et al., 2009; Thomas and Baker, 2013), as well as lesser metabolic distress related to reduced sedentary behaviors (Yanagibori et al., 1998; Hamilton et al., 2004; Demiot et al., 2007; Hamburg et al., 2007). Our longitudinal results suggest, similar to our previous cross-sectional findings (Burzynska et al., 2014), that only exercise and avoiding sedentariness can slow down WM age-related WM decline.

We acknowledge that there may be other factors not addressed in the current study, such as genetic polymorphisms or diet that influence the magnitude of WM decline in aging. For example, greater amyloid burden was found to explain faster FA decline in parahippocampal cingulum, body corpus callosum, and forceps minor in healthy older adults (Rieckmann et al., 2016), and those carrying the APOE-ε4 risk allele may also preferentially benefit from PA (Etnier et al., 2007; Smith et al., 2013). Future randomized clinical trials on larger samples are needed to understand individual differences in WM deterioration in healthy aging.

CONCLUSIONS

In conclusion, we provided first evidence for a dance intervention resulting in increased FA. We attribute this to the fact that dance is a combined cognitive, physical and social training, known to boost intervention outcomes. We found no relation of fornix FA to memory, but a rather unexpected relation to processing speed, suggesting a role of the fornix beyond the memory systems in healthy individuals. Importantly, knowing fornix FA can be increased with dance training may lead to new avenues for early treatments, for example, in genetically inherited dementias, characterized by reduced fornix FA at preclinical, asymptomatic stages (Ringman et al., 2007). We also provided first evidence for robust decline in WM integrity in healthy older adults over only 6-months. Patterns of change in different diffusivity parameters may reflect region-specific histological mechanisms of decline. Our findings support previous reports of accelerated decline with advancing age and for greater susceptibility of anterior than posterior corpus callosum fibers. However, we found no evidence for gender differences or anterior-to-posterior or superior-to-inferior gradient of decline in the whole WM. Importantly, less time spend sitting and more time spent engaging in MVPA was associated with less negative change in FA, providing the first evidence of objectively measured lifestyle activities on change in WM health.

AUTHOR CONTRIBUTIONS

AB, designed and conducted the study, preprocessed the data, carried out the analyses and wrote the manuscript; YJ, analyzed the data and wrote the manuscript; AMK, collected and preprocessed data; JF, EA, and NG, collected and preprocessed data; TC, preprocessed data; MV assisted in study design, data collection and preprocessing; EM and AFK, designed the study and wrote the manuscript.

FUNDING

This work was supported by National Institute on Aging (https://www.nia.nih.gov/; R37 AG025667; AFK) and the Center for Nutrition Learning and Memory at the University of Illinois at Urbana-Champaign (http://cnlm.illinois.edu/; AFK). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ACKNOWLEDGMENTS

We thank Jenna Klippenstein and Jane Gill for help with data organization, Holly Tracy and Nancy Dodge for MRI data collection, and Susan H. Herrel for project coordination.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnagi.2017.00059/full#supplementary-material

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 23 March 2017
doi: 10.3389/fnagi.2017.00069

Limited Effects of Set Shifting Training in Healthy Older Adults

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Our ability to flexibly shift between tasks or task sets declines in older age. As this decline may have adverse effects on everyday life of elderly people, it is of interest to study whether set shifting ability can be trained, and if training effects generalize to other cognitive tasks. Here, we report a randomized controlled trial where healthy older adults trained set shifting with three different set shifting tasks. The training group ($n = 17$) performed adaptive set shifting training for 5 weeks with three training sessions a week (45 min/session), while the active control group ($n = 16$) played three different computer games for the same period. Both groups underwent extensive pre- and post-testing and a 1-year follow-up. Compared to the controls, the training group showed significant improvements on the trained tasks. Evidence for near transfer in the training group was very limited, as it was seen only on overall accuracy on an untrained computerized set shifting task. No far transfer to other cognitive functions was observed. One year later, the training group was still better on the trained tasks but the single near transfer effect had vanished. The results suggest that computerized set shifting training in the elderly shows long-lasting effects on the trained tasks but very little benefit in terms of generalization.

Keywords: set shifting, task switching, cognitive training, executive functions, normal aging

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Received: *14 September 2016*
Accepted: *07 March 2017*
Published: *23 March 2017*

Citation:
Grönholm-Nyman P, Soveri A, Rinne JO, Ek E, Nyholm A, Stigsdotter Neely A and Laine M (2017) Limited Effects of Set Shifting Training in Healthy Older Adults. Front. Aging Neurosci. 9:69. doi: 10.3389/fnagi.2017.00069

INTRODUCTION

Executive functions represent higher-level cognitive control processes that are crucial for everyday activities. Different models of the mental architecture of executive functions have been put forth, but a particularly influential model by Miyake et al. (2000) that is based on data from young adults postulates three major executive functions that are separable but strongly interrelated. These functions are (1) working memory updating, (2) inhibition of task-irrelevant responses, and (3) shifting between tasks and mental sets. A later study gave support for the tripartite model of executive functions also in older adults (Vaughan and Giovanello, 2010). All three functions, including the third one that is at the focus of the present study, have been found to decline with older age (Cepeda et al., 2001; Kray et al., 2004; Zelazo et al., 2004). Little research interest has been directed to the trainability of set shifting in late adulthood, despite the fact that the ability to switch sets or tasks quickly is important in our everyday life (Monsell, 2003; Vaughan and Giovanello, 2010). Moreover, as the risk of cognitive impairment is enhanced in late adulthood due to, for example, dementing disorders, there is a need for finding suitable compensatory interventions for older adults. Therefore, we set out to study the effects of set shifting training in older adults with a 5-week adaptive training regime.

Although the generalizability of set shifting training in healthy elderly adults has been scarcely studied, there is an increasing number of studies on the effects of computerized working memory and multidomain training in healthy elderly (Buschkuehl et al., 2008; Dahlin et al., 2008b; Borella et al., 2010; Brehmer et al., 2011, 2012; Barnes et al., 2013; Zinke et al., 2013; Sandberg et al., 2014). In addition to improvement on the trained task itself, many of these recent training studies have shown that training can lead to *near transfer*, that is, improvement on tasks that are closely related to the intervention (e.g., working memory training leading to improved performance on another working memory task). Some findings suggest that training may even show *far transfer*, that is, generalization to other cognitive domains (e.g., working memory training leading to improved performance on a task measuring fluid intelligence). The results from a recent meta-analysis by Karbach and Verhaeghen (2014) indicated that training of working memory and executive functions was effective in older persons both with regard to near and far transfer, albeit the latter transfer effect was more modest. However, a re-analysis by Melby-Lervåg and Hulme (2016) found no convincing support for far transfer following working memory training in older age.

The results from the few existing set shifting training studies investigating transfer effects have varied, but most of them have found near transfer effects (Minear and Shah, 2008; Karbach and Kray, 2009; Pereg et al., 2013; Soveri et al., 2013). To our knowledge, only Karbach and Kray (2009) have included elderly adults in their set shifting training study. They found near transfer effects in reaction times to a set-shifting task structurally similar to the trained task for children, young adults, and older adults both with regard to switching cost and mixing cost when compared with the respective active control groups. *Switching cost* refers to mean reaction times (RTs) of switch trials minus mean RTs of non-switch trials within a mixed block, i.e., within the task block where switching takes place. *Mixing cost* refers to mean RTs of nonswitch trials in a mixed block minus mean RTs of single task trials where no switching takes place (see also the next paragraph for more information about switching and mixing cost). The effects were most pronounced in children and older participants on the mixing cost. Additionally, far transfer was found to inhibition, verbal and spatial working memory, and fluid intelligence in all age groups. The training tasks of Karbach and Kray (2009) were later used by Zinke et al. (2012) who studied transfer effects of set shifting training in adolescents. They found that compared to controls, set shifting training resulted in transfer to the mixing cost in a similar but untrained set shifting task, but far transfer was limited to a speed task and a tendency toward faster performance in an updating task. Thus, their transfer results were more limited than those of Karbach and Kray (2009). Also Pereg et al. (2013), studying set shifting training in young adults, used the same paradigm as Karbach and Kray (2009) and found only limited transfer effects. One could also note that the results from a recent multidomain (updating, shifting, and inhibition) training study conducted with young and old adults showed only near transfer effects (Sandberg et al., 2014). Soveri et al. (2013) studied set shifting training with young adults and found no significant transfer effects. As regards performance on the trained tasks following set shifting training, only Soveri et al. (2013) reported these effects, finding that the training group outperformed the control group on an accuracy measure.

Set shifting represents a rather well-studied construct in cognitive psychology. In set shifting experiments, participants are first asked to perform more simple tasks (=single tasks) with just one instruction in mind (for example, determining if the number in a number-letter pair is even or odd). In addition, the task includes a mixed task block where the participants have to perform different tasks depending on different properties of the stimuli. For example, they may need to determine if the number in a number-letter pair is even or odd when the pair is presented in a certain location, or to determine if the letter in the pair is a vowel or consonant when the pair is presented in another location. Key measures of set shifting ability include switching cost and mixing cost measures both in RTs and accuracy that were defined in the previous paragraph. A switching cost reflects the generally longer RTs and higher error rates to switching trials compared with repetition trials within the mixed block. In turn, the repetition trials of the mixed block tend to elicit slower and more error-prone responses than the single block trials. This effect is coined as the mixing cost and it is thought to reflect increased monitoring demands in the mixed block (Monsell, 2003). All in all, set shifting calls for several executive processes, such as shifting attention between different aspects of the stimulus, shifting between instructions, retrieving instructions from long-term memory and acting upon them, inhibiting the previous instruction or task set, and overall monitoring (Monsell, 2003). There is also a growing number of neuroimaging studies on set shifting (for a review, see e.g., Ruge et al., 2013). These studies have used different procedures that require participants to shift between varying stimulus-response mappings, spatial locations, abstract goals etc. Recent neuroimaging studies employing multiple types of shifts within a paradigm have revealed both domain-independent as well as domain-specific neural correlates of set shifting (Ravizza and Carter, 2008; Chiu and Yantis, 2009; Muhle-Karbe et al., 2014). One further theoretical division in set shifting tasks is the separation into perceptual vs. rule-based switching. Perceptual switching tasks require reorienting of visuospatial attention, that is, "what/where one should address one's attention," whereas rule-based switching tasks call for changing goal-directed information (rules), that is, "what one should do" (Ravizza and Carter, 2008). There is evidence that these two aspects of switching differ in terms of behavioral effects and neural recruitment, meaning that one cannot draw general conclusions only on the basis of a single type of a set shifting task.

As mentioned above, set shifting ability declines with age, but there are differences as to which type of switching costs are most affected by age (Verhaeghen and Cerella, 2002; Wasylyshyn et al., 2011). Wasylyshyn et al. (2011) investigated in their meta-analysis the relationships between aging and switching and mixing costs (labeled as local vs. global switch cost in their paper). They found that in general, the switching cost does not seem to be affected by age. In other words, selective attention processes needed for the deactivation and activation of cognitive

processes in order to perform switches do not seem to be age-sensitive. However, Wasylyshyn et al. (2011) found that the mixing cost that reflects the ability to maintain two task sets was enhanced in older age, and the effect was not explained by general age-related slowing. Wasylyshyn et al. (2011) speculated that the larger mixing cost in late adulthood could be related to impaired working memory, as previous studies have shown a strong relationship between age-related cognitive deficits and working memory processes. In other words, working memory demands might adversely affect set shifting performance in older adults.

The aim of the present study was to investigate transfer effects of set shifting training in older adults, as only one previous set shifting training study reviewed above has included elderly subjects (Karbach and Kray, 2009), and the extent of the generalization effects of set shifting training is controversial. First, we presumed that the training group would outperform the control group on the trained tasks. Second, in the light of previous studies, we expected to find near transfer effects to untrained set shifting tasks. Here, we also wanted to explore if the expected near transfer effects would show differential results regarding perceptual vs. rule-based set shifting. Third, far transfer effects were expected to be less plausible but possible. Measures of inhibition and working memory updating were included as far transfer measures, as these executive functions are related to set shifting (Miyake et al., 2000). Also, Karbach and Kray (2009) found transfer to these domains in their set shifting training study. Cognitive training studies often include measures of fluid intelligence as far transfer measures, as working memory updating and fluid intelligence are strongly correlated (Engle, 2002). In fact, Karbach and Kray (2009) reported that set shifting training generalized to fluid intelligence. Therefore, we also included measures of fluid intelligence among our far transfer measures. In addition, verbal fluency was included as a far transfer measure, as set shifting, working memory updating and response inhibition, in addition to lexical retrieval ability, are important components for optimal performance on verbal fluency tasks (Henry and Crawford, 2004; Flanagan et al., 2014; Shao et al., 2014), and therefore set shifting training might have an effect even on verbal fluency performance. In addition, memory measures were included as transfer measures because in aging research, one has argued for an interplay between executive and memory functions (Bisiacchi et al., 2008). Finally, the visuomotor speed measure was included as a measure of processing speed. In order to explore how long-lasting the possible training-induced effects were, a one-year follow-up was included.

In the present randomized controlled trial, we used a 15-session long adaptive training regime, and included an active control group. We also wanted to look more closely at perceptual vs. rule-based switching (cf. Ravizza and Carter, 2008), as that has not been investigated in previous set shifting training studies. Therefore, the set shifting measures in our pre-post test battery included both a perceptual part, where responses were given according to location of target, and a rule-based part, where responses required the retrieval of appropriate stimulus-response mappings. Untrained tasks tapping set shifting served as near transfer measures. Far transfer tasks included measures of inhibition, working memory updating, fluid intelligence, verbal fluency, episodic memory, and visuomotor speed. We included at least two tests per cognitive domain (apart from visuomotor speed) to ensure that possible transfer effects are not task-specific (see Shipstead et al., 2012).

MATERIALS AND METHODS

Participants

Thirty-six healthy Finnish-speaking older adults recruited from various sources (an adult education center, a sports club for seniors, on bulletin boards etc.) volunteered for the experiment. Initial screening of potential participants was conducted over the phone to exclude those with self-reported neurological or psychiatric diseases. Thereafter, a short neuropsychological assessment was conducted, consisting of a semi-structured interview probing the participants' education, occupation, vision, hearing, possible illnesses, traumatic brain injuries, medication, alcohol and/or drug abuse, and possible alcohol intake during the 24-h period preceding the testing, as well as the Finnish version of Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Welsh et al., 1994; Hänninen et al., 2010), the Logical Memory immediate and Logical Memory delayed subtests of Wechsler Memory Scale—Revised (WMS-R; Wechsler, 1996), the Similarities subtest of Wechsler Adult Intelligence Scale—Revised (WAIS-R; Wechsler, 1992), and Memo-Boston Naming Test (Memo-BNT; Karrasch et al., 2010). Before the neuropsychological assessment, the participants were asked to give their written informed consent. After the assessment, they filled in a Finnish translation of the Edinburgh Handedness Inventory (Oldfield, 1971), the Godin Leisure-Time Exercise Questionnaire[1] (Godin and Shephard, 1997), and Behavior Rating Inventory of Executive Function–Adult Version (BRIEF-A)[2] (Roth et al., 2005). They also filled in the Beck Depression Inventory-II (BDI-II; Beck et al., 2004) at home before the pretesting in order to rule out major depressive symptoms, as well as the PK-5 Personality test[3] (Psykologien Kustannus Oy, 2007). Two participants were excluded after the neuropsychological assessment as they performed below cut-off on several memory measures, and one participant dropped out during the training period, bringing the final number of participants to 33 (19 females and 14 males). The study was approved by the Ethics Committee of the Hospital District of Southwest Finland. The follow-up part of the study was approved by the Ethics Committee of the Departments of Psychology and Logopedics at the Åbo Akademi University. The participants did not receive monetary compensation for their participation.

The participants were first matched in pairs and then randomly allotted to the training group ($n = 17$; 10 women/7 men) or to the active control group ($n = 16$; 9 women/7 men). Variables that were taken into account during matching were

[1] The results of this questionnaire will be reported elsewhere.
[2] BRIEF-A was also filled in at the end of the post testing.
[3] The results of this test will be reported elsewhere.

education, WAIS-R (Wechsler, 1992) Similarities score[4], age, and gender. The participants were not aware of their group membership. The groups were comparable in terms of years of education $t_{(31)} = 0.348$, $p = 0.730$ (training group $M = 14.91$, $SD = 3.55$, control group $M = 14.44$, SD = 4.27) performance on the WAIS-R Similarities $t_{(31)} = -0.196$, $p = 0.853$ (training group $M = 29.53$, $SD = 2.40$, control group $M = 29.29$, $SD = 2.21$), and age $t_{(31)} = 0.173$, $p = 0.864$ (training group $M = 68.76$, $SD = 6.68$, control group $M = 68.31$, $SD = 8.28$).

Procedure

The experimental procedure including the tasks that were administered is depicted in **Figure 1**. A randomized controlled trial with a pretest-posttest design was used. Both the training group and the active control group participated in 15 training sessions, 45–60 min/session, three times a week for 5 weeks. The training took place at the university in groups with maximally four people, or individually when needed. All participants underwent the individually administered extensive pre-posttest battery. The posttest was performed maximally 11 days after training, and there was no group difference with regard to the number of days between the last training (or "pseudo-training") session and posttest $t_{(31)} = 0.535$, $p = 0.596$. The training tasks were adaptive for both the training group and the control group, with the tasks becoming more difficult as the participants advanced. At pretest, at every training session, and at posttest, all participants rated their level of motivation (on a scale 1–5, where 1 = not at all motivated; 5 = very motivated) and fatigue/alertness (on a scale 1–5, where 1 = very tired; 5 = very alert).

Procedure and Training Tasks for the Training Group

Three computerized set shifting training tasks were used: (1) a Categorization Task (CT) that was a modified version of the Wisconsin Card Sorting Test (Berg, 1948; Soveri et al., 2013), (2) a Number-Letter (NL) task (Soveri et al., 2013), adapted from Rogers and Monsell (1995), and (3) a Dot-Figure (DF) task that was a modified non-verbal version of the Number-letter task.

All training tasks included four difficulty levels. To advance to the next difficulty level, the participants had to pass a level test. The level test was a version of the CT that was at the same difficulty level as the previous week's training task, and it was performed after the last training session of the week. The participants who made <20% errors advanced to the next difficulty level. Exceeding this error criterion would have implied staying at the same level for at least 1 week, but all participants advanced after each level test. As there were four difficulty levels, there were three level tests. After the participants had reached the highest difficulty level (level 4), they stayed on that level for the remaining training sessions. The participants were asked to perform as fast and as accurately as possible throughout training. The order of trials in the training tasks and the level tests was randomized.

[4]The WAIS-R Similiarities score was included as a matching criteria, as it is an indicator of general mental ability (Lezak et al., 2012).

The Categorization Task (CT) in Training

In this task, four stimulus cards appeared in a horizontal line at the top of the computer screen. The task was to match response cards, appearing one at a time, with the stimulus cards, based on different sorting rules that were given. At levels 1 and 2, the four stimulus cards included different *shapes* (cross, circle, triangle, or square), *colors* (red, blue, yellow, or black), and *quantities* (one, two, three, or four figures), and the figures were placed at the center of the cards. The task was to sort the response cards according to these features by deciding which stimulus card had figures of the same shape, color, or number, as the figures on the response cards, based on the sorting rule that was shown underneath each response card. At levels 3 and 4, *location* (upper left, upper right, lower left, or lower right corner) was added as a fourth sorting rule and feature on the stimulus cards. Thus, at levels 3 and 4, the figure was always placed in one of the four corners of the card (**Figure 2A**). At levels 1 and 3, the sorting rule changed randomly after four to six response cards and at levels 2 and 4 after one to three response cards, regardless of whether the responses were correct or incorrect. Level 1 employed three sorting rules with less frequent shifts (after 4–6 trials with altogether 270 trials), level 2 three sorting rules with more frequent shifts (after 1–3 trials with altogether 270 trials), level 3 four sorting rules with less frequent shifts (after 4–6 trials with altogether 300 trials) and level 4 four sorting rules with more frequent shifts (after 1–3 trials with altogether 288 trials). Task completion took about 15 min. Each difficulty level was preceded by a short practice sequence including all relevant sorting rules. The four response keys, 1, 2, 3, and 4 on the keyboard corresponded spatially to the stimulus cards. The sorting rule was presented for 1,000 ms at the beginning of each trial, and the response card was presented simultaneously until a response was given, or maximally for 3,000 ms. Before moving on to the next response card, audio-visual feedback was given for 1,500 ms. A correct response elicited a high pitch tone and a bright screen, while an incorrect response or no response elicited a low pitch tone and a dark screen. Feedback was given at all difficulty levels. After the task, the number of correct responses, incorrect responses and missed responses were shown on the computer screen. The task included two 1-min pauses, which the participants could end sooner by pressing the Enter key.

The Number-Letter (NL) Task in Training

At levels 1 and 2 in this task, black number-letter pairs on white background were presented in one of two squares on the computer screen, one square above the other (**Figure 2B**). When the number-letter pair was presented in the upper square, the participant had to determine if the number was even or odd, and when it was presented in the lower square, the task was to determine if the letter was a vowel or a consonant. Thus, the location of the number-letter pair served as a cue for which task to perform. Number-letter pairs were constructed by combining the vowels A, E, I, U and the consonants G, K, M, R, with the even numbers 2, 4, 6, 8 and the uneven numbers 3, 5, 7, 9. The participants could not anticipate when a number-letter pair shifted from one square to another (switching trial), or when it was shown in the same square as the previous pair

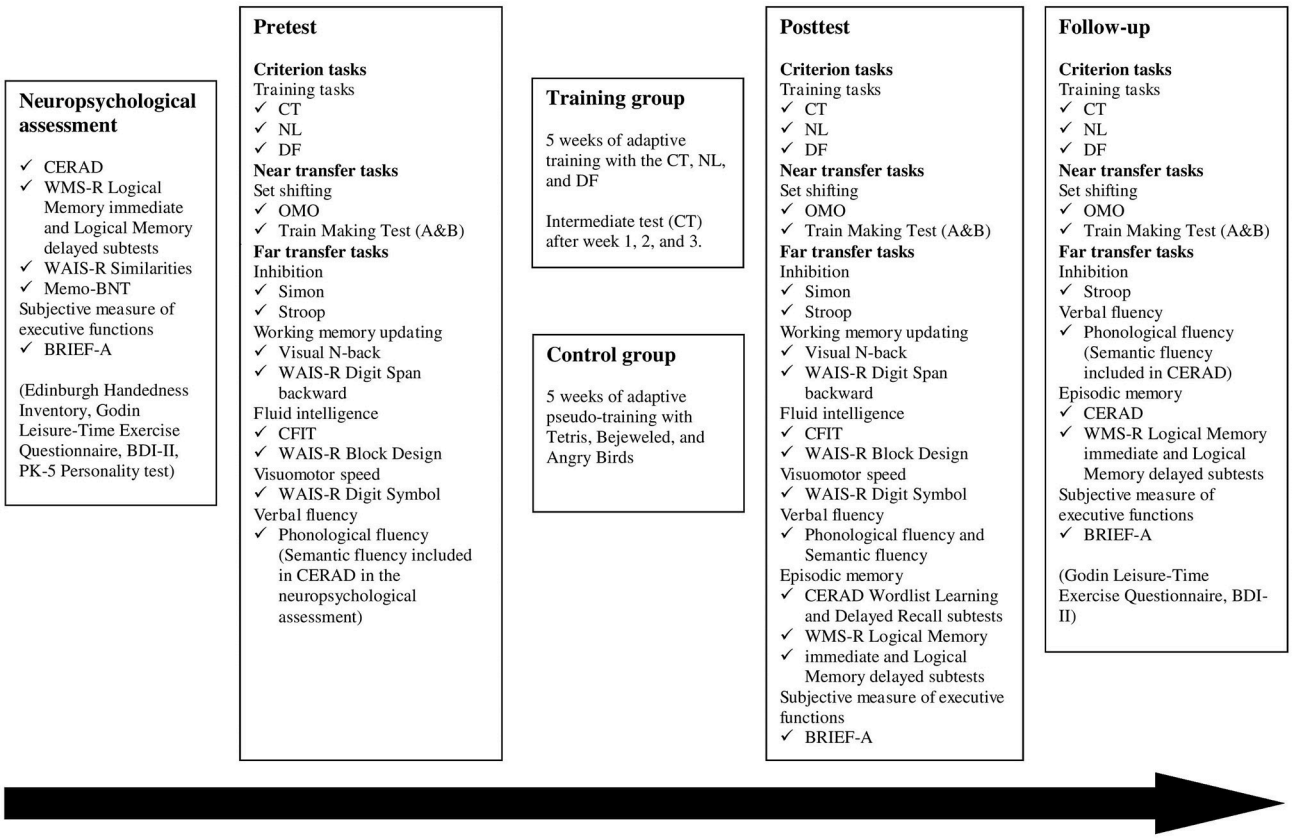

FIGURE 1 | The experimental procedure including tasks that were administered. For more detailed information on the procedure and the tasks, see Section Material and Methods.

(repetition trial, **Figure 2B**). At levels 3 and 4, a third square was added that was placed underneath the upper two squares, and the number-letter pairs appeared in red or blue. If the pair was presented in the lowest square, the participant had to decide whether the color of the pair was red or blue. Two response keys on the computer keyboard were used, with one response key for vowels, even numbers and red color, and the other for consonants, odd numbers, and blue color. As in the CT, switching trials occurred less frequently at levels 1 and 3 (after 3–5 trials) and more frequently at levels 2 and 4 (after 1–3 trials), thus yielding two squares/less frequent shifts at level 1, two squares/more frequent shifts at level 2, three squares/less frequent shifts at level 3, and three squares/more frequent shifts at level 4. The number of trials at each level was 288, and it took ∼15 min to complete the task. Each difficulty level was preceded by a short practice sequence. Every trial began with a blank screen. After 150 ms, a fixation cross appeared in the middle of the screen, being replaced by two or three squares (one of which contained a number-letter pair) after 300 ms. The squares remained on the screen until a response had been given or 3,000 ms had passed. Audiovisual feedback and information about the responses was given in the same manner as in the CT task, and two 1-min pauses were included that could be cut short by pressing Enter.

The Dot-Figure (DF) Task in Training

This task was identical to the NL task, except that instead of number-letter pairs, dot-figure pairs were used (**Figure 2C**). At levels 1 and 2, a dot-figure pair presented in the upper square prompted the participant to decide whether the number of dots (that varied between 1 and 4 dots) was even or uneven. When the dot-figure pair was presented in the lower square, the task was to decide whether the figure that was either a triangle, square, circle or oval had an angular or round shape. At levels 3 and 4, a third square was added under the upper two squares (**Figure 2C**), and at these levels the dot-figure pairs appeared in red or blue. If the pair was presented in the lowest square, the participants had to decide whether the pair was red or blue. Two response keys on the computer keyboard were used: one for even number of dots/angular shape/red color, and the other for uneven number of dots/round shape/blue color. The four difficulty levels followed the same logic as in the NL task.

Pseudo-Training Procedure & Computer Games for the Active Control Group

Three puzzle computer games were used: (1) Tetris (Tetris Worlds, THQ), (2) Bejeweled (Bejeweled 2, PopCap Games), and (3) Angry Birds (version 3.0.0, Rovio Entertainment Ltd). Each game was played for 15 min per session. The games were

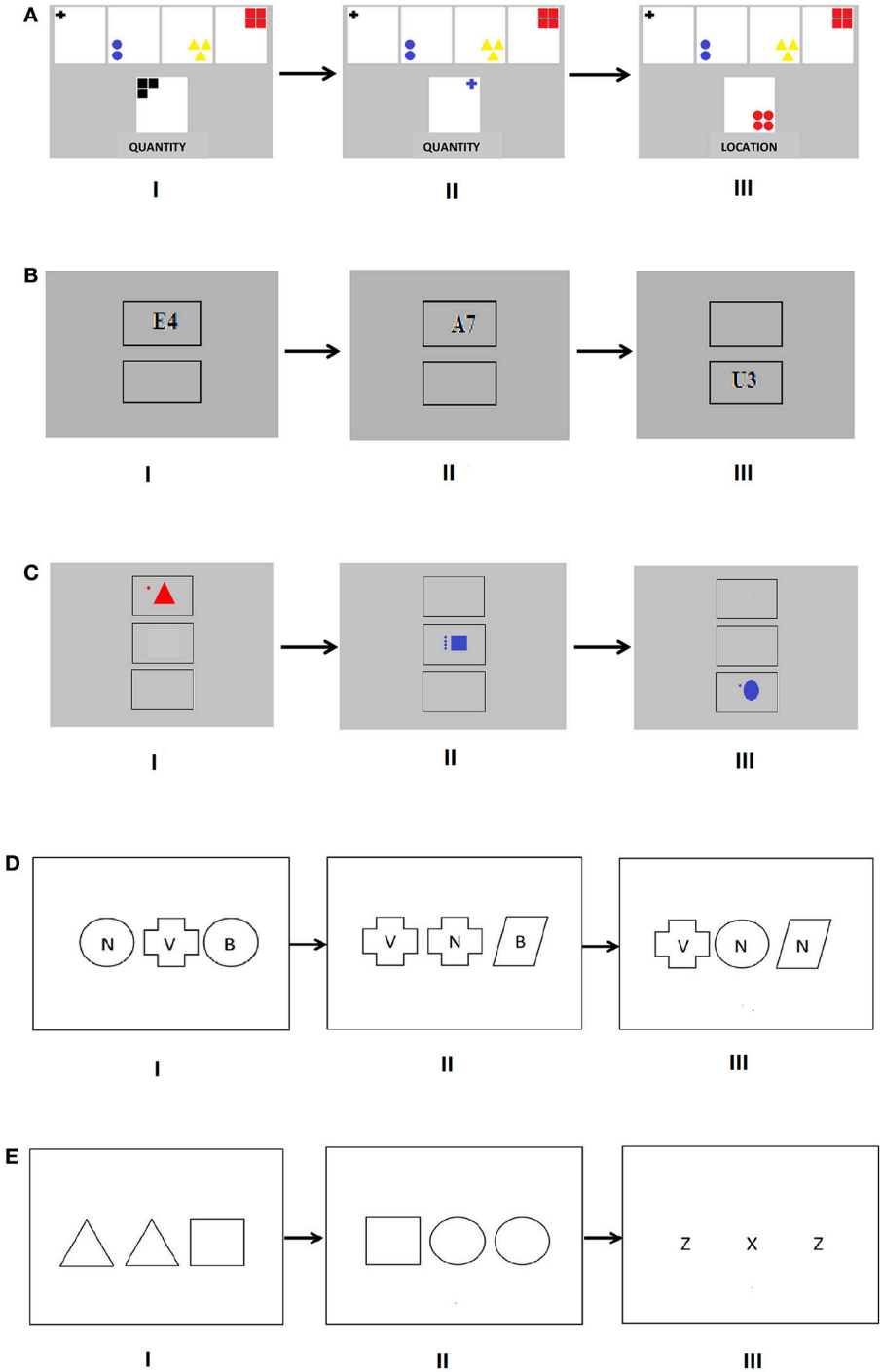

FIGURE 2 | (A) *The Categorization Task.* The more difficult version of the task (level 3 and 4). The stimulus cards are at the top of the screen and the response cards appear at the bottom half of the screen, and the written cue is given underneath the response card at each trial. In (I) the given sorting rule is "quantity," that is, the participant should press "3." In the repetition trial (II), the participant should press "1," and in the switching trial (III) the participant is given a new cue "location" and should press "3." **(B)** *The Number-Letter task.* The easier version of the task (level 1 and 2). Two squares are placed vertically on the screen and the number-letter pair is presented in either one of them. In (I) the participant's task is to decide whether the number is "even" (correct response) or "odd." In the repetition trial (II) the correct response is "odd," and in the shifting trial (III) the participant is to decide whether the letter is a "vowel" or a "consonant." **(C)** *The Dot-Figure task.* The more difficult version of the task (level 3 and 4). Three squares are placed vertically on the screen and the dot-figure pair is presented in one of them. In (I) the participant's task is to decide whether the number of dots is "even" or "odd" (correct). In the switching trial (II) the participant's task is to decide whether the figure is "angular" (correct) or "round," and in the switching trial (III) the participant is to decide whether the figure is "red" or "blue" (correct). **(D)** *The perceptual part of the OMO task (mixed task),*

(Continued)

FIGURE 2 | Continued
where the participant responds by pressing the key that corresponds to the spatial location of the odd stimulus. In trial (I), the correct choice is the middle key that corresponds to the cross. In the repetition trial (II) the correct response is the figure to the right, that is, the parallelogram. In the switching trial (III) the correct choice is the letter "v." **(E)** *The rule-based part of the OMO task (mixed task)*, where the participant responds by pressing a previously memorized key for that letter or figure (1 = z and triangle, 2 = x and square, and 3 = c and circle). In trial (I), the correct choice is the square. In the repetition trial (I) the correct choice is again the square. In the switching trial (III) the correct response is the letter "x."

selected based on their limited demands on set shifting and other executive functions, as well as their appeal to a wide audience. There were 3 difficulty levels in Tetris and Angry Birds. Bejeweled did not have separate difficulty levels, but the game became more difficult due to time pressure, so that the participants had to respond faster as they advanced in the game. Tetris served as a criterion task, in other words, when the participants advanced in Tetris, they could move to the next difficulty level in Angry Birds as well. The participants were asked to perform as fast and as accurately as possible throughout training.

Tetris

In Tetris, geometric shapes composed of square blocks each fall down in a matrix, and the participant's task is to move these shapes with the aim to create a horizontal line without gaps. When such a line is created, it disappears and blocks above will fall. When enough lines are cleared, a new level is entered. Difficulty level 1 represented the easiest version of Tetris, and if the participant improved his/her performance in this version during sessions 1–3, the participant moved to the next difficulty level on session 4. Otherwise the participant stayed at the same level until his/her performance improved, whereafter the participant moved to the next level either on session 8 or 12. When the participant improved his/her performance on level 2, the participant moved to the most difficult level either on session 8 or 12, and played at this level for the remaining sessions.

Bejeweled

In this game, the participant was to swap one gem with an adjacent gem to form a chain of 3 or more gems either horizontally or vertically. Gems disappeared when chains were formed and gaps were filled by gems falling from the top. Bejeweled was played in a so-called action mode, with the game becoming gradually more difficult due to time pressure.

Angry Birds

Here the participant used a slingshot to launch birds at pigs in different environments, aiming to destroy all the pigs. As the participant advanced, new sorts of birds became available that had special abilities, which the participant could activate. This game had three difficulty levels. If the participants advanced to the next difficulty level in the criterion task, namely Tetris, they moved to the next difficulty level in Angry Birds as well.

Pre/Post Testing

We employed an extensive cognitive test battery including pre/posttest versions of all three training tasks, and tests measuring near and far transfer. Near transfer effects were measured by two set shifting tasks: a modified version of a set shifting test ("odd-man-out" test) previously used by Ravizza and Carter (2008), and the Trail Making Test (A&B; Tombaugh, 2004)[5]. Based on the model of Miyake et al. (2000), tasks measuring inhibition and working memory updating were regarded as far transfer tasks, as were tasks measuring fluid intelligence, verbal fluency and visuomotor speed. Far transfer to inhibition was measured by the Simon task (Simon and Rudell, 1967) and the Stroop task (Lezak et al., 2012). Working memory updating was tapped by the visual n-back task (Cohen et al., 1994) and the WAIS-R (Wechsler, 1992) Digit span subtest (only the backward span is reported here). Fluid intelligence was assessed by the Culture Fair Intelligence Test (CFIT, 1973) and the WAIS-R Block design subtest. Visuomotor speed was measured by the WAIS-R Digit symbol subtest. Furthermore, verbal fluency that taps executive functioning was tested by phonological fluency and semantic fluency tasks. Two episodic memory tests (CERAD wordlist learning/delayed recall and WMS-R Logical Memory immediate/delayed recall) were also performed. Semantic fluency and the memory measures were included in the neuropsychological assessment that was performed already before the pretest session. At posttest, the CERAD wordlist learning and the WMS-R immediate recall were always administered first due to the delayed recall, but the remaining pre/posttests were administered in a random order, both at pre- and post-test[6]. The participants were asked to perform as fast and as accurately as possible when the task at hand required it.

Training Tasks at Pre/Posttest

The pre/posttest version of the *Categorization Task (CT)* represented the most difficult level (level 4) of the training task. Four single tasks were always performed first (20 trials each). The sorting rule (shape, color, quantity, or location) was always the same within a single task. The single task was preceded by a practice sequence, in which all the four sorting rules were presented twice, and the practice sequence was presented until the participant made less than 25% errors. After the single tasks, the mixed task block including switching trials was administered, in which the sorting rule changed after 1–3 trials. The number of trials was 144 (72 switching trials, 72 repetition trials). The mixed task block was preceded by a short practice sequence that was repeated once if the participant made more than 20% errors. The order of trials was randomized, but each sorting category and repetitions of the same sorting rule (one, two, or three trials) was presented the same amount of times. Audiovisual feedback

[5]A third set shifting measure was also performed, i.e., the CANTAB Attention switching task (AST) (Cambridge Cognition, 2013, www.cambridgecognition.com/academic/cantabsuite/executive-function-tests), but severe problems in the functionality of that test as a set shifting measure led to its exclusion.

[6]However, The CANTAB AST test that had to be discarded was always administered last at pre/posttest due to technical reasons.

was given also in the pre/posttest version of the task. In order to control for situations where the participant might have made a perseveration error that by chance led to the correct answer, the cards were sorted so that the sorting rule could not match with both the previous and the present sorting category. The *switching cost* (the difference between switching trials and repetition trials within the mixed task block) and the *mixing cost* (the difference between repetition trials and single-task trials) in RTs and in the proportions of correct answers were calculated for the CT task.

The *Number-Letter (NL) task* and the *Dot-Figure (DF) task* were administered as follows at pre/posttest. Both tasks started with three single task blocks (32 trials each). In the first single task, number-letter/dot-figure pairs were always shown in the uppermost square (even number/even number of dots or odd number/odd number of dots), in the second single task in the middle square (vowel/angular shape or consonant/round shape), and in the third single task in the lowest square (red or blue color). In all single task blocks, there was an equal number of trials for the two response options. Each single task was preceded by a short practice sequence. If the participant made more than 20% errors, the practice sequence was repeated once. After the single tasks, the mixed task block was performed with 72 switching trials and 72 repetition trials. The order of trials was randomized, and the sequences were balanced for the number of trials per square and for the number of occurrences for each response alternative. The mixed task block was also preceded by a practice sequence that the participant could perform at own pace (max. 10 s per trial). This practice sequence was repeated until the participant made fewer than 20% errors, whereafter a practice sequence with the same ISI as in the actual task was administered once. Audiovisual feedback was given. Similar to the CT, switching cost (the difference between switching trials and repetition trials) and the mixing cost (the difference between repetition trials and single-task trials) in RTs and in the proportions of correct answers were calculated for the NL and DF tasks. All RT measures for the training tasks were based on correct responses only.

To provide more global and possibly more reliable measures of the training tasks, the switching cost, and mixing cost in RTs and in the proportions of correct answers were averaged across the three training tasks. Combining tasks that differ in terms of paradigm and content but nevertheless aim to tap the same domain (here set shifting) has been argued to be a better strategy than combining only homogenous tasks (Schmiedek et al., 2014). The following composits were constructed for the pre/post analyses: composite switching cost in RTs, composite mixing cost in RTs, composite switching cost of proportions of correct answers, and composite mixing cost of proportions of correct answers.

Near Transfer Measures (Set Shifting)

An *"odd-man-out" (OMO) task* (adapted from Ravizza and Carter, 2008) was used in this study as a near transfer measure of set shifting. The task taps both perceptual and rule-based set shifting, which is of interest here concerning the nature of possible near transfer, as our training tasks required both visuospatial attention and the use of contextual rules. Sets of letters and shapes served as stimuli in the OMO task. The order of trials was randomized. In the *perceptual* part of the task, letters were presented inside figures, three in a row (**Figure 2D**). The letters used in this task were B, N, and V, and the figures used were a circle, cross, and a parallelogram. The participant was to identify which letter or figure did not match with the other letters or shapes. In a switching trial, the odd stimulus shifted from letter to figure or vice versa. When the odd stimulus was a letter, all the shapes were different and vice versa. Responses in the perceptual task corresponded to the spatial location of the odd stimulus. For example, if the letter or shape in the middle was the odd one, the participant responded by pressing the middle key of the three response keys (1, 2, and 3 on the keyboard). The perceptual task started with two single task blocks (32 trials each). On the first single task block it was always a letter that was the odd one, while on the second single task block it was always a shape. The mixed task block in the perceptual task consisted of 144 trials (72 switching trials, 72 repetition trials). In 72 trials the odd stimulus was a letter while in 72 trials it was a shape. Shifts occurred after one to three trials. Both the single tasks and the mixed task were preceded by a short practice sequence that was repeated once if the participant made more than 20% errors. In the *rule-based* part, the participant's task was to press a key that had previously been memorized for that letter or shape (1 = z and triangle, 2 = x and square, and 3 = c and circle; **Figure 2E**). In this part of the task, only one feature set was present, i.e., three letters in a row or three figures in a row were shown at a time, and the letters were thus not inside the figure as in the perceptual part of the task. Right before performing the rule-based part of the task, a practice task was performed, requiring the participant to memorize the stimulus-response mappings. In the practice task, the participant received one stimulus at a time, either a letter or a shape, and the task was to respond according to the correct response mapping for that stimulus. First the participant was allowed to perform at own pace (maximum 10 s per stimulus), whereafter the practice task was given with the same ISI as the actual task. This was repeated until the participant made less than 20% errors. The participant received auditory and visual feedback in the practice task: a correct response elicited a high pitch tone and a bright screen, while an incorrect response or no response elicited a low pitch tone and a dark screen. When the participant had memorized the response mappings, the rule-based part with two single task blocks and a mixed task block was performed. Both the single task and the mixed task blocks were preceded by a short practice sequence that was repeated once if the participant made more than 20% errors. In the first single task block, only letters were shown, and the participant had to identify the odd stimulus and respond according to the memorized keys (1 = z, 2 = x, and 3 = c). In the second single task block, only figures were presented, and the response was given according to the memorized keys (1 = triangle, 2 = square, and 3 = circle). In the mixed task block, feature sets (either letters or shapes) alternated (144 trials, of which 72 were switching trials and 72 repetition trials), with shifts occurring after 1–3 trials. All task blocks, both perceptual and rule-based, began with a blank screen. After 150 ms, a fixation cross appeared in the middle of the screen. The fixation cross was replaced by the feature set after

300 ms. The feature set remained on the screen until a response had been given or until 3,000 ms had passed. In the OMO task, the dependent variables were the switching and mixing cost in RTs and the proportion of correct responses in the perceptual and rule-based task, respectively. We also explored possible overall task effects by including the average RTs and accuracy across all task blocks as dependent measures in the analyses. All RT measures were based on correct responses only.

The second set shifting measure was the *Trail Making Test A&B* (Tombaugh, 2004). In part A of the test, the participant's task was to draw in ascending order a line as quickly as possible between numbers 1 and 25 that were placed inside circles on a paper sheet. In part B, the circles contained either numbers or letters, and the task was to draw the line alternating between numbers and letters in the sequence, 1-A-2-B etc., as quickly as possible. The processing cost caused by the alternating between numbers and letters, that is, the total completion time of part B (in seconds) minus total completion time of part A, was analyzed.

Far Transfer Measures

Inhibition

The computerized Simon task (Simon and Rudell, 1967) and a paper version of the Stroop Test (Lezak et al., 2012) were used as far transfer measures of inhibition. In the Simon task, a red, or a blue square was presented on either side of the computer screen, and the task was to respond according to the color of the square, irrespective of its position that either matched or not with the position of the correct response key. The task was performed by pressing the left key with the left index finger when the square was blue and the right key with the right index finger when the square was red. The task included both congruent (square on the same side as the relevant response key, e.g., red square on the right side) and incongruent trials (square on the opposite side of the relevant response key, e.g., blue square on the right side. Out of the 100 trials, half were congruent and half incongruent. The order of the trials was randomized. The trials were divided into four equally long blocks with a 5-s break in-between. A practice sequence (eight trials) was administered before starting the actual task. A fixation cross was presented at the beginning of each trial. The cross disappeared after 800 ms, replaced by a blank screen for 250 ms. After this, a blue or red square was presented on either the left or the right side of the screen. The stimulus remained on the screen until a response key was pressed or until 1,000 ms had passed. Then the screen went blank for 500 ms before moving on to the next trial. The dependent variables were the Simon effect in RTs and in proportion of correct responses. The Simon effect is the difference between incongruent and congruent trials, and taps the processing cost related to the incompatible location of the stimulus. In the Stroop task, the dependent variable was the Stroop effect, that is, the difference in completion time between naming ink color of conflicting color words (100 trials on a paper sheet) and naming the ink color of sequences of the letter "x" (90 trials on a paper sheet).

Working memory updating

Possible transfer effects to working memory updating were measured by the computerized n-back task (Cohen et al., 1994) and the Digit span backward subtest of the WAIS-R (Wechsler, 1992). In the n-back task, numbers from one to nine were presented one at a time at the center of the screen. The task was to remember the previous number (1-back) or the one presented two trials back (2-back). Two response keys were used: the left key for a target, that is, the number was the same as the previous number (1-back) or the one two trials back (2-back), and the right key for a non-target, that is, the number did not match. The total amount of trials was 240 (120 1-back trials, 120 2-back trials). The numbers were divided into 12 blocks of 20 trials each, so that six blocks were 1-back blocks and six were 2-back blocks. The presentation order of the stimuli was pseudorandomized. The 1-back blocks consisted of nine targets and 11 non-targets, and the 2-back block included six targets and 14 non-targets. Before each block, a written prompt informing whether the following block was a 1-back or a 2-back block appeared on the screen together with a picture of a hand indicating the corresponding response keys. After 5,000 ms, the first number was shown, remaining on the screen for 1,500 ms. After this, the number was replaced by a fixation cross for 450 ms. The fixation cross was then followed by the next number. On each trial, the response had to be given within 2,000 ms. The first trial in the 1-back condition and the first two trials in the 2-back condition were excluded from the analysis. The difference in RTs and in the proportion of correct responses between the 2-back and the 1-back conditions were used as the dependent variables for this task. These measures reflect the processing cost caused by the demands on working memory updating in the 2-back condition. In the Digit span backward test, the task was to orally repeat sequences of digits in reversed order. The total score for backward span was analyzed.

Fluid intelligence

Fluid intelligence was measured using the Culture Fair Intelligence Test (CFIT, 1973) scales 2 and 4, and the WAIS-R subtest Block design. In CFIT, the participant's task was to find logical relationships between different shapes and figures that were presented on paper. Performance time was limited to 240 s for scale 2 and 180 s for scale 4. Each scale had two equivalent versions, A and B. At pretest, version A of scale 2 and 4 were administered to 17 of the participants (roughly the same number of participants from both groups) and version B to the remaining 16 participants, and vice versa. The dependent variable was the sum of correct responses (scale 2 + scale 4). In the Block design test, the total score of the 9 trials of advancing difficulty (maximum score 51) was analyzed.

Verbal fluency

Semantic fluency (producing as many animal names as possible within 60 s) that was included in the neuropsychological screening was performed at posttest as well, and thus also used as a transfer measure. Also phonological fluency (producing words beginning with the phoneme "s" within 60 s) was used as a transfer measure. For both fluency tasks, the number of correct responses was used as the dependent variable.

Episodic memory

The CERAD (Welsh et al., 1994; Hänninen et al., 2010) wordlist learning and delayed recall and the WMS-R (Wechsler, 1992) Logical Memory immediate and delayed recall, which were included in the neuropsychological screening, were performed also at posttest and thus used as transfer measures. For the CERAD, we analyzed wordlist learning sum score, delayed recall raw score, and savings score in percent computed by dividing the number of words retrieved on delayed recall by the number of words recalled on the third learning trial (x 100). For the WMS-R Logical Memory, we analyzed immediate and delayed recall.

Follow-Up

The follow-up was conducted 1 year after posttest (plus minus 3 weeks). One participant from the control group declined to participate, and thus 32 out of 33 participants were tested in the follow-up. The follow-up was otherwise similar to the posttest, but the following tests were not included: the Simon task, the visual n-back task, the WAIS-R Digit span, Block design and Digit symbol subtests, the Culture Fair Intelligence Test. The whole CERAD (Welsh et al., 1994; Hänninen et al., 2010) was conducted at follow-up in order to control for possible memory deterioration[7]. Before the follow-up session, the participants were asked to give their written informed consent and after the assessment, they filled in the Godin Leisure-Time Exercise Questionnaire (Godin and Shephard, 1997), and BRIEF-A (Roth et al., 2005), as well as BDI-II (Beck et al., 2004). Motivation and alertness was also surveyed, and some questions concerning the participants' gaming/computer habits were included as well.

Statistical Analyses

ANCOVAs with posttest performance as the dependent variable, pretest performance as the covariate, and group as the between-subjects factor were run on all dependent measures (see Dimitrov and Rumrill, 2003; Senn, 2006). Effect sizes reported as adjusted Cohen's d were calculated using estimated values from the ANCOVA model. For the follow-up, ANCOVAs with follow-up performance as the dependent variable, pretest performance as the covariate, and group as the between-subjects factor were run only on the dependent measures of the training tasks and the OMO task that had been statistically significant or had an $F > 2$ at posttest. Each task was reviewed independently regarding possible exclusion of individual cases. In all tests, the exclusion criteria were being an extreme outlier in accuracy or RTs at pretest or showing evidence of misunderstanding test instructions. Concerning accuracy in the computerized tests, outliers were defined as chance level performance. Regarding RTs in the computerized tests and performance in the paper and pencil tests, outliers were defined as performance laying more than three times the interquartile range above or below the 1st or the 3rd quartile, respectively. There were no outliers regarding RTs.

[7]Two participants performed below cut-off in the CERAD wordlist delayed recall at follow-up, but as they performed adequately in the other memory measures, they were included the analyses.

RESULTS

Training Results

The means and standard deviations for the composite training scores at pre/posttest and at the follow-up are presented in **Table 1**, and they are also shown separately for each training task in **Table 2** (CT), **Table 3** (NL), and **Table 4** (DF)[8].

Both the ANCOVA on the composite switching cost in RTs, $F_{(1, 30)} = 26.671$, $p < 0.001$, $d = -1.84$, 95% CI [−2.56, −1.11], as well as on the composite mixing cost in RTs $F_{(1, 30)} = 59.874$, $p < 0.001$, $d = -2.80$, 95% CI [−3.54, −2.06], were statistically significant, due to the smaller switching and mixing costs of the training group at posttest compared with the control group. We also controlled for multiple comparisons with a Bonferroni correction, setting the alpha level to 0.05/4 = 0.0125. Both the switching and mixing cost effects in RTs survived the Bonferroni correction. The corresponding analysis regarding accuracy showed that the composite switching cost was somewhat smaller for the training group $F_{(1, 30)} = 6.824$, $p = 0.014$, $d = 0.93$, 95% CI [0.20, 1.66], but the group effect did not quite reach significance after the Bonferroni correction. The group effect of the composite mixing cost on accuracy did not reach statistical significance, $F_{(1, 30)} = 2.517$, $p = 0.123$, $d = 0.56$, 95% CI [−0.16, 1.27].

Tasks Measuring Near Transfer (Set Shifting)

With regard to the near transfer tasks, we corrected for multiple comparisons by setting the alpha level to 0.05/13 = 0.0038

The OMO Task: Perceptual Subtest

No significant near transfer effects were seen in the perceptual subtest of the OMO task. Neither the switching cost nor the mixing cost in RTs or accuracy showed significant training-related group differences (Fs < 1). ANCOVAs were performed also on overall performance both regarding RTs as well as accuracy. The control group performed somewhat faster than the training group in absolute terms, but this was not significant $F_{(1, 30)} = 2.696$, $p = 0.111$, $d = 0.59$, 95% CI [−0.14, 1.33]. The training group performed somewhat better regarding overall accuracy compared with the control group, but this difference did not reach statistical significance, $F_{(1, 30)} = 3.596$, $p = 0.068$, $d = 0.67$, 95% [−0.05, 1.38] (**Table 5**).

The OMO Task: Rule-Based Subtest

The switching cost and the mixing cost in RTs or accuracy did not differ between groups at posttest as analyzed by ANCOVAs (all Fs < 2). As above, ANCOVAs were performed also on overall performance, both for RTs and accuracy. No significant group difference in overall RTs was found, $F_{(1, 30)} = 2.444$, $p = 0.128$, $d = 0.56$, 95% CI [−0.17, 1.29]. Regarding overall accuracy, the training group outperformed the control group

[8]The pretest intercorrelations on switching and mixing cost in RTs were low between the CT and NL task, as well as between the CT and DF task across both groups. In turn, the NL and DF task that represent the same task paradigm showed a positive correlation (Pearson's r) regarding both switching cost ($r = 0.68$) and mixing cost ($r = 0.41$).

TABLE 1 | Composite set shifting switching cost and mixing cost scores of the training tasks.

			Training (n = 17)		Control (n = 16)[a]		
		Session	Mean	*SD*	Mean	*SD*	Sig.
Reaction times (ms)	Switching cost	Pretest	320.90	119.58	276.11	106.47	N/A
		Posttest	174.46	60.99	287.27	110.99	*
		Follow-up	271.60	112.75	287.80	131.31	ns
	Mixing cost	Pretest	400.63	52.51	366.63	72.19	N/A
		Posttest	159.69	53.03	310.81	85.00	*
		Follow-up	216.30	81.78	305.33	99.15	*
Correct responses (%)	Switching cost	Pretest	−3.94	3.72	−2.36	3.21	N/A
		Postest	−0.69	0.90	−2.15	2.34	ns
		Follow-up	−0.62	1.88	−2.08	2.43	*
	Mixing cost	Pretest	−2.33	2.84	−1.50	3.77	N/A
		Posttest	−0.25	1.20	−0.88	1.34	ns
		Follow-up	−0.39	1.17	−1.16	2.43	ns

*Between-group differences at posttest and follow-up were analyzed with ANCOVA. [a]One participant in the control group declined to participate in the follow-up, leading to a sample size of 15 at that measurement point. *Alpha level is Bonferroni corrected (p = 0.0038 at posttest), ns = not significant.*

at posttest, $F_{(1, 30)} = 14.950$, $p = 0.001$, $d = 1.35$, 95% CI [0.64, 2.06] (**Table 5**; **Figure 3**), and this finding also survived the Bonferroni correction. In other words, near transfer effects were seen on the rule-based part of the OMO task regarding accuracy.

Trail Making Test A & B

No significant group difference on the switching effect (TMT B minus A) at posttest was seen ($F < 1$; **Table 6**).

Tasks Measuring Far Transfer

Inhibition

No generalization of training gains was observed *n* the *Simon task,* as the main effect of group was non-significant at posttest both with regard to the Simon effect in RTs ($F < 1$) and accuracy ($F < 2$). Nor did the main effect of group on the incongruency effect (word-color conflict completion time minus color completion time) on the *Stroop Test* reach significance, $F_{(1, 29)} = 2.553$, $p = 0.121$, $d = -0.57$, 95% CI [−1.30, 0.16] (**Table 7**). For *Working memory updating*, no far transfer was not seen, as the n-back effect did not show differentiate the groups on either RTs (both targets and non-targets included), $F_{(1, 28)} = 2.146$, $p = 0.154$, $d = 0.53$, 95% CI [−0.21, 1.28], or accuracy ($F < 1$). The main effect of group on the *WAIS-R Digit span backward* subtest was also non-significant ($F<1$; **Table 7**). *Fluid intelligence* tasks showed no significant group difference either on the *Culture Fair Intelligence Test (CFIT; F* < 1) or on the *WAIS-R Block Design* subtest ($F < 1$; **Table 8**). With regard to *Episodic memory*, the main effect of group on wordlist learning (sum) of the *CERAD* was non-significant, $F_{(1, 30)} = 2.063$, $p = 0.161$, $d = 0.52$, 95% CI [−0.22, 1.26]. Same was true for the main effect of group on the CERAD delayed recall (raw score) and the savings score (both *Fs* < 1). The *WMS-R Logical Memory* immediate recall did not show a group difference either ($F < 1$), and nor did the WMS-R logical memory delayed recall, $F_{(1, 30)} = 2.917$, $p = 0.098$, $d = 0.60$, 95% CI [−0.12, 1.31] (**Table 8**). *Verbal fluency* tasks showed no group differences on semantic fluency ($F < 1$), or on phonological fluency $F_{(1, 30)} = 2.701$, $p = 0.111$, $d = 0.57$, 95% CI [−0.14, 1.28] (**Table 8**). *Visuomotor speed* was measured with the *WAIS-R Digit Symbol* subtest that did not show any group difference at posttest ($F < 1$; **Table 8**).

Motivation, Alertness and Subjective Set Shifting Ability

In order to investigate possible changes in motivation or alertness across the intervention, the relevant survey responses were analyzed with a mixed model ANOVA with motivation/alertness (3 levels: motivation/alertness at pretest, across training sessions[9], and at posttest) as within-subjects factors and group as a between-subjects factor. A significant main effect of motivation was found $F_{(2, 62)} = 5.265$, $p = 0.008$, as the participants were more motivated at pretest compared with the training sessions/posttest. The motivation x group interaction was non-significant ($F < 1$). The main effect of alertness was not significant ($F < 2$), but the alertness x group interaction was statistically significant $F_{(2, 62)} = 7.191$, $p = 0.002$. Subsequent one-way ANOVAS showed that there were no group differences concerning alertness at pretest or across training sessions (both *Fs* < 1), but at posttest a significant group difference was found, $F_{(1, 31)} = 6.308$, $p = 0.017$, with the training group reporting a higher degree of alertness ($M = 4.32$, $SD = 0.68$) compared with the controls ($M = 3.50$, $SD = 1.15$). The set shifting index (raw score) of the BRIEF-A self-report form that was analyzed with an ANCOVA, did not show a statistically significant group

[9]The motivation/alertness score was missing for one participant in the training group for one training session and the mean was thus calculated based on 14 sessions instead of 15 sessions for that participant.

TABLE 2 | Performance on the Categorization Task (CT).

			Training (n = 17)		Control (n = 16)[a]	
		Session	Mean	*SD*	Mean	*SD*
Reaction times (ms)	Switching trials	Pretest	1765.16	288.39	1664.82	247.99
		Posttest	1252.02	188.66	1546.84	243.33
		Follow-up	1433.37	248.93	1578.49	247.33
	Repetition trials	Pretest	1591.12	232.83	1495.24	235.11
		Posttest	1141.50	186.68	1394.55	219.47
		Follow-up	1281.42	190.07	1418.19	222.51
	Single-task trials	Pretest	1301.28	257.79	1214.46	271.76
		Posttest	1007.01	164.18	1156.05	196.77
		Follow-up	1139.02	202.16	1212.46	233.20
	Switching cost	Pretest	174.04	115.84	169.59	88.41
		Posttest	110.52	50.31	152.28	86.73
		Follow-up	151.96	109.07	160.30	112.10
	Mixing cost	Pretest	289.83	128.13	280.78	173.36
		Posttest	134.49	76.55	238.50	146.62
		Follow-up	142.40	121.03	205.74	172.63
Correct responses (%)	Switching trials	Pretest	84.89	10.81	89.67	4.65
		Posttest	96.98	4.77	93.75	4.94
		Follow-up	98.04	2.25	93.61	5.67
	Repetition trials	Pretest	89.54	7.27	93.84	4.78
		Posttest	98.04	3.58	95.49	4.26
		Follow-up	98.12	1.83	93.70	5.55
	Single-task trials	Pretest	91.25	5.10	94.45	4.40
		Posttest	99.04	0.94	97.34	2.70
		Follow-up	98.24	2.21	96.00	4.28
	Switching cost	Pretest	−4.66	7.12	−4.17	4.89
		Posttest	−1.06	1.87	−1.74	2.98
		Follow-up	−0.08	2.43	−0.09	3.26
	Mixing cost	Pretest	−1.71	5.57	−0.62	5.52
		Posttest	−1.00	3.85	−1.86	2.77
		Follow-up	−0.11	3.00	−2.30	5.97

[a] *One participant in the control group declined to participate in the follow-up, leading to a sample size of 15 at that measurement point.*

difference[10], $F_{(1, 29)} = 2.678$, $p = 0.112$, $d = -0.62$, 95% CI [−1.39, 0.15].

Follow-Up

Training Results

The same analyses were run for the follow-up as for the posttest, using pretest as a covariate. The main effect of group on the composite switching cost in RTs did not reach the level of significance at follow-up, $F_{(1, 29)} = 2.825$, $p = 0.104$, $d = -0.61$, 95% CI [−1.36, 0.13], but there was a significant group difference with regard to the composite mixing cost in RTs $F_{(1, 29)} = 10.900$, $p = 0.003$, $d = -1.21$, 95% CI [−1.95, −0.46], due to the smaller mixing cost of the training group at follow-up compared with the control group. Regarding accuracy, a significant group difference for the composite switching cost was seen at follow-up, $F_{(1, 29)} = 7.292$, $p = 0.011$, $d = 0.99$, 95% CI [0.24, 1.73], with the cost being relatively smaller for the training group compared to the control group, but the group effect of the composite mixing cost of accuracy was non-significant ($F < 2$; **Table 1**). Both statistically significant findings survived Bonferroni correction (0.05/4 = 0.0125).

[10] One participant from the control group was excluded from the analysis due to a highly inconsistent score.

The OMO Task

ANCOVAs were run for the overall RTs and overall accuracy at follow-up for both subtests using pretest as a covariate. *Perceptual subtest.* The control group was somewhat faster than the training group at follow-up, $F_{(1, 29)} = 5.778$, $p = 0.023$, $d = 0.87$, 95% CI [0.13, 1.61], but this difference did not survive Bonferroni correction (0.05/4 = 0.0125). The main effect of group regarding overall accuracy did not reach statistical significance ($F < 1$; **Table 5**). *Rule-based subtest.* No significant group difference on either overall RTs ($F < 1$) or overall accuracy $F_{(1, 29)} = 2.892$,

TABLE 3 | Performance on the Number-Letter (NL) task.

			Training ($n = 17$)		Control ($n = 16$)[a]	
		Session	Mean	*SD*	Mean	*SD*
Reaction times (ms)	Switching trials	Pretest	1499.47	193.32	1368.75	218.12
		Posttest	963.29	140.07	1347.07	159.30
		Follow-up	1262.27	171.81	1364.23	177.00
	Repetition trials	Pretest	1135.99	150.57	1061.81	167.74
		Posttest	751.88	117.28	981.266	150.38
		Follow-up	920.68	139.24	1038.23	149.68
	Single-task trials	Pretest	674.47	90.22	625.53	99.79
		Posttest	590.07	71.92	620.19	81.08
		Follow-up	676.24	99.90	651.21	93.45
	Switching cost	Pretest	363.48	159.29	306.94	185.47
		Posttest	211.41	102.03	365.80	149.52
		Follow-up	341.59	185.86	326.00	154.30
	Mixing cost	Pretest	461.52	100.24	436.28	123.44
		Posttest	161.80	58.71	361.08	115.97
		Follow-up	244.44	121.58	387.03	101.62
Correct responses (%)	Switching trials	Pretest	93.29	7.96	95.33	3.91
		Posttest	99.34	0.72	96.57	4.30
		Follow-up	98.34	1.88	94.65	4.77
	Repetition trials	Pretest	95.83	4.68	97.57	3.27
		Posttest	99.67	0.61	99.13	1.51
		Follow-up	98.86	1.01	97.78	1.73
	Single-task trials	Pretest	98.67	2.07	98.32	1.75
		Posttest	99.75	0.81	99.19	0.92
		Follow-up	99.68	0.51	99.21	1.18
	Switching cost	Pretest	−2.54	6.89	−2.23	2.85
		Posttest	−0.34	0.93	−2.57	3.76
		Follow-up	−0.51	1.86	−3.13	4.30
	Mixing cost	Pretest	−2.84	4.60	−0.75	3.30
		Posttest	−0.07	0.80	−0.06	1.74
		Follow-up	−0.83	1.05	−1.43	1.67

[a] *One participant in the control group declined to participate in the follow-up, leading to a sample size of 15 at that measurement point.*

$p = 0.100$, $d = 0.60$, 95% CI [−0.12, 1.33] was found at follow-up (**Table 5**).

Motivation and Alertness

At the follow-up, one-way ANOVAS showed no group differences on motivation or alertness ratings (both $Fs < 1$; **Table 5**).

DISCUSSION

The present study addressed a potentially important but only scarcely studied area, namely the effects of set shifting training in healthy elderly. In the light of previous training studies, we expected to find improvement on the trained tasks and near transfer effects. Nevertheless, we also wanted to explore whether far transfer effects could be observed. In brief, what we found were strong and long-lasting training effects on the trained tasks, very limited evidence for near transfer, and no far transfer. These results are summarized and discussed in detail below.

Concerning the trained tasks, the training group showed the expected improvement compared to the controls. Our training group outperformed the control group at posttest regarding both switching as well as mixing costs in reaction times. The corresponding posttest effects on accuracy were not statistically significant, although the switching cost accuracy showed a trend for significance in favor of the training group. The analyses on the follow-up performances showed that the training group outperformed the control group on the mixing cost in reaction times and switching cost in accuracy even after 1 year. Thus, the follow-up findings confirmed that the training regime worked, and a 5-week set shifting training can create long-lasting training effects on the practiced tasks. With regard to near transfer, no statistically significant effects were observed on the switching cost or mixing cost in reaction times or accuracy in either part

TABLE 4 | Performance on the Dot-Figure (DF) task.

			Training ($n = 17$)		Control ($n = 16$)[a]	
		Session	Mean	*SD*	Mean	*SD*
Reaction time (ms)	Switching trials	Pretest	1552.03	242.75	1371.69	158.06
		Posttest	971.15	139.48	1288.76	237.39
		Follow-up	1239.90	197.96	1351.75	216.96
	Repetition trials	Pretest	1126.84	172.38	1019.89	109.05
		Posttest	769.69	116.75	945.05	138.55
		Follow-up	918.65	154.10	974.64	114.82
	Single-task trials	Pretest	676.30	114.79	637.04	85.87
		Posttest	586.92	74.11	612.20	68.23
		Follow-up	656.60	107.88	651.40	94.08
	Switching cost	Pretest	425.19	199.40	351.80	137.49
		Posttest	201.46	87.72	343.71	176.24
		Follow-up	321.24	154.10	377.12	183.27
	Mixing cost	Pretest	450.55	112.81	382.85	68.84
		Posttest	182.77	75.76	332.85	99.51
		Follow-up	262.06	101.58	323.24	113.62
Correct responses (%)	Switching trials	Pretest	91.05	7.40	94.63	5.15
		Posttest	99.17	1.00	96.21	3.28
		Follow-up	98.01	3.27	95.49	5.69
	Repetition trials	Pretest	95.67	3.29	95.31	4.67
		Posttest	99.84	0.46	98.35	1.77
		Follow-up	99.26	1.40	98.52	1.53
	Single-task trials	Pretest	98.10	2.45	98.45	1.36
		Posttest	99.49	0.55	99.06	1.03
		Follow-up	99.49	0.67	98.28	1.51
	Switching cost	Pretest	−4.62	5.98	−0.68	6.22
		Posttest	−0.67	1.00	−2.14	2.86
		Follow-up	−1.25	2.98	−3.03	4.53
	Mixing cost	Pretest	−2.43	3.61	−3.14	4.92
		Posttest	0.34	0.83	−0.71	1.83
		Follow-up	−0.23	1.44	0.24	1.86

[a] *One participant in the control group declined to participate in the follow-up, leading to a sample size of 15 at that measurement point.*

of the odd-man-out task. The switching cost in reaction times in the rule-based part was very small, and the mixing cost was negative. Concerning the overall accuracy and reaction time measures across all task blocks of the odd-man-out task, the rule-based part showed a statistically significant training effect on overall accuracy with a very large effect size ($d = 1.35$). The corresponding overall reaction time measures did not yield a group difference at posttest. Furthermore, no near transfer effects were observed on the Trail Making Test. To sum up, only one measure, overall accuracy on the rule-based part, showed near transfer, indicating a very limited transfer effect. We found no evidence for far transfer on the extensive test battery tapping other executive domains, fluid intelligence, episodic memory, verbal fluency, or visuomotor speed.

Only one of the earlier set shifting training studies (Soveri et al., 2013) has addressed both transfer effects and training effects on the training tasks themselves. Naturally enough, the goal of cognitive training is to obtain improvement on untrained tasks, but verification of training effects on the trained tasks serves as a proof that the training program as such works. In the present study, these effects were verified. In general, improvements on the trained tasks have been the most robust finding in brain training studies (for reviews, see Melby-Lervåg et al., 2016; Simons et al., 2016). This is also true for cognitive training studies that have specifically addressed elderly individuals (Karbach and Verhaeghen, 2014). The fact that these effects were maintained in the follow-up concurs with the largest cognitive training study conducted thus far: the Advanced Cognitive Training for Independent and Vital Elderly study found long-lasting effects on the trained tasks 2 years, 5 years, and even 10 years after training (Ball et al., 2002; Willis et al., 2006; Rebok et al., 2014).

The present results concerning near transfer are broadly in line with most previous set shifting training studies (Minear and Shah, 2008; Karbach and Kray, 2009; Zinke et al., 2012;

TABLE 5 | Performance on the "odd-man-out" (OMO) task.

			Training (n = 17)		Control (n = 16)[a]		
		Session	Mean	*SD*	Mean	*SD*	Sig.
PERCEPTUAL TASK							
Reaction times (ms)	Switching trials	Pretest	1954.12	213.14	1819.95	253.20	N/A
		Posttest	1915.15	227.04	1740.81	262.03	N/A
		Follow-up	1997.32	255.51	1787.47	247.05	N/A
	Repetition trials	Pretest	1711.42	272.99	1576.36	199.70	N/A
		Posttest	1688.65	264.87	1498.50	236.60	N/A
		Follow-up	1751.13	312.10	1517.92	287.41	N/A
	Single-task trials	Pretest	1273.27	224.92	1221.41	256.95	N/A
		Posttest	1277.56	233.00	1141.53	213.82	N/A
		Follow-up	1297.83	191.31	1150.99	184.31	N/A
	Switching cost	Pretest	242.70	171.57	243.59	142.76	N/A
		Posttest	226.49	170.00	242.31	112.79	ns
	Mixing cost	Pretest	438.14	192.62	354.95	206.13	N/A
		Posttest	411.10	183.41	356.98	182.71	ns
	Overall RTs	Pretest	1646.27	215.29	1539.24	211.83	N/A
		Posttest	1627.12	221.59	1460.28	219.02	ns
		Follow-up	1682.09	235.29	1485.46	221.04	ns
Correct responses (%)	Switching trials	Pretest	82.52	12.27	85.30	8.23	N/A
		Posttest	88.32	10.48	88.64	8.33	N/A
		Follow-up	84.26	15.90	87.32	12.21	N/A
	Repetition trials	Pretest	85.21	11.48	88.54	7.65	N/A
		Posttest	91.26	6.11	90.71	7.95	N/A
		Follow-up	85.78	14.88	90.56	6.67	N/A
	Single-task trials	Pretest	97.05	3.53	96.47	3.39	N/A
		Posttest	97.72	1.98	96.27	4.15	N/A
		Follow-up	97.91	2.60	96.56	3.39	N/A
	Switching cost	Pretest	−2.69	7.52	−3.24	2.59	N/A
		Posttest	−2.94	6.22	−2.07	2.80	ns
	Mixing cost	Pretest	−11.85	9.95	−7.93	6.28	N/A
		Posttest	−6.46	4.95	−5.56	5.98	ns
	Overall accuracy	Pretest	88.26	8.17	90.10	5.97	N/A
		Posttest	92.43	5.80	91.88	6.40	ns
		Follow-up	89.32	10.42	91.48	6.38	ns
RULE-BASED TASK							
Reaction times (ms)	Switching trials	Pretest	1508.15	246.03	1416.79	279.80	N/A
		Posttest	1440.95	224.01	1314.69	177.53	N/A
		Follow-up	1470.90	192.68	1369.72	228.98	N/A
	Repetition trials	Pretest	1422.61	235.08	1309.70	247.84	N/A
		Posttest	1353.17	201.09	1236.49	149.38	N/A
		Follow-up	1402.97	207.29	1296.28	194.20	N/A
	Single-task trials	Pretest	1438.85	238.39	1319.55	186.00	N/A
		Posttest	1375.20	193.77	1249.20	174.01	N/A
		Follow-up	1389.19	191.01	1319.43	199.44	N/A
	Switching cost	Pretest	85.53	54.43	107.08	75.66	N/A
		Posttest	87.78	62.25	78.20	63.96	ns
	Mixing cost	Pretest	−16.23	78.93	−9.84	145.20	N/A
		Posttest	−22.04	75.82	−12.72	109.88	ns
	Overall RTs	Pretest	1456.54	235.59	1348.68	228.79	N/A
		Posttest	1389.77	202.59	1266.79	157.13	ns
		Follow-up	1421.02	191.67	1328.48	201.72	ns

(Continued)

TABLE 5 | Continued

			Training ($n = 17$)		Control ($n = 16$)[a]		
		Session	Mean	*SD*	Mean	*SD*	Sig.
Correct responses (%)	Switching trials	Pretest	92.96	6.32	94.63	6.47	N/A
		Posttest	98.18	1.78	93.84	5.58	N/A
		Follow-up	97.02	2.90	96.34	2.86	N/A
	Repetition trials	Pretest	95.42	3.21	95.40	3.89	N/A
		Posttest	98.04	2.09	94.79	3.88	N/A
		Follow-up	97.39	1.69	96.67	3.31	N/A
	Single-task trials	Pretest	96.87	3.58	95.87	3.81	N/A
		Posttest	99.05	1.52	96.88	3.46	N/A
		Follow-up	98.39	2.13	96.45	3.29	N/A
	Switching cost	Pretest	−2.47	4.91	−0.77	5.22	N/A
		Posttest	0.14	2.41	−0.95	4.01	ns
	Mixing cost	Pretest	−1.44	4.25	0.47	2.74	N/A
		Posttest	−1.01	2.04	−2.08	4.36	ns
	Overall accuracy	Pretest	95.08	3.36	95.30	4.09	N/A
		Posttest	98.42	1.32	95.17	3.67	*
		Follow-up	97.60	1.65	96.49	2.50	ns

*Between-group differences at posttest and follow-up were analyzed with ANCOVA. [a]One participant in the control group declined to participate in the follow-up, leading to a sample size of 15 at that measurement point. *Alpha level is Bonferroni corrected ($p = 0.0038$ at posttest), ns, not significant.*

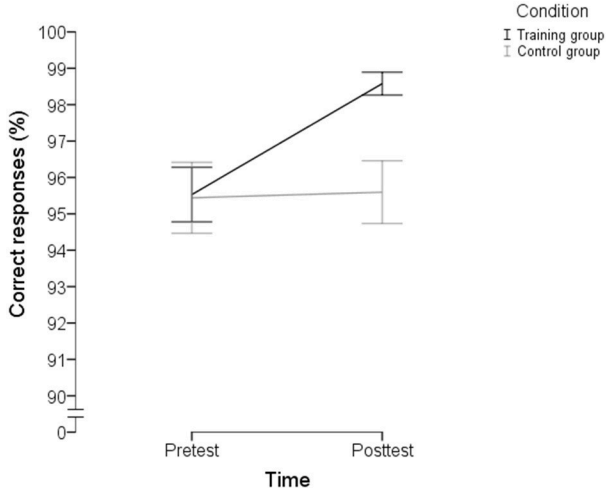

FIGURE 3 | Number of correct responses (%) across single tasks, switching trials and repetition trials of the rule-based part of the "odd-man-out" near transfer task for the training group and the control group, including standard errors (scale 90–100%).

Pereg et al., 2013) insofar that they have also reported selective near transfer effects. The results also fit well with recent results from an executive process training study including set shifting training that also found limited near transfer effects (Sandberg et al., 2014). A possible reason for the observed near transfer to the rule-based odd-man-out task is that the training tasks may have recruited similar cognitive resources. In general, it has been argued that transfer can take place only if the training and transfer tasks depend upon partly the same cognitive processes and neural systems (e.g., Dahlin et al., 2008a; Waris et al., 2015), and in most executive training studies conducted with older participants that have reported transfer, the transfer has been seen on tasks that are very similar to the trained tasks (Morrison and Chein, 2011; Buitenweg et al., 2012). The Number-Letter and Dot-Figure tasks employed arbitrary cues (placement of number-letter/dot-figure pairs), and the participants had to learn and update the response rules during task performance. Also the Categorization Task and the rule-based odd-man-out task may share some underlying cognitive mechanism(s) as they are both complex in nature, and require several executive processes (Ravizza and Carter, 2008; Naglieri and Otero, 2014). Ravizza and Carter (2008) found that rule-switching in their odd-man-out task that was similar to ours, was related to greater activity in the dorsolateral prefrontal cortex, which in turn has been linked to rule-guided behavior and to context maintenance. Also the Wisconsin Card Sorting Test that the Catergorization Task is based on has been linked to dorsolateral prefrontal cortex activation (Nyhus and Barceló, 2009), and the lateral prefrontal findings in relation to the Wisconsin Card Sorting Test are thought to reflect maintenance of task-set units (e.g., "color") in working memory (Miller and Cohen, 2001). It might thus be that the near transfer finding in the present study reflects active maintenance of task-relevant information (cf. also Pereg et al., 2013) rather than set shifting. In other words, it is possible that the shared cognitive component between the three training tasks and the rule-based odd-man-out task is working memory updating, an executive process that is required to a higher degree by the rule-based than the perceptual odd-man-out task. This would also be in line with the study by Pereg et al. (2013), as the results from their study suggested that what had been trained as a "set shifting ability" in the study by Karbach and Kray (2009) was

TABLE 6 | Performance on the Trail Making Test A & B.

		Training ($n = 16$)		Control ($n = 15$)		
	Session	**Mean**	***SD***	**Mean**	***SD***	**Sig.**
A (numbers). duration in seconds	Pretest	44.44	13.86	37.27	14.35	N/A
	Posttest	38.94	11.60	37.07	12.78	N/A
B (numbers+letters). duration in seconds	Pretest	90.81	32.10	86.20	27.31	N/A
	Posttest	80.19	25.03	74.80	22.19	N/A
Switching cost (B − A)	Pretest	46.38	30.97	48.93	20.25	N/A
	Posttest	41.25	19.66	37.73	17.33	ns

Between-group differences at posttest were analyzed with ANCOVA; ns, not significant.

TABLE 7 | Performance on the far transfer tasks measuring inhibition and working memory updating.

		Session	**Mean**	***SD***	**Mean**	***SD***	**Sig.**
SIMON TASK							
			Training ($n = 17$)		**Control ($n = 15$)**		
Reaction times (ms)	Congruent	Pretest	546.94	76.68	520.02	53.71	N/A
		Posttest	546.69	75.75	508.82	70.26	N/A
	Incongruent	Pretest	586.64	89.61	565.46	68.30	N/A
		Posttest	561.62	81.83	531.71	61.57	N/A
	Simon effect	Pretest	39.70	37.00	45.45	23.61	N/A
		Posttest	14.93	34.33	22.91	39.47	ns
Correct responses (%)	Congruent	Pretest	96.71	3.36	96.93	3.28	N/A
		Posttest	96.94	4.01	96.40	7.10	N/A
	Incongruent	Pretest	95.53	3.84	94.67	4.12	N/A
		Posttest	97.65	2.94	95.33	8.57	N/A
	Simon effect	Pretest	−1.17	4.19	−2.27	4.46	N/A
		Posttest	0.71	3.08	−1.10	3.45	ns
STROOP TASK							
			Training ($n = 16$)		**Control ($n = 16$)**		
Duration in seconds	Color	Pretest	69.44	9.95	64.38	12.75	N/A
		Posttest	67.81	11.05	63.37	11.42	N/A
	Word-color conflict	Pretest	139.44	23.81	129.63	33.14	N/A
		Posttest	125.63	14.39	124.75	30.12	N/A
	Incongruency cost	Pretest	70.00	18.81	65.25	24.21	N/A
		Posttest	57.81	11.11	61.38	21.44	ns
N-BACK TASK							
			Training ($n = 15$)		**Control ($n = 16$)**		
Reaction times (ms)	1-back	Pretest	838.86	124.08	757.86	104.40	N/A
		Posttest	762.52	119.15	733.73	111.66	N/A
	2-back	Pretest	1065.36	168.20	951.30	155.55	N/A
		Posttest	979.36	111.17	903.50	113.11	N/A
	N-back effect	Pretest	226.50	114.47	193.44	86.92	N/A
		Posttest	216.84	84.09	169.78	70.52	ns
Correct responses (%)	1-back	Pretest	92.92	4.82	91.34	7.86	N/A
		Posttest	97.19	2.25	95.34	4.20	N/A
	2-back	Pretest	77.53	10.09	74.25	14.81	N/A
		Posttest	82.96	7.31	82.18	10.66	N/A
	N-back effect	Pretest	−15.39	11.38	−17.09	14.70	N/A
		Posttest	−14.47	6.90	−13.16	8.52	ns
WAIS-R Digit span							
			Training ($n = 17$)		**Control ($n = 16$)**		
Total score	Backward	Pretest	6.06	1.56	6.38	1.31	N/A
		Posttest	6.12	1.69	6.69	1.99	ns

Between-group differences at posttest were analyzed with ANCOVA; ns, not significant.

TABLE 8 | Performance on the far transfer tasks measuring fluid intelligence, episodic memory, verbal fluency, and visuomotor speed.

		Session	Mean	*SD*	Mean	*SD*	Sig.
			Training ($n = 17$)		Control ($n = 16$)		
CULTURE FAIR INTELLIGENCE TEST							
Part 2 + Part 4	Total raw score	Pretest	12.71	2.80	12.18	1.94	N/A
		Posttest	12.24	2.86	12.50	2.56	ns
WAIS-R BLOCK DESIGN							
	Total raw score	Pretest	26.29	10.62	29.94	7.68	N/A
		Posttest	28.53	9.60	32.25	6.98	ns
CERAD							
Wordlist sum score		Pretest	21.12	2.98	23.00	3.52	N/A
		Posttest	23.76	2.68	23.37	4.33	ns
Wordlist delayed recall		Pretest	7.59	1.18	8.13	1.31	N/A
		Posttest	8.06	1.03	8.38	1.45	ns
Wordlist savings score (%)		Pretest	92.35	11.17	97.56	12.06	N/A
		Posttest	94.35	13.31	97.06	15.65	ns
WMS-R							
Logical Memory immediate	Total raw score	Pretest	27.35	4.73	26.06	3.57	N/A
		Posttest	30.24	4.93	29.94	3.73	ns
Logical Memory delayed	Total raw score	Pretest	23.53	4.61	23.69	4.38	N/A
		Posttest	28.82	4.52	26.81	4.48	ns
VERBAL FLUENCY							
Semantic fluency	60 seconds	Pretest	28.53	5.78	28.56	5.78	N/A
		Posttest	28.53	6.26	27.63	7.26	ns
Phonological fluency	60 seconds	Pretest	17.35	6.30	17.06	6.69	N/A
		Posttest	19.18	7.28	16.25	5.36	ns
WAIS-R DIGIT SYMBOL							
	Total raw score	Pretest	45.88	10.48	48.81	14.53	N/A
		Posttest	49.47	10.16	50.44	12.77	ns

Between-group differences at posttest were analyzed with ANCOVA; ns, not significant.

not a broad ability, but rather a specific skill related to the unique working memory updating requirements of the training tasks. It is of interest to note that set shifting deficits in late adulthood are usually found when participants have to maintain and coordinate two task sets in working memory (Wasylyshyn et al., 2011). The transfer effect found in the rule-based part of the odd-man-out task was no longer significant at the 1-year follow-up. The fact that no near transfer effects were found on the Trail Making Test may have been due to the fact that this paper-and-pencil test is a rough measure compared with computerized tests that can reveal more subtle performance changes.

The results regarding far transfer effects have been mixed in previous set shifting studies. Minear and Shah (2008) did not include far transfer measures in their study at all, Zinke et al. (2012) found only modest far transfer effects, and Soveri et al. (2013) did not find any far transfer effects. However, Karbach and Kray (2009) found transfer effects to tasks measuring working memory updating, inhibition, and fluid intelligence. Our study differs from the study by Karbach and Kray (2009) in that we used an adaptive training paradigm, and we had a higher number of switches that were distributed somewhat differently in the training. Additionally, Pereg et al. (2013) used the same protocol as Karbach and Kray (2009), but were not able to replicate the far transfer findings of Karbach and Kray (2009). It has recently been argued that especially the far transfer effects seen in executive training studies are not consistent (Shipstead et al., 2010, 2012; Morrison and Chein, 2011; Buitenweg et al., 2012; Melby-Lervåg and Hulme, 2013, 2016), and several previous executive training studies have suffered from methodological shortcomings (e.g., not including an active control group, not using an adaptive training regime, or not including enough transfer measures). We tried to take these criticisms into account by employing an active control group, using an adaptive and long enough training paradigm, and by including at least two transfer tasks per cognitive domain. Still we found only very limited statistically significant near transfer effects.

Some limitations of the present study should be pointed out. First, the sample size was small, which decreases the statistical power and increases the risk for Type II errors. Given the practical challenges of cognitive training studies, Internet-based training experiments that enable larger sample sizes offer one promising way to study further the transfer effects of executive training in the future (e.g., Ngandu et al., 2015). Second, some of the participants performed at ceiling in parts of the training tasks and the odd-man-out task (mainly in the single task blocks), limiting the sensitivity of these tasks in showing possible

training-related effects. Third, to rule out possible expectancy effects, future studies should also examine whether the active control group has the same expectations of improvement on the pre/post tasks as the experimental group, as only then can we more confidentially attribute differential improvements to the shifting training (Boot et al., 2013). Fourth, while no motivational differences were found between the groups, the control group reported being less alert than the training group at posttest. However, as the groups were equally alert during pretest and training, alertness was not a confounding factor for the training period. It is unlikely that the higher subjective alertness level of the training group at posttest reflected a general training effect, as in that case one might have expected more widespread transfer. One possibility is that it could be an after-effect of the posttest where the training group performed tasks that were very familiar to them and where they could excel (i.e., the training tasks), whereas the control group had no similar tasks to perform as the computer games were not included in the pre-post test battery. Nevertheless, in absolute terms, both groups displayed adequate levels of subjective alertness at posttest.

In conclusion, we found that set shifting training in the elderly yielded reliable and long-lasting effects on the trained tasks. However, the near transfer effects from this training were very limited.

ETHICS STATEMENT

All participants gave their written informed consent to participate in the study. The consent forms were also reviewed by the Ethics Committee of the Hospital District of Southwest Finland, i.e., the subjects were among other things informed that they could quit their participation in the study at any time without a reason, and that the collected data was confidential and kept in a safe place. The follow-up part of the study was approved by the Ethics Committee of the Departments of Psychology and Logopedics at the Åbo Akademi University. No additional considerations, the subjects were healthy.

AUTHOR CONTRIBUTIONS

All authors listed have made substantial, direct and intellectual contribution to the work, and approved it for publication. More specifically, PG-N designed the study, performed the experiments, analyzed and interpreted the data, and drafted the manuscript. AS, JR, ASN, and ML contributed to the conception of the experiments and they critically reviewed the manuscript. AS and ML also contributed to the interpretation of the data. EE and AN performed the experiments together with PG-N and critically reviewed the manuscript.

ACKNOWLEDGMENTS

We would like to thank the participants for their time and effort. Prof. Lars Bäckman is thanked for his comments on this study. Nea Holmberg, Jennifer Söderholm, Benjamin Wärnå and Eric Karlsson are thanked for their much appreciated inputs. PG-N was funded by the Academy of Finland (Grant No. 251788) and the Folkhälsan Foundation. ML received funding from the Academy of Finland (Grant No. 260276) and the Abo Akademi University Endowment (grant to the BrainTrain project). JR received funding from Sigrid Juselius Foundation and Turku University Hospital clinical grants.

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Conflict of Interest Statement: JR is serving as a neurology consultant for CRST Ltd. None of the aforementioned had any role in the present study, including data collection, preparation or analysis. None of the other authors have any commercial or financial relationships to declare that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 18 April 2017
doi: 10.3389/fnagi.2017.00103

Individual Differences in Cognitive Function in Older Adults Predicted by Neuronal Selectivity at Corresponding Brain Regions

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Relating individual differences in cognitive abilities to neural substrates in older adults is of significant scientific and clinical interest, but remains a major challenge. Previous functional magnetic resonance imaging (fMRI) studies of cognitive aging have mainly focused on the amplitude of fMRI response, which does not measure neuronal selectivity and has led to some conflicting findings. Here, using local regional heterogeneity analysis, or H_{corr}, a novel fMRI analysis technique developed to probe the sparseness of neuronal activations as an indirect measure of neuronal selectivity, we found that individual differences in two different cognitive functions, episodic memory and letter verbal fluency, are selectively related to H_{corr}-estimated neuronal selectivity at their corresponding brain regions (hippocampus and visual-word form area, respectively). This suggests a direct relationship between cognitive function and neuronal selectivity at the corresponding brain regions in healthy older adults, which in turn suggests that age-related neural dedifferentiation might *contribute to* rather than *compensate for* cognitive decline in healthy older adults. Additionally, the capability to estimate neuronal selectivity across brain regions with a single data set and link them to cognitive performance suggests that, compared to fMRI-adaptation—the established fMRI technique to assess neuronal selectivity, H_{corr} might be a better alternative in studying normal aging and neurodegenerative diseases, both of which are associated with widespread changes across the brain.

Keywords: neuronal selectivity, episodic memory, verbal fluency, hcorr, aging

OPEN ACCESS

Edited by:
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University of East Anglia, UK

Reviewed by:
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Institute of Molecular Biology and Biotechnology, Greece
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Received: *18 August 2016*
Accepted: *30 March 2017*
Published: *18 April 2017*

Citation:
Jiang X, Petok JR, Howard DV and Howard JH Jr. (2017) Individual Differences in Cognitive Function in Older Adults Predicted by Neuronal Selectivity at Corresponding Brain Regions. Front. Aging Neurosci. 9:103. doi: 10.3389/fnagi.2017.00103

INTRODUCTION

Cognitive abilities are highly heterogeneous among individuals, and this variance is typically even higher in older compared to middle-aged adults (Morse, 1993; Spreng et al., 2010). Because individuals with lower cognitive performance are at a higher risk of Alzheimer's disease (AD) and other age-related dementias (Masur et al., 1994; Albert et al., 2001; Riley et al., 2005), identifying the neural bases of these individual cognitive differences in older adults might reveal potential neural targets for interventional therapies. These could in turn help to preserve or even improve cognitive function, thereby reducing the risk of AD and other types of dementia. However, relating individual

differences in cognitive performance to neural substrate remains a major challenge.

Previous work on object recognition has suggested that individual differences in behavioral performance might be accounted for by differences in neuronal selectivity in corresponding brain regions, with higher neuronal selectivity associated with higher behavioral performance, and vice versa (Sigala et al., 2002; Freedman et al., 2006; Jiang et al., 2007). Meanwhile, computational simulation and theoretical works have suggested that aging leads to a decrease in neuronal selectivity, often referred to as neural "dedifferentiation" (Li et al., 2001; Park and Reuter-Lorenz, 2009). This neural dedifferentiation in aging is thought to be a key contributor to cognitive decline in older adults (Li et al., 2001). That is, neurons in the aged-brain become less selective, leading to increasing overlap in the neuronal response to different stimuli. This, in turn, contributes to diminished behavioral performance as well as to an increase in the workload of executive/attention circuits. Recent single-unit recording studies in animals (Schmolesky et al., 2000) and functional magnetic resonance imaging (fMRI) studies in human subjects (Goh et al., 2010; Lee et al., 2011; Park et al., 2012) have lent support to this neural dedifferentiation theory of aging. For instance, using fMRI-adaptation (fMRI-A) and morphed face stimuli with varying shape similarity, two independent groups of researchers showed that, compared to young adults, neuronal selectivity in the fusiform face area, or FFA, a critical region in face processing (Kanwisher et al., 1997), is reduced in healthy older adults (Goh et al., 2010; Lee et al., 2011). In addition, using a different fMRI technique, multi-voxel pattern analysis (MVPA) (Norman et al., 2006), it has been shown that the distinctiveness of neuronal response to preferred vs. non-preferred stimulus classes is reduced in aged brain (Carp et al., 2010). Taken together, these studies reveal a general reduction in the distinctiveness of neural representations with healthy aging, i.e., age-related neural dedifferentiation.

While these previous studies have provided converging evidence in support of the age-related neural dedifferentiation theory, one key element is missing. To our knowledge, none of these studies has established a direct relationship between cognitive function and neuronal selectivity (or neural distinctiveness Carp et al., 2010) at corresponding brain regions in older adults. In other words, it is not clear whether the individual differences in neuronal selectivity in older adults can be used to predict individual differences in cognition, thereby providing some insight into inter-individual heterogeneity of cognitive function with age.

Recent theoretical studies of aging—inspired by findings of increased activity and/or recruitment of additional brain regions in functional neuroimaging studies of healthy older adults—propose that neural dedifferentiation might serve as a compensatory mechanism in older adults. That is, neurons in the aged brain may become more broadly tuned so that they might be recruited to support cognitive process in other tasks (Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Park, 2010; but see Reuter-Lorenz and Park, 2014), suggesting the decrease in neuronal selectivity in aging brain might be beneficial, that is, it might help to *compensate for* cognitive decline in older adults.

In direct contrast to this idea that dedifferentiation *compensates for cognitive decline*, studies of object recognition suggest that lower neuronal selectivity is associated with lower cognitive performance, i.e., a positive correlation between neuronal selectivity and cognitive performance (Freedman et al., 2006; Jiang et al., 2007, 2013; Scholl et al., 2014). That is, the decrease in neuronal selectivity in aging brain *contributes to* rather than *compensate for* cognitive decline in older adults. Furthermore, experimental data and computational models of object recognition suggest that a decrease in neuronal selectivity would lead to an increase in unspecific neuronal response (Freedman et al., 2006; Jiang et al., 2006), suggesting that the increase in fMRI signal in additional brain regions often seen in older adults might be—at least partially—due to the decrease in neuronal selectivity (in addition to modulations due to attention, task difficulty, and effort), as *a consequence of cognitive decline rather than a compensation to cognitive decline*. Thus, additional research is warranted to investigate the relationship between age-related neural dedifferentiation, general age-related cognitive decline, and individual differences, and to reconcile the inconsistency between the two competing hypotheses.

Here we studied this question by examining the relationship between different cognitive functions and neuronal selectivity at corresponding brain regions in older adults, using a novel fMRI data analysis technique, *local regional heterogeneity analysis*, or H_{corr}, which we recently developed to estimate neuronal selectivity based on fMRI activation patterns (Jiang et al., 2013). Briefly, this technique calculates the variance (heterogeneity) of local voxel-wise correlations in a region of interest (ROI), also termed H_{corr}, to assess the sparseness of neuronal activations as an indirect measure of neuronal selectivity. Higher H_{corr} indicates larger inter-voxel variance and hence greater neuronal sparseness, which in turn suggests sharper neuronal tuning, and vice versa. This technique is motivated by earlier computational, behavioral, imaging, and single-unit studies that suggest the sparseness of activation patterns is related to neuron selectivity (Freedman et al., 2006; Jiang et al., 2006): neurons with high selectivity produce a sparse neural code, as each neuron only responds to a small set of stimuli that are highly similar to its preferred stimulus. In contrast, less selective neurons respond to a greater number of dissimilar stimuli, leading to greater overlap in responses and less sparse neural representations. For instance, single-unit studies in monkeys have shown that learning produces sparser codes, with neurons responding to fewer stimuli after training (Kobatake et al., 1998; Freedman et al., 2006). Therefore, when neuronal selectivity is measured using our technique with fMRI, a lower local regional heterogeneity of correlations (H_{corr}) should be associated with a lower neuronal selectivity and thus a poorer behavioral performance. Conversely, greater heterogeneity implies higher neuronal selectivity and thus better behavioral performance across subjects. Indeed, we have found that behavioral face discrimination in adults with autism spectrum disorders can be quantitatively predicted by neuronal selectivity in FFA, estimated via both the novel H_{corr} and the established fMRI-A techniques (Jiang et al., 2013). This suggests that H_{corr} reliably estimates neuronal selectivity.

In the present study, we investigated whether the novel H_{corr} technique can effectively assess neuronal selectivity across brain regions in older adults and whether the H_{corr}-estimated neuronal selectivity can selectively predict individual differences in behavioral performance on two cognitive functions, episodic memory and letter verbal fluency. Both of these show declines in healthy aging (Fleischman et al., 2004; Cansino, 2009; Elgamal et al., 2011; Stokholm et al., 2013) as well as in neurodegenerative disease, such as AD (Henry et al., 2004; Rémy et al., 2005). Specifically, we used H_{corr} to assess neuronal selectivity at two brain regions, the hippocampus, which is associated with episodic memory (Tulving, 2002; Squire and Wixted, 2011), and the visual word form area (VWFA), an area in the left ventral occipitotemporal cortex that is important for lexical aspects of language skills (McCandliss et al., 2003) and has been associated with letter verbal fluency (Gleissner and Elger, 2001). Critically, based on previous studies of object recognition in animal and human subjects and computational modeling, we predicted a double dissociation, such that H_{corr} at the hippocampus would predict individual differences in episodic memory, but not letter verbal fluency, whereas H_{corr} at the VWFA would show the opposite pattern. Further, we predict a positive correlation in both cases. In addition, it would predict there is no correlation between letter verbal fluency performance and H_{corr} at the VWFA homologous region in the right hemisphere (R-VWFA), which is typically associated with face processing in young adults (Kanwisher et al., 1997). By contrast, the neural dedifferentiation-related compensation theory would predict a negative correlation between cognitive performance and H_{corr} at other brain regions, i.e., a better performance in letter verbal fluency would correlate with a lower H_{corr} at R-VWFA. That is, while R-VWFA and nearby regions are typically associated with face processing, the reduced neuronal selectivity due to age-related neural dedifferentiation might help to recruit neurons in this region to assist language processing (e.g., letter verbal fluency) in healthy older adults, with a direct contrast to the prediction of the computational theories of object recognition. Here we tested the two hypotheses by applying the novel H_{corr} technique to a previously collected data set (Simon et al., 2011).

EXPERIMENTAL PROCEDURES

Participants

Twelve healthy older adults (age range: 63–72 years old, mean age: 67.5 ± 3.2 years old, nine women) participated in the study. Experimental procedures were approved by Georgetown University's Institutional Review Board, and written informed consent was obtained from all subjects prior to the experiment. The data from one additional subject were excluded due to missing data.

Participants were screened for MRI safety, neurological disease or disorder, and drugs known to influence cognition. In addition, subjects were excluded from the study if they met criteria for dementia (i.e., a score of below 27 on the Mini-Mental State Examination) or had abnormal intelligence status (i.e., scores outside the expected age range on neuropsychological measures of processing speed, cued recall, free recall, verbal memory, vocabulary, and reading ability (n = 0).

The demographic info and neuropsychological test scores are shown in **Table 1**.

Neuropsychological Tests

A comprehensive neuropsychological test battery was administered to all participants 1 day or 2 days after the MRI scan (see **Table 1** for the complete list). Here we focused on episodic memory performance measured with the Logical Memory subtest of the Weschsler Memory Scale–Third Edition (WMS-III), and language skills measured with FAS verbal fluency and Wood-Johnson III Word Identification test.

Implicit Sequence Learning Scans

The Hcorr data were derived from MRI images collected during an event-related design consisting of three runs for each subject while they performed a shortened and simplified version of the Triplets Learning Task (TLT) (Howard et al., 2008). The details of task design can be found elsewhere (Simon et al., 2011) and are not described here because the task itself is not the focus of the current paper. Briefly, three open circles were displayed against a gray background on the screen (**Figure 1**). Each trial or "triplet" began with two sequentially presented cue events (circles filling in red—displayed for 200 ms each), which were followed by a target (a circle filling in green—displayed for 850 ms). Each event

TABLE 1 | Demographic and neuropsychological data (n = 12).

Demographic	Range	Mean (STD)
Age	63, 72	67.5 (3.2)
Gender	9 Female, 3 Male	
Education	12, 21	17.2 (2.4)
Neuropsychological tests	**Scores**	
MMSE	28, 30	29.3 (0.8)
*COWAT-FAS Sum	27, 65	46.0 (12.5)
WAIS-III vocabulary	57, 77	67.9 (5.7)
WAIS-III digit symbol coding	31, 83	60.7 (13.7)
WAIS-III digit symbol pairing	4, 18	10.4 (5.0)
WAIS-III digit symbol recall	5, 9	7.0 (1.4)
*WAIS-III logical memory (unit)	34, 55	45.8 (6.4)
WAIS-III logical memory (thematic)	16, 21	19.0 (2.0)
WAIS-III digit span forward	9, 15	11.8 (2.0)
WAIS-III digit span backward	4, 12	9.0 (2.6)
WJ-III Word Attack SS	24, 29	27.5 (1.4)
*WJ-III Word Identification SS	70, 76	74.2 (1.7)
USC-REMT free recall correct	15, 37	24.9 (5.1)
USC-REMT free recall repetitions	90, 13	2.7 (3.6)
USC-REMT free recall intrusions	0, 2	1.0 (0.9)

MMSE, Mini-Mental State Examination; WAIS-III, Wechsler Adult Intelligence Scale, 3rd ed.; COWAT-FAS, Controlled Oral Word Association Test-FAS; USC-REMT, University of Southern California-Repeatable Episodic Memory Test; WJ-III, Woodcock-Johnson, 3rd ed.

**Tests used for the H_{corr} correlation analyses.*

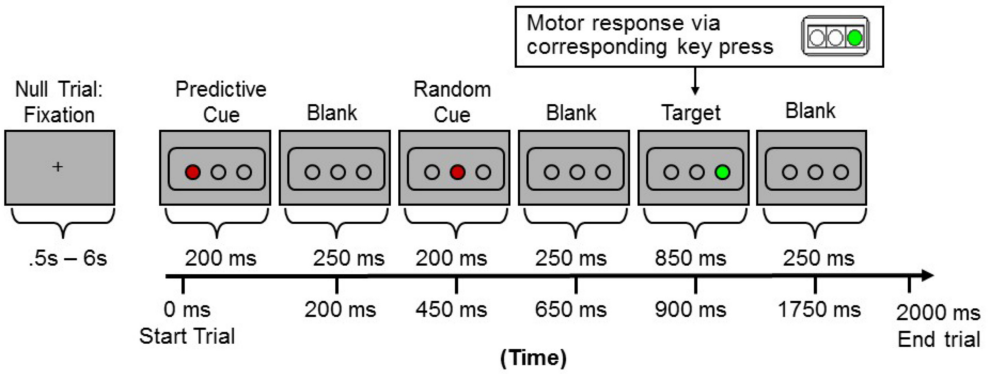

FIGURE 1 | Sample presentation of one trial (or "triplet") during the event-related fMRI scans.

was immediately followed by a 250 ms blank screen, and each trial lasted 2000 ms. Participants passively viewed the first two red events and responded to the third, green target event location as quickly and as accurately as possible via a corresponding button (one of three buttons on a button box held in the right hand). Each run consisted of 135 trials and lasted 6 m and 30 s. Within each run, trial orders and trial durations were implemented using OptSeq2 (Dale, 1999), resulting in a rapid event-related design with a temporally jittered intertrial interval (0.5–6 s, mean = 1.36 s). The overall accuracy was 98.4 ± 0.04%, and the reaction time was 482.72 ± 41.76 ms.

MRI Data Acquisition and Analysis

MRI data were acquired at Georgetown University's Center for Functional and Molecular Imaging using an echo-planar imaging (EPI) sequence on a 3.0 Tesla Siemens Trio scanner (Flip angle = 90°, TR = 2.5 s, TE = 30 ms, FOV = 256 × 256 mm, 64 × 64 matrix) with a twelve-channel head coil. Fifty descending axial slices (thickness = 3.7 mm, 0.3 mm gap; in-plane resolution = 4.0 × 4.0 mm^2) were acquired. At the end, three-dimensional T1-weighted MPRAGE images (resolution 1 × 1 × 1 mm^3) were acquired from each subject.

The EPI images were spatially realigned and unwrapped using the SPM2 software package (http://www.fil.ion.ucl.ac.uk/spm/software/spm2/), then all images were resliced to 2 × 2 × 2 mm^3, normalized to a standard MNI reference brain in Talairach space, and smoothed with 6 mm Gaussian kernel using SPM2.

The hippocampal formation and parahippocampal regions of interest (ROIs) were defined using the AAL toolbox (Tzourio-Mazoyer et al., 2002), and the voxels from the surface of ROIs were removed before analyzing data to limit the possibilities of including voxels from other nearby regions. The VWFA ROI was defined as a 4-mm sphere centered at (MNI: −42 −54 −18) (Glezer et al., 2009), and right-hemispheric symmetrical region (R-VWFA) was defined as a 4-mm sphere centered at (MNI: 42 −54 −18), though similar results were obtained when the VWFA and R-VWFA ROIs were defined with different radius (3 or 5 mm).

Results using conventional fMRI data analysis can be found elsewhere (Simon et al., 2011). Here we reported results using a novel fMRI data analysis technique (see below).

Local Regional Heterogeneity Analysis

For the local regional heterogeneity and synchronization analysis, we first extracted the raw time series data in each of ROIs from the three runs of ER scans for each subject, followed by removing any linear trends and low frequency variations. The fMRI data were used in a pair-wise correlation analysis between each voxel, which resulted in a set of pairwise correlation coefficients (for n voxels), r_{ij}.

$$r_{ij} = corr(Vox_i, Vox_j),\ i,j \in 1..n \tag{1}$$

We then calculated a measure of local heterogeneity, H_{corr}, as the standard error of the mean (SEM) of those averaged correlation coefficients (r_{ij}, $i < j$, because $r_{ij} = r_{ji}$, and $r_{ii} = 1$).

$$H_{corr} = \sqrt{\frac{\sum_{i=1}^{n-1}\sum_{j=i+1}^{n}\left(r_{ij}-u\right)^2}{N\times(N-1)}}\ where\ N=\sum_{i=1}^{n-1} i\ u = \frac{1}{N}\sum_{i=1}^{n-1}\sum_{j=i+1}^{n} r_{ij} \tag{2}$$

The H_{corr} of each individual run and each individual ROI was calculated separately, and the averaged values of three runs (and for hippocampus and parahippocampus, mean of both hemispheres) were used in the main analysis, but similar results were observed with data from each run and each hemisphere (see Supplementary Materials).

RESULTS

Three runs of fMRI data were acquired while subjects (N = 12) performed an implicit sequence learning task (Simon et al., 2011) (also see **Figure 1**). The neuronal selectivity at VWFA and bilateral hippocampal formation were estimated using the H_{corr} technique, and then correlated with verbal fluency and episodic memory. For comparison, H_{corr} at the bilateral parahippocampal region and the right-hemispheric symmetrical region of VWFA

(R-VWFA) (Cohen et al., 2003) were also obtained (to serve as control regions) (see Experimental Procedures).

Episodic Memory Performance Is Predicted by H_{corr} at Hippocampus but Not the VWFA and Parahippocampal Region

Episodic memory is one of the most commonly affected cognitive functions in elderly adults (Fleischman et al., 2004; Cansino, 2009). While it is well-known that reduced episodic memory is mainly driven by neuronal dysfunction in the hippocampal region, the exact neural mechanisms remain unknown. Given recent findings suggesting that neurons in hippocampus are highly selective with a sparse neural representation (Quiroga et al., 2005; Viskontas et al., 2009), we hypothesized that, in healthy older adults, poor episodic memory is due to reduced neuronal selectivity in the hippocampus and individual differences in episodic memory can be related to variations in neuronal selectivity in the hippocampus.

To test this hypothesis, we examined the relationship between neuronal selectivity in hippocampus and episodic memory in these older adults. Episodic memory was assessed outside of the MRI scanner with the Logical Memory subtest (LMS) of the Weschsler Memory Scale–Third Edition (WMS-III), using the total unit score of immediate recall. Neuronal selectivity at the hippocampal region was estimated via H_{corr} (using the mean of both hemispheres and three runs, similar results were observed using data from each hemisphere and each run separately). Pearson's correlation analyses revealed that episodic memory performance was significantly correlated with H_{corr} in the hippocampus; with higher selectivity (i.e., a higher H_{corr} value) associated with better performance on episodic recall (total units, $r = 0.73$, $p < 0.007$, **Figure 2A**). In contrast, there was no significant correlation between episodic memory performance and the H_{corr} at either the VWFA ($r = 0.30$, $p > 0.34$, **Figure 2B**) or the parahippocampal region ($r = 0.23$, $p > 0.46$, **Figure 2C**). Thus, episodic memory performance in older adults is closely, and selectively, related to the neuronal selectivity in hippocampus as estimated by H_{corr}.

The neural mechanisms underlying reduced episodic memory have been the focus of many neuroimaging studies of aging (Corkin, 1998; Chhatwal and Sperling, 2012), which generally suggest that neuronal dysfunction at hippocampus might underlie reduced episodic memory in older adults. For instance, reduced hippocampal volume has been linked to lower memory performance in both older adults and patients with probable AD (Petersen et al., 2000). However, the link between episodic memory deficits and neuronal dysfunction at hippocampus remains elusive. For instance, fMRI studies of episodic memory in healthy older adults have revealed conflicting reports; while some studies revealed decreased neural activity in hippocampus of older than younger adults (Daselaar et al., 2006; Antonova et al., 2009), others have reported the opposite (Yassa et al., 2011). These conflicting reports might reflect the technical limitations of conventional fMRI techniques: in fMRI, higher response amplitude can result from either fully functioning neurons or broadly tuned neurons (which will increase the number of neurons responding), while lower response amplitude may reflect loss of neurons responding or sharply tuned neurons (which will also lead to a decrease in number of neurons responding). These two scenarios have very different implications for performance, but cannot be differentiated with conventional fMRI techniques that rely on response amplitude, which does not measure neuronal selectivity. Furthermore, the relationship between individual differences in episodic memory and neuronal function in hippocampus remains an open question of high interest. In contrast, the H_{corr} technique we use here is sensitive to neuronal selectivity, and reveals a selective association between neuronal selectivity at hippocampus and a measure of episodic memory. This suggests that age-related decline in episodic memory might be related to region-specific age-related neural dedifferentiation, with a poorer episodic memory associated with a lower neuronal selectivity in hippocampus, and potentially a higher risk of dementia. These results are in line with a previous study of amnestic mild cognitive impairment (aMCI), which found that neuronal selectivity (estimated via fMRI-A) is lower in the hippocampus of aMCI than that of healthy controls (Johnson et al., 2004).

Moreover, here we found there was no significant correlation between episodic memory and H_{corr} at parahippocampal region. This finding is a bit surprising, as previous studies have suggested the involvement of parahippocampus in memory encoding and retrieval (Hayes et al., 2007). However, our lack of correlation in the present study is consistent with those showing that the parahippocampus is not related verbal or semantic related memory (what was assessed via LMS) but rather spatial

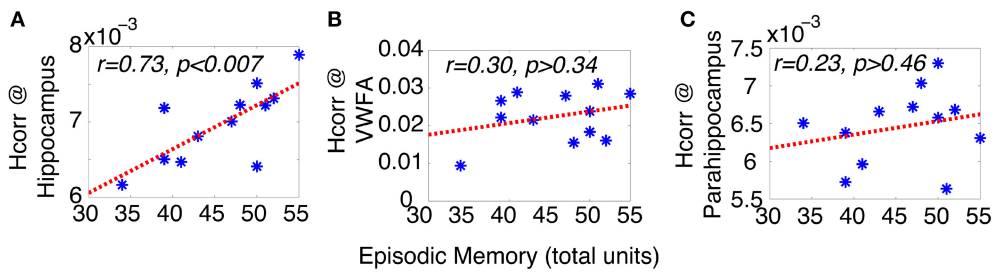

FIGURE 2 | Episodic memory performance of older adults can be predicted by H_{corr} at hippocampal formation (A), but not VWFA **(B)**, nor parahippocampal region **(C)**, suggesting the episodic memory performance in older adults is closely coupled with neuronal selectivity in hippocampus. *Represents data from each individual subject.

memory processes (Moscovitch et al., 2006; Aminoff et al., 2013).

Letter Verbal Fluency Predicted by H_{corr} at VWFA but Not Hippocampus and R-VWFA

Verbal fluency tasks have been widely used to assess both language- and executive-related cognitive performance in several populations (McDowd et al., 2011), and studies have found that verbal fluency declines in healthy aging (Elgamal et al., 2011; Stokholm et al., 2013), as well as in Alzheimer's disease (Henry et al., 2004; Clark et al., 2009) and other neurological disorders (Henry and Beatty, 2006; McDowd et al., 2011). However, the neural bases of verbal fluency remain to be elucidated. For instance, while neuroimaging studies of letter and semantic verbal fluency have consistently revealed the involvement of left inferior frontal gyrus (Costafreda et al., 2006), supporting the critical role of executive function in verbal fluency tasks (Bolla et al., 1990), the majority of neuroimaging studies of letter and semantic verbal fluency have failed to reveal the involvement of the left ventral occipitotemporal region (including VWFA) (Costafreda et al., 2006; Wagner et al., 2014). This stands in contrast to findings from neuropsychological studies that have found lesions of the left but not right temporal lobe impair letter verbal fluency (Gleissner and Elger, 2001). Furthermore, using a different experimental design, a recent fMRI study (Birn et al., 2010) reported significant activations in VWFA (MNI: −45 −51 −11) related to letter verbal fluency tests, consistent with the lesion studies. Nevertheless, the functional role and relationship between verbal fluency and VWFA are still poorly understood. Given the previous findings suggesting the critical role of VWFA in language (McCandliss et al., 2003) and the sharp tuning of VWFA neurons (Glezer et al., 2009), here we hypothesized that there is a relationship between neuronal selectivity in the VWFA and verbal fluency, whereby poorer verbal fluency in older adults is related to reduced neuronal selectivity in VWFA.

To test these hypotheses, we examined the relationship between letter verbal fluency and H_{corr} in VWFA and other comparison brain regions. Verbal fluency was assessed with the letter verbal fluency test (FAS), measured as the total number of words beginning with a given letter (F, A, and S) reported within 1 min. Pearson's correlation analyses revealed a significant correlation between verbal fluency and H_{corr} at VWFA ($r = 0.77$, $p < 0.004$, **Figure 3A**), but not at the hippocampus ($r = 0.28$, $p > 0.38$, **Figure 3B**). In addition, there was no significant correlation between verbal fluency and H_{corr} at the R-VWFA ($r = 0.17$, $p > 0.60$, **Figure 3C**), a right-hemispheric homolog of the VWFA that is not part of the language brain network (Cohen et al., 2003). These results suggest that, in older adults, verbal fluency is associated with neuronal selectivity in the VWFA, a key language region in the left ventral occipitotemporal cortex, but not the hippocampus and the R-VWFA. Similar results were obtained with Woodcock-Johnson III–Word Identification scores (see **Figure 4**), as well as using data from each of the three runs separately (data not shown here). In addition, the correlation coefficients between performance of two cognitive functions (episodic memory and verbal fluency) and H_{corr} at two brain regions (hippocampus and VWFA) were Z-transformed and shown in **Figure 5**, which revealed a clear interaction that is consistent with the double dissociation prediction.

Despite the fact that the VWFA was not found to be strongly activated in most previous neuroimaging studies of verbal fluency, here we provide evidence that letter verbal fluency is closely related to H_{corr} estimated neuronal selectivity in the VWFA, suggesting a critical role of the VWFA in letter verbal fluency. This is consistent with the lesion studies summarized above (Gleissner and Elger, 2001) as well as with the recent fMRI study that revealed a strong involvement of the VWFA during a letter verbal fluency test (Birn et al., 2010). In addition, the strong correlation between H_{corr} at the VWFA and verbal fluency suggests that neuronal selectivity (estimated via H_{corr}) at the VWFA might be a reliable predictor of lexical access ability. This hypothesis is further supported by the significant correlation between H_{corr} at the VWFA and WJ Word ID scores (**Figure 4**). In contrast, the lack of significant correlation between verbal fluency and H_{corr} at the hippocampus suggests that, at least in healthy older adults, letter verbal fluency might not be a reliable measurement of neuronal function at the hippocampus (Baldo et al., 2006 but also see Gleissner and Elger, 2001). In addition, the lack of correlation between verbal fluency and H_{corr} at the R-VWFA is consistent with the argument that the R-VWFA is not critical for verbal fluency or language in general (Cohen et al., 2003), even though this R-VWFA region is often strongly activated by visually presented words and letters, with an even further increased activity in older adults (compared to young adults). These results thus argue against the neural dedifferentiation-related compensation hypothesis, but are in

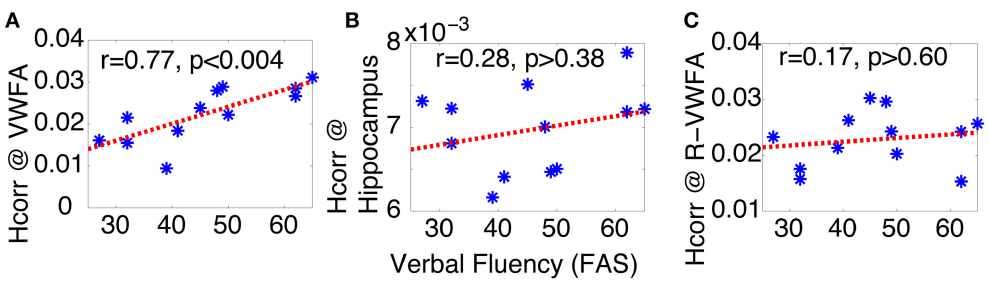

FIGURE 3 | Verbal fluency (FAS) of older adults can be predicted by H_{corr} in the VWFA (A), but not hippocampus **(B)**, nor the R-VWFA **(C)**, confirming the key role of VWFA in language skills. *Represents data from each individual subject.

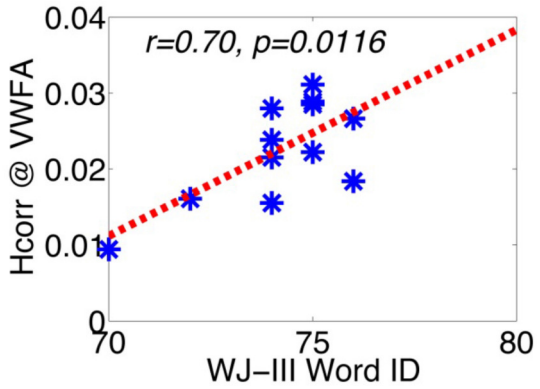

FIGURE 4 | The correlation between WJ-III Word ID and H_{corr} in VWFA. *Represents data from each individual subject.

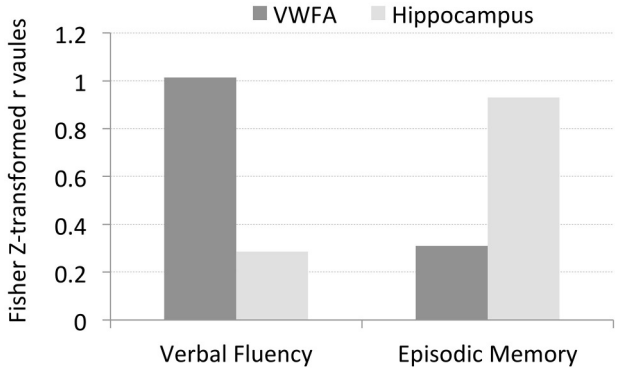

FIGURE 5 | The Z-transformed correlation coefficients between performance of two cognitive functions (episodic memory and verbal fluency) and H_{corr} at two brain regions (hippocampus and VWFA), respectively. The data suggests a double disassociation, that is, H_{corr} at hippocampus predicts episodic memory but not verbal fluency, while H_{corr} at VWFA predicts verbal fluency but not episodic memory.

line with the theories of object recognition. These results provide further support that fMRI response amplitude, compared to neuronal selectivity (estimated via H_{corr} here), might be a poor measure of behavioral performance (Grill-Spector et al., 2006; Mahon et al., 2007). On the contrary, it has been proposed that neurons in the right fusiform area (similar to R-VWFA's location) might be involved in face processing and belong to a largely specialized functional region, the fusiform face area, or FFA (Kanwisher et al., 1997). Consistent with this, we and others found that face discrimination performance can be predicted by neuronal selectivity in the FFA (estimated via fMRI-A or H_{corr}) (Jiang et al., 2006, 2013).

Taken together, the strong correlation between H_{corr} at the VWFA and letter verbal fluency performance suggests that VWFA is not only critical in reading (to process the visual inputs of letter strings), but also important for retrieving the letter string of words, in consistent with the hypothesis that VWFA might serve as a word "dictionary" responsible for the processing, learning, storing, and retrieving of word letter strings (Dehaene et al., 2005; Glezer et al., 2009, 2015), even in congenitally blind adults (Striem-Amit et al., 2012). However, it remains an open question about the role of VWFA in semantic or action verbal fluency, which does not necessarily involve the retrieval of word letter string.

DISCUSSION

Despite its significant scientific and clinical interest, relating individual differences in cognitive abilities to neural substrate in older adults remains a major challenge. Here by reanalyzing fMRI data from previously published work (Simon et al., 2011) in which subjects were participating in an implicit sequence learning task, we found that the novel H_{corr} technique (Jiang et al., 2013) can reliably estimate neuronal selectivity across different brain regions in healthy older adults with a single data set (even when subjects were performing an irrelevant task) and that individual differences in a specific cognitive function correlated with H_{corr} measures at the corresponding–but not other–brain regions. That is, we observed a double dissociation whereby individual differences in episodic memory performance were related to differences in neuronal selectivity in the hippocampus but not the VWFA, whereas the reverse was true for letter verbal fluency. In addition, there was no correlation between letter verbal fluency and H_{corr} measure at R-VWFA, the VWFA homologous region in the right hemisphere. These results suggest that individual differences in neuronal selectivity at specific brain regions might underlie individual differences in corresponding cognitive functions in healthy older adults. Furthermore, the ability to estimate neuronal selectivity across brain regions with a single data set and to estimate neuronal selectivity at a specific brain region (e.g., VWFA) even when subjects were performing an irrelevant task (implicit sequence learning) suggests that the novel H_{corr} technique has potential for studying healthy cognitive aging, and age-related neurological disease, such as Alzheimer's Disease, both associated with widespread change across brain regions.

Our findings here support theoretical work in cognitive aging suggesting that age-related neural dedifferentiation, i.e., a reduced neuronal selectivity in aged brain, is a key contributor of cognitive function in older adults (Li et al., 2001). In contrast, our results are not consistent with proposals that neural dedifferentiation might serve as a compensatory mechanism (Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Park, 2010), but see (Reuter-Lorenz and Park, 2014). The neural dedifferentiation-related compensation hypotheses, such as the original STAC (the Scaffolding Theory of Aging and Cognition) model were inspired by findings from functional neuroimaging studies that often revealed greater activation of prefrontal and parietal regions in older adults (Gutchess et al., 2005; Davis et al., 2008), as well as an increase in bilateral recruitment (compared to more lateralized activity in younger adults) (Dolcos et al., 2002). Basically these theories argue that, to perform a specific cognitive task, age-related neural dedifferentiation might help older adults to recruit additional neurons/regions to compensate

for the reduced neuronal function at the brain regions that are typically associated with the specific cognitive task/domain. While this compensatory mechanism might indeed underlie the increased activations in task circuits, such as frontal cortices in older adults (Reuter-Lorenz et al., 2000; Cabeza et al., 2002), the increased activity or recruitment of additional brain regions could also be due to factors like effort, attention, and task difficult levels, which are known to modulate fMRI response.

In addition, it is difficult to reconcile this dedifferentiation-related compensation hypothesis with findings from computational neuroscience of object recognition, and neuropsychological studies of patients with lesions.

First, computationally it is difficult to reconcile this compensation idea in the posterior regions that contain neurons highly selective to different features or object classes (e.g., face processing in FFA, vs. visual word processing in VWFA). That is, it is difficult to argue that FFA neurons selective to faces in young brain are now so broadly tuned in aged brain that these neurons can now be recruited to assist processing words or houses. Computationally the cost would be too high (i.e., the FFA neurons are now so broadly tuned that they are no longer highly efficient in processing faces) and the gain would be too small (i.e., again the FFA neurons are so broadly tuned that they would not be very effective for processing words or houses), suggesting that neural dedifferentiation at FFA is unlikely to be able to compensate for reduced word processing function due to neural dedifferentiation at VWFA, and vice versa, supporting by the lack of correlation between letter verbal fluency performance and H_{corr}–measured neuronal selectivity in the right occipital-temporal region.

Second, lesions in the left hemisphere often lead to deficits in varying aspects of language processing, including aphasia. While patients might recruit homologous brain regions in the intact right hemisphere to retain some language capabilities (Basso et al., 1989; Turkeltaub et al., 2011), several functional neuroimaging studies of these left-hemisphere stroke patients have found that increased fMRI response at the right hemisphere homologous language regions may actually correlate with poorer language performance (Heiss et al., 1999; Postman-Caucheteux et al., 2010), suggesting the recruitment of homologous regions in the right hemisphere might be *detrimental* rather than *beneficial* in language processing, *even in patients with left hemisphere lesions along with an intact right hemisphere*. In addition, using the low frequency repetitive transcranial magnetic stimulation (rTMS) technique, which inhibits neural activity at targeted brain regions, studies have shown that inhibiting the right-hemisphere homologous language regions actually help with regaining language function in aphasia patients with left-hemisphere lesions (Hamilton et al., 2010), and can even help healthy adults to learn new words (Nicolo et al., 2016)–again against the dedifferentiation-related compensation hypothesis. Taken together, the data from these previous neuropsychology and rTMS studies suggest that, the increased bilateral fMRI response in healthy older adults (compared to younger adults) likely does not serve as a compensation mechanism, but rather it might be due to increased attentional load or task engagement, or decreased neuronal selectivity. While increased task engagement would lead to an increase in performance, decreased neuronal selectivity would correlate with a lower cognitive performance, along with a more complex relationship between increased attentional load and performance, which could be positive or negative.

Therefore here we argue that the present study provides evidence against some aspects of this compensation hypothesis, for two reasons: First, in contrast to the lack of correlation between performance and age-related neural dedifferentiation in previous studies, the double disassociation between episodic memory/verbal fluency and the hippocampus/VWFA in the present study suggest that cognitive function is directly, and positively, related to neuronal selectivity (measured via H_{corr}) at corresponding, but not other brain regions, even in older adults; Second, the compensation hypothesis would predict a negative correlation between cognitive performance (e.g., verbal fluency) and neuronal selectivity at task-irrelevant regions (e.g., R-VWFA), but we did not observe any negative correlation (not even a trend) between varying cognitive abilities and H_{corr} at different brain regions. Therefore, we propose that age-related neural dedifferentiation has a *detrimenta*l rather than *compensatory* effect on cognitive performance in healthy older adults, i.e., the lower the neuronal selectivity at a brain region (e.g., hippocampus), the worse the corresponding cognitive function (e.g., episodic memory). The observed increase in activity or the recruitment of additional brain regions in healthy older adults might be more likely a consequence of cognitive decline, which would lead to neural dedifferentiation, increased attentional demand and task difficulty levels (all could lead to an increase in fMRI response), rather than a compensatory mechanism. However, compensation mechanisms might indeed help healthy older adults in some aspects of cognitive functions, such as the increased involvement of hippocampus in implicit learning in healthy older adults, which is typically associated with striatum in younger adults (Dennis and Cabeza, 2011). Future studies are needed to differentiate the increased activity due to age-related compensation or other factors (such as increased attentional demand), which might help to develop better cognitive training paradigms to preserve/improve cognitive function in aging.

Future studies are also needed to verify the Hcorr technique in a large and more heterogeneous sample, because the current sample is small. Longitudinal studies are also needed to examine the trajectory of change in neuronal selectivity from young to middle-aged to very older adults, along with detailed cognitive assessment, to provide definitive evidence on the relationship between neural dedifferentiation, aging, and cognitive performance. Furthermore, while the majority of previous studies on the correlation analysis of fMRI time series have been focusing on the correlations between time series at different brain regions—which have revealed impaired interregional connectivity due to aging (Chen et al., 2009), we and others have provided data suggesting that local voxel-wise correlations can help to uncover neuronal function/dysfunction at an intraregional level, using techniques like H_{corr} or ReHo (regional homogeneity) (Zang et al., 2004). For instance, using the fMRI ReHo and the [18F]-fluorodeoxyglucose (PET-FDG)

techniques, a recent study revealed a tight correlation between the ReHo scores and the glucose metabolism across brain regions (Bernier et al., 2017), suggesting that local voxel-wise correlation might have the potential to serve as a non-invasive tool to study brain function/dysfunction. Therefore, combining interregional techniques like resting state functional connectivity analysis with this novel intraregional H_{corr} technique in future studies is expected to lead to a more complete and accurate understanding of the neural mechanisms underlying cognitive decline due to aging and/or age-related neurodegenerative disease.

Furthermore, compared to other well-established like techniques like fMRI-A and MVPA–both of which have been successfully applied to examine age-related decreases in neuronal selectivity (Carp et al., 2010; Goh et al., 2010; Lee et al., 2011), the novel H_{corr} technique offers several advantages for studying aging. First, both fMRI-A and MVPA techniques usually require lengthy scanning time, which is not ideal for research on older populations. In contrast, H_{corr} is highly sensitive and can be accomplished with much shorter scans (Jiang et al., 2013). Second, by design, previous techniques can only probe neural dedifferentiation in task-related brain regions, while aging is associated with changes across a broad range of brain regions (Levy, 1994; Hedden and Gabrieli, 2004; Grady, 2012). In contrast, H_{corr} has the potential to estimate neuronal selectivity across brain regions from a single data set, including resting state scans. More specifically, because previous single unit recording studies (Bair et al., 2001; Jermakowicz et al., 2009; Lin et al., 2014) found that pair-wise correlations between two neurons in the presence of visual stimuli can be detected in the absence of stimuli, thus the voxel-wise correlations and H_{corr} within a given region should be similar with or without a task. Similar neural mechanisms might also underlie the findings from fMRI studies of resting state (Fox and Raichle, 2007; Smith et al., 2009). These unique advantages suggest H_{corr} has strong potential for studying cognitive aging and cognitive neuroscience in general, and that this technique could be applied to rich sets of fMRI data that have already been collected. However, future studies that directly link neuronal activity and selectivity (through single or multiple unit recordings), H_{corr}, and behavioral performance, are warranted to verify and validate this technique.

In summary, using a novel H_{corr} technique, we found a double dissociation in a sample of relatively homogeneous healthy older adults, such that episodic memory performance correlates with neuronal selectivity at hippocampus, but not VWFA, whereas verbal fluency shows the reverse pattern. In addition, there was no correlation between episodic memory and neuronal selectivity at the parahippocampal region, nor between verbal fluency and the R-VWFA. These results suggest that individual differences in cognitive abilities in healthy older adults are tightly linked to differences in neuronal selectivity at corresponding brain regions, and age-related neural dedifferentiation might be a *contributing* rather than *compensating* factor to age-related cognitive decline. However, this conclusion needs to be taken with caution as this study has several limitations. As this study was conducted from reanalyzing the data collected in a previously published study (Simon et al., 2011), the available behavioral and fMRI data was limited, the sample size was small, and the original experiment was not designed to test the hypotheses proposed here. Furthermore, the small sample size made it impossible to examine the potential difference due to gender, education, and other factors that might affect brain function and/or contribute to risks of certain age-related neurodegenerative diseases. Therefore, the present study should be treated as hypothesis generating rather than hypothesis testing, and future studies are warranted. However, the results we have reported here clearly demonstrate the sensitivity and applicability of this technique in studying cognitive aging, especially its heterogeneity, and we hope this study, as a proof or concept, will open a door for others to reanalyze the rich data that have already been collected, especially those with comprehensive neuropsychological assessments and a large and well-documented cohort.

ETHICS STATEMENT

Experimental procedures were approved by the Georgetown University's Institutional Review Board, and written informed consent was obtained from all subjects prior to the experiment.

AUTHOR CONTRIBUTIONS

JP, DH, and JH designed the original study. JP conducted the original study. XJ reanalyzed the data. XJ, JP, DH, and JH wrote the paper.

ACKNOWLEDGMENTS

This research was supported by grants R01AG036863, R37AG15450, and F31AG034691 from the National Institute on Aging, National Institutes of Health; grant M01 RR023942-01 from the Georgetown Clinical Research Center; a dissertation grant to JP from the American Psychological Association; a startup fund from Saint Olaf College to JP; and a startup fund from Georgetown University to XJ.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

REVIEW
published: 01 May 2017
doi: 10.3389/fnagi.2017.00115

Body–Brain Connections: The Effects of Obesity and Behavioral Interventions on Neurocognitive Aging

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Obesity is a growing public health problem in the United States, particularly in middle-aged and older adults. Although the key factors leading to a population increase in body weight are still under investigation, there is evidence that certain behavioral interventions can mitigate the negative cognitive and brain ("neurocognitive") health consequences of obesity. The two primary behaviors most often targeted for weight loss are caloric intake and physical activity. These behaviors might have independent, as well as overlapping/synergistic effects on neurocognitive health. To date obesity is often described independently from behavioral interventions in regards to neurocognitive outcomes, yet there is conceptual and mechanistic overlap between these constructs. This review summarizes evidence linking obesity and modifiable behaviors, such as physical activity and diet, with brain morphology (e.g., gray and white matter volume and integrity), brain function (e.g., functional activation and connectivity), and cognitive function across the adult lifespan. In particular, we review evidence bearing on the following question: *Are associations between obesity and brain health in aging adults modifiable by behavioral interventions?*

Keywords: aging, brain health, intervention, obesity, physical activity

OPEN ACCESS

Edited by:
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George Mason University, USA

Reviewed by:
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Received: *06 January 2017*
Accepted: *10 April 2017*
Published: *01 May 2017*

Citation:
Stillman CM, Weinstein AM, Marsland AL, Gianaros PJ and Erickson KI (2017) Body–Brain Connections: The Effects of Obesity and Behavioral Interventions on Neurocognitive Aging. Front. Aging Neurosci. 9:115. doi: 10.3389/fnagi.2017.00115

INTRODUCTION

Obesity is an epidemic in the United States, affecting over one-third of American adults. Rates of obesity in middle aged (adults aged 45–64) and older adults (adults aged 65 and older) are amongst the highest of all age categories (Ogden et al., 2014) and are increasing. This upward trend is in sharp contrast to the declining or stable rates recently reported for other age categories (Ogden et al., 2016).

In addition to conferring risk for cardiovascular disease, recent evidence links obesity with unfavorable changes in brain morphology and function, as well as impairments in cognitive performance. When examined in older adults, these obesity-related effects go above-and-beyond the changes seen during normal aging. Whether associations between obesity, brain, and cognitive measures are a *consequence* of weight gain or are the *cause* of behaviors that subsequently lead to weight gain (i.e., hedonic overeating) remains a matter of speculation and rich debate (Schwartz and Porte, 2005; McEwen and Morrison, 2013). Nonetheless, there is now evidence for causal

links between obesity and adverse changes in brain morphology and function. Accordingly, it is plausible that adulthood obesity may accelerate the onset of late-life neurocognitive impairments and disorders.

Although the factors leading to a population-wide increase in body weight are still under investigation (e.g., see Luke and Cooper, 2013; Blair, 2015; Malhotra et al., 2015 for debate), there is evidence that certain behaviors that reduce obesity could in turn improve aspects of neurocognitive health. The two primary behaviors most often targeted for promoting weight loss are diet (energy intake) and physical activity levels (energy expenditure). These behaviors might have independent or overlapping/synergistic effects on neurocognitive health.

Physical activity (PA) is a modifiable lifestyle factor shown to improve physical and neurocognitive health throughout the lifespan. PA has been associated with elevated cognitive performance and enhanced brain function in both neurologically healthy and impaired adults (Hughes and Ganguli, 2009; Bherer et al., 2013b; Gajewski and Falkenstein, 2016). For example, cross-sectional, prospective longitudinal, and randomized controlled trials have demonstrated that PA is associated with increased gray matter volume in the hippocampus and prefrontal cortex (Colcombe et al., 2006; Erickson et al., 2011; Ruscheweyh et al., 2011; Weinstein et al., 2012; Maass et al., 2015). These brain changes are sometimes associated with improvements in cognitive function, including memory and executive function (e.g., Erickson et al., 2011; Ruscheweyh et al., 2011; Weinstein et al., 2012; but see Young et al., 2015). Hence, the brain appears to have an enduring capacity for plasticity, and even modest changes in behavior can alter the size and functioning of the brain.

Prior reviews and meta-analyses have described the associations between obesity and behavioral interventions that promote neurocognitive health independently, and in parallel, from one another. This is striking since obesity and certain modifiable lifestyle behaviors (e.g., PA and energy intake) are closely linked both conceptually and physiologically. For example, obesity and PA levels are often correlated and predict many similar health outcomes (i.e., cardiovascular health). They also exert effects on similar physiological pathways and brain networks, as will be discussed further below. At the same time, there is also evidence that PA, diet, and obesity may influence different organ and disease endpoints, such as brain or cardiovascular health, through distinct pathways.

In this review, we first summarize evidence linking obesity, diet, and PA activity with brain morphology (e.g., gray and white matter volume and integrity) and function (e.g., functional activation and connectivity) across the adult lifespan. These sections are followed with a summary of the possible mechanisms of obesity and select behavioral interventions on neurocognitive health. In particular, we summarize evidence bearing on the following question: *Are associations between obesity and neurocognitive health in aging adults modifiable through behavioral intervention?*

EFFECTS OF OBESITY ON NEUROCOGNITIVE HEALTH

Obesity is a condition where there is an excess proportion of body fat in relation to lean mass, resulting from excess energy intake. Obesity status is typically assessed by measuring body mass index (BMI), which refers to the ratio of a person's weight to their height. According to the World Health Organization, a BMI of at least 30 kg/m^2 is considered obese, between 25 and 30 is considered overweight, between 18.5 and 25 is considered healthy weight, and below 18.5 is considered underweight (National Institutes of Health, 1998). However, BMI is not actually a measure of body fat, but rather is a relatively crude measure used as a proxy for body composition. The correspondence between BMI and actual body composition varies by age and gender. For instance, even when holding BMI constant, healthy women and older adults tend to have more body fat than men and younger adults, respectively (Prentice and Jebb, 2001). Therefore, BMI is a rough, and sometimes poor, approximation of adipose vs. lean tissue. Other, more accurate measures of body fat exist (e.g., central adiposity metrics) and are more predictive of negative health outcomes (Sahakyan et al., 2015), but the methods for collecting these metrics are often more costly and/or time-intensive than calculating BMI. Thus, despite the well-known limitations of BMI, many of the studies described in this review have used BMI as the primary measure of obesity in adulthood.

Obesity and Brain Health

Gray Matter

Many studies have shown that obesity (typically assessed via BMI) is associated with reduced gray matter volume in both neurologically healthy and cognitively impaired older adults. This relationship has been noted consistently in the hippocampus (Ho et al., 2010a; Raji et al., 2010; Cherbuin et al., 2015). For example, Raji et al. (2010) compared the brain volumes of 94 obese, overweight, or healthy weight adults. Compared to healthy weight individuals, the obese adults had reduced gray matter volume in several brain regions, including the hippocampus, prefrontal cortex, and other subcortical regions. The group differences remained significant, even after controlling for comorbid conditions, such as diabetes, suggesting a unique role of excess body fat to brain atrophy. The hippocampus is of particular interest for considering the health trajectories of obese older adults because it is a region supporting episodic and relational memory functions. Moreover, this region is known to be particularly sensitive to pro-inflammatory proteins, metabolic disruptions, stress, and aging (Sudheimer et al., 2014). In fact, smaller hippocampal volumes are predictive of a future Alzheimer's Disease (AD) diagnosis in cognitively healthy older adults (e.g., Elias et al., 2000).

Obesity is also inversely related to the volume of gray matter regions in other brain areas. These patterns have been reported in a number of regions including the anterior cingulate and dorsolateral prefrontal cortex, orbitofrontal cortex, hypothalamus, basal ganglia, supplementary motor area, lateral occipital cortex, cerebellum, and brainstem (Jagust et al., 2005;

Debette et al., 2010, 2014; Ho et al., 2010a; Raji et al., 2010; Walther et al., 2010; Brooks et al., 2013a; Medic et al., 2016). In one study, Medic et al. (2016) examined associations between BMI and cortical thickness in a sample of 203 adults (mean age 32 years) with no known physical or metabolic morbidities. There were no associations between BMI and global measures of brain health, such as average cortical thickness or total surface area. However, higher BMI was associated with reduced gray matter volume in a large cluster in the ventromedial prefrontal cortex, extending into the anterior cingulate and frontopolar cortex, as well as with a cluster in the lateral occipital cortex. The anterior frontal regions identified in this work support diverse behaviors such as reward and salience detection, autonomic nervous system control, decision making, and executive functioning. Posterior occipital areas are critical for functions such as visual attention. Thus, excess adiposity is associated with cortical thinning in brain regions underlying diverse cognitive functions, even in a sample free of the various comorbid health conditions associated with obesity. Of course, one caveat of the Medic study and others is that these studies are correlational and/or cross-sectional nature. The causal associations between brain health and obesity are difficult to determine because it is conceivable that degeneration of regions supporting visual attention and feeding behavior could be either a cause or consequence of overeating. Nonetheless, it is clear from this literature that obesity is consistently associated with lower gray matter volume in many cortical and subcortical brain areas.

Yet, not all studies have shown that obesity is associated with reduced brain volume. For example, Taki et al. (2008) reported both positive and negative correlations between BMI and gray matter volume in a sample of 1,428 middle-aged Japanese adults. BMI was negatively associated with total gray matter volume, as well as with volume in the medial temporal, occipital, and frontal lobes of older men (but not women). However, higher BMI was also associated with *greater* volume in other regions of the frontal, temporal, and cerebellar cortices in the same male sample. These findings are not consistent with the majority of other studies and could be explained by a number of factors, including differences across studies in sample size, analytical approach, or presence of comorbidities (e.g., diabetes).

White Matter

There is mixed evidence regarding the direction of the associations between obesity and white matter volume. For example, while many studies find that greater BMI is associated with lower white matter volume in many subcortical and cortical regions (Ho et al., 2010a,b; Raji et al., 2010; Driscoll et al., 2012; van Bloemendaal et al., 2016), other studies fail to find a relationship between BMI and white matter volume (Gunstad et al., 2008; Soreca et al., 2009; Debette et al., 2010), and still others have reported a positive relationship (Pannacciulli et al., 2006).

Positive associations between obesity and white matter volume have been reported in the basal ganglia, frontal lobes, medial temporal lobe, precuneus, cerebellum, brainstem, and parts of the occipital cortex (Pannacciulli et al., 2006; Haltia et al., 2007; Walther et al., 2010). Although it is possible that these are merely spurious positive correlations, losing weight through dietary changes reduces white matter volume in similar regions (Haltia et al., 2007). For example, in a group of 30 obese and 16 lean middle-aged adults (mean age = 37 years), obese adults had greater white matter volume in the frontal lobes, fusiform gyrus, brainstem, and cerebellum than their lean peers. A subset of the obese group ($n = 16$) then underwent a 6-week, calorie restrictive diet that resulted in a reduction of white matter volume throughout some of the regions that had previously been larger in the obese compared to lean adults. These experimental data indicate that the positive relationships between white matter volume and adiposity in obese individuals may not be spurious since it can be experimentally reduced with only 6 weeks of dieting.

One possible explanation for the paradoxical reduction in white matter volume following caloric restriction is that morphometric analyses of white matter might be extracting information about local inflammation in addition to the integrity and volume of the axonal sheaths themselves. For example, both rodent and human studies find evidence of reactive gliosis in the hypothalamus, an area critical for body weight maintenance. In mice, a high fat diet induced hypothalamic inflammation both transiently and chronically, and obese humans exhibited increased gliosis, which was detectable on MRI images of the hypothalamus (Thaler et al., 2012). If morphometric measures of white matter volume are detecting glial cell density in the lipid-based myelin sheath, then a higher volume could indicate poorer white matter health (via more inflammation).

Diffusion tensor imaging (DTI) is a newer, more granular method of assessing white matter, which has led to a more consistent picture of obesity and white matter associations. The structural integrity of white matter tracts connecting various brain regions is generally reduced in obesity (e.g., Mueller et al., 2011; Verstynen et al., 2012; van Bloemendaal et al., 2016). Fractional Anisotropy (FA) is the most common measure of white matter integrity and indicates the shape of water diffusion in a given voxel. FA is calculated by taking the ratio of axial diffusivity (DA; along the axon) to radial diffusivity (DR; perpendicular to the axon). Lower FA can result from either a drop in DA (indicating less diffusion down the length of the axon) or an increase in DR (indicating more diffusion, or "leaking," out of the axon).

Recent DTI work has shown that obesity-linked decreases in FA are due to both an increase in DR throughout the brain, as well as a decrease in DA (Mueller et al., 2011; Verstynen et al., 2012). For example, in a sample of 28 neurologically healthy adults (aged 18–69 years), Verstynen et al. (2012) demonstrated a consistent negative relationship between BMI and FA across diffuse WM pathways. Then, by controlling for overall water diffusion, they demonstrated that the decreases in FA were attributable to differences in both DA and DR (i.e., decreased DA and increased DR). Another study reported a similar association between increasing BMI and decreasing FA and, further, showed that increased DR accounted for a greater proportion of the difference in FA for females compared to males (Mueller et al., 2011). Across both sexes, obesity-related decreases in FA are most consistently observed in tracts connecting the frontal and

temporal lobes, as well as those connecting limbic regions (for review see Kullmann et al., 2015). Interestingly, such a pattern of increased DR is also associated with demyelination in mouse models of inflammatory disorders, such as Multiple Sclerosis (Klawiter et al., 2011). Thus, the systemic increases in circulating inflammatory cytokines reported in obesity may contribute to the increases in DR signal (and resulting decreases in FA) observed in MRI studies of white matter integrity in obese adults (Song et al., 2005; Klawiter et al., 2011).

Demyelination also compromises the health of the remaining tissue within white matter tracts. White matter hyperintensities (WMH) are lesions in white matter, which are readily visible in MRI and could be a sign of demyelination processes. These lesions are observed more often in groups with ischemic and cardiovascular disease, conditions highly prevalent in obesity (Chimowitz et al., 1989). In addition, WMHs are positively associated with BMI (Jagust et al., 2005; Ho et al., 2010a) and visceral adiposity (Pasha et al., 2016) in cognitively normal middle aged and older adults. For example, in a sample of 126 middle aged adults (aged 40–62), Pasha et al. (2016) demonstrated across several objective measures of adiposity—e.g., waist circumference, and percent body fat—that higher body fat is associated with a greater WMH burden throughout the brain. Thus, multiple measures of both obesity and white matter provide converging evidence that excess adiposity is associated with poorer health and integrity of white matter. The fact that the participants in many of these studies are cognitively normal suggests that these associations may precede any detectable cognitive changes in these groups.

Together, these studies in aging adults suggest that obesity is associated with reduced health and integrity of gray and white matter in the brain. Given that normal aging is also associated with decreased gray and white matter integrity and increased WMH burden (Bennett et al., 2010; Raz et al., 2012), these findings suggest that obesity may accelerate the characteristic features of brain aging. However, some notable caveats of the studies described above are that they are predominantly cross-sectional in nature and have small-to-modest sample sizes. Thus, although they have provided provocative and somewhat consistent associations between obesity and brain health, they are ultimately limited in their ability to draw causal associations that are generalizable to larger populations. In particular, there are many conditions that often co-exist with obesity (e.g., diabetes, hypertension) that could be confounding or mediating these associations (e.g., Verstynen et al., 2013; Onyewuenyi et al., 2014). It is only with well-designed interventions or prospective longitudinal studies that the direction and temporality of these associations can be determined.

Functional Brain Activation

Functional neuroimaging studies comparing obese vs. healthy-weight individuals have identified obesity-related abnormalities in a wide range of brain areas. Most of these studies to date have been in younger and/or middle aged adults and have examined brain responses to food-related cues. In a systematic review, Pursey et al. (2014) reviewed 60 studies of obesity including functional magnetic resonance imaging (fMRI) outcomes. Compared to healthy-weight controls, obese adults consistently exhibit increased activation to food compared to non-food items in limbic and orbitofrontal brain regions associated with decision making, satiety, motivation, and reward (Pursey et al., 2014). While most studies have reported *hyper*activation of various brain regions (e.g., orbitofrontal cortex), there are also some regions in which *hypo*activation has been observed in a different set of reward-related (e.g., striatum) and cognitive control-related (e.g., dorsolateral prefrontal cortex) regions, suggesting general dysfunction in reward circuits in obesity with some regions showing greater and others less activation compared to healthy-weight individuals (Brooks et al., 2013b). Notably, functional activation differences between obese and healthy-weight groups are typically largest in response to high calorie food items, and have also been shown to scale with individual differences in BMI (Rothemund et al., 2007; Grosshans et al., 2012; Martens et al., 2013). This pattern suggests that obesity is associated with altered functional brain activation compared to healthy-weight counterparts, particularly in the context of food-related stimuli.

Consistent differences in brain activation of obese compared to healthy weight older adults have been reported as well, with some notable divergences from the pattern seen in younger groups. For example, Green et al. (2011) compared older and younger adults' functional responses to pleasant (sucrose) vs. aversive (caffeine) taste stimuli. In both age groups, BMI was negatively associated with activation of the caudate, a region of the striatum involved in motivation and reward during pleasant stimuli. However, in older adults BMI was also negatively associated with activation of the nucleus accumbens (NA), another central reward-related region. The NA is a key region initiating the reinforcing effects of addictive substances, such as drugs and highly palatable foods, as it receives dense innervation of dopamine producing neurons of the ventral tegmental area of the mesencephalon. Thus, the hypoactivation of certain reward-related regions in response to pleasant taste stimuli in obese older adults, coupled with the fact that dopamine declines in normal aging (Volkow et al., 2000), may indicate that older adults are particularly susceptible to food-related reward insensitivity and weight gain.

There is also evidence for aberrant brain function in obese adults, even outside of the context of food. In a fMRI study by Gonzales et al. (2010), cognitively normal obese and overweight middle-aged adults were scanned while completing a two-back working memory task in which participants indicated when a letter presented was the same as the one occurring two trials back. The authors then examined the functional activation across obese and non-obese groups in a set of *a priori* task-relevant regions. The obese group showed significantly lower activation in the right parietal cortex, a region involved in executive functioning, compared to the non-obese group, as well as worse performance on the working memory task. Further, both BMI and parietal activation covaried with individual differences in insulin sensitivity (assessed via blood draw by comparing levels of fasting glucose and insulin), and insulin insensitivity statistically mediated the relationship between BMI and parietal activation. Other groups have shown similar obesity-related hypoactivation using fMRI and peripheral markers of metabolic health and

have also shown that obesity-related impairments in cognitive performance are linked to changes in neuronal viability and metabolism (Gonzales et al., 2010, 2012; Haley et al., 2013). These findings add to a growing body of literature demonstrating that obesity is associated with decreases in brain and cognitive health, which can be linked to mechanisms involving peripheral and central metabolic dysfunction.

Obesity and Cognitive Function

As might be predicted given the negative links between obesity and the various aspects of brain morphology and function described above, obese adults generally perform more poorly on cognitive tasks compared to their healthy weight counterparts. Cognitive functioning in obesity is particularly impaired in the domains of executive functioning and memory. A recent review examined the relationship between obesity and cognitive function across a variety of cognitive domains during different developmental life stages (Smith et al., 2011). Across 15 cross-sectional and four prospective studies, in adults aged 19–65, greater body mass was associated with poorer performance on measures of global cognitive functioning, semantic and episodic memory, motor/processing speed, and, most consistently, executive function. Indeed, these studies were remarkably consistent, with 14 of the cross-sectional studies and three of the prospective studies showing negative associations. The remaining two studies were conducted in older adults aged 72 years or older and reported a positive association between BMI and cognitive functioning, which will be discussed further below.

There is also evidence that more time spent in an obese state has a cumulative negative effect on cognitive performance in adults (Sabia et al., 2009). A meta-analysis of 16 prospective studies concluded that midlife obesity, as defined by BMI, significantly increased the risk of developing dementia as compared to being normal weight in midlife (Anstey et al., 2011). Being underweight is also associated with dementia risk in late life (Beydoun et al., 2008). Maintenance of a healthy weight throughout adulthood (not simply *lower* weight) may therefore represent a critical component in preventing late life cognitive impairment.

Mechanisms of Obesity on Neurocognitive Health

The relationships between obesity and peripheral health can be linked to those found in the brain. In particular, excess adipose tissue has negative vascular and metabolic consequences on the body, including increased risk for atherosclerotic heart disease and Type II diabetes (Sharma and Chetty, 2005). Moreover, declines in vascular health lead to executive cognitive dysfunction (e.g., Forman et al., 2008), further supporting the potential role of vascular mechanisms in obesity-cognition associations. One major pathway by which obesity, especially central adiposity, can engender risk for heart disease is through associations with elevated blood pressure (e.g., Krauss et al., 1998). The relationship between heart disease and blood pressure is thought to occur because being overweight or obese is associated with activation of the renin-angiotensin-aldosterone system, elevated sympathetic nervous system activity, renal sodium retention, and increased levels of procoagulants in systemic circulation. These physiological changes can combine to increase cardiac output, endothelial dysfunction, and vessel stiffening (atherosclerosis and artiolosclerosis)—likely all consequences of the increased blood volume needed to maintain excess adipose tissue (e.g., Pausova, 2006).

Obesity can also lead to peripheral insulin resistance and hyperinsulemia, both conditions leading to increased circulating glucose levels. Importantly, insulin resistance and hyperinsulemia affect kidney function in a manner that increases sodium reabsorption and, consequently, blood pressure (Wickman and Kramer, 2013). An individual presenting with all of the above conditions—excess adiposity (particularly in central regions), elevated blood pressure, and glucose/lipid dysregulation—is considered to have metabolic syndrome (MeS; Grundy et al., 2004). Several studies have shown that the risk for MeS increases with age, suggesting that understanding its widespread health consequences in middle-aged and older adults will be important for future health care planning (Ford et al., 2002; Ravaglia et al., 2006; Hildrum et al., 2007). Most relevant to the present review, this particular clustering of diabetes mellitus and cardiovascular risk factors, referred to as MeS, has been linked to cognitive impairment, including dementia, as well as functional and structural changes in brain systems important for memory and higher order cognitive functions (Yaffe et al., 2003; Yaffe, 2007; Hassenstab et al., 2010; Yates et al., 2012).

Obesity has also been linked to central insulin resistance. That is, individuals with peripheral insulin resistance often also show reduced insulin sensitivity in the brain, and this can negatively impact cognitive functioning (Heni et al., 2015). Central insulin resistence has negative consequences on hippocampal-dependent and executive functions since the brain regions that support these functions (e.g., medial temporal and dorsolateral prefrontal cortices) have high concentrations of insulin receptors (Blázquez et al., 2014; Mainardi et al., 2015). Research in rodent models of obesity and Type II Diabetes support this idea, demonstrating that learning and memory functions are selectively impaired in insulin resistant rodents compard to healthy controls (Biessels and Reagan, 2015). In humans, regions essential for memory, including the hippocampus and dorsolateral prefrontal cortex, show reduced activation in obese compared to healthy-weight participants, and the degree of insulin resistance is negatively correlated with memory performance (Cheke et al., 2017). Together, the emerging research from both animals and humans converge on the idea that there are detrimental effects on brain insulin signaling as a result of obesity which are closely tied to peripheral metabolic dysfunction.

Compounding the negative effects of these metabolic conditions, excess adipose tissue secretes proteins, called adipokines, that can change the functioning of nearby tissues, signal the central nervous system, and ultimately have detrimental effects on brain health through inflammatory pathways (Mohamed-Ali et al., 1997; Xu et al., 2003). Circulating levels of inflammatory mediators covary positively with adiposity and systemic metabolic dysregulation (Ouchi et al., 2011). Converging animal and human evidence suggests that systemic inflammation plays a role in neurocognitive function by crossing

the blood brain barrier and stimulating the production of central proinflammatory cytokines in discrete brain regions (Schöbitz et al., 1994; Vitkovic et al., 2000; Takeda et al., 2014). These central inflammatory mechanisms subsequently result in hippocampal neurodegeneration, impairment in memory function, and even heightened risk for dementia (Bellinger et al., 1995; Takeda et al., 2014). Further, cross-sectional evidence shows that among midlife adults, higher circulating markers of inflammation are associated with higher BMI, poorer working memory and executive function, and lower hippocampal volume (Marsland et al., 2006, 2008, 2015; Gianaros et al., 2015). Thus, peripheral inflammation—and interwoven metabolic dysregulation—is likely an important mechanism linking obesity to the neurocognitive outcomes discussed above.

Interim Summary

From the literature reviewed above it is clear that obesity is generally associated with reduced brain structure and function throughout the adult lifespan, and these associations likely have negative consequences for cognitive function. Physiological pathways, including inflammation, blood pressure, insulin resistance, and other cardiometabolic pathways, are also linked to brain structure and function. We therefore speculate that the effects of obesity on the more macroscopic aspects of brain and cognitive health may be mediated by these physiological systems. The critical question, however, is what can be done to reverse the negative consequences of obesity, or at least stall their progression.

Unfortunately, we still have a poor understanding of the broader behaviors driving the obesity epidemic and the interventions required to reverse this trend. For example, it is not clear to what extent obesity is attributable to decreases in energy expenditure (i.e., PA) vs. increases in caloric intake. This is a potentially important distinction as it might influence the effectiveness of certain types of interventions over others. In the following sections, we examine how PA interventions, as well as those that change body composition without targeting increased energy expenditure (e.g., dieting) may act through both overlapping and independent pathways to improve peripheral, brain, and cognitive health in obese adults.

EFFECTS OF BEHAVIORAL WEIGHT-LOSS INTERVENTIONS ON NEUROCOGNITIVE HEALTH

If obesity is causally related to cognitive decline, then a reduction of body fat may attenuate obesity-related cognitive deficits. One well-known strategy to lose weight is via caloric restriction—i.e., dieting. The literature on diet-induced weight loss and cognition is still in its infancy, but preliminary evidence supports that weight-loss through caloric restriction can change aspects of cognitive functioning (**Table 1**). A meta-analysis examined seven randomized trials and five non-randomized studies of intentional weight loss in overweight and obese adults who were otherwise healthy (Siervo et al., 2011). While somewhat variable across studies, diet-induced weight loss improved attention and executive control. These effects were moderated by initial BMI, such that the strongest effects occurred in the most obese individuals, while overweight individuals showed no change in cognitive performance. Diet-induced weight loss also had a modest, marginally significant effect on memory function across the studies, but this trend disappeared when only studies including a control group were analyzed. While this meta-analysis examined the impact of diet-induced weight loss on cognitive performance, it is possible that dieting individuals also increased their PA levels in concert with healthier eating habits. Since PA is often prescribed in addition to diet for effective weight loss, it is unclear from these studies whether increased PA levels moderate (or mediate) fat loss-associated benefits on cognitive health.

Although limited, there is also evidence that dieting may change brain structure and functioning. Jakobsdottir et al. (2016) conducted a prospective dietary intervention in 18 obese, but otherwise healthy, post-menopausal women (mean age 57 years; mean BMI = 32.2 kg/m^2). The women were placed on a calorie-restrictive diet for 4 weeks and lost an average of 4.8% of their body weight. Participants completed a visual food cue task during functional magnetic resonance imaging (fMRI) before and after the caloric restriction intervention while in a fasting state. Compared to the baseline scan, following the intervention women showed less activation in response to food cues in some brain regions supporting motivation, salience and reward processing (e.g., amygdala) and more activation in other brain regions, including those supporting cognitive control (e.g., prefrontal cortex), suggesting that the functioning of cognitive control networks increases following dietary restriction. Since the amygdala is involved in motivational functions such as food craving, the authors suggested that the intervention modified signaling of satiety, perhaps via increased cognitive control signaling. These activation changes were also correlated with reductions in peripheral metabolic health markers (e.g., inflammatory cytokines, leptin), supporting the potential mediating role of peripheral systems on brain health. Unfortunately, while obesity-related comorbidities were controlled for (i.e., because all obese participants were otherwise physically healthy at baseline) participants' PA levels were not assessed, so it is possible that changes in PA may contribute to the reported effects (e.g., if participants also increased their PA during the intervention). Further, the existing study had a very small sample size (N = 18). Thus, there was not sufficient power to examine the potential mediating or moderating role of the peripheral metabolic biomarkers assessed. Despite these limitations, the findings reported in this initial interventional study support that diet-induced weight loss increases functioning in brain regions underlying executive control and decreases those implicated in food-related reward responses. Cross-sectional studies comparing obese to normal weight control groups support this conclusion, showing similar patterns of increased activation (McCaffery et al., 2009) and increased gray matter volume (Hassenstab et al., 2012) in cognitive control networks in healthy weight compared to obese groups. Given the paucity of studies in this area, future research is needed in order to further clarify the

TABLE 1 | Inervention studies showing effects of PA and/or caloric restriction on neurocognitive health in adults.

References	Type/Duration intervention	PA, Diet, or Both	Age group	Results
Colcombe et al., 2004	6-month PA intervention	PA	Older adults	Greater activation in prefrontal, parietal, and anterior cingulate cortex, and well as increased cognitive control performance in higher aerobically fit (study 1) or aerobically trained (study 2) individuals.
Colcombe et al., 2006	6-month aerobic exercise trial	PA	Older adults	Aerobic exercise increased gray matter in the right middle frontal gyrus, left superior temporal lobe, and bilateral regions of the anterior cingulate and supplementary motor area, as well as in anterior white matter tracts.
Erickson et al., 2011	1-year aerobic walking intervention	PA	Older adults	Volume of the anterior hippocampus and memory performance increased following a 12-month aerobic exercise intervention.
Espeland et al., 2016	10-year "lifestyle" intervention involving PA and diet	Both	Older adults	Mean white matter hyperintensity volume was 28% lower among lifestyle intervention participants compared with those receiving diabetes support and education. The lifstyle intervention group also exhbited smaller ventricle volume compared to the education control group.
Haltia et al., 2007	6-week dietary restriction	Diet	Young-middle aged adults	White matter volumes were greater in obese compared to lean subjects in several basal brain regions. Positive correlation between white matter volume in basal brain structures and waist to hip ratio in obese individuals. The detected white matter expansion was partially reversed by dieting. Regional gray matter volumes did not differ significantly in obese and lean subjects, and dieting did not affect gray matter.
Honea et al., 2016	3-month intervention involving caloric restriction, increased PA, and behavioral modification	Both	Middle aged adults	Percent weight loss was positively correlated with baseline gray matter volume in right parahippocampal and orbitofrontal gyri in sccessful obese dieters. Successful dieters showed greater volume loss in the left precentral gyrus and the insula compared with unsuccessful dieters. A negative correlation was found between weight loss and pre-post-intervention volume change in left prefrontal regions.
Jakobsdottir et al., 2016	8 week diet (2 week isocaloric, 4 weeks caloric retriction, 2 weeks isocaloric); prospective intervention (no control)	Diet	Older adults	Activity in the amygdala and correlations between peripheral metabolic factors with activity in brain areas involved in food reward processing differ substantially before and after weight loss.
Krogh et al., 2014	3-month aerobic PA intervention	PA	Older adults	No Group × Time interactions (potentially due to poor adherence in intervention group). However, positive association between change in hippocampal volume and changes in memory.
Legget et al., 2016	6-month aerobic walking program	PA	Obese Young-middle aged adults	PA-related changes in communication between large-scale brain networks and integrative netowrk "hub" regions.
Maass et al., 2015	3-month aerobic PA intervention	PA	Older adults	Hippocampal volume, perfusion, and memory increases following a 3-month aerobic exercise intervention; Changes in perfusion statistically mediate relationship between volume and memory.
McFadden et al., 2013	6-month aerobic exercise intervention	PA	Middle aged adults	The intervention was associated with a reduction in DMN activity in the precuneus, which was associated with greater fat mass loss.
Niemann et al., 2014	12-month PA intervention	PA	Older adults	Increased hippocampal volume in both PA and control (coordinative training) groups.
Pajonk et al., 2010	3-month aerobic PA intervention	PA	Young-middle aged adults (schizophrenic patients)	Hippocampal volume and short-term memory improve following 3-month aerobic exercise intervention; Changes in volume correlate with changes in memory.
Paolini et al., 2015	6-month intensive weight loss RCT	Diet	Middle-older adults	After accounting for known correlates of weight loss (e.g., baseline weight, age, sex, and self-regulatory efficacy), greater global effiency in the HBN-A was associated with an additional 19% of the variance in weight loss.
Prehn et al., 2017	12-week caloric restriction	Diet	Older adults	In the caloric restriction group, found improved recognition memory, paralleled by increased gray matter volume in inferior frontal gyrus and hippocampus, and augmented hippocampal resting-state functional connectivity to parietal areas.
Rosano et al., 2010	12-month PA intervention	PA	Older adults	2 years after conclusion of intervention, PA group showed higher processing speed scores and significantly greater activation in processing-speed-related brain regions.
Rosano et al., 2016	24-month PA intervention	PA	Older adults	Greater hippocampal volume in PA compared to control group following moderate intensity exercise intervention, even after controlling for dementia-related covariates.

(Continued)

TABLE 1 | Continued

References	Type/Duration intervention	PA, Diet, or Both	Age group	Results
Ruscheweyh et al., 2011	6-month PA intervention	PA	Older adults	Positive association between changes in PA and episodic memory following a 6-month mixed-intensity intervention no longer significant after accounting for the variance associated with change in anterior cingulate gray matter volume.
ten Brinke et al., 2015	6-month aerobic exercise intervention	PA	Older adults	Hippocampal volume increases following 6-month aerobic exercise intervention. Changes in volume negatively associated with changes in short-term memory.
Voss et al., 2010	6-month aerobic PA intervention	PA	Older adults	Connectivity of large-scale brain networks and executive functioning improve following 6-month aerobic exercise intervention; changes in connectivity correlate with changes in executive functioning.
Voss et al., 2013	1-year aerobic walking intervention	PA	Older adults	Overall, no significant white matter changes, but percent change in VO2 positively predicted percent change in white matter FA in prefrontal, parietal, and temporal regions in the exercise group; FA did not relate to cognition.
Voss et al., 2013	12-month PA intervention	PA	Older adults	Improved fitness is associated with changes in prefrontal and temporal white matter integrity following a 12-month aerobic exercise intervention; no changes in short-term memory.

For brevity, only interventions including brain outcomes are included; numerous interventions have shown cognitive (only) outcomes. FA, fractional anisotropy; PA, physical activity; VO_2, maximal volume oxygen consumption.

complex relationships between adiposity, cognitive control, and reward.

Interestingly, brain morphometry in cognitive control-related regions also increases following weight *gain* in individuals recovering from anorexia nervosa, a condition in which individuals are severely underweight (Seitz et al., 2013, 2016). This work serves to further bolster findings from dietary weight loss interventions in obesity because it suggests that the brain morphology differences observed across normal and overweight/underweight individuals are linked to unhealthy (either too high or too low) levels of adiposity rather than to another, unknown variable covarying with weight status.

Mechanisms of Caloric Restriction on Neurocognitive Health

Although the mechanisms by which caloric restriction leads to changes in neurocognitive health in humans are not well-understood, it has become increasingly clear that proteins involved in metabolic regulation are likely key mediators of diet-induced neurocogniitve plasticity. This is because during an energetic challenge, the body switches from using liver glycogen to using adipose-derived fatty acids (Longo and Mattson, 2014). A host of metabolic benefits arise from this switch. For example, insulin sensitivity in the hippocampus increases following a period of caloric restriction (with or without exercise) in obese young and middle-aged adults (Larson-Meyer et al., 2006; Weickert, 2012), and intermittent fasting improves cardiovascular and hormonal responses to stress in rats (Wan et al., 2003). Fasting has also been shown to improve learning and memory consolidation in rodent models (Fontán-Lozano et al., 2007). However, more research in both animals and humans is needed to clarify the underlying cellular and molecular mechanisms of caloric restriction on brain health outcomes.

Interim Summary

Although limited, there is evidence that dietary interventions can improve cognition and brain functioning in areas that overlap with those showing associations with obesity. This pattern of results suggests that PA may not be a necessary component to interventions designed to reverse obesity-related neurocognitive dysfunction. However, none of the studies of dietary interventions to date have controlled for PA levels, and obesity-related health comorbidities have not been consistently accounted for, making it impossible to determine whether the effects attributed to diet are moderated or mediated by PA or other health-related factors. This possibility needs to be examined in the context of future dietary intervention studies.

In addition to dietary interventions, there are other ways to change body composition. PA is commonly prescribed alongside weight loss interventions for effective weight management. It can be difficult to disentangle the overlapping vs. independent effects of PA compared to other weight-loss strategies on neurocognitive health. However, doing so is important for increasing our understanding of which intervention components are most critical for promoting and preserving brain health.

EFFECTS OF PHYSICAL ACTIVITY ON NEUROCOGNITIVE HEALTH

As shown in **Table 1**, the majority of behavioral intervention research to date has focused on modifying physical activity (PA) levels to preserve neurocognitive health in older adulthood. PA is an umbrella term for bodily movement requiring energy (Caspersen et al., 1985). PA interventions are particularly attractive for promoting and preserving brain health in adulthood as they are low cost and widely accessible. PA has even been prescribed by some as the key ingredient for reversing the obesity trend, inadvertently perpetuating a common public

misconception that you can "out run" poor dietary behaviors (Donnelly et al., 2009). However, there is also evidence that PA is not particularly effective compared to other types of interventions (e.g., dieting) at decreasing weight, especially in the dosage included in most intervention studies (e.g., see Wing, 1999; Donnelly et al., 2009). Instead, PA interventions more reliably change body composition (i.e., increase lean muscle mass and decrease adiposity), which can help prevent weight gain (Jakicic et al., 2008; Jakicic, 2009). These characteristics make PA interventions an interesting test bed in which to tease apart the key ingredients of interventions designed to mitigate the neurocognitive consequences of obesity.

In typical aerobic PA interventions, relatively inactive adults (typically older adults) are assigned to either an aerobic PA group or non-aerobic control group. Cognitive and brain functioning is assessed prior to and following the intervention period, which lasts 6–12 months in most PA studies. We review the evidence from aerobic PA interventions in the following sections and compare these effects, when possible, to the effects of intentional energy restriction (i.e., dieting). By doing this, we aim to get a better sense of the effects unique to aerobic PA (hereafter referred to as PA) vs. those that can be achieved from other interventions that change body composition without influencing cardiovascular health status.

PA and Brain Health

Gray Matter

Intervention studies that randomly assign adults to either receive PA or a control condition find that increased engagement in PA can alter the size and function of several different brain areas. For example, in one study, 59 older adults were randomly assigned to either a moderate intensity walking group or to a stretching and toning control group for 6-months (Colcombe et al., 2006). After the intervention, the aerobic exercise group showed increased gray matter volume in the frontal cortex (anterior cingulate cortex, middle frontal gyrus, and supplementary motor area), as well as in anterior callosal white matter tracts (also see Ruscheweyh et al., 2011). In contrast, the control group showed volumetric decreases that were consistent with normal aging. Similar effects were also found for a 1-year exercise intervention when examining the size of the hippocampus. In a sample of healthy older adults (mean age ∼66 years), walkers showed a 2% increase in hippocampal volume as compared to their stretching and toning peers, who lost ∼1.4% of their hippocampal volumes over this same period (Erickson et al., 2011). These exercise effects were relatively specific to the hippocampus in that the caudate nucleus and thalamus volumes were unaffected by the aerobic exercise intervention. A similar increase in hippocampal volume was recently replicated in a sample of 86 healthy female older adults following a 6-month aerobic PA intervention (ten Brinke et al., 2015), as well as following a similar 24-month intervention in 26 older adults with impaired mobility and cardiovascular health conditions (Rosano et al., 2016). Increases in hippocampal volume were also observed in a separate sample of 96 older adults following 12-months of aerobic or coordination training (Niemann et al., 2014). Thus, in as little as 6-months, PA can increase regional gray matter volume in adults, especially in the hippocampus and frontal cortex. Although not the focus of the present review, results of cross-sectional and correlational studies relating gray matter volume to PA and/or cardiovascular fitness generally support the findings from randomized PA interventions (e.g., see Colcombe et al., 2006; Hillman et al., 2008; Hayes et al., 2013; Erickson et al., 2014). Therefore, PA appears to be a promising method for increasing gray matter volume in adulthood, particularly in regions in which obesity and aging are associated with decreased gray matter volume.

White Matter

White matter volume and integrity have been less often studied as outcome variables from randomized PA interventions. However, recent evidence supports that white matter integrity increases following experimental increases in cardiovascular fitness. In the first DTI study to examine changes in white matter integrity in the context of a PA intervention, Voss et al. (2013) evaluated the effects of a 12-month aerobic exercise program in 70 healthy older adults in which hippocampal gray matter had been shown to increase post-training (Erickson et al., 2011). Participants were randomly assigned to either an aerobic walking or toning/stretching (control) group and participated in their respective activities for 40 min per day, 3 days per week. Intervention-induced changes in cardiovascular fitness were associated with increases in FA in tracts connecting temporal and prefrontal brain regions. Although interventional evidence of PA-induced changes in white matter integrity is limited, there is a wealth of cross-sectional and correlational evidence supporting a link between these two variables (e.g., see Erickson and Kramer, 2009; Bherer et al., 2013a; Oberlin et al., 2016). Thus, as with the gray matter findings above, the interventional and cross-sectional findings converge on the idea that white matter integrity may improve with PA and increasing fitness.

There is also evidence that PA interventions can decrease the progression of WMH burden in adults. In a recent study, Espeland et al. (2016) evaluated the effects of a 10-year weight loss intervention involving both diet and physical activity on WMHs in a subset of 319 older adults from the Look Ahead trial, a randomized controlled trial of PA in older adults with Type II diabetes. All participants were overweight or obese and had diabetes at enrollment. At year 10, mean WMH volume was 28% lower in older adults who had participated in the intervention compared to a control group who had received educational classes on the same topics. These findings suggest that a long-term intervention involving PA may delay the progression of WMH burden associated with obesity and comorbid conditions, such as diabetes. However, it is not possible to disentangle the contribution of PA from those of diet in the effects observed, as the intervention involved both PA and nutritional counseling. Similarly, it is not possible to link *change* in WMH burden to PA, as baseline WMH measurements were not available. Nonetheless, the randomized controlled design of this study makes it less likely that the group difference in WMH burden observed were due to preexisting differences between the intervention and control groups.

In the case of WMH, cross-sectional and longitudinal studies of WMH do not provide any additional clarity regarding

whether PA slows their progression in the brain. A recent meta-analysis examined the association between physical activity and WMH in individuals without advanced disease associated with WMH, such as stroke, depression, and dementia (Torres et al., 2015). Across 12 studies using WMH as an outcome variable, 6 studies reported that more PA was associated with less WMH burden in older adults, while the other 6 reported no association. The studies were more likely to find an association between PA and WMH if they used a longitudinal design, took PA across the lifespan into consideration (i.e. as opposed to only assessing PA at one time point), used a slightly younger older adult sample (mean age 68.5 vs. 72.8), used objective measures of PA (i.e., as opposed to self report), and performed multivariate analyses to control for risk factors associated with WMH. Thus, the null effects found in some studies examining the relationship between PA and WMH could be the result of design or analytical limitations, rather than a true null effect. Further, few PA studies have taken potential confounders, such as BMI and/or adiposity or obesity-related comorbid conditions into consideration. More research is therefore needed in this area before firm conclusions about a causal relationship between PA and WMH, and whether PA can reduce WMH burden in the same regions in which WMHs increase with obesity.

Functional Brain Activation

PA-related changes in brain function have been examined in the context of several PA interventions (e.g., Voss et al., 2010; Kamijo et al., 2011; Chaddock-Heyman et al., 2013; Hillman et al., 2014; Krafft et al., 2014). Unlike randomized intervention studies examining structural outcomes, most RCTs including functional outcomes have focused on changes in prefrontal cortex functioning rather than in the hippocampus. For example, 2 years after completing a 12-month aerobic PA intervention, a subsample of older adults who had continued to adhere to the intervention showed increased activation in bilateral prefrontal regions supporting executive control compared to those who has been in the control group (Rosano et al., 2010). Since bilateral activation in older adults could be compensatory (e.g., Cabeza, 2002), these results suggest that PA may lead to behaviorally relevant changes in the allocation of neural resources. These findings also suggest that the functional brain changes observed following PA interventions are sustained, even years after the termination of the intervention.

Functional connectivity between brain regions has also been shown to change in adults following PA interventions. Using fMRI, Voss et al. (2010) showed that a 12-month walking intervention increased functional connectivity among regions within two large-scale brain networks in older adults: The default mode and the frontal executive networks (FEN). The increased functional connectivity in the FEN, a network that includes several prefrontal brain regions, was associated with improvements in executive control performance. A seminal study by Colcombe et al. (2004) reported similar findings in the functioning and recruitment of the FEN following a shorter, 6-month exercise intervention in older adults, supporting the claim that changes to large scale brain networks may occur relatively soon after the commencement of exercise training. Since large-scale brain networks are known to become less efficient and less flexible with age, these results suggest that exercise may exert more global effects on the efficiency and flexibility in which networks of brain regions interact in older adults, leading to preserved cognitive performance.

PA and Cognitive Function

The effects of PA on cognitive functioning are summarized extensively elsewhere (e.g., Cotman and Berchtold, 2007; Kramer and Erickson, 2007; Laitman and John, 2015), and so we only provide a summary of the cognitive effects here. The majority of research on PA and cognition focuses on whether this behavior can improve late-life, as opposed to midlife, cognitive performance. In a meta-analysis of 18 randomized PA interventions with older adults (ages 55–80), those involving aerobic PA training showed significant improvements on tasks of visuospatial processing, learning and memory, processing speed, and executive function when compared to non-aerobic control groups (Colcombe and Kramer, 2003).

While many domains of cognitive performance have been shown to improve with PA exposure, executive function tasks typically exhibit the largest and most consistent benefits (Colcombe and Kramer, 2003; Deary et al., 2006). Executive control is typically the first cognitive domain to show age-related decline and is also a cognitive domain in which obese adults are especially impaired. Therefore, the fact that executive functions are especially sensitive to the effects of PA suggests that PA interventions may be able to preserve and even enhance functioning in cognitive domains that exhibit impairments in both obesity and aging. This might make PA interventions particularly suitable for altering the course of brain function in obese adults. However, not all studies have reported significant changes in cognitive functioning following PA interventions (e.g., Sink et al., 2015; Young et al., 2015), thus the critical components of successful PA interventions (e.g., dosage, frequency, and duration) are still unknown.

Mechanisms of PA on Neurocognitive Health

As with obesity, to understand the effects of PA on the more macroscopic neurocognitive outcomes discussed above, we again turn to peripheral processes. Regular PA confers protection against cardiovascular disease, Type 2 diabetes mellitus, and hypertension (e.g., Espeland, 2007; Jackson et al., 2014; Soares-Miranda et al., 2016). As mentioned above, cardiometabolic disorders are also associated with chronic systemic inflammation, as well as peripheral and central insulin resistance. One proposed mechanism of PA on the brain is through the reduction in systemic inflammation. PA interventions reduce pro-inflammatory and increase anti-inflammatory cytokines, and they may help to protect against chronic low-grade systemic inflammation (Petersen and Pedersen, 2005). This later point is especially important because levels of systemic inflammation increase in normal age-related cognitive decline and incident dementia (Engelhart et al., 2004; Rafnsson et al., 2007; Marioni et al., 2009). Specifically, cognitive dysfunction, especially

Alzheimer's disease (AD), is associated with elevated blood levels of pro-inflammatory markers, such as C-reactive protein and interleukin-6 (e.g., Ravaglia et al., 2007). Rodent models offer a potential mechanism for the PA-dementia relationship in that reducing peripheral inflammation through PA-related decreases in amyloid-beta deposits in the brain, a hallmark of AD pathology and a putative cause of dementia (Nichol et al., 2008). Additional work has found that PA may also increase peripheral amyloid clearance mechanisms, suggesting that it may increase the overall ability of the body to regulate levels of proteins associated with neuropathology (Stranahan et al., 2012).

Other possible pathways by which PA improves neurocogntinve function involve increasing insulin and neurotrophic factor signaling in both the brain and periphery. In regards to insulin signaling, middle aged adults with higher levels of objectively measured PA have been shown to have higher insulin sensitivity compared to those with lower PA levels (Balkau et al., 2008), and those with greater insulin sensitivity exhibit better memory and more activation in memory-related brain networks than those with lower sensitivity (Cheke et al., 2017). Regarding neurotrophic factor signaling, PA interventions in rodent models have consistently shown increased levels of peripheral and central neurotrophins (e.g., brain derived neurotrophic factor) following periods of increased PA (e.g., Cotman et al., 2007; van Praag et al., 2014). However, measuring levels of neurotrohic factors in humans following PA is much more difficult. As a consequence, far less evidence on PA and neurotrophic factor signaling in humans exisits, although there is indirect evidence that neurotropic signaling may mediate the positive effects of PA on neurocogntion (Huang et al., 2014; Leckie et al., 2014; Mueller et al., 2015).

Together, the mechanistic evidence described above suggests that increased PA influences similar physiological pathways (i.e., inflammation, vascular health, metabolic signaling) as that of obesity, albeit in the opposite direction. Such patterns could suggest mechanisms by which changes in body composition through an increase in PA influences brain health.

Interim Summary

PA interventions involving even moderate-vigorous levels of PA are not particularly effective at reducing body weight. Rather, these interventions change cardiovascular fitness levels, as well as the body's composition of fat to lean muscle mass. Improvements in neurocognitive health observed following PA interventions in obese adults typically depend on changes in cardiovascular fitness rather than in weight loss or body composition *per se*. This suggests that weight and adiposity are not the most critical components for PA-related neurocognitive improvements.

Complicating this conclusion, however, is the fact that dietary interventions do not improve cardiovascular fitness nor increase lean muscle mass, yet improvements in neurocognitive health are still observed following these interventions. Although the evidence is limited, the effects of dieting appear to overlap with, but may be more selective than, the effects of PA interventions. This pattern highlights a potential unique role of cardiovascular fitness to brain and cognitive heath. A key caveat of the existing literature is that measures of BMI or adiposity are rarely included as covariates in PA studies. Conversely, PA is rarely included as a covariate in dietary restriction studies. This limits the causal links that can be drawn between these interventions and improvements in neurocognitive health.

DISCUSSION

Both aging and obesity contribute to increased health care costs. Consequently, an increase in the proportion of middle-aged and older adults who are obese may predict a compounded health care spending crisis in the future. Finding cost-effective, non-pharmacological interventions to attenuate the negative consequences of obesity on neurocognitive health is therefore a major public health priority. Until now, research examining the association between obesity and neurocognitive function has been mostly discussed separately from results relating PA and fitness to neurocognitive function. As described in the introduction, although PA and obesity are not simply inverse constructs of one another, there are clear physiological and conceptual similarities between them. Hence, this review brought these two literatures together to examine whether associations between brain and obesity are similar to those between brain and PA.

Convergence and Divergence in the Effects of Obesity vs. PA

PA interventions have been shown to increase neurocognitive health in similar areas as those affected by obesity and aging. In terms of brain health, the effects of PA are especially robust in the hippocampus and prefrontal cortex, as well as the white matter tracts connecting these regions. In the cognitive realm, PA interventions exert the largest and most consistent effects on executive control, while some less consistent effects are also observed in learning and memory processes. In addition, at the physiological level, there is evidence that PA works through similar mechanisms, albeit in the reverse direction, as obesity. For example, obesity is associated with increased peripheral inflammation and insulin resistance, as well as increased risk for cardiovascular (e.g., hypertension, diabetes) and neurodegenerative disease (e.g., dementia). Conversely, PA interventions decrease inflammation, increase insulin sensitivity, and decrease risk for a similar set of diseases (e.g., see Ertek and Cicero, 2012), suggesting that the mechanisms underlying obesity and PA converge. Such an overlap in underlying mechanisms could help explain the overlap in brain regions and cognitive functions most strongly linked to obesity and PA.

There are also some areas in which the effects of obesity and PA diverge. For example, as reviewed above, obesity has consistently been shown to affect the structure and functioning of limbic and reward-related brain networks, including regions such as the striatum and nucleus accumbens. On the other hand, PA studies have not shown consistent effects in the striatum or in limbic regions other than the anterior cingulate cortex. Therefore, the effects of obesity

and PA on brain outcomes may not be merely opposites of each other. Further supporting this point, interventions (e.g., dietary interventions) that combat obesity by decreasing body fat composition, but do not also increase fitness levels or lean muscle mass show more selective improvements in cognitive performance (e.g., increases in episodic memory, but not executive functioning) and brain health (e.g., diffuse increases in white matter, but only select increases in gray matter structure) compared to PA interventions. This pattern suggests that there are unique benefits of PA interventions on neurocognitive health that are not necessarily attributable to changes in body composition. Similarly, there may be unique negative consequences of obesity that are not attributable to physical inactivity, such as altered reward sensitivity and responses to food-related stimuli.

Converging Cellular and Molecular Mechanisms

At the cellular and molecular level, several mechanisms emerge that could explain the pathways for obesity on brain function, while PA and energy restriction positively impact, neurocognition during aging. We do not go into great detail on these mechanisms here as they are summarized extensively in numerous reviews (e.g., Cotman et al., 2007; Neufer et al., 2015; Stranahan, 2015; Raefsky and Mattson, 2017). However, some commen themes are worth reiterating. First, obesity decreases metabolic function (e.g., impairs insulin signaling, decreases mitochondrial efficiency), increases glutocorticoid and inflammatory signaling, and decreases structural and functional integrity of brain circuits (most consistently in medial temporal and frontal lobes). As a consequence of these deleterious cellular and molecular effects, obesity is associated with deficits in cognitive functioning.

Fortunately, there is a wealth of evidence that behavioral interventions, such as PA or caloric restriction, work in opposition to obesity in each of the mechanistic cellular/molecular domains mentioned above (Neufer et al., 2015; Raefsky and Mattson, 2017). For example, PA improves metabolic function in both brain and periphery by increasing insulin sensitivity and mitochondrial biogenesis/efficiency. PA also decreases glutocorticoid secretion and central and peripheral inflammation (e.g., for review see Neufer et al., 2015). Finally, PA selectively increases neural plasticity (e.g., by increasing brain-plasticity-promoting neurotrophins) and cognitive functioning in domains similar to those affected in obesity, including memory and learning and executive control (e.g., Erickson and Kramer, 2009).

Caloric restriction has also been found to have positive effects on the cellular and molecular level (Longo and Mattson, 2014; Raefsky and Mattson, 2017). For example, dietary restriction or intermittent fasting increases mitochondrial biogenesis and efficiency, reduces oxidative stress, and enhances neurogenesis and the synaptic plasticity of neurons. These findings suggest that bioenergetically challenging the body, either through PA or through dieting/fasting have positive consequences at the cellular/molecular level which promote a healthier body and brain. These interventions hold considerable promise for reversing the negative consequences of obesity and associated metabolic diseases.

Optimizing Obesity Interventions

A critical point of debate arising from these literatures is whether fatness or fitness matters more in terms of preserving neurocognitive health in adulthood. The answer to this question could inform the design of interventions for obesity in order to optimize neurocognitive health outcomes. Speaking to this point, the salutary effects of PA can be dissociated from changes in body composition in several ways. For example, PA can attenuate disease risk in individuals with varying levels of body fat, ranging from lean to obese (Church et al., 2005; Lee et al., 2005). Relatedly, neurocognitive changes have been observed following PA interventions, even in the absence of weight loss (Erickson et al., 2011; e.g., Erickson and Kramer, 2009). For example, following a 12-month aerobic exercise intervention, Erickson et al. (2011) reported improvements in spatial memory, as well as in hippocampal volume in a sample of cognitively normal older adults. These changes were associated with changes in fitness, but not with changes in body weight. This evidence again supports the notion that the mechanisms underlying PA and obesity are not just opposites of one another. That is, weight loss may not be a *necessary* component to mitigate the negative neurocognitive consequences of obesity. This signifies a potentially unique contribution of PA-induced changes in cardiovascular fitness (and not necessarily body composition) to the peripheral mechanisms discussed above. If this is the case, the associations between obesity and brain outcomes reported in the obesity studies above may not in fact be causal. Rather, they could be at least partially attributable to obesity-related health comorbidities, or to poor cardiovascular fitness (as a result of physical inactivity).

Related to the idea of whether fat loss is necessary for effective neurocognitive interventions is the notion of the obesity paradox (e.g., Hainer and Aldhoon-Hainerová, 2013; Wang et al., 2016). That is, having a higher BMI actually appears to be protective for some groups. This phenomenon has been observed in older adults aged 73 or older, referred to as the "oldest old" age group. Both cross-sectional and prospective longitudinal studies have reported that there is a positive relationship between BMI and cognitive performance in the oldest old, whereas there is a negative relationship between these two variables in adults ages of 55 and 72 (Luchsinger et al., 2007; Smith et al., 2011; Kim et al., 2016). One possible explanation for this pattern is that lower BMIs in the oldest old may reflect unintentional weight loss due to co-morbid health conditions, rather than healthful lifestyle-related weight maintenance. It's also possible that a reduced BMI could be the *result of* rather than the *cause of* cognitive impairment in this age group (e.g., memory problems could lead to poor nutrition). Individual differences, such as age are therefore complex, yet important, moderators to consider when discussing the effects of obesity on brain and cognition. It's possible that the optimal intervention for

promoting and preserving neurocognitive health could differ by age group. For example, increasing cardiovascular fitness and lean muscle may be the critical component for the oldest-old, while other interventions may be just as effective for younger age groups. Regardless, the obesity paradox literature is consistent with the idea that *increased fitness* rather than *decreased fatness* may be the key to successful neurocognitive interventions. In fact, sedentary time and poor cardiovascular health are consistently found to be more predictive of all-cause mortality than obesity (Lee et al., 2010; Sui et al., 2013; Ekelund et al., 2015), a finding that further bolsters this conclusion.

Limitations and Recommendations

Our review should be considered in light of several limitations. First, we chose to focus on interventional evidence to draw our conclusions regarding whether obesity-related neurocogntive outcomes can be reversed via behavioral modifications. In doing so, we chose not to include a detailed summary of the wealth of cross-sectional and correlational evidence that is relevant to this question. However, evidence from interventions in which effects are measured before and after a behavioral modification provide stronger evidence of causal links than correlational or cross-sectional observations. A second limitation of our review is that we are not able to draw precise conclusions regarding the overlap of brain regions showing effects related to obesity, diet, and PA because we did not have access to the data from individual studies. A meta-anlysis on this topic would be useful in order to draw more firm conclusions and to overcome the heterogeneity observed across individual studies.

There are also several limitations in the field that limit more specific conclusions about the associations between obesity, PA, and brain health. One overarching limitation is that it is difficult to separate the role of PA and cardiovascular fitness from the role of body composition when evaluating the effects of weight loss interventions, such as diet. PA levels affect the general health status of an individual and thus may be a confounding variable in all obesity-brain and obesity-cognition relationships reported. On the surface, for instance, the results of dietary interventions for weight loss seem to suggest that increased fitness is not necessary to reverse obesity-related neurocognitive dysfunction. To our knowledge, however, no studies of dietary weight-loss interventions have simultaneously assessed PA levels in the same individuals in order to evaluate whether PA behaviors had also changed. It is therefore not possible to rule out the possibility that PA mediates or moderates the neurocognitive effects observed in these interventions. Future studies of dietary interventions should consider objectively tracking PA levels in order to control for this possibility.

Another limitation of the obesity literature is that many studies use BMI as their main measure of adiposity. However, as mentioned above, BMI is a poor proxy for body composition and it can vary by age and gender. Future studies should therefore make use of more specified methods of measuring body composition (e.g., DEXA) in the future.

Studies of PA are also subject to these same limitations; the majority do not control for adiposity/BMI and peripheral health conditions, such as diabetes and hypertension. This makes separating the contributions of physical activity/fitness from those of weight and body composition difficult, at best. PA interventions in which both activity levels and adiposity measures were collected in the same individuals would help to better disentangle these relationships.

Despite these limitations, this review raises several interesting questions for future research. For instance, would a combined diet and exercise intervention benefit neurocognitive health more than diet or exercise alone? What is the appropriate dose of PA to maximize neurocognitive outcomes? What are the shared mechanisms of both obesity and PA on brain health?

CONCLUSIONS

While PA and obesity share many associations with neurocognitive function, they also differ in several respects. For example, obesity is not merely the instantiation of physical inactivity, nor is physical fitness necessarily indicative of a healthy weight. Understanding the interplay between body composition and physical activity on cognition promotes a more "complex systems" view of cognitive health. In this sense, the brain does not work in isolation of the periphery but instead acts as part of a complex interaction between physiological networks that sustain life. Appreciating how physical health of the entire body impacts brain health is crucial when considering complex public health problems, such as neurocognitive decline. The purpose of this review was to consider together obesity and behavioral interventions as they relate to neurocognitive outcomes in aging. This comparison demonstrated overlap between the neurocognitive mechanisms affected by obesity and those affected by certain behavioral interventions (namely, diet and PA), suggesting that some of the negative neurocognitive consequences of this public health crisis can be reversed. However, our comparison also exposed a need for more rigorous studies directly examining the common and dissociable mediating pathways, cumulative effects, and dose-response relationships in order to fully understand how obesity and promising behavioral interventions, such as PA, affect neurocognitive outcomes. While there are still many unanswered questions, this review highlights that it is important to consider physical health when examining the brain in order to understand how body and brain function act together as a complex system, particularly in the context of aging.

AUTHOR CONTRIBUTIONS

CS, AW, AM, PG, and KE have seen and approved this manuscript for submission and are accountable for all aspects of the work. CS, AW, AM, PG, and KE made substantial contributions to conceptualizing, drafting, and revising this manuscript.

FUNDING

CS is supported by NIH/NIMH T32 MH109986. KE was supported by National Institutes of Health grants R01 DK095172, R01 CA196762, R01 AG053952, P30 MH90333, and P30 AG024827. PG was supported by R01 HL089850. AW was supported by P30 AG024827.

ACKNOWLEDGMENTS

The lead author would like to thank Ryan Ghallagher, an undergraduate research assistant in the Brain Aging and Cognitive Health laboratory for his help organizing the literature review and tables for this manuscript.

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Conflict of Interest Statement: The handling Editor declared a past collaboration with one of the authors KE and states that the process nevertheless met the standards of a fair and objective review.

The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 09 May 2017
doi: 10.3389/fnagi.2017.00133

Active Experiencing Training Improves Episodic Memory Recall in Older Adults

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Active experiencing (AE) is an intervention aimed at attenuating cognitive declines with mindfulness training via an immersive acting program, and has produced promising results in older adults with limited formal education. Yet, the cognitive mechanism(s) of intervention benefits and generalizability of gains across cognitive domains in the course of healthy aging is unclear. We addressed these issues in an intervention trial of older adults (N = 179; mean age = 69.46 years at enrollment; mean education = 16.80 years) assigned to an AE condition (n = 86) or an active control group (i.e., theatre history; n = 93) for 4 weeks. A cognitive battery was administered before and after intervention, and again at a 4-month follow-up. Group differences in change in cognition were tested in latent change score models (LCSM). In the total sample, several cognitive abilities demonstrated significant repeated-testing gains. AE produced greater gains relative to the active control only in episodic recall, with gains still evident up to 4 months after intervention. Intervention conditions were similar in the magnitude of gains in working memory, executive function and processing speed. Episodic memory is vulnerable to declines in aging and related neurodegenerative disease, and AE may be an alternative or supplement to traditional cognitive interventions with older adults.

Keywords: aging, cognition, memory, intervention, acting, theater

OPEN ACCESS

Edited by:
Carryl L. Baldwin, George Mason University, USA

Reviewed by:
Bogdan O. Popescu, Colentina Clinical Hospital, Romania
Richard Camicioli, University of Alberta, Canada

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Received: *29 October 2016*
Accepted: *20 April 2017*
Published: *09 May 2017*

Citation:
Banducci SE, Daugherty AM, Biggan JR, Cooke GE, Voss M, Noice T, Noice H and Kramer AF (2017) Active Experiencing Training Improves Episodic Memory Recall in Older Adults. Front. Aging Neurosci. 9:133. doi: 10.3389/fnagi.2017.00133

INTRODUCTION

Age-related cognitive declines are associated with the development of dementia (National Institutes of Health, 2011) and impact the ability of older adults to live safely and independently (Blake et al., 1988; Grundstrom et al., 2012; Boelens et al., 2013). The rate and magnitude of decline differs across cognitive functions; whereas crystalized intelligence is relatively stable, for example, episodic memory follows a steep negative trajectory (Horn and Donaldson, 1980; Lindenberger et al., 1993; Park, 2000; Bherer et al., 2013). Further, a multitude of factors appear to shape an individual's aging trajectory (Raz and Kennedy, 2009), suggesting the possibility of intervening upon the process to potentially slow decline and promote successful aging. With this aim, various behavioral interventions have been proposed such as physical activity (Colcombe and Kramer, 2003) and cognitive training (Jaeggi et al., 2008; Karbach and Kray, 2009).

AE as a form of mindfulness training has been recently identified as a promising avenue for short-term intervention that produces lasting gains in cognitive function among older adults (Noice et al., 2004; Noice and Noice, 2009). These studies provide a good initial framework for examining AE, though, the evidence of gains is limited; the use of small samples that included individuals with elevated risk factors for cognitive decline and limited assessment of multiple cognitive abilities make the generalizability of this finding across cognitive functions in healthy aging unclear. Here, we report the largest study to date of this promising intervention in healthy older adults, including an extensive test battery of cognitive tests.

AE is a mindfulness exercise that encourages the individual to be cognizant of the immediate environment and internal state, and is commonly used as preparation for acting (Noice et al., 2004). AE was designed based on interactions with professional actors (Noice, 1996; Noice and Noice, 1999, 2001; Noice et al., 2000). The AE intervention for cognitive aging was developed by extrapolating acting strategies, including motor cues and mnemonic devices (Noice, 1996; Noice and Noice, 1999, 2006), which are often not explicitly demanded of actors but can contribute to successful script performance. AE interventions use a two-stage process of preliminary examination of the script, and engaging the character in rehearsal and performance (Noice et al., 2004). In an AE intervention, older adults with no prior acting experience are instructed to become their character and work to achieve the character's goals (Noice et al., 2004). They do this by "actively experiencing" the character on cognitive, emotional, and physiological levels.

Previous evidence suggests that this activity may promote memory functions. Following a 4-week intervention, older adults participating in AE performed better than a no-contact control group on standardized tests of episodic memory and working memory span, but only problem solving ability was significantly improved relative to an active control that completed a visual arts course (Noice et al., 2004). Intriguingly, the AE intervention group maintained higher performance levels in these domains, with potential continued gains in episodic memory (Noice et al., 2004; Noice and Noice, 2009). Thus, AE may be an example of a brief, inexpensive, and enjoyable intervention that can have a sustainable impact on cognitive functions that typically decline during aging. Yet, in part due to the limited scope of cognitive batteries used in these prior reports, the potential mechanism(s) and specificity of AE benefits to memory function over other cognitive abilities are unclear. Unlike cognitive training regimens, AE interventions do not train participants on any specific cognitive tasks or provide any pertinent strategies that are specific to assessment.

Instead, older adults indirectly memorize a script by actively engaging in their character and in response to their acting partner (Noice et al., 2015). The intent of this exercise is to use the dialog to achieve the character's motivation, before continuing to the next line of dialog. For example, if the script indicates a character flatter another character, then the first actor attempts to *sincerely flatter* the second actor using the exact wording in the script. Naturally, with repetition, this type of rehearsal leads to memorization of a short script (e.g., one-three pages), although it is not the explicit goal. In this manner, the AE intervention is a type of mindfulness exercise with the goal of verbatim memorization and recall of complex information, but deliberate memorization independent of the mindfulness exercise is discouraged.

Based upon the intervention design, there are two plausible routes of cognitive gains: one, promoting executive control function that is expected to have more general benefits to cognition; another, bolstering mnemonic encoding and recall that would produce more specific gains in memory and problem solving ability. For example, AE as a form of mindfulness may be similar to meditation that is hypothesized to improve attentional control in executive function (Tang et al., 2015) to confer gains in memory and reasoning abilities (Zeidan et al., 2010; Tang et al., 2012), much like the prior reports of AE. However, unlike mindfulness meditation, participants in AE have an explicit task to engage and sincerely act out a script during every rehearsal. A second hypothesized mechanism is specific to memory function. The evaluation of a character's motivation based upon the written script and subsequent performance, and the requirement to respond in character to a dynamic scene, can be conceived as forms of memory training that encourage working memory function and episodic encoding and retrieval. The AE intervention does not explicitly train mnemonic devices, but it is plausible that the acting exercise itself promotes the use and practice of associative memory strategies that aid performance on laboratory memory tasks in older adults (Shing et al., 2008). Yet, for the lack of comprehensive assessment in previous reports, the mechanism(s) and specificity of benefits from AE to cognitive ability in older age is uncertain.

We examined these hypothesized cognitive mechanisms of AE benefits by testing intervention-related changes in several cognitive functions—executive function, episodic and working memory, and processing speed—as well as the interaction between changes in different cognitive domains. These aims are aided by a sizable sample of older adults that is the largest study of AE to date. A substantial portion of the extant evidence has come exclusively from samples drawn from the same geographic region, of older age, low-middle socioeconomic status, some living in government-subsidized retirement communities, and on average achieving a high school level education (Noice et al., 2004; Noice and Noice, 2009). Each of these factors can impact cognitive function (Jefferson et al., 2011) and it is logical that carriage of greater risk may produce larger intervention effects. The present study addresses this limitation by implementing a 4-week, randomized control trial of AE intervention among community-dwelling older adults who, on average, obtained a university degree. This sample of older adults is also double the group size of those used in previous AE studies, providing greater power to detect effects and broader representation of the general population. Further, previous reports employed an ANCOVA approach to test intervention gains, which cannot evaluate individual differences in change or the relationship between concurrent and future changes in cognition (see McArdle, 2009). Here, we use latent change models for intent-to-treat analyses, which is the gold standard (McArdle, 2009) to test

changes in cognition following intervention and up to 4 months later. Within this framework, we expect the AE group to experience greater gains in cognitive function as compared to the active control group. Additionally, evidence of correlated gains in executive function, working memory and episodic memory may lend insight into the underlying mechanism of AE.

MATERIALS AND METHODS

Participants

The participants in this study were 179 community-dwelling adults aged 60–89 years (M = 69.46, SD = 6.59; 62% female), who on average had a college education (M = 16.80 years, SD = 3.48). For study enrollment, participants were right-handed, scored at least 23 on the MMSE (M = 28.69, SD = 1.39; Folstein et al., 1975), had no contraindication to MRI (not reported in the present article), and provided written consent for study participation. This study was carried out in accordance with the recommendations of the Institutional Review Board at the University of Illinois at Urbana-Champaign with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Institutional Review Board. Based on enrollment criteria and initial phone screening, 235 persons were enrolled in the study: 179 completed the intervention and were included in analysis; another 56 individuals were removed from the study due to violations of enrollment criteria that were identified retrospectively (**Figure 1**). Upon successful entry into the study, participants were assigned to either the active control (n = 86) or the AE condition (n = 93). Group assignment was pseudo random depending on the participant's time of enrollment. Attendance was monitored and participants were required to attend 75% of class sessions. The two groups were similar in age ($t_{(176)} = -0.79$, $p = 0.43$), MMSE ($t_{(176)} = 0.22$, $p = 0.82$) and years of education ($t_{(176)} = 0.86$, $p = 0.39$), as well as representation of sex ($\chi^2_{(1)} \leq 0.15$, $p \geq 0.70$). After completing the 4-week intervention, participants returned for a post-intervention assessment (delay from the first assessment M = 51.48 days, SD = 14.78) and a follow-up 4 months later (delay from post-intervention assessment M = 127.89 days, SD = 10.35). The AE condition experienced a longer delay at post-intervention than the control ($t_{(169)} = -3.53$, $p < 0.001$) but groups were similar in follow-up delay ($t_{(143)} = 1.78$, $p = 0.08$) and delays between assessments were included as covariates in the model to account for this. Of the 179 individuals included in analyses, 33 did not return for the follow-up assessment, but were similar in demographic characteristics (all $t < 1.55$, $p > 0.12$) as those who did return and attrition was similar between the conditions ($\chi^2_{(1)} = 0.76$, $p = 0.38$). Thus, intent-to-treat analyses were conducted on the total sample and missing data were handled via full information maximum likelihood (FIML) estimation with the assumption of missing at random—a non-imputation approach that leverages all available data during latent model estimation (Muthén and Khoo, 1998).

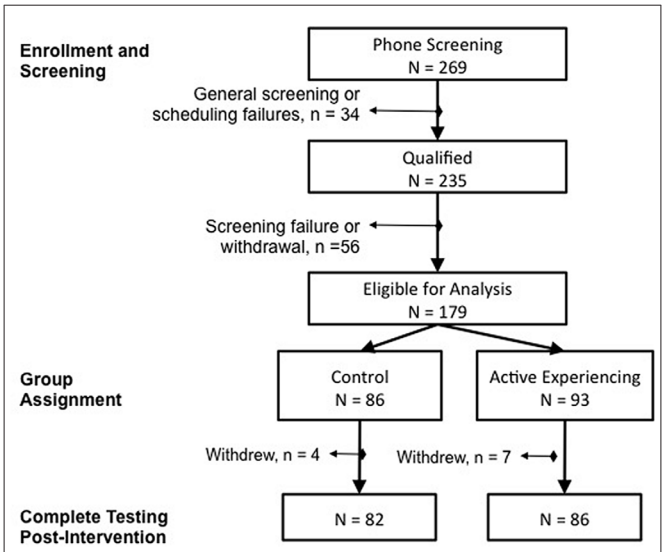

FIGURE 1 | CONSORT Flow diagram of participant recruitment, enrollment and attrition over the course of the intervention trial.

Intervention

Participants were assigned to one of two groups: the Active Control that attended an Understanding the Art of Acting class or the intervention AE class. The control and intervention sessions occurred over a period of 4 weeks with both groups meeting two times a week for 75-min sessions, including a 15-min coffee break to encourage additional social interaction among the participants. Researchers with experience administering AE interventions chose the content of the classes and trained all outside instructors (TN and HN).

The Active Control was designed as a theater appreciation class including talks, demonstrations and video clips of stage and film performances. The course topics included the styles of acting, in addition to the history of theater. The Active Control condition was designed to rule out the possibility that learning about a popular art form like acting, along with the social interaction of being engaged in a class, are sufficient to produce the significant improvement in cognitive functioning observed in the previous theatre interventions.

The active experience training in the AE group was designed to be internally rewarding and non-competitive (Noice and Noice, 2009). The intervention has been described in detail in previous reports (Noice and Noice, 2009; Noice et al., 2015). Participants performed short scenes with a partner and scripts were 1–3 pages (large print) in length. The activities conducted in the class integrated four key concepts to teach the AE construct. First, participants were discouraged from "pretending" during sessions and instead instructed to perform every action as if it were real life. Second, participants were required to use their imaginations to mentally create the scenario in which they are asked to act. Third, participants were taught to be goal-driven by the scripted scenario and work through difficulties to achieve the character's goal. During the first 2 weeks of

AE classes, participants were not required to memorize the scripts but were encouraged to spontaneously pursue the script, by responding to interactions or alterations immediately and naturally. During the training, participants were encouraged to access each of these concepts cognitively, emotionally, and physically. These main constructs were implemented in a range of lessons throughout the intervention period. Finally, during the last 2 weeks of class, participants were expected to perform their assigned scene verbatim from memory. All participants were in the same room during classes, and the training directors circulated to provide active feedback to the acting partners. In previous studies, participants learned very short scenes in less than 1 h and longer scenes in two or three 1-h sessions (Noice and Noice, 2009; Noice et al., 2015).

Cognitive Measures

Tasks were selected to address a range of cognitive domains including episodic memory, working memory, semantic knowledge, executive function and processing speed. All computer-based tasks were designed in E-prime version 1.1 (Psychology Software Tools, Pittsburgh, PA, USA) and administered on computers with 17 inch cathode ray tube (CRT) monitors. The same tests were repeated at pre- and post-intervention, and at the follow-up after 4 months. All assessments were administered and scored by research assistants who were blinded to group assignment.

Episodic Memory

The Logical Memory task was taken from the Virginia Cognitive Aging Project (Salthouse and Ferrer-Caja, 2003; Salthouse, 2004, 2005, 2010). Two recorded stories were played for the participant. Each story contained 25 specific story details and eight thematic details. Immediately following the story, participants were asked to recall the story in as much detail as possible. Following the second story, participants were asked to recall as much detail as possible from the first story without having it played back, providing a measure of delayed recall. Number of details recalled for the specific story and thematic categories were used as separate measures of episodic memory. Latent constructs for story and thematic recall were each defined by immediate and delayed recall.

Spatial Working Memory

The computerized spatial working memory (SWM) task was administered at variable difficulty memory loads of two, three and four target dots, randomly arranged on the computer screen. Participants completed 12 practice trials followed by 120 test trials. The dots were visible for 500 ms or 1000 ms, replaced with a fixation cross for 3000 ms. Following the fixation, a red dot either appeared in the same location where one of the black dots was or in an altered location. Participants indicated whether the dots were in the original or altered positions. Accuracy of responses for each of the three conditions was used as measures to identify the latent construct.

Verbal Working Memory

In the computerized N-back test, participants viewed a series of letters presented sequentially for 500 ms with an inter-trial interval of 2000 ms. Participants performed both a 1-back and a 2-back condition, with five runs of 20 letters presented for each condition. In the 1-back condition, participants were instructed to respond by pressing a button when the currently presented letter was the same as the previously presented letter (match trial), but to press a different button when the current letter did not match the previously presented letter. Instructions were similar for the 2-back condition that required participants to indicate if the currently presented letter was the same or different to the letter presented 2 trials previously. For both 1- and 2-back conditions, 50% of trials met the match rule. Response accuracy on each the 1- and 2-back conditions were used as measures to identify the latent construct.

Semantic Memory

Category fluency of animals and fruits/vegetables was administered to measure semantic memory. Participants were prompted with a category and orally recalled as many items as possible in that category within 1 min. The total number of correct responses per category was used as indicators of category fluency.

Executive Function

The computerized Task Switching test consisted of two individual tasks, each presenting a single digit (1–9, excluding 5) for 2500 ms. Participants were required to make a judgment about the presented digit based upon the background color. When presented on a pink background, participants were instructed to indicate if the digit was more or less than 5. When presented on a blue background, participants indicated if the digit was odd or even. Participants completed one block of 40 trials of each task rule individually followed by a block of 160 trials that required switching between response rules, designed to present randomly. The latent construct was defined by accuracy on the switch block and average accuracy of the non-switch blocks.

Processing Speed

The latent processing speed construct was defined by two measures: Part A of the Trail Making Test and Digit Symbol Substitution Task. In Part A of the Trail Making Test, the participant was required to connect a total of 25 numbers (1–25) in ascending and alphabetical order, as quickly as possible without removing the pencil from the page. Longer completion time indicates slower processing speed. In the Digit Symbol Substitution Task participants were provided nine pairs of numbers and symbols, and then were required to fill in the matching symbol for a provided number using the key as a reference. There were 133 possible items and participants were given 2 min to complete as many items as possible working from left to right without leaving any blank. Greater number of correct responses was an index of faster processing speed.

Statistical Analyses

All analyses were completed in a latent modeling framework, estimated in MPlus software (v. 7; Muthen and Muthen). Changes in cognitive ability from pre- to post-intervention, and from post-intervention to follow-up after 4 months, were estimated in latent change score models (LCSM). A LCSM is similar to a difference score, but because it is determined by latent constructs, estimates of change and individual differences therein are free of measurement error (McArdle, 2009). In this model construction, sequential changes between measurement occasions were correlated, and pre-intervention performance was allowed to correlate with subsequent change.

To construct the LCSM, several measurement features were imposed. Latent constructs were each determined by multiple measures, fixing one measure factor loading to 1, the other loadings were freely estimated, and all measurement residuals were freely estimated. The following latent constructs were estimated (*italics indicates factor loading fixed to* 1 f*or latent identification*): story and thematic recall were each defined by *immediate* and delayed recall; category fluency by accuracy of recall for *animal* and vegetable/fruit categories; SWM by accuracy on the *one*, two and three dot conditions; verbal working memory by accuracy on *2-back* and 1-back; task switching by accuracy on the *switch* and non-switch blocks; and processing speed by performance on *digit symbol* and Trails Part A (see **Table 1**). To ensure measurement invariance longitudinally, several constraints were added to the LCSM: estimated factor loadings were constrained to be equal over time, measure intercepts and variances were equal at each time point, and repeated measures were allowed to correlate but the magnitude of the correlation was constrained to be equal between occasions. There were a few exceptions: measurement variance of the 3-dot condition of the SWM task was freely estimated and measure intercepts of the task switching block were freely estimated.

Prior to model construction, all measures were normed to pre-intervention scores in the total sample. Thus, change scores can be interpreted as standardized change from pre-intervention. All reported effects are unstandardized coefficients. A standardized effect size of mean latent change was calculated: d = (Mean Latent Change)/$\sqrt{}$(Pre-intervention Latent Variance). Cognitive constructs that evidenced significant individual differences in change were further tested for covariates, including age, sex, delay between occasions, as well as group differences. Intervention group differences were tested in a grouped LCSM that included constraints for measurement invariance also between groups. Only the means and variances tested for group differences were freely estimated. To test whether changes in one cognitive ability predict change in another following intervention, parallel change score models were constructed. These included correlated change in cognitive constructs at each assessment occasion, as well as change from pre- to post-intervention in one cognitive ability predicting future change from post-intervention to follow-up in another ability. Model fit was determined by several accepted indices (Hu and Bentler, 1999): non-significant normal theory weighted chi-square (χ^2), comparative fit index (CFI $>$ 0.90), root mean square error of approximation (RMSEA $<$ 0.05), and standardized root mean residual (SRMR $<$ 0.08). Model fit was determined for the total sample and with grouped modeling procedures.

Analyses were completed with the assumption of intent-to-treat and included the total sample. Missing data were handled via FIML—a non-imputation approach that leverages all available data during effect estimation (Muthén and Khoo, 1998; Larsen, 2011), and the current recommended practice for longitudinal studies with attrition (Little and Card, 2013). To avoid spurious results due to a smaller sample size, all LCSM were bootstrapped with bias-correction (5000 draws; Hayes and Scharkow, 2013) to produce 95% confidence intervals (BS 95% CI) of unstandardized effects. Due to the limitation on the number of parameters that can be reasonably estimated in proportion to the sample size, each cognitive construct was evaluated in a separate model. A Bonferroni correction was made for multiple comparisons (α' = 0.01).

RESULTS

Longitudinal Consistency in Measures

Prior to testing longitudinal change, longitudinal consistency of the measures was evaluated with Pearson correlations between pre-intervention measures and subsequent testings. Performance

TABLE 1 | Mean latent change at post-intervention and the 4-month follow-up in the total sample.

Construct	Pre-intervention variance	Post-intervention		*d*	4 Month follow-up		*d*
		Mean change [BS 95% CI]	Variance in change		Mean change [BS 95% CI]	Variance in change	
Story recall	0.73*	0.32* [0.21/0.42]	0.49*	0.37	0.12 [0.02/0.25]	0.50*	0.14
Thematic recall	0.73*	0.18† [0.04/0.32]	0.87*	0.21	0.12 [0.01/0.26]	0.60*	0.14
Category fluency	0.61*	0.07 [−0.10/0.23]	1.00*	0.09	0.21* [0.09/0.36]	0.59*	0.27
Spatial WM	0.89*	−0.04 [−0.20/0.12]	1.04*	−0.04	0.12 [−0.02/0.26]	1.00*	0.13
Verbal WM	0.25*	0.09 [−0.03/0.19]	0.27*	0.18	0.06 [−0.01/0.17]	0.17*	0.12
Task switching	1.00*	0.14† [0.02/0.26]	0.70*	0.14	0.16† [0.03/0.30]	0.77*	0.16
Processing speed	0.85*	0.21* [0.13/0.28]	0.07	0.23	0.07 [−0.01/0.14]	0.08	0.08

Note: Unstandardized change scores reported for measures normed to the mean and standard deviation of the total sample at pre-intervention. All constructs are latent composites of multiple measures.$p < 0.01$, †$p < 0.05$, $\alpha' = 0.01$. d is a standardized coefficient of change: d = Mean Change/$\sqrt{}$(Pre-intervention Variance). BS 95% CI, bias-corrected bootstrapped 95% confidence intervals; WM, working memory.*

on all tasks had acceptable longitudinal consistency: the highest consistency in performance on digit symbol (r = 0.85 and 0.83), and the lowest on n-back task 1-back (r = 0.30 and 0.59) and 2-back conditions (r = 0.55 and 0.49).

Latent Longitudinal Change in Cognitive Ability

Within the entire sample, mean changes from pre- to post-intervention and from post-intervention to the follow-up 4 months later were tested in sequential LCSM. All models had excellent fit: $\chi^2_{(7-31)}$ = 8.73–40.49, p = 0.05–0.79; CFI = 0.97–1.00; RMSEA = 0.00–0.07; SRMR = 0.02–0.05. Story recall improved at post-intervention (mean = 0.32, $p < 0.001$, α' = 0.01; BS 95% CI: 0.21/0.42), as did thematic recall (mean = 0.18, p = 0.03, α' = 0.01; BS 95% CI: 0.04/0.32), although the effect did not survive correction for multiple comparisons. Both tasks evidenced additional gains at follow-up 4 months later, supported by BS 95% CI that do not overlap with zero, but neither effect reached statistical significance (**Table 2**). Task switching also showed nominal gains at post-intervention (mean = 0.14, p = 0.04, α' = 0.01) and follow-up (mean = 0.16, p = 0.04, α' = 0.01), whereas category fluency only improved at follow-up (0.21, p = 0.005, α' = 0.01; BS 95% CI: 0.09/0.36). Performance on all other tasks was stable over the course of study (**Table 2**). However, individuals varied in the magnitude of gains in performance on all constructs, except processing speed, and we went on to test possible intervention group differences in performance changes. In addition to intervention group differences, several covariates were tested to explain individual differences in change: pre-intervention performance, age, sex and the delay between assessments as control variables, as well as correlated changes at post-intervention and follow-up. See **Table 2** for a summary of all covariates to change. Better performance at pre-intervention was associated with lesser gain at post-intervention in all constructs (r = −0.48 to −0.10, $p < 0.001$); the same pattern was not consistently observed at follow-up, but individuals who showed greater gains at post-intervention experienced lesser gain at follow-up (r = −0.34 to −0.23, $p < 0.001$). Final models of covariates had good fit: $\chi^2_{(28-55)}$ = 31.11–59.45, p = 0.01–0.33; CFI > 0.95; RMSEA < 0.06; SRMR < 0.06. Possible intervention effects were tested as group differences in the magnitude of change in each cognitive domain, accounting for pre-intervention performance, age and delay between assessments as covariates.

Intervention Group Differences

Prior to evaluating group differences in latent change, groups were confirmed to be statistically similar in performance on cognitive measures at pre-intervention (all $t_{(176)}$ = −1.28 to 1.90, $p > 0.06$), except the AE condition performed worse on immediate story recall ($t_{(176)}$ = 2.09, $p < 0.04$) and immediate ($t_{(176)}$ = 2.39, p = 0.02) and delayed ($t_{(176)}$ = 3.18, p = 0.002) thematic recall. In latent models testing group differences in change, we constrained pre-intervention latent episodic memory scores to be equal between groups to confirm that this was not a bias in the analysis.

The AE intervention produced greater gains in episodic memory than Active Control. Grouped models of episodic memory had excellent fit (story and thematic recall, respectively): $\chi^2_{(62)}$ = 78.51 and 65.78, p = 0.08 and 0.35 (AE = 39.49 and 43.23; Active Control = 39.02 and 22.55); CFI = 0.97 and 0.99; RMSEA = 0.06 and 0.03; SRMR = 0.06. The AE condition experienced significant improvement in story recall at post-intervention (0.44, $p < 0.001$; BS 95% CI: 0.31/0.59) and a trend for the same at follow-up (0.20, p = 0.05, BS 95% CI: 0.04/0.37) whereas the Active Control group showed no significant change in performance over the study (**Table 3**). Indeed, the intervention produced significantly greater gains at post-intervention as compared to Active Control (difference = 0.26, p = 0.04, BS 95% CI: 0.07/0.46), but additional gains at follow-up were similar between groups (difference = 0.16, p = 0.25, BS 95% CI: −0.06/0.38; **Figure 2**). A similar pattern was observed for thematic recall—the AE intervention produced greater gains at post-intervention (difference = 0.49, p = 0.002, BS 95% CI: 0.23/0.75) but not at follow-up (difference = 0.04, p = 0.78, BS 95% CI: −0.19/0.29). Although the magnitude of change did not significantly differ between groups at follow-up,

TABLE 2 | Covariates of latent change.

Construct	Change score	Pre-intervention performance	Age	Sex	Delay
Story recall	Post-intervention	−0.23*	−0.08	0.18	−0.02
	Follow-up	−0.10	0.14†	−0.03	−0.08
Thematic recall	Post-intervention	−0.59*	0.06	0.23	−0.10
	Follow-up	−0.20	−0.01	−0.24	0.01
Category fluency	Post-intervention	−0.56*	0.33*	−0.08	0.00
	Follow-up	0.44*	−0.39*	0.21	0.01
Spatial WM	Post-intervention	−0.30*	−0.05	0.08	−0.06
	Follow-up	0.06	−0.10	0.00	−0.05
Verbal WM	Post-intervention	−0.10*	−0.11†	0.12	0.00
	Follow-up	0.01	0.10†	−0.13	0.02
Task switching	Post-intervention	−0.33*	−0.04	0.22	−0.08
	Follow-up	−0.24*	0.07	−0.16	−0.01

*Note: All covariate effects estimated in latent change score models. Unstandardized coefficients reported for measures normed to pre-intervention means and standard deviations in the total sample. *$p < 0.01$,†$p < 0.05$, $\alpha' = 0.01$. Constructs are latent composites of multiple measures. WM, working memory.*

TABLE 3 | Intervention group differences in change at post-intervention and 4-month follow-up.

	Change at Post-Intervention			Change at Follow-up		
Construct	**AE [BS 95% CI]**	**Control [BS 95% CI]**	**Difference [BS 95% CI]**	**AE [BS 95% CI]**	**Control [BS 95% CI]**	**Difference [BS 95% CI]**
Story recall	0.44* [0.31/0.59]	0.18 [0.02/0.33]	0.26† [0.07/0.46]	0.20† [0.04/0.37]	0.04 [−0.10/0.19]	0.16 [−0.06/0.38]
Thematic recall	0.41* [0.22/0.64]	−0.07 [−0.21/0.09]	0.49* [0.23/0.75]	0.13 [−0.05/0.33]	0.09 [−0.06/0.24]	0.04 [−0.19/0.29]
Category fluency	0.06 [−0.15/0.28]	0.09 [−0.17/0.33]	−0.03 [−0.35/0.31]	0.15 [−0.01/0.32]	0.26† [0.07/0.47]	−0.10 [−0.39/0.13]
Spatial WM	−0.07 [−0.28/0.13]	−0.06 [−0.27/0.16]	−0.01 [−0.29/0.27]	0.11 [−0.06/0.31]	0.12 [−0.12/0.36]	−0.01 [−0.31/0.29]
Verbal WM	0.11 [−0.05/0.26]	0.21* [0.07/0.36]	−0.10 [−0.32/0.09]	0.05 [−0.05/0.19]	−0.03 [−0.10/0.09]	0.07 [−0.07/0.22]
Task switching	0.10 [−0.14/0.27]	0.18† [0.04/0.32]	−0.08 [−0.34/0.15]	0.20 [0.03/0.41]	0.09 [−0.10/0.32]	0.11 [−0.18/0.38]

Note: Intervention group comparisons were made in a grouped latent change score model, including covariates and constraints to ensure measurement invariance longitudinally and between groups. Unstandardized coefficients are reported for measures normed to pre-intervention means and standard deviations of the total sample.$p < 0.01$; †$p < 0.05$; $\alpha' = 0.01$. AE, active experiencing intervention condition; Control, active control condition; BS 95% CI, bias-corrected bootstrapped 95% confidence intervals; WM, working memory.*

the intervention produced a different pattern of gains in episodic memory over the course of study—suggesting better maintenance (and potentially continued gains) of recall ability up to 4 months after the intervention. To ensure that this intervention-related effect was not an artifact of group differences in pre-intervention performance level, we imposed additional model constraints that held groups to be equal at pre-intervention, and the AE condition still demonstrated greater gains in thematic recall at post-intervention (difference = 0.40, $p = 0.01$; BS 95% CI: 0.14/0.66) and the test of the effect in story recall (difference = 0.19, $p = 0.10$; BS 95% CI: 0.00/0.38) was likely underpowered based upon the BS 95% CI that slightly overlapped with zero. Therefore, the evidence of group differences in repeated-testing gains in episodic memory is likely an intervention effect and not a bias from a possible ceiling effect in performance.

Group differences were only detected in episodic memory ability and groups were equivalent in changes in all other constructs (**Table 3**). All other group models of cognitive ability had excellent fit: $\chi^2_{(46-117)} = 46.65–131.46$, $p = 0.17–0.45$ (AE = 25.17–54.55, Active Control = 21.48–76.91); CFI > 0.98;

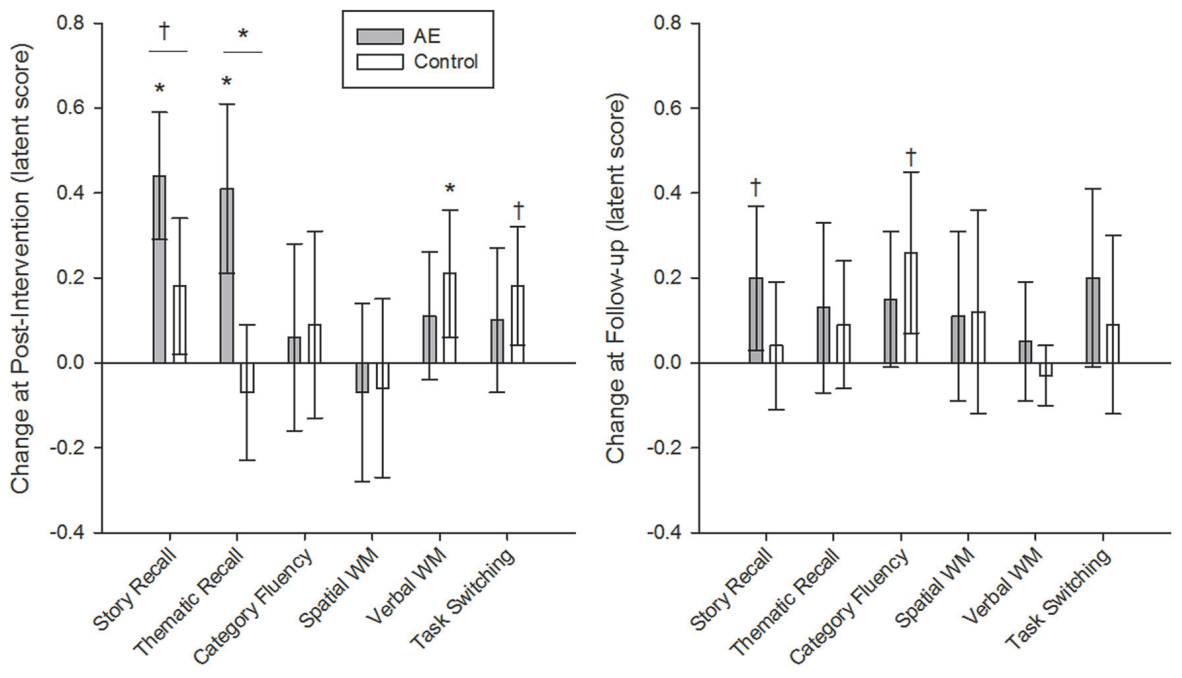

FIGURE 2 | Intervention group differences in latent change in cognitive ability at post-intervention and at follow-up, 4 months later. The Active experiencing (AE) condition produced significantly greater gains in story and thematic recall in episodic memory as compared to the control group at post-intervention, but not at follow-up. Groups were similar in the magnitude of change in all other cognitive constructs. Intervention group comparisons were made in a grouped latent change score model, including covariates and constraints to ensure measurement invariance longitudinally and between groups. Unstandardized coefficients are reported for measures normed to pre-intervention means and standard deviations of the total sample. Error bars represent bias-corrected bootstrapped 95% confidence intervals; *$p < 0.01$; †$p < 0.05$; $\alpha' = 0.01$. AE, AE intervention condition; Control, active control condition.

RMSEA < 0.04; SRMR < 0.07. Except the model of task switching that had less-than-optimal fit due to violations to the assumption of measurement invariance between groups: $\chi^2_{(55)} = 96.33, p < 0.001$; CFI = 0.96; RMSEA = 0.09; SRMR = 0.09.

Correlated Changes in Cognition

Although groups did not differ in the magnitude of change in any domain besides episodic memory, individuals varied in changes in several cognitive domains and the pattern of correlated changes across domains may lend insight into the mechanism of AE intervention benefits. In a parallel latent change score model, we evaluated correlations between concurrent changes in cognitive constructs, including story and thematic recall, executive function and working memory. This was first examined in the total sample. As expected, individuals who experienced greater gains in story recall also showed gains in thematic recall immediately following the intervention ($r = 0.25, p < 0.001$) and at follow-up ($r = 0.19, p < 0.001$). Greater gains in executive function from post-intervention to follow-up also correlated with concurrent gains in thematic recall ($r = 0.11, p = 0.03$) but not in story recall at that time ($r = 0.07, p = 0.17$), and changes from pre- to post-intervention were not correlated with concurrent changes in thematic ($r = 0.001, p = 0.99$) or story recall ($r = 0.04, p = 0.44$). Changes in working memory were unrelated to concurrent change in episodic recall at post-intervention ($r = -0.06$ and $r = 0.02$, $p > 0.09$, story and thematic recall, respectively) or at follow-up ($r = 0.01$ and $r = 0.00$, $p > 0.77$, respectively). Thus, while performance on story and thematic recall was correlated, it did not consistently associate with concurrent changes in executive function or working memory.

To further evaluate a possible cognitive mechanism of AE intervention gains in episodic memory, the parallel change score model included a test of change in executive function and working memory from pre- to post-intervention predicting future change in episodic recall from post-intervention to follow-up. However, there was no evidence of change in one cognitive domain predicting future change in another. Change in executive function immediately after the intervention did not predict future change in episodic recall assessed 4 months later ($b = -0.11$ and $b = -0.06$, $p > 0.29$, story and thematic recall, respectively), nor did change in working memory ($b = -0.17$ and $b = -0.12$, $p > 0.46$, story and thematic recall, respectively). Due to the lack of evidence for these effects in the total sample, intervention group differences were not further tested. Taken together, group intervention effects were limited to episodic recall and gains in this cognitive domain were unrelated to changes in executive function and working memory.

DISCUSSION

Typical aging is characterized by cumulative and progressive declines in cognition (Horn and Donaldson, 1980; Lindenberger et al., 1993; Park, 2000; Bherer et al., 2013) and the prospect of interventions to slow this decline is intriguing. AE, a form of mindfulness, is a promising intervention that has not been widely explored. Here, we find that a group of older, community-dwelling adults who completed a 4-week AE intervention experienced greater repeated-testing gains in episodic memory recall than the Active Control group. These gains in function were maintained up to 4 months later, although the intervention groups did not significantly differ in performance at follow-up. This is the largest study of AE to date and included a broad range of cognitive assessments. Yet, there was no evidence of intervention benefits to other cognitive abilities, suggesting that AE may specifically bolster episodic memory in healthy aging. Thus, the mechanism of the AE intervention is likely closely related to mnemonic encoding and recall to confer gains within this domain, albeit without additional global cognitive benefits.

The pace and magnitude of declines during aging vary across cognitive domains and episodic memory appears to be particularly sensitive (Horn and Donaldson, 1980; Lindenberger et al., 1993; Park, 2000; Bherer et al., 2013). Thus, short-term interventions that bolster this function with sustained benefits could have major implications for public health. Several intervention approaches, including aerobic exercise (Colcombe and Kramer, 2003; Smith et al., 2010; Roig et al., 2013), cognitive training (Melby-Lervåg and Hulme, 2013), and mindfulness meditation (Tang et al., 2015) have been tested and produce mixed results in improving memory function in older adults. Here, we partially replicate previous reports of AE improving memory function relative to active control groups (Noice et al., 2004; Noice and Noice, 2009). Importantly, the present study reports an extensive range of cognitive assessments never before administered in this type of intervention, of which only episodic memory showed improvements. This result indicates a potential selective intervention benefit via a mechanism specific to mnemonic function, and not global improvements in executive function or working memory, for example.

Although we find evidence for a selective effect, we can only speculate on the precise mechanism by which AE bolsters memory ability, and it is plausible that it relates to improved use of mnemonic strategies for encoding and retrieval. The AE training required the participant to evaluate a character's motivation and affect in the course of performing a script. Although participants were not instructed to deliberately memorize the script, the repetition and creative development of the character in relation to the scene performance is conceptually similar to elaborative mnemonic strategies that improve subsequent recall in the laboratory (Hertzog and Dunlosky, 2004; Preston and Eichenbaum, 2013). Older adults appear to spontaneously use such strategies less frequently and less effectively than their younger counterparts do, partially explaining worse recall accuracy in later life (Kausler, 1994; Verhaeghen and Marcoen, 1994). Moreover, age-related deficits in episodic recall can be mitigated by supplying deep encoding strategies (Shing et al., 2008) that are similar to those derived from AE training. AE does not explicitly train mnemonic strategies or specific cognitive functions, yet rehearsal over 4 weeks may have encouraged older adults to spontaneously use deep encoding strategies more frequency and effectively when performing tasks other than acting. In this regard, AE training may have implicit benefits to episodic memory function. Moreover, these benefits were sustained up to 4 months later,

similar to the long-term benefits of mnemonic strategy training evidenced years after intervention (Gross and Rebok, 2011). However, without independent reports of strategy use, we can only speculate on the source of gains in episodic recall.

An alternative hypothesized mechanism of AE benefits to memory and problem solving that have been reported previously (Noice et al., 2004; Noice and Noice, 2009) is a boost in executive control functions that, in turn, promotes cognitive ability, similar to the putative mechanism of benefits following mindfulness meditation (Tang et al., 2012, 2015). However, we found no evidence of intervention gains in other cognitive abilities, including executive function and working memory, and individual differences in the magnitude of change in these domains did not predict subsequent change in episodic recall. Thus, the AE intervention does not appear to directly target executive function *per se*.

The present results are not completely consistent with previous reports of AE (Noice et al., 2004; Noice and Noice, 2009). This may in part be due to differences in sample characteristics. Although the health of previously reported samples was not thoroughly documented (Noice et al., 2004; Noice and Noice, 2009), previous reports were on samples that were older, of lower SES and education level than participants in the current study. Each of these demographics are proxies for multifarious processes in aging that have been shown to predict steeper cognitive declines (Jefferson et al., 2011). Because greater risk can moderate the magnitude of intervention effects (e.g., Colcombe and Kramer, 2003; Smith et al., 2010; Danielsson et al., 2015), the generalizability of AE benefits in cognition to samples with lesser concomitant risk can be questioned. Here, we partially replicate the previous reports in a college-educated and healthy aging sample, and failure to find effects outside of episodic memory may reflect the sample selection. Future studies should consider additional health factors that may account for individual differences in responsiveness to the intervention. Moreover, individual differences in brain structure and function may interact with health factors and demonstrate change in response to the intervention to further explain cognitive function, as has been documented with mindfulness meditation (Tang et al., 2015). We aim to address these hypotheses in future reports and intentionally limited this initial report to the analysis of primary cognitive outcomes. Nonetheless, the moderate effect sizes within episodic memory function measured in this sample and the sustained effect 4 months later demonstrate the promise of the AE intervention in the course of normal cognitive aging.

The current report replicates and expands the extant literature on AE and employs a robust analytic approach. Yet, the evidence should be interpreted with consideration of several limitations. In addition to the possible bias introduced by strict sample selection from the Champaign-Urbana, IL metro area, the sample was compromised by some attrition. However, this is the largest sample to date testing the effects of AE. Further, intent-to-treat analyses were completed on the entire sample and we handled missing data via FIML—a non-imputation approach that leverages all covariance information available during model estimation. To avoid spurious results from the smaller sample size, estimated effects were bootstrapped with bias-correction to produce 95% confidence intervals. Yet, we cannot completely eliminate possible bias related to sampling characteristics. A second limitation of the study is pseudo randomization of group assignments, which may be reflected in group differences in episodic memory performance at pre-intervention. The latent models that assessed intervention group differences included constraints to account for this, but we cannot completely account for this possible source of bias. Future studies should consider a true randomization scheme. A third limitation is our assessment of sustained benefits only 4 months after intervention. Longer delays with multiple measurement occasions are necessary to evaluate this further. Despite these limitations, we offer promising evidence of AE intervention benefits to episodic memory function in healthy aging and identify propitious avenues of future study.

CONCLUSION

Previous reports of AE identified it as a promising intervention to promote cognitive function into older age, yet the mechanism of intervention benefits as well as the generalizability of gains across cognitive domains in the course of healthy aging had not yet been examined. Here, we identified specific gains in episodic recall from AE relative to the Active Control, but no other evidence of intervention gains in cognition. The cognitive mechanism of AE intervention benefits appears to be specific to mnemonic encoding and retrieval, as individual differences in executive function and working memory were unrelated to subsequent change in episodic recall. Episodic memory is particularly vulnerable to decline in aging and here we find promising evidence of intervention benefits in a healthy aging sample that is larger than any previously reported in an AE intervention. Because sustainable benefits were seen after a relatively brief intervention, AE may be a promising activity to slow episodic memory declines that are typical in aging. However, despite the extensive neuropsychological battery, no other cognitive domains exhibited benefits from the AE intervention, in contrast to expectations and previous reports. Future studies that include additional measures of brain structure and function, and other health factors, may substantiate AE as an effective intervention to promote successful aging.

AUTHOR CONTRIBUTIONS

SEB, AMD, JRB, GEC, MV, TN, HN and AFK: manuscript preparation and editing; SEB, AMD, JRB, GEC and MV: data analysis and interpretation; GEC, MV, TN, HN and AFK: study design; AFK, TN and HN: study funding.

ACKNOWLEDGMENTS

This study was supported by funding from the National Institute on Aging to AFK, HN and TN. AMD and JRB were supported by Beckman Institute Postdoctoral Fellowships at the University of Illinois at Urbana-Champaign, with funding provided by the Arnold and Mabel Beckman Foundation.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 22 May 2017
doi: 10.3389/fnagi.2017.00152

Age-Related Differences in Dynamic Interactions Among Default Mode, Frontoparietal Control, and Dorsal Attention Networks during Resting-State and Interference Resolution

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Resting-state fMRI (rs-fMRI) can identify large-scale brain networks, including the default mode (DMN), frontoparietal control (FPN) and dorsal attention (DAN) networks. Interactions among these networks are critical for supporting complex cognitive functions, yet the way in which they are modulated across states is not well understood. Moreover, it remains unclear whether these interactions are similarly affected in aging regardless of cognitive state. In this study, we investigated age-related differences in functional interactions among the DMN, FPN and DAN during rest and the Multi-Source Interference task (MSIT). Networks were identified using independent component analysis (ICA), and functional connectivity was measured during rest and task. We found that the FPN was more coupled with the DMN during rest and with the DAN during the MSIT. The degree of FPN-DMN connectivity was lower in older compared to younger adults, whereas no age-related differences were observed in FPN-DAN connectivity in either state. This suggests that dynamic interactions of the FPN are stable across cognitive states. The DMN and DAN were anti correlated and age-sensitive during the MSIT only, indicating variation in a task-dependent manner. Increased levels of anticorrelation from rest to task also predicted successful interference resolution. Additional analyses revealed that the degree of DMN-DAN anticorrelation during the MSIT was associated to resting cerebral blood flow (CBF) within the DMN. This suggests that reduced DMN neural activity during rest underlies an impaired ability to achieve higher levels of anticorrelation during a task. Taken together, our results suggest that only parts of age-related differences in connectivity are uncovered at rest and thus, should be studied in the functional connectome across multiple states for a more comprehensive picture.

Keywords: brain networks, functional connectivity, interactions, interference resolution, resting-state

OPEN ACCESS

Edited by:
Pamela M. Greenwood, George Mason University, United States

Reviewed by:
Stefano Delli Pizzi, University of Chieti-Pescara, Italy
Isabella C. Wagner, University of Vienna, Austria

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Received: *30 September 2016*
Accepted: *03 May 2017*
Published: *22 May 2017*

Citation:
Avelar-Pereira B, Bäckman L, Wåhlin A, Nyberg L and Salami A (2017) Age-Related Differences in Dynamic Interactions Among Default Mode, Frontoparietal Control, and Dorsal Attention Networks during Resting-State and Interference Resolution. Front. Aging Neurosci. 9:152. doi: 10.3389/fnagi.2017.00152

INTRODUCTION

Resting-state fMRI (rs-fMRI) measures temporal correlations in spontaneous blood oxygen level-dependent (BOLD) signal fluctuations of discrete brain regions. Coherence in spontaneous activity among brain regions is referred to as functional connectivity, and provides an important measure of information transfer and dynamics in the brain (Shmuel and Leopold, 2008; Damoiseaux and Greicius, 2009). Several studies have shown coherent spontaneous activity within neuroanatomical systems, revealing large-scale functional networks (Damoiseaux et al., 2006; Chen et al., 2008; Biswal et al., 2010; Allen et al., 2011; Power et al., 2011; Yeo et al., 2011; van den Heuvel and Sporns, 2013; Salami et al., 2014a,b). These resting-state networks (RSNs) show strong within-network connectivity and have a particular topological signature. A number of RSNs are now recognized, including the default mode network (DMN; Raichle et al., 2001; Buckner et al., 2008; Andrews-Hanna et al., 2010), the frontoparietal control network (FPN; Vincent et al., 2008; Spreng et al., 2010; Niendam et al., 2012), and the dorsal attention network (DAN; Corbetta and Shulman, 2002; Fox et al., 2006). The latter two are part of the task-positive network (TPN; Fox et al., 2005) and show increased activation during externalized attention-demanding cognitive tasks (Cabeza and Nyberg, 2000; Fox et al., 2005; Dosenbach et al., 2007). In contrast, the DMN has been shown to deactivate during externally focused tasks (Raichle et al., 2001; Buckner et al., 2008), and is instead active during internally focused tasks (Spreng et al., 2010; Spreng and Schacter, 2012) and unconstrained cognition (e.g., mind-wandering; Mason et al., 2007; Buckner et al., 2008; Christoff et al., 2009; Spreng et al., 2009).

The topology of the brain is similar across different cognitive states (Calhoun et al., 2008; Smith et al., 2009; Cole et al., 2014; Krienen et al., 2014). That is, the same functional networks, including TPNs and the DMN, are present during both rest and a number of cognitive tasks. Functional interactions among these networks are critical for integrating resources from distinct brain systems, in order to support complex cognitive functions (Fransson, 2006; Kelly et al., 2008; Hampson et al., 2010; Spreng et al., 2010; Spreng and Schacter, 2012; Elton and Gao, 2014). However, the way in which interactions between TPNs and the DMN are modulated across cognitive states is not well understood. On the one hand, previous studies report moment-to-moment anticorrelations (i.e., negative correlations) between the DMN and some parts of the TPN, particularly the DAN, during both rest (Fox et al., 2005, 2009; Fransson, 2005; Keller et al., 2015) and task (Fornito et al., 2012; Elton and Gao, 2014, 2015). Importantly, the degree of anticorrelation tends to increase from rest to task and is associated with level of cognitive performance (Kelly et al., 2008; Hampson et al., 2010; Rieckmann et al., 2011; De Pisapia et al., 2011). On the other hand, positive functional coupling between the DMN and FPN has also been observed during rest and goal-directed internally focused cognitive tasks (Simons et al., 2008; Spreng et al., 2010; Spreng and Schacter, 2012; Bluhm et al., 2011; Gerlach et al., 2011; Leech et al., 2011; Gao and Lin, 2012; Di and Biswal, 2014). Yet, the extent to which these opposite connectivity trends reflect increases or decreases in connectivity as a function of cognitive demands is not clear. This diverse pattern of functional connectivity may reflect that different parts of the TPN serve different functions across different cognitive states. Hence, their dynamic profile and coupling with the DMN may also change. In support of this view, Spreng et al. (2010) provided a first indication that the FPN facilitates the relation between the DMN and DAN, by coupling its activity with one or the other in support of internally or externally-oriented cognition. As the FPN is anatomically interposed between the DMN and DAN, it is well placed to integrate information from both networks (Vincent et al., 2008). Although this model was initially suggested for two different types of goal-directed tasks (autobiographical vs. visuospatial planning), it could be extended to become a hypothetical model of dynamic changes from rest to task. Thus, the first aim of this study is to investigate how dynamic interactions among the DMN, FPN and DAN differ between rest and an external goal-directed task.

Functional interactions between large-scale networks, particularly between the DMN and DAN/FPN during both rest and task, are altered in aging (Grady et al., 2006, 2010, 2016; Andrews-Hanna et al., 2007; Sambataro et al., 2010; Wu et al., 2011; Chan et al., 2014; Geerligs et al., 2014a,b; Li et al., 2015). However, the underlying cause of these disruptions is still under debate. Some studies have reported that older adults show lower levels of within-network connectivity in the DMN when performing external attention-demanding tasks, which might lead to disruptive interactions between the DMN and TPNs (Lustig et al., 2003; Grady et al., 2006; Persson et al., 2007; Damoiseaux et al., 2008; Sambataro et al., 2010). Others, however, have suggested that age-related alterations in inter-network connectivity are not caused by dysfunction within the DMN itself, but rather reflect lower flexibility of network interactivity and reduced range of network modulation to changing task demands (Spreng and Schacter, 2012). Thus, this would indicate that there are age-related functional connectivity deficiencies in interactions between the DMN and other networks.

Moreover, the way in which these RSNs are affected by aging may not be identical during rest and task. For some networks, functional connectivity can represent a stable characteristic of the brain, whereas for others it can change depending on cognitive state. Previous studies suggest that both stability and variability are important in shaping individual functional connectivity profiles (Cole et al., 2014; Geerligs et al., 2015). Still, it remains unclear whether the degree of functional connectivity between TPNs and the DMN is stable or whether it differs across states. Geerligs et al. (2015), showed that average functional connectivity among several RSNs was highly similar across mental states, whereas age-related differences remained similar for some RSNs, but different for others. This dichotomy could reflect underlying differences in connectivity nature. Still, regardless of the role of the FPN in supporting internal or external goal-directed cognition, results from previous studies show that the level of functional connectivity within these TPNs and between the FPN and DMN is positive (Spreng et al., 2010; Spreng and Schacter, 2012; Elton and Gao, 2015). On the other

hand, the DMN and DAN have been consistently reported to be anticorrelated, reflecting the extent to which the DMN is suppressed and the DAN is engaged (Fox et al., 2005, 2009; Elton and Gao, 2014, 2015). Hence, it is possible that age-related alterations in connectivity between the FPN and DMN/DAN behave differently from those involving the DMN and DAN and, subsequently, exhibit distinct stability patterns. The second aim of our study is to investigate this possibility, by exploring whether possible age-related differences in dynamic interactions among the DMN, FPN and DAN are modulated when switching from rest to task. This allows us to discriminate if age-related differences are readily observed during rest, or whether networks need to be engaged in a task for them to be detected.

We used fMRI data from 29 younger and 30 older participants scanned during rest and while performing the Multi-Source Interference task (MSIT, Bush et al., 2003). To complete the MSIT, subjects need to ignore irrelevant information and deal with multiple dimensions of cognitive interference. This type of conflict resolution is known to decline in aging, with older adults being less able to inhibit irrelevant information (Hasher et al., 1991; Stoltzfus et al., 1993; Madden et al., 2004; Gazzaley et al., 2008; Greenwood and Parasuraman, 2012; Salami et al., 2014b). To investigate how dynamic interactions among these networks change from rest to the MSIT, we used independent component analysis (ICA) to identify the three RSNs. First, we hypothesized that the FPN is more coupled to the DMN during rest, and to the DAN during the MSIT. Second, we predicted that the dynamic coupling between the FPN and DMN during rest and between the FPN and DAN during task is less expressed in older adults. Thus, finding age-related differences during both rest and task would indicate that the functional connectivity profile among these networks is stable across states. If these differences were to vary from rest to task, it would rather imply that functional connectivity changes in a state-dependent manner. Third, we expected the DMN and DAN to be negatively correlated during both states, but that the degree of anticorrelation would be greater during the task. In agreement with past work (Hampson et al., 2010; Rieckmann et al., 2011; Hermundstad et al., 2014), we also examined possible associations between DMN-DAN functional connectivity and cognitive performance. Complementary analyses were carried out to investigate whether resting cerebral blood flow (CBF) within the DMN relates to the level of anticorrelation between the DMN and DAN during the MSIT (Riedl et al., 2014). This would clarify whether lower DMN neural activity during rest underlies an impaired ability to achieve higher levels of anticorrelation during a task.

MATERIALS AND METHODS

Participants

Twenty-nine younger (mean age 25.0 ± 3.4 years, range 20–31, 16 women) and 30 older (mean age 68.2 ± 2.6 years, range 65–74, 16 women) adults from Stockholm, Sweden were sampled. All participants were right-handed, native Swedish-speakers, had normal or corrected to normal vision and no history of neurological illness. None of them reported or was diagnosed with cognitive impairment. There were no significant differences in years of education (young: 14.8 ± 2.1; old: 14.4 ± 3.7), the Mini Mental Status Examination (MMSE; Folstein et al., 1975; young: 29.3 ± 0.7; old: 29.0 ± 0.9), depressive symptoms as assessed using the Swedish version of the Geriatric Depression Scale (Brink et al., 1982; Gottfries, 1997; young: 1.4 ± 1.6; old: 1.5 ± 2.5), or in the state scale of the State-Trait Anxiety Inventory (Spielberger et al., 1983; young: 30.5 ± 5.4; old: 27.9 ± 8.0). We used a cutoff of 24 for MMSE (Folstein et al., 1975) and performed additional behavioral analyses, where older participants showed typical patterns, with worse performance in working memory ($p < 0.001$), but better performance in semantic memory ($p < 0.001$), compared with their younger counterparts. All 59 subjects underwent 6 min of rs-fMRI and 57 subjects also completed the MSIT in the scanner. Three persons (two old, one young) were excluded from analysis due to low task performance (3 SD ± mean). Another two older subjects were excluded for not performing the task at all. One young subject was excluded due to technical error. Thus, the effective MSIT sample included 26 younger and 25 older participants. All subjects gave written informed consent. The protocol was approved by the Karolinska Institutet Ethics Committee in accordance with the recommendations of the Declaration of Helsinki.

Data Acquisition

Brain imaging data were acquired with a 3T fMRI Siemens Magnetom TrioTim scanner at Huddinge Hospital, Stockholm, Sweden, with a 32-channel head coil. Functional data were obtained with a gradient-echo planar imaging (EPI) sequence as follows: TR = 2.5 s, 39 slices (3.0 mm thick), voxel size 3 × 3 × 3 mm, FOV = 230 mm, flip angle = 90°, TE = 40 ms. Four dummy scans were obtained to allow for equilibration of the fMRI signal. Structural high-resolution T1-weighted images (200 slices, 1 mm thickness, FOV = 256 mm, voxel size = 1 × 1 × 1 mm^3) were collected after the functional images.

Participants underwent 6 min of rs-fMRI, during which they were instructed to keep their eyes open and lie still. In addition, they performed the MSIT (Bush et al., 2003), a task that consists of detecting and reporting the number that is different (target) from two other numbers (distracters) presented simultaneously on a screen. It includes 16 blocks of control and interference trials, which alternate during the session. Within each block, 12 stimuli were presented for 2 s each. Participants were given a button box and told that the keys corresponded to numbers 1, 2 and 3, from left to right. They were instructed to indicate the number that was different by pressing the key that spatially corresponded to the target number, regardless of its position on the screen. During control trials, distracters were always zero and the target number corresponded to its position on the button box (e.g., the number 1 always appeared in the leftmost position). In contrast, during interference trials, distracters were 1, 2, or 3 and the target never matched its position on the keyboard. Participants were instructed to respond as accurately and quickly as possible (**Figure 1**). Stimuli were presented on a computer

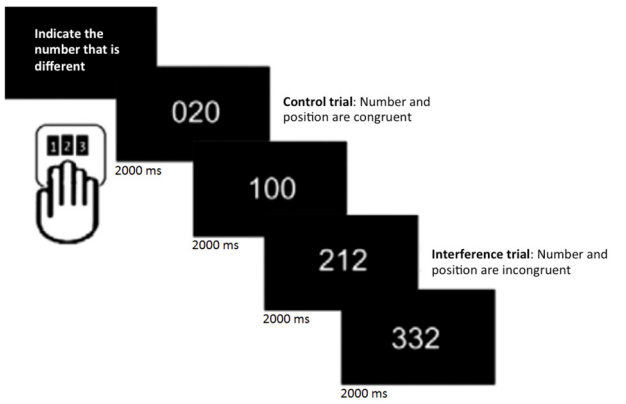

FIGURE 1 | Multi-Source Interference task (MSIT; Bush et al., 2003). In each trial, participants were asked to indicate the number that was different by pressing the spatially corresponding key on the button pad.

screen that was seen by participants through a tilted mirror attached to the head coil. E-prime (Psychology Software Tools, Inc., Pittsburgh, PA, USA[1]) was used for presentation of stimuli and responses were made on custom-built MRI-compatible response pads (MAG Design and Engineering, Sunnyvale, CA, USA).

CBF data were acquired using a pseudo-continuous arterial spin labeling (pCASL) sequence with the following settings: TE/TR = 18/3500 ms, 18 slices (6.0 mm thick), FOV = 230 × 230, flip angle = 90°, labeling duration = 1600 ms, post-labeling delay = 1170 ms, matrix size = 64 × 64, inter-slice gap = 0.9 mm, bandwidth = 2790 Hz/pixel, with 70 control/label acquisitions.

Data Analysis

Preprocessing

Functional and structural images were preprocessed using Statistical Parametric Mapping Software (SPM12; Wellcome Department of Imaging Science, Functional Imaging Laboratory, University College London). All functional images were first corrected for differences in slice-time acquisition within each volume using the middle slice as reference. The resulting slice-timing corrected images were rigidly aligned to the first volume to correct for head motion. These images were then despiked with 3dDespike in AFNI[2], which minimizes the effect of outliers by eliminating spikes in the time-series signal. Despiking is very similar to the scrubbing method proposed by Power et al. (2012), but rather than removing the affected time points, the outliers are replaced with estimates derived from a third-order spline fit. Next, a within-subject rigid registration was conducted in order to align functional and structural images. T1-weighted images were then segmented into gray matter (GM) and white matter (WM), and a group-specific template was created with Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra (DARTEL; Ashburner, 2007). GM and WM images were imported into the DARTEL space using the normalization parameter previously generated during segmentation, followed by resampling to isotropic voxels. A first template was produced as a mean of GM/WM across all subjects. Then a deformation from this template was computed to each of the subject-specific GM/WM images. The inverse of the deformation was applied to the subject-specific GM/WM images. A second template was produced as the mean of the deformed subject-specific GM/WM images. This included six iterative steps of increasingly improved group-specific templates. The realigned fMRI and segmented GM/WM images were then non-linearly normalized to a sample-specific template, affine aligned to the Montreal Neurological Institute (MNI) template, and smoothed using a 6 mm full-width at half-maximum (FWHM) Gaussian filter. For smoothing, we followed the theory of Gaussian random fields, according to which reliable estimates of statistical significance can only be obtained when smoothing kernels have at least twice the voxel size (Worsley and Friston, 1995).

The pCASL postprocessing was based on scripts provided in the ASL toolbox[3]. It included motion correction by rigid body transformation, creation of a mean image, coregistration between the mean image and anatomical T1, realigning the pCASL images to match the mean, spatially smoothing the data (6 mm FWHM Gaussian filter), and calculating a CBF map in ml/100 g/min. The maps were spatially normalized in analogy to the functional scans. Finally, a threshold map was used to calculate subject specific CBF in the DMN. As a control analysis, a similar procedure was undertaken to calculate CBF in the primary visual network.

Statistical Analyses

ICA was applied to the resting-state preprocessed images using the group ICA fMRI toolbox (GIFT v2.0a; Calhoun et al., 2001; Allen et al., 2011). ICA is a multivariate data-driven technique that decomposes the fMRI dataset into independent spatial maps and respective time courses. This is done by first reducing the intensity-normalized data from each subject using principal component analysis (PCA), which decreases computational complexity while keeping most of the information. The resulting volumes were then temporally concatenated and PCA was performed again. After these two steps of data reduction, ICA was performed using the Infomax algorithm to identify 21 independent components (ICs), estimated by minimum description length criteria (MDL), on a group level. Finally, a back reconstruction using an improved version of dual regression (GICA3, Erhardt et al., 2011) was carried out, and spatial maps and corresponding time courses were computed for each subject. After visually inspecting all 21 ICs and comparing their topology to those of previous studies, 13 were considered to represent relevant RSNs (Raichle et al., 2001; Damoiseaux et al., 2006; Andrews-Hanna et al., 2007; Smith et al., 2009; Biswal et al., 2010; Allen et al., 2011; Salami et al., 2014b). These networks exhibited spatial overlap with RSNs identified in previous studies (Biswal et al., 2010; Di and Biswal, 2014; Salami et al., 2014b), showed peak activation in the GM, and had little to no overlaps with ICs known to reflect vascular, ventricles, motion and susceptibility

[1]www.pstnet.com/eprime

[2]http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dDespike.html

[3]https://cfn.upenn.edu/~zewang/ASLtbx.php

artifacts. Out of the 13 relevant networks, we identified and further analyzed the right and left FPN, DMN and the DAN. The inter-network functional connectivity, which reflects the degree of cross talk between two specific networks, was then computed. This was carried out using Fisher's z-transformed Pearson correlation coefficients between pairs of time courses that were previously detrended, despiked, and filtered using a fifth-order Butterworth low-pass filter ($f < 0.15$). Importantly, given that previous studies have shown that head motion in the scanner can have a strong effect on functional connectivity during rest (Power et al., 2012; Buckner et al., 2013), additional preprocessing steps and control analyses were carried out in order to distinguish noise sources from the signal of interest. Outliers from subjects' time courses were identified based on the median absolute deviation and replaced with the best estimate using third-order spline fit. Previous work has shown that this method is efficient in reducing the effect of head motion from ICA time courses (Allen et al., 2014; Geerligs et al., 2014a; Salami et al., 2016). As a control analysis, an additional step was carried out where 24-motion parameters using the Friston model (Yan et al., 2013) were regressed out before performing the ICA.

Because we were also interested in investigating the degree of change in functional connectivity during the interference resolution task, a constrained ICA (Calhoun et al., 2005) was applied to the preprocessed MSIT fMRI images, using the templates derived from the resting-state ICA analyses. The inter-network connectivity between the components of interest was also computed. Then, in order to assess whether connectivity between these networks changes from rest to task, a 3 (connectivity: FPN-DMN; FPN-DAN; DMN-DAN) by 2 (state: rest vs. task) repeated-measures analysis of variance (ANOVA) was conducted. The ANOVA was first carried out for the younger group only, to assess how inter-network connectivity changes in a canonical sample composed by healthy young individuals. This was followed by a 3 (connectivity: FPN-DMN; FPN-DAN; DMN-DAN) by 2 (state: rest vs. task) by 2 (group: young vs. old) ANOVA, in order to compare connectivity differences between the two groups. When appropriate, results were followed by *post hoc* *t*-tests (Bonferroni corrected for multiple comparisons).

In addition, we calculated the degree of task-relatedness for each of these networks with the temporal sorting option in GIFT. This method uses a multiple regression fit to each subjects' ICA time courses. First, regressors modeling both the control and interference conditions were computed using SPM12, by convolving the ideal timing of the events with a canonical hemodynamic response function. Then, these regressors were fit to subjects' time courses and the average percent signal change was computed. Task-relatedness was measured by analyzing the fit parameters. A network would be task-related if the regressor parameter fit survived a one-sample *t*-test (Calhoun et al., 2008). Finally, to test for an association between functional connectivity and MSIT performance, we computed change-change correlations for inter-network functional connectivity (connectivity during rest—connectivity during task) and MSIT accuracy (accuracy in control condition—accuracy in interference condition). This analysis was carried out for the FPN-DMN, FPN-DAN and DMN-DAN. We also tested whether resting CBF in the DMN was associated with the level of DMN-DAN anticorrelation during task performance.

RESULTS

Cognitive Performance

A 2 (condition: control vs. interference) by 2 (group: young vs. older) ANOVA was conducted on the accuracy data. The analysis showed a main effect of condition ($F_{(1,104)} = 16.146$, $p < 0.0001$), a main effect of age ($F_{(1,104)} = 4.397$, $p = 0.038$) and a significant age × condition interaction ($F_{(1,104)} = 4.239$, $p < 0.05$). Older subjects' were less accurate during interference than during the control condition ($p = 0.002$), but this effect was only at trend level in younger adults ($p = 0.08$). The older group was also less accurate compared to the young during interference ($p < 0.05$), but not during control ($p = 0.9$). A similar ANOVA was run for latency for correct trials, showing significant main effects of condition ($F_{(1,108)} = 108.912$, $p < 0.0001$) and age ($F_{(1,108)} = 21.830$, $p < 0.0001$), but no interaction ($F < 1$). Reaction times were longer for interference compared to control trials for both groups ($p < 0.0001$), and longer for older adults than for the young in both conditions ($p < 0.05$; for more details see Salami et al., 2014b).

Mapping Resting-State Networks

ICA estimated a total of 21 components, 13 of which represented RSNs. We identified the DMN, bilateral FPN and DAN (**Figure 2**), by comparing the topology of all ICA components with those of previous studies (Spreng et al., 2010; Di and Biswal, 2014; Salami et al., 2014b).

The two components identified as the DMN were averaged, and consisted of brain regions traditionally known to be part of this network such as the ventral medial prefrontal cortex (vmPFC), inferior parietal lobule (IPL) and posterior cingulate cortex (PCC). The FPN included the rostrolateral prefrontal cortex (rlPFC), anterior extent of the inferior parietal lobule (aIPL), and middle frontal gyrus (MFG). Finally, the DAN consisted, among others, of the dorsolateral prefrontal cortex (dlPFC) and superior parietal lobule (SPL). These networks had little to no overlap with known artifacts or with each other (**Figure 3**).

Inter-Network Connectivity in the Younger Group

We first investigated whether the degree of functional connectivity among the DMN, FPN (averaged across the two hemispheres), and DAN changed from rest to the MSIT in the group of younger subjects. This also served as a check to assess whether functional connectivity levels fell within the expected range. The ANOVA revealed a main effect of connectivity ($F_{(2,54)} = 305.76$, $p < 0.0001$), a main effect of state ($F_{(1,27)} = 23.02$, $p < 0.0001$) and a connectivity × state interaction ($F_{(2,54)} = 44.67$, $p < 0.0001$). Pairwise comparisons showed that FPN-DMN connectivity was higher ($t_{(27)} = 7.34$,

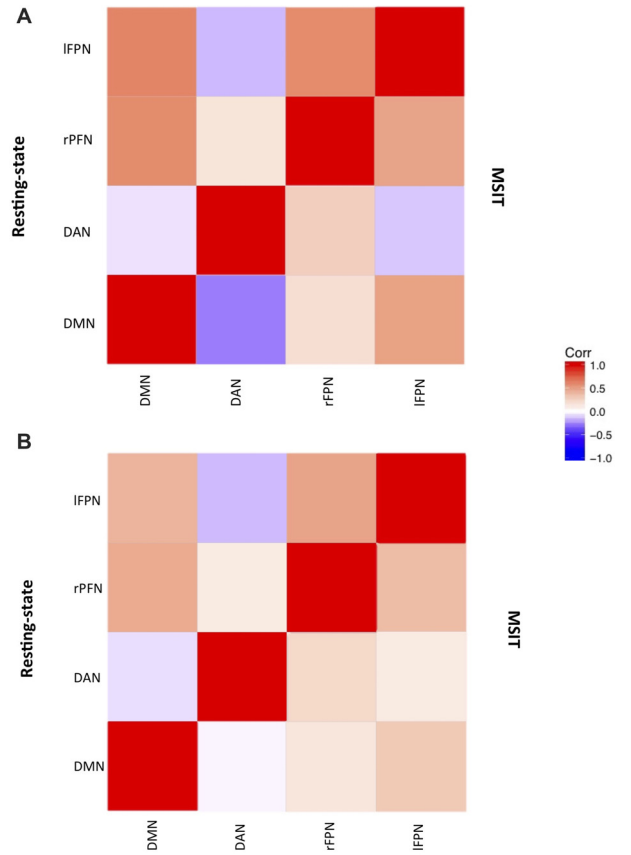

FIGURE 2 | Networks correlation matrix during resting-state (upper-case diagonal) and interference resolution (lower-case diagonal) for (A) young and **(B)** old.

$p < 0.0001$) at rest compared to task, whereas the opposite pattern was seen for the FPN and DAN, where functional connectivity was higher ($t_{(27)} = -2.57$, $p = 0.016$) during the MSIT as compared to rest. Moreover, the level of DMN-DAN anticorrelation also increased ($t_{(27)} = 5.13$, $p < 0.0001$) from rest to task.

In summary, younger adults had lower FPN-DMN and higher FPN-DAN connectivity during the MSIT, as compared to rest. They also showed a task-related increase in the level of DMN-DAN anticorrelation. However, the degree of correlation between the FPN and DAN was lower ($r < 0.1$) than expected during both states, when compared to the other networks or results found in previous studies (Spreng et al., 2010; Spreng and Schacter, 2012; **Figure 4**).

We further examined possible reasons for low FPN-DAN connectivity. The magnitude of the correlation between the FPN and DAN was significantly different from zero, but quite low when compared to other networks. Thus, we hypothesized that the FPN—the network responsible for coupling itself with the DMN or DAN according to task demands—could be differentially modulated (i.e., engaged or disengaged) between the right and left hemisphere given the nature of the task.

To investigate this, a multiple regression fit with control and interference conditions as regressors was carried out on subjects' ICA time courses. We found that the right FPN (rFPN) was strongly and positively related to both control and interference, whereas the left FPN (lFPN) was not significantly associated with any of the two conditions (**Table 1** for results across groups). The DAN and DMN were positively and negatively associated to the task, respectively. Finally, the rFPN and DAN were the most task-related networks in our study.

Results from the task-relatedness analysis are indicative of a lateralized effect regarding FPN connectivity during the MSIT. Hence, rather than analyzing connectivity with the averaged bilateral FPN, we repeated the analyses for the rFPN and lFPN separately (**Figure 5**, left panel). When including the rFPN, the ANOVA showed a main effect of connectivity ($F_{(2,54)} = 160.89$, $p < 0.0001$), a main effect of state ($F_{(1,27)} = 38.27$, $p < 0.0001$) and a connectivity × state interaction ($F_{(2,54)} = 58.62$, $p < 0.0001$). In line with the initial results, these data also indicate that rFPN-DMN connectivity was higher ($t_{(27)} = 10.25$, $p < 0.0001$) during rest compared to the MSIT, whereas connectivity between the rFPN and DAN was higher during task ($t_{(27)} = -3.29$, $p = 0.003$) compared to rest. When the model included the lFPN instead, results also showed a main effect of connectivity ($F_{(2,54)} = 290.25$, $p < 0.0001$), a main effect of state ($F_{(1,27)} = 10.00$, $p = 0.004$), and a connectivity × state interaction ($F_{(2,54)} = 10.94$, $p < 0.0001$). Connectivity between the lFPN and DMN was again higher ($t_{(27)} = 2.53$, $p = 0.018$) during rest than during task. However this was not the case for connectivity between the lFPN and DAN, which was not different between the two states ($t_{(27)} = -0.71$, $p = 0.483$).

In sum, similar effects to our previous analysis were found regarding rFPN/lFPN connectivity with the DMN, such that connectivity between the networks decreased from rest to task. Likewise, connectivity between the rFPN and DAN was also consistent with the initial results, showing an increase from rest to task. However, connectivity between the lFPN and DAN remained identical in both states. Thus, in order to facilitate interpretation in the following analyses, we averaged right and left FPN connectivity concerning the DMN. Because connectivity between the FPN and DAN showed distinct unilateral patterns, this could not be done for the DAN.

Inter-Network Connectivity in the Younger vs. Older Group

Our second aim was to investigate whether functional connectivity changes among the DMN, FPN and DAN were differentially expressed in young and older adults. Hence, a 3 (connectivity) by 2 (state) by 2 (group) ANOVA was conducted using the right lateralized and task-related rFPN-DAN connectivity. This revealed a main effect of connectivity ($F_{(2,110)} = 382.96$, $p < 0.0001$), a main effect of state ($F_{(1,55)} = 14.91$, $p < 0.0001$), but not of group ($F_{(1,55)} = 1.90$, $p = 0.174$), as well as a connectivity × group interaction ($F_{(2,110)} = 21.20$, $p < 0.0001$), a state × group interaction ($F_{(1,55)} = 7.57$, $p = 0.008$), a connectivity × state interaction ($F_{(2,110)} = 54.89$, $p < 0.0001$) and a connectivity × state × group

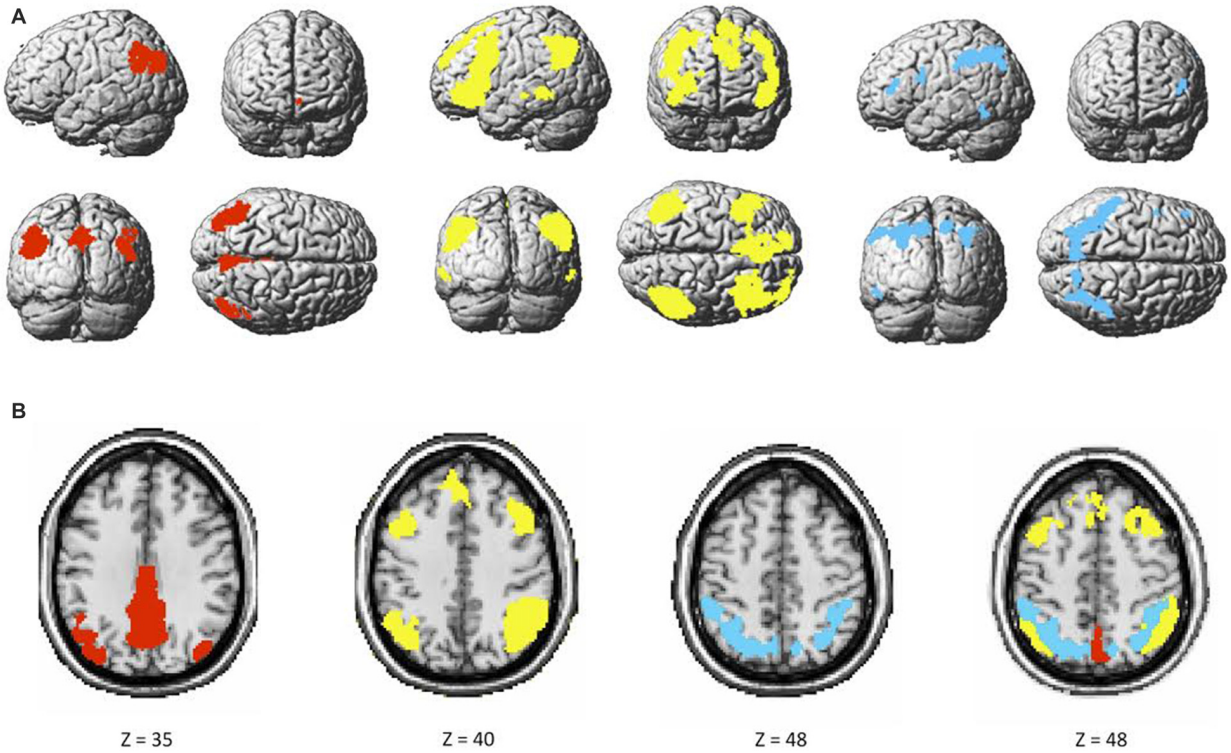

FIGURE 3 | (A) Maps of the default mode (DMN; red), bilateral frontoparietal control (FPN; yellow), and dorsal attention (DAN; blue), and **(B)** overlap among the three networks.

interaction ($F_{(2,110)} = 6.74$, $p = 0.002$). Specifically, FPN-DMN connectivity was higher during rest than during the MSIT for both the young ($t_{(27)} = 7.34$, $p < 0.0001$) and the old ($t_{(28)} = 4.43$, $p < 0.0001$). The younger group had higher connectivity levels during both rest ($t_{(57)} = -4.15$, $p < 0.0001$) and task ($t_{(55)} = -0.247$, $p = 0.017$) when compared to the older group. In summary, the older group showed significantly lower connectivity during rest and the MSIT when compared to the young, but exhibited the same pattern of results by decreasing the degree of FPN-DMN connectivity during task performance.

Connectivity between the two task-related networks, the rFPN and DAN, was higher during MSIT as compared to rest for both young ($t_{(27)} = -0.33$, $p = 0.003$) and old ($t_{(28)} = -3.12$, $p = 0.004$). Moreover, younger subjects had slightly higher rFPN-DAN connectivity compared to the old, but this difference did not approach conventional significance in either state (rest: $t_{(45.555)} = -0.99$, $p = 0.329$; MSIT: $t_{(45.220)} = -1.34$, $p = 0.186$). Hence, both young and old showed higher connectivity between the rFPN and DAN during the MSIT than during rest, but there were no age-related differences in either state.

Despite not being task-related, pairwise t-tests were carried out in order to compare lFPN and DAN connectivity. During rest, the younger and older groups' connectivity was not different ($t_{(57)} = 0.16$, $p = 0.872$), but during the MSIT, the old showed significantly higher connectivity ($t_{(55)} = 4.95$, $p < 0.0001$), compared to the young. Whereas the young group showed no significant difference in lFPN-DAN connectivity between rest and task ($t_{(27)} = -0.71$, $p = 0.483$), the old group showed an increase in functional connectivity during

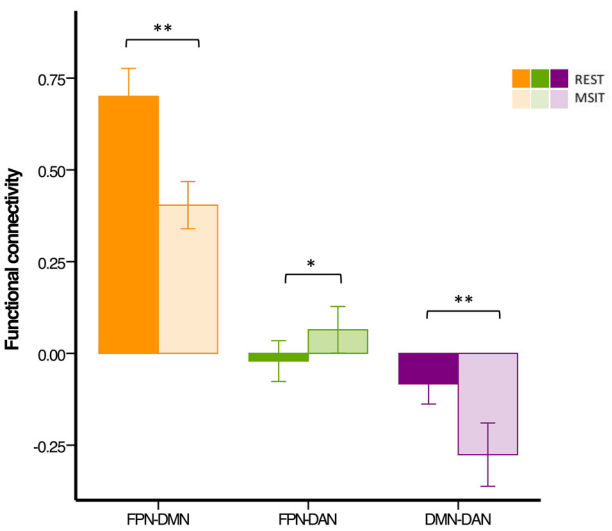

FIGURE 4 | Functional connectivity among the DMN, FPN and DAN during rest and the MSIT for the younger group. Connectivity between the FPN and DMN significantly decreased from rest to task, whereas the opposite trend can be seen for coupling between the FPN and DAN. The DMN and DAN were significantly more anticorrelated during task performance than during rest. *$p < 0.05$; **$p < 0.001$.

TABLE 1 | Network task relatedness across both age groups.

	Interference		Control	
	t-value	*p*-value	*t*-value	*p*-value
Default mode network (component 1)	−9.748	1.145e-13	−5.834	2.821e-07
Default mode network (component 2)	−6.151	8.596-08	−5.779	3.466e-07
Right frontoparietal network	7.679	2.614e-10	8.457	1.374e-11
Left frontoparietal network	−1.528	0.132	−0.668	0.507
Dorsal attention network	11.175	6.999e-16	3.411	0.001

the MSIT ($t_{(28)} = -7.42$, $p < 0.0001$). This indicates that connectivity between the lFPN and DAN remained the same during both states for the young, but increased during the task for the old.

Finally, the level of DMN-DAN anticorrelation indicated that the younger and older groups' connectivity was not significantly different during rest ($t_{(57)} = -0.14$, $p = 0.888$), but that the young had higher negative DMN-DAN connectivity compared to the old during the MSIT ($t_{(55)} = 4.56$, $p < 0.0001$). From a different angle, connectivity levels did not differ between the two states in the older group ($t_{(28)} = -1.48$ $p = 0.151$), whereas the degree of anticorrelation increased in the young during the MSIT ($t_{(27)} = 5.13$, $p < 0.0001$). As such, the young showed greater task-related modulation in DMN-DAN anticorrelation compared to the old (**Figure 5**).

Correlations with MSIT Performance and Perfusion

To test for an association between functional connectivity and MSIT performance, we computed change-change correlations for inter-network functional connectivity (connectivity during

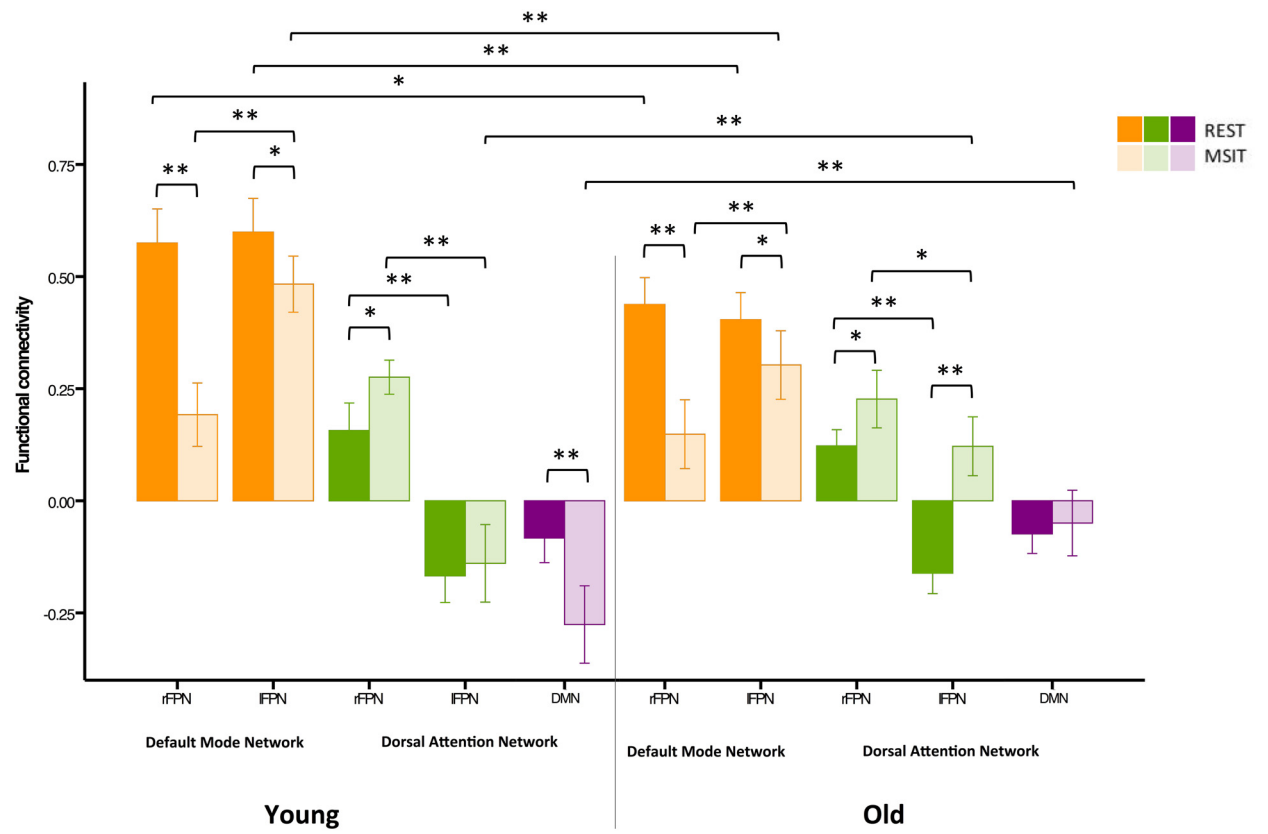

FIGURE 5 | Functional connectivity among the DMN, FPN and DAN during rest and the MSIT for younger and older adults. The young had higher FPN-DMN connectivity than the old in both conditions. However, both groups showed a decrease in inter-network functional connectivity during the MSIT when compared to rest. Both groups also showed an increase in right FPN (rFPN)-DAN connectivity during the MSIT compared to rest, but there were no differences between young and old. Although there were also no differences between the groups in lFPN-DAN connectivity during rest, the old showed increased connectivity during the MSIT, whereas the young group retained similar levels of (negative) connectivity. DMN-DAN connectivity levels did not significantly differ between the age groups at rest, but the young showed increased negative connectivity during the MSIT, whereas the old did not. *$p < 0.05$; **$p < 0.001$.

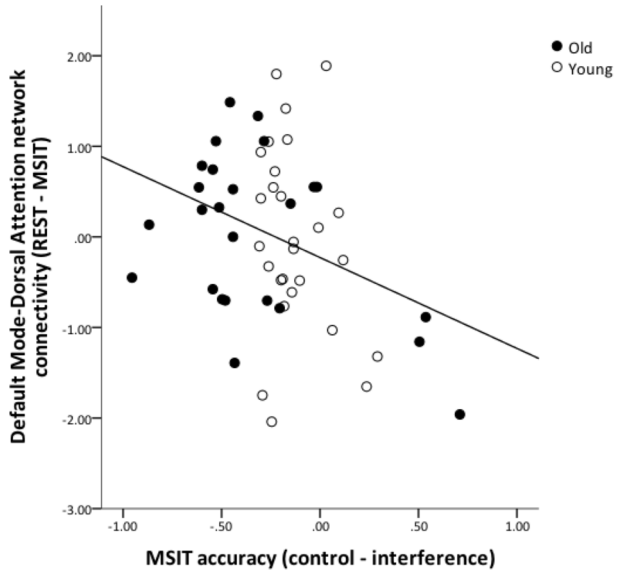

FIGURE 6 | The relation between DMN and DAN coupling and MSIT accuracy. The graph shows the residuals of the change-change age-partialed correlation between DMN-DAN connectivity (rest—task) and accuracy during the MSIT (correct responses for control items—correct responses for interference items).

rest—connectivity during task) and MSIT accuracy (accuracy in control condition—accuracy in interference condition) for all connectivity pairs (FPN-DMN, FPN-DMN and DMN-DAN). Due to the relatively small sample size, these analyses were carried out across all subjects, while controlling for age. The increases in DMN-DAN anticorrelation were significantly correlated with accuracy performance ($r = -0.339$, $p = 0.015$), indicating that better interference resolution was associated with a greater increase in DMN-DAN anticorrelation from rest to MSIT (**Figure 6**). No other associations were found between inter-network connectivity and performance ($p > 0.05$).

Finally, we investigated whether the degree of anticorrelation between the DMN and DAN during task was related to resting CBF in the DMN. The results showed that higher resting CBF in the DMN was associated with a stronger DMN-DAN anticorrelation during the MSIT ($r = -0.30$, $p = 0.047$, after adjusting for age, DMN gray-matter volume, and CBF in the visual cortex). The old had significantly lower global gray-matter CBF than the young (41 ± 9 vs. 57 ± 12 ml/100 g/min, $p < 10^{-7}$). This indicates that high absolute DMN activity during rest contributes to the ability to increase the level of DMN-DAN anticorrelation during a task (Riedl et al., 2014).

Motion and Age-Related Differences in Connectivity

Previous studies have indicated that head motion can create confounds in functional connectivity (Power et al., 2012; Buckner et al., 2013). As such, we have already motion-corrected subjects' ICA time courses, which were then used to compute inter-network connectivity. However, in order to further investigate whether our results were confounded by motion, we carried out an additional control analysis where 24-motion parameters using the Friston model were regressed out, before the ICA—as opposed to motion correction on the ICA time courses. This analysis revealed very similar results to our previous findings (see **Figure 7**).

DISCUSSION

The primary aim of this study was to investigate state-dependent changes in dynamic interaction patterns of three large-scale brain networks in younger and older adults. By comparing inter-network functional connectivity during rest and the MSIT, we demonstrated that interactions within TPNs (i.e., FPN and DAN) and between TPNs and the DMN differ between rest and task in both young and old. Specifically, the FPN was more coupled to the DMN during rest, and more coupled to the DAN during the MSIT in both age groups. Past research has shown increased functional connectivity between the FPN and DMN during autobiographical planning and between the FPN and DAN during visuospatial planning (Spreng et al., 2010; Spreng and Schacter, 2012). Our results further demonstrate that the interposition of the FPN between the DMN and DAN represents a robust effect, and support a switching role for the FPN by dynamically interacting with one or the other depending on task demands. Past work using graph theory has provided more direct evidence for this switching function, by showing that the FPN includes brain regions that flexibly and rapidly update their connectivity in a task-dependent manner, but also that its connectivity pattern shifts more than that of other networks across a variety of tasks (Cole et al., 2013). Moreover, a study by Spreng et al. (2013) identified FPN nodes that exhibit distinct preferred connectivity with the DMN, DAN, or both. These nodes changed their network affiliation and showed realignment from rest to task, which suggests a more flexible connectivity profile.

Our second aim was to investigate age-related differences among the DMN, FPN and DAN. We found that older adults had lower FPN-DMN functional connectivity during both rest and the MSIT, but still exhibited greater FPN-DMN connectivity at rest compared to task. A similar trend was observed for interactions between the rFPN and DAN, with older adults showing numerically lower connectivity values for both states compared to the young, but these did not reach conventional significance. Older adults also had greater rFPN-DAN connectivity during the MSIT compared to rest. These findings suggest that, similarly to what was observed in younger adults, the FPN serves as a switch to actively engage other networks and facilitate cognition in older adults. This pattern is in line with previous studies indicating that normal aging is accompanied by a lower degree of flexible network interactivity (Spreng and Schacter, 2012; Chan et al., 2014; Grady et al., 2016).

Additional analyses revealed that the DMN and DAN were anticorrelated during both states for young and old, but that

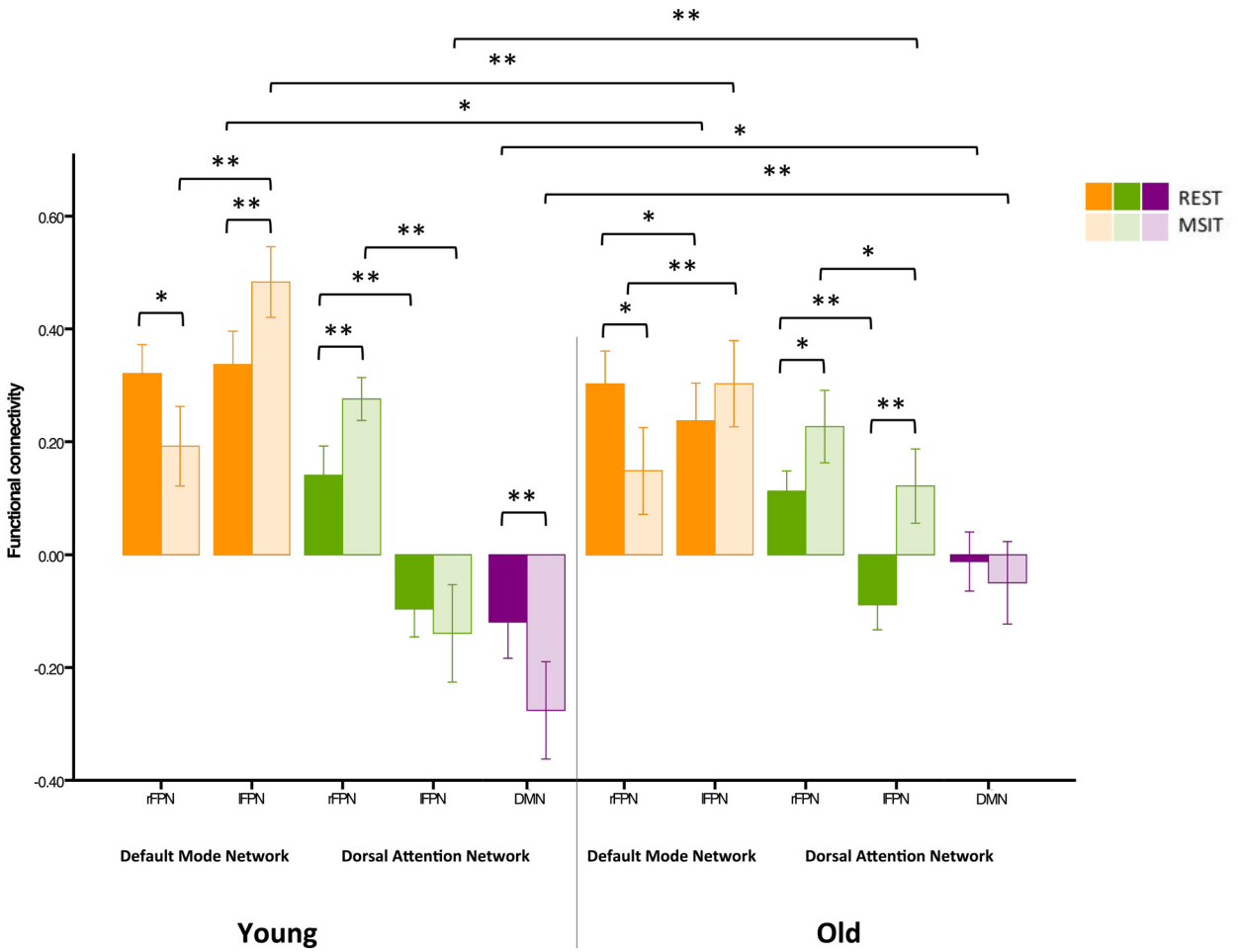

FIGURE 7 | Control analysis on functional connectivity levels among the DMN, FPN and DAN during rest and the MSIT for younger and older adults. Connectivity between the rFPN and DMN decreased for both groups from rest to task. The younger also had higher connectivity between the lFPN and DMN during the MSIT when compared to rest, whereas the old showed no connectivity differences between states. Importantly, there were no differences in rFPN-DMN connectivity between groups during both states, whereas connectivity between the lFPN and DMN was higher for young during both rest and task. Hence, despite exhibiting seemingly opposite effects, the same trend is still observed—an age-related difference that is present during one state is also present during the other and vice-versa. In line with our previous findings, both groups showed an increase in rFPN-DAN connectivity during the MSIT compared to rest, and there were no differences between groups. Young also showed negative connectivity between the lFPN and DAN, with no significant difference between rest and task, whereas the old group's connectivity increased during the MSIT. This is also consistent with our previous results, where young and old similarly increased rFPN-DAN connectivity during the MSIT, but there were no age-related differences in either state. The same trends are also present for the lFPN and DAN, indicating that the young did not change their connectivity levels from one state to the other, whereas the older group did. Finally, both groups had negative connectivity between the DMN and DAN, but the young showed increased anticorrelation during the task while older subjects did not. Importantly, the correlation between DMN-DAN connectivity changes and MSIT performance remained after regressing out motion ($r = -0.408$, $p = 0.003$). $^{*}p < 0.05$; $^{**}p < 0.001$.

the degree of anticorrelation increased from rest to the MSIT in the young only. Several studies indicate that these two networks subserve different cognitive functions, with the DMN being more engaged in internally-directed attention (Simons et al., 2008; Spreng et al., 2010; Spreng and Schacter, 2012; Bluhm et al., 2011; Gerlach et al., 2011; Leech et al., 2011; Gao and Lin, 2012; Di and Biswal, 2014), and the DAN being more engaged in externally-directed attention (Corbetta and Shulman, 2002; Fox et al., 2005; Fransson, 2005; Corbetta et al., 2008; Fox et al., 2009; Keller et al., 2015). Our results corroborate that DMN-DAN anticorrelation transcends cognitive states. We also found that changes in DMN-DAN connectivity levels between rest and task were associated with MSIT accuracy, further supporting its behavioral relevance. Changes in connectivity between cognitive states have been associated with performance in the past (Hermundstad et al., 2014); however studies investigating the relationship between DMN-DAN anticorrelation and task performance have mostly focused on memory (Hampson et al., 2010; Rieckmann et al., 2011). Our results extend these patterns to the domain of interference resolution. Furthemore, the degree of anticorrelation during the MSIT was associated with CBF in the DMN during rest. This suggests that DMN activity at rest is a helpful indicator of the degree of change in DMN-DAN connectivity.

In contrast with previous studies, there were no age-related differences in the level of anticorrelation between the DMN and DAN at rest (e.g., Wu et al., 2011; Keller et al., 2015). However, most of these studies report differences in connectivity between the DAN and the anterior, but not posterior, part of the DMN. Likewise, some previous observations regarding age-related differences in anticorrelation levels should be interpreted with caution due to the use of global signal regression, a method that mitigates physiological noise in resting-state but has been shown to mathematically generate anticorrelations (Murphy et al., 2009). A recent study by Spreng et al. (2016) has similarly demonstrated that DMN-DAN anticorrelation is reduced in older adults during both rest and task, which supports the notion that altered network dynamics is a central feature of brain aging. Our results also showed increased anticorrelation from rest to MSIT in the young only. This finding is in agreement with past work showing that both DMN deactivation and increased anticorrelation levels are related to elevated task demands (Kelly et al., 2008; Hampson et al., 2010). The lack of task modulation in the degree of DMN-DAN anticorrelation in the older group is also in line with the view that aging is accompanied by impaired flexible network interactivity (Spreng et al., 2016).

Our task-relatedness analysis indicated that only the rFPN was involved in MSIT performance. Connectivity between the lFPN and DAN was not significantly different between the age groups at rest, although the older group showed increased lFPN-DAN connectivity during the task and the younger group did not. This finding is in line with a previous study where older adults showed increased activity in the left prefrontal cortex (PFC) and parietal regions during sustained visual attention (Cabeza et al., 2004), a necessary component when performing the MSIT. Furthermore, some PFC regions that show lateralized activation in young adults also show more bilateral activity in older adults (Bäckman et al., 1997; Cabeza, 2002; Cabeza et al., 2002). Likewise, previous research has found that older subjects show increased bilateral functional connectivity in the PFC during task performance (Grady et al., 2010; Rieckmann et al., 2011). Thus, older adults might need increased bilateral connectivity in order to adequately perform the task, although this pattern could also reflect less selective recruitment of brain networks, consistent with the concept of dedifferentiation in cognitive aging (Li and Lindenberger, 1991).

The impact of task demands on functional connectivity was also investigated using task-relatedness analyses, where we found that the level of modulation in the three networks differed. Whereas rFPN/DAN and DMN were positively and negatively task-related, the lFPN was task-unrelated. Previous research has indicated that the MSIT activates the cingulo-frontal-parietal attention network bilaterally and does not show a lateralized pattern of activation (Bush et al., 2003; Bush and Shin, 2006) like the one found in our study. The current finding of lateralization within the FPN contrasts with past work, but it should be noted that previous MSIT studies examined activation, and not connectivity. Moreover, sustained attention processes have been associated with the right PFC, which provides a plausible explanation for the lateralization effect found in the current study (Pardo et al., 1991; Lewin et al., 1996; Cabeza and Nyberg, 2000). Finally, whereas the rFPN showed little modulation between conditions (i.e., interference vs. control), the DAN was more involved during interference than control trials, indicating a higher degree of modulation and increased recruitment when task difficulty increased.

We found that age-related differences in functional connectivity were not always consistent across cognitive states, and might be dependent on task demands (Di et al., 2013; Gonzalez-Castillo et al., 2015; but see Tavor et al., 2016). There is a strong body of evidence relating aging to disruptions in network interactions, but it remains unclear whether age-related differences in RSNs are consistently found across cognitive states. Previous research has found that age-related differences in inter-network dynamics are not static across cognitive states (Geerligs et al., 2015). However, this contrasts against other studies showing that individual differences in cognitive tasks may be a stable trait marker (Tavor et al., 2016), or that age differences may be more readily observed when there are no external demands on cognitive processing (Grady et al., 2016). This work provides novel insights as to whether age-related differences in network interactions can be easily identified during rest, or whether networks should be momentarily engaged in a cognitively demanding task to elicit patterns of age-related differences. In our study, age-related differences in connectivity were stable between rest and task for FPN-DMN and FPN-DAN interactions (Tavor et al., 2016). This finding, along with well-known age differences in cognitive control (Buckner, 2004; de Frias et al., 2009), suggests that the dynamic functional connectivity of the FPN with other large-scale networks remains similar across cognitive states and can be readily observed during resting-state. In contrast, DMN-DAN connectivity showed a distinct pattern in the two groups. Although young people had increased negative connectivity during the MSIT, older people had similar connectivity levels in both rest and task. This indicates that age differences in the interactions between the two networks function in a state-dependent manner. Previous studies suggest that the DMN exhibits a general dynamic reorganization of its functional connectivity pattern in a task-specific manner (Gao et al., 2013; Elton and Gao, 2015). According to this view, we would expect that the degree of DMN-DAN anticorrelation would vary across cognitive states.

Despite alterations in the degree of modulation, functional connectivity between the FPN and DMN/DAN remained positive and was stable. In contrast, connectivity between the DMN and DAN was negative and varied between rest and the MSIT. These opposite trends could indicate that DMN suppression is highly state-dependent, whereas positive connectivity between other networks, particularly those involving the FPN, has a more stable pattern across states. Moreover, if we wish to argue that cognitive demands are responsible for connectivity differences in young and old from rest to the MSIT, we would expect similar effects when comparing two tasks differing in cognitive load (Grier et al., 2003; Caggiano and Parasuraman, 2004). This needs to be further investigated across different cognitive domains and using different measures of individual differences.

A limitation of this work is that we cannot address all potentially relevant mechanisms by which changes in cerebrovascular physiology in aging (e.g., changes in neurovascular coupling) could impact connectivity measures. There are many factors that can potentially confound group differences in fMRI studies. Given its nature, the BOLD signal is affected by elements that are unrelated to neural activity, such as changes in cerebrovascular reactivity (CVR), CBF and cerebral blood volume (CBV). Because aging is associated with cerebrovascular physiological changes, controlling for such differences is of particular importance when comparing age groups. However, we did not collect information regarding subjects' vascular profile or compliance with the resting-state protocol. We took this issue into account, by controlling for resting-state fluctuation amplitude (RSFA) in additional analyses that are not reported here. RSFA is a measure that gives comparable results to CO_2 challenges and breath-hold (BH) tasks (Liu et al., 2013) and is capable of capturing differences between younger and older participants (Kannurpatti et al., 2011). As expected, older subjects had significantly lower RSFA and therefore reduced CVR. However, the basic pattern of age-related differences remained unaltered. This indicates that neurovascular factors are not driving the main pattern in our findings, although we cannot rule out the possibility that these factors are, at least partly, responsible for our results. Our findings could also be biased by scan length, because the resting-state and task sessions had different durations (145 vs. 180 volumes). Still, this was not the case, as we ran the same analyses using only the first 145 task volumes, and results were identical.

Finally, previous work using the same pool of subjects has shown that older persons have marked GM reductions in several brain regions, particularly in anterior parts of the brain (Salami et al., 2014b). There is also evidence that age-related differences in GM and WM affect the brain's ability to engage and coordinate large-scale functional networks, including the DMN and FPN (Greicius et al., 2009; Horn et al., 2014; Marstaller et al., 2015). Thus, it was expected that GM differences would account for part of the results found in the present study. After controlling for the effects of GM volume on functional connectivity, the overall pattern of age-related differences was identical to the one found before controlling for atrophy, with only FPN-DMN connectivity showing a similar trend but not reaching statistical significance. Indeed, if functional connectivity is a measure of brain integrity, then structural brain changes should account for age-related changes in interactions among large-scale networks (Marstaller et al., 2015).

In summary, our results provide three main findings. First, our analyses of inter-network connectivity support a model in which the FPN dynamically interacts with the DMN or DAN depending on cognitive state in both younger and older adults. Second, the degree of FPN-DMN connectivity during both rest and the MSIT was lower in older compared to younger adults, whereas no age-related difference was observed in FPN-DAN connectivity in either state. These data suggest that dynamic interactions of the FPN are stable across cognitive states. Third, the DMN and DAN were anticorrelated, and the degree of anticorrelation was age-sensitive only during the MSIT (and predictive of task performance), suggesting that it varies in a state-dependent manner. In addition, low DMN-DAN anticorrelation during task was related to low resting metabolism in the DMN, providing further characterization of the physiological underpinnings of these interactions.

AUTHOR CONTRIBUTIONS

BA-P contributed to writing the manuscript, as well as analyzing and interpreting the data. AS contributed to writing the manuscript and assisted in analyzing the results. LB and LN supervised the project and contributed to scientific discussions and manuscript writing. AW analyzed and helped interpret the CBF-related data. All authors critically reviewed the content and approved the final version for publication.

ACKNOWLEDGMENTS

This work was supported by a donation from the Swedish Research Council (AS), the Stichting af Jochnick Foundation (LB), the Torsten and Ragnar Söderberg's Foundation (LN), and the Karolinska Institutet doctoral (KID) grant. We want to thank the research participants for their contribution to our study, and Håkan Fischer and Anna Rieckmann for data collection.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 08 August 2017
doi: 10.3389/fnagi.2017.00256

The Effects of Home-Based Cognitive Training on Verbal Working Memory and Language Comprehension in Older Adulthood

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Effective language understanding is crucial to maintaining cognitive abilities and learning new information through adulthood. However, age-related declines in working memory (WM) have a robust negative influence on multiple aspects of language comprehension and use, potentially limiting communicative competence. In the current study ($N = 41$), we examined the effects of a novel home-based computerized cognitive training program targeting verbal WM on changes in verbal WM and language comprehension in healthy older adults relative to an active component-control group. Participants in the WM training group showed non-linear improvements in performance on trained verbal WM tasks. Relative to the active control group, WM training participants also showed improvements on untrained verbal WM tasks and selective improvements across untrained dimensions of language, including sentence memory, verbal fluency, and comprehension of syntactically ambiguous sentences. Though the current study is preliminary in nature, it does provide initial promising evidence that WM training may influence components of language comprehension in adulthood and suggests that home-based training of WM may be a viable option for probing the scope and limits of cognitive plasticity in older adults.

Keywords: cognitive training, working memory, language, aging

OPEN ACCESS

Edited by:
Pamela M. Greenwood, George Mason University, United States

Reviewed by:
Alexandra B. Morrison, University of Miami, United States
Jerri D. Edwards, University of South Florida, United States

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Received: *09 August 2016*
Accepted: *19 July 2017*
Published: *08 August 2017*

Citation:
Payne BR and Stine-Morrow EAL (2017) The Effects of Home-Based Cognitive Training on Verbal Working Memory and Language Comprehension in Older Adulthood. Front. Aging Neurosci. 9:256. doi: 10.3389/fnagi.2017.00256

INTRODUCTION

Literacy and effective language comprehension are crucial to maintaining cognitive abilities and learning from text through adulthood (Manly et al., 2003; Stern, 2009; Payne et al., 2012a; Stine-Morrow et al., 2015). However, normative age-related cognitive changes have a profound influence on language understanding, especially for effortful comprehension and memory processes (Wingfield and Stine-Morrow, 2000; Wlotko et al., 2010; Payne and Stine-Morrow, 2016; Stine-Morrow and Payne, 2016). Working memory (WM) — the ability to temporarily store, maintain, and organize task-relevant information— is often implicated as a domain-general mechanism responsible for such age-related changes in language understanding (Stine and Wingfield, 1987; Van der Linden et al., 1999; Borella et al., 2011; Kemper, 2012; Payne et al., 2014a). Although virtually all models of language comprehension include some mechanism to account for WM constraints

(see Pickering and van Gompel, 2006; Caplan and Waters, 2013 for reviews), the degree to which the WM system directly supports comprehension and the role of WM in language understanding is a topic of ongoing debate (see, e.g., Just and Carpenter, 1992; Carpenter et al., 1994; Caplan and Waters, 1999, 2013; Just and Varma, 2002, 2007; MacDonald and Christiansen, 2002).

The majority of research examining the influence of WM on language comprehension has relied on either dual-task paradigms to examine the effects of manipulated WM constraints on language comprehension (Smiler et al., 2003; Fedorenko et al., 2006; Kemper and Herman, 2006), or correlational approaches that test the relationship between individual differences in WM and language comprehension (King and Just, 1991; Just and Carpenter, 1992; Caplan and Waters, 1999; DeDe et al., 2004; Stine-Morrow et al., 2008; Noh and Stine-Morrow, 2009; Caplan et al., 2011; Payne et al., 2014a). In contrast, the current study used home-based cognitive training as an experimental approach to examining the degree to which the verbal WM system underlies language comprehension (cf. Novick et al., 2013; Hussey et al., 2016).

Aging, Working Memory, and Language Comprehension

Working memory limitations have historically been invoked in models of language understanding to explain comprehension difficulties for linguistically complex material (Miller and Chomsky, 1963). Current research activity has focused on performance on complex WM span tasks, which have been argued to underpin performance on a wide range of both complex and everyday tasks (Engle, 2010; Baddeley, 2012). While there are many contemporary models of WM, each of which make slightly different predictions or have slightly different foci (e.g., Cowan, 2000; Engle, 2002, 2010; Kane et al., 2007a,b), most models converge on a similar account that the WM system supports "the ability to simultaneously maintain information in an active and readily accessible state, while concurrently and selectively processing new information..." (Conway et al., 2007; p. 3). Complex WM span measures such as the *reading span* (Daneman and Carpenter, 1980; Wingfield et al., 1988) and the *operation span* (Turner and Engle, 1989) task share the requirement to simultaneously hold information in memory while performing some concurrent processing. This dual-task nature of complex span tasks critically sets them apart from simple STM tasks that are not predictive of higher-order cognition (reviewed in Baddeley, 2012). In contrast, performance on complex WM span tasks predict individual differences in a number of higher-order cognitive abilities including reasoning, episodic memory, attentional control, and intelligence (see Conway et al., 2007 for reviews). WM is also related to comprehension, with meta-analytic correlations ranging between $r = 0.41$ and $r = 0.52$ (Daneman and Merikle, 1996). Theoretical accounts of such relationships center on the reliance on WM for constructing, storing, retrieving, and integrating an incremental representation of the text's meaning as decoding and parsing of the surface input is ongoing (e.g., Just and Carpenter, 1992; Gibson, 1998; Lewis and Vasishth, 2005).

Performance on complex span tasks declines with aging (e.g., Bopp and Verhaeghen, 2005), as does comprehension and memory for language (Kemper, 1987; DeDe et al., 2004; Payne et al., 2014b). For example, a meta-analysis by Johnson (2003) revealed that on average, older adults perform at about the 22nd percentile of the distribution of younger adults in text memory. Similar effect sizes for age-related declines in immediate language memory have been found in a longitudinal study tracking changes in older adults' auditory discourse memory over a 10-year period (Payne et al., 2014b). Although there is considerable debate regarding the impact of WM deficits on on-line measures of real-time language processing in aging (Caplan and Waters, 1999; Kemper and Liu, 2007; Caplan et al., 2011; Payne et al., 2014a), verbal WM has been found to reliably mediate age-related changes in "off-line" measures of language comprehension and language memory (Kwong See and Ryan, 1995; Van der Linden et al., 1999; Hertzog et al., 2003; DeDe et al., 2004; Stine-Morrow et al., 2008; Borella et al., 2011).

Moreover, age differences in sentence comprehension accuracy are larger for sentences that are more semantically or syntactically complex, and these differences in performance have been found to be dependent upon individual differences in verbal WM capacity (Kemper, 1987; Stine and Hindman, 1994; Stine-Morrow et al., 2000; Christianson et al., 2006; Payne et al., 2014a). For example, "garden path" sentences such as (1) introduce a temporary syntactic ambiguity.

(1) *The experienced soldiers warned about the dangers conducted the midnight raid.*

Typically, the first verb *warned* is initially (and incorrectly) interpreted as the main verb of the sentence (rather than as the verb of the reduced relative clause), creating difficulty when the reader encounters the second verb *conducted*; resolution thus requires a revision of the initial analysis (Bever, 1970; Clifton et al., 2003), which entails maintaining the alternate parse of the sentence during processing. WM capacity is an important predictor of resolution in garden-path ambiguities in younger (Just and Carpenter, 1992; MacDonald et al., 1992; Just and Varma, 2002) and older (Kemtes and Kemper, 1997; Kemper et al., 2004; Christianson et al., 2006) adults, as well as in other syntactically complex constructions, such as object-relative clauses (Stine-Morrow et al., 2000; DeDe et al., 2004), and long distance dependencies (King and Kutas, 1995; Caplan et al., 2011; Payne et al., 2014a).

Cognitive Training in Aging

Cognitive training has a long history in aging research, dating back over 30 years. Studies have reliably demonstrated that older adults show targeted improvements in trained abilities, including episodic memory, inductive reasoning, task switching, psychomotor speed, and WM capacity (Willis et al., 1981; Baltes and Willis, 1982; Willis and Nesselroade, 1990; Ball et al., 2002; Rebok, 2008; cf. Stine-Morrow and Basak, 2011; Rebok et al., 2014, for a review). Importantly, the demonstration that targeted

training in a cognitive domain can improve performance in that domain in older adults is not trivial considering evidence of age-related declines in plasticity (Lövdén et al., 2010). At the same time, there is considerable debate regarding whether and how cognitive training may produce "far" transfer, that is, improvements on untrained tasks that are distal from the trained ability—with studies demonstrating variable effect sizes for transfer (Melby-Lervåg and Hulme, 2013, 2016; Melby-Lervåg et al., 2016; Simons et al., 2016; but see Karbach and Verhaeghen, 2014; Au et al., 2015, 2016; Greenwood and Parasuraman, 2016). Note that there is considerable variability in cognitive training programs as well as what constitutes a target of transfer across the literature (Kelly et al., 2014; Simons et al., 2016)—the focus of the current study is on whether targeted cognitive training in one domain can produce transfer *across other cognitive domains*. Training effects on other outcomes (e.g., instrumental activities of daily living, self-rated health; e.g., Rebok et al., 2014, see Kelly et al., 2014; Simons et al., 2016 for recent reviews) are beyond the scope of this study and are not discussed in further detail. In the cognitive aging literature, cognitive training has most reliably produced narrow transfer across untrained cognitive domains (see reviews in Stine-Morrow and Basak, 2011; Simons et al., 2016). For example, the ACTIVE trial (Ball et al., 2002; Willis et al., 2006; Rebok et al., 2014), was the largest cognitive intervention study to date ($N = 2{,}832$) and arguably remains the benchmark cognitive training study, conforming to many of the best practices for intervention research. Healthy older adult participants' completed 10 sessions of training in either processing speed, episodic memory (targeting strategy use), or inductive reasoning. Although evidence of transfer to measures of functional and clinical outcomes (e.g., instrumental activities of daily living, depressive symptoms, driving mobility, and others) has been reported from ACTIVE (e.g., Willis et al., 2006; Wolinsky et al., 2010; Rebok et al., 2014), the effects of the transfer of cognitive training across cognitive outcomes was narrow, with large and maintained effects of training on measures proximal to the training (e.g., memory training improved episodic memory) with little evidence of transfer across other cognitive domains (e.g., memory training had no impact on processing speed or inductive reasoning).

Some researchers have noted that training regimens that target executive control and WM functions have shown more promise in stimulating cognitive improvements beyond near transfer and practice effects in older adults (Karbach and Verhaeghen, 2014; Greenwood and Parasuraman, 2016). For example, a number of studies have demonstrated that WM training increases performance not only on span tasks that are untrained but proximal to WM, but also some (limited) evidence for transfer to other cognitive domains such as inhibitory control, memory, and reasoning (Buschkuehl et al., 2008; Li et al., 2008; Borella et al., 2010, 2017; Brehmer et al., 2011; Richmond et al., 2011; Zinke et al., 2014, see Karbach and Verhaeghen, 2014 for a recent meta-analysis). On the other hand, there is an active debate regarding whether such WM training can produce reliable broad-based transfer across cognitive domains, such as transfer to fluid intelligence, in younger and older adults, with studies producing overall inconsistent results (e.g., Shipstead et al., 2012; Harrison et al., 2013; Melby-Lervåg and Hulme, 2013; Simons et al., 2016; but see Karbach and Verhaeghen, 2014; Au et al., 2015, 2016).

One limitation of these reviews and meta-analyses is that there is considerable heterogeneity in the tasks used to train and measure WM, making it difficult to evaluate efficacy in the aggregate (cf. Morrison and Chein, 2011; Shipstead et al., 2012; Melby-Lervåg and Hulme, 2013). At the same time, a full understanding of the effects of WM training has been obscured by a literature that is rife with methodological short-comings. Calls for improved methodological and quantitative standards in cognitive training research are abundant (e.g., Shipstead et al., 2012; Melby-Lervåg and Hulme, 2013; Walton et al., 2014; Simons et al., 2016). Some of the issues clouding the extant literature include the lack of adequate control groups and very small sample sizes. Moreover, any effect of improved WM on other abilities hinges on the assumption that these constructs rely on overlapping cognitive and neural resources that are engaged across multiple domains (cf. Dahlin et al., 2008; Hussey et al., 2016; Lindenberger et al., 2017) and yet there exists a surprising lack of consideration of theoretical mechanisms of training effects and transfer in the literature (cf. Shipstead et al., 2012). One recent attempt to elucidate the benefits of WM training in aging in the context of substantial heterogeneity of training outcomes came from Borella et al. (2017), who performed an integrative data analysis of four training intervention studies from their group that used an identical complex WM training protocol, the same target outcome measures, and similar samples of healthy older adults (total N across studies $= 148$). This study showed that, in aggregate, there was evidence for near transfer of WM training that was maintained for at least 6–8 months. In addition, they found evidence for immediate transfer of complex span training to measures of reasoning and processing speed, but also showed considerable individual differences in responsiveness to the training (cf. Payne et al., 2012b).

The Current Study

The current study aimed to capitalize on the principles of vertical transfer to examine the degree to which training-related improvements in WM modulate targeted language comprehension functions that putatively rely heavily on WM. Older adults were randomly assigned to either a cognitive training program targeting complex verbal WM or an active control targeting decision speed, both of which were home-based programs delivered via electronic tablets.

Our goal was to address three key issues. First, we were interested in the extent to which WM, as a critical underpinning for language, is plastic and responsive to training-related improvements. Second, we wanted to test the causal hypothesis that WM capacity is a critical resource for language comprehension and memory. Manipulating WM capacity through training and examining its effects on language outcomes afforded the opportunity to directly examine the causal link that is often assumed based on correlational results (Daneman and Merikle, 1996). A number of studies have examined language comprehension as an outcome of cognitive training interventions

(Chein and Morrison, 2010; Shiran and Breznitz, 2011; Carretti et al., 2013a,b; Novick et al., 2013; Karbach and Verhaeghen, 2014; Hussey et al., 2016) but nearly all of this work has focused on healthy young college adults or child populations with specific reading difficulties (e.g., Shiran and Breznitz, 2011; Karbach et al., 2015). Karbach et al. (2015) found evidence in children that adaptive WM training benefited standardized measures of reading comprehension but not measures of math performance or executive control (e.g., inhibition, task switching), suggesting a potentially unique pathway of WM training to comprehension. To our knowledge, only one study, by Carretti et al. (2013b), has specifically examined the effects of WM training on language outcomes among older adults. The training in this study consisted of multiple components, which included not only complex span tasks but also retrieval tasks incorporated into text processing tasks. As such, the improvements observed in language performance may have derived from direct instruction in components of reading comprehension rather than WM processes. In other words, the substantial overlap between the training and transfer task in the Carretti colleagues experiment makes it difficult to evaluate the isolated effects of WM improvement on language. Thus, there has not as yet been a definitive test of the hypothesis that WM training can modulate language performance in older adults, to our knowledge.

Finally, our goal was to develop a model of home-based training using technology that would both offer potential for scaling up for wider use and provide a medium for effective placebo control. In fact, home-based training in other domains has demonstrated good adherence and gains comparable to those observed in the laboratory in older adults (Margrett and Willis, 2006; Payne et al., 2012b; Stine-Morrow et al., 2014). Training tasks were designed to closely match the properties of complex verbal WM tasks in a mobile electronic format that was not only appealing for users, but also provided a detailed record of adherence to the study protocol as well as daily performance gains. We contrasted this with an active-component control group that was comparable to the training task in surface features, feedback, and engagement. Outcomes were measures of complex span tasks that were not directly trained as well as tasks that assessed various aspects of language performance. We were specifically interested in the degree to which WM training would impact immediate memory for sentences, comprehension of sentences that differed in their syntactic complexity, and discourse comprehension and memory.

MATERIALS AND METHODS

Participants

Volunteers were recruited from the Champaign-Urbana community through flyer advertisements, information booths at the farmer's market and related events, e-mail lists, and through phone recruitment from a database of older adult volunteers in the community who had previously participated in studies at the Beckman Institute.

A CONSORT (CONsolidated Standards of Reporting Trials) diagram is presented in **Figure 1** (Altman et al., 2001), which provides a graphical representation of the recruitment process and the flow of participants through the study, from eligibility to post-testing. A total of 240 individuals were contacted either by phone or e-mail from our recruitment database, or after expressing interest in the study. Of those, 134 did not follow-up or reply to our invitation to participate in the study. A total of 106 individuals were then assessed for eligibility. Participants were required to be 60 years of age or older, native English speakers with no exposure to other languages before the age of five, normal or corrected-to-normal vision (self-reported), no history of cancer treatment, closed head injury, or traumatic brain injury, no history of Alzheimer's disease, Parkinson's disease, Schizophrenia, or other neurological or psychiatric disorders, not currently taking any psychoactive medications (e.g., anti-depressant, anti-anxiety, anti-seizure), and had not participated in a physical, social, or cognitive intervention study within the previous 3 years. Of those assessed for eligibility, 39 refused to continue participation after learning more about the study, 22 were excluded for not meeting one or more of the inclusion criteria above ($N = 9$ recently participated in an intervention study; $N = 8$ self-reported history of neurological or psychiatric disease; $N = 4$ currently taking a psychoactive medication; $N = 1$ did not meet the age requirement), and three were excluded for other various reasons (e.g., loss of contact, restrictive scheduling constraints).

Thus, a total of 42 individuals were pre-tested. One participant did not meet inclusion criteria at baseline, based on an inability to complete the pre-test cognitive assessment. Thus 41 individuals were randomly assigned to either a treatment ($n = 22$) or control ($n = 19$) group. Of those, 21 in the training group, and 17 in the control group, completed at least 80% of the training sessions. **Table 1** presents demographics at baseline in the control and treatment groups. As can be seen in **Table 1**, differences between the two groups in age, $t(39) = 0.29$, education, $t(39) = 0.53$, sex, $\chi^2(1) = 0.005$, MoCA score (a clinical tool used for assessing risk for mild cognitive impairment, Nasreddine et al., 2005), $t(39) = 0.42$, and vocabulary score (ETS extended range vocabulary task administered at baseline only), $t(39) = 0.78$ were negligible. Importantly, we adopted an intention-to-treat analysis approach (Hollis and Campbell, 1999; Gupta, 2011), whereby individuals who did not complete the training were actively recruited to participate in post-testing and were included in all analyses. This method results in a conservative test of the treatment effect by de-confounding any potential treatment effects on outcome measures truly due to non-adherence.

Experimental Design and Overview

A pretest–postest randomized controlled experimental design with an active control group was used to examine the effects of WM training. Participants were asked to complete a total of five 30-min sessions in each week, for a total of 15 sessions over a 3-week period (or 7.5 h of total training). The interval between pre-test and post-test sessions was held constant across participants such that post-testing occurred no more than 4 weeks from the pre-test dates.

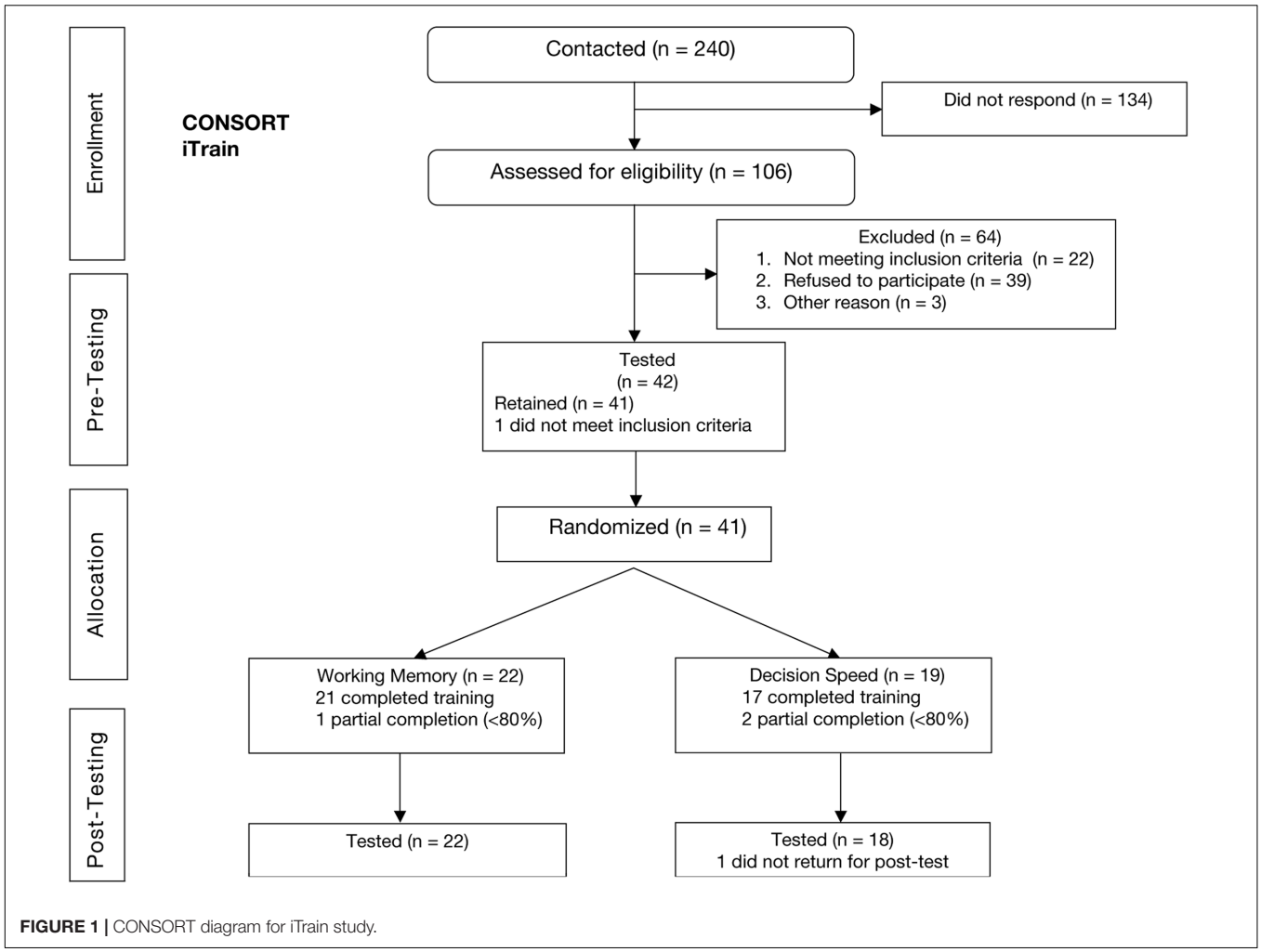

FIGURE 1 | CONSORT diagram for iTrain study.

TABLE 1 | Baseline demographics in control and treatment groups.

	Control		Treatment			
	***M* or count**	***SD* or %**	***M* or count**	***SD* or %**	***Diff***	***95% CI***
(1) Age	68.11	6.24	67.68	2.77	−0.42	[−2.55, 3.41]
(2) Years of education	17.47	2.38	17.09	2.20	−0.38	[−1.83, 1.07]
(3) MoCA	27.21	2.39	27.77	1.93	0.56	[−0.81, 1.92]
(4) Vocabulary	0.63	0.23	0.68	0.18	0.04	[−0.09, 0.17]
(5) % Female	14	74%	16	73%	0.01	[−0.26, 0.26]

MoCA is Montreal Cognitive Assessment (Maximum = 30, Range = 24–30). Vocabulary is scored as the proportion of accurate items on the ETS Extended Range Vocabulary Test. Diff = mean difference between groups at baseline. There were no significant differences between the treatment and control groups at baseline.

Experimental Groups

Working Memory Training

A novel home-based complex verbal WM training program called iTrain was designed for the study. It was written in Objective-C and implemented for use on iPad tablet computers via the Xcode environment. The program was designed for home-based training to allow participants to complete training sessions without having to make daily visits to the lab while also allowing us to monitor adherence. Prior studies suggest that home-based cognitive training shows gains on the same order of magnitude as lab-based training (Margrett and Willis, 2006; Stine-Morrow et al., 2014), and also results in high retention rates in healthy older adults in part because participants do not have to travel to the lab daily throughout the course of the intervention.

The three tasks in iTrain – Category Span, Lexical Decision Span, and Sentence Span— were designed to exercise verbal WM by requiring a dual-task load of concurrent language processing and memory storage. In the *Category Span task*, participants were

presented with a semantic category at the top of the screen (e.g., weather) along with a set of single words for which they made validity judgments (e.g., humidity – Yes; chocolate – No). Each trial consisted of the category and target word presented for 4 s. At any point within this duration, participants could decide if the target matched or did not match the category by pressing a "Yes" button or "No" button at the bottom of the screen. Once participants made a decision, the target word would disappear and participants would be presented with accuracy feedback (a green check mark if correct, or a red cross if incorrect) for 1 s. The program would then progress to the next trial within the set. If participants took longer than 4 s to respond, then the target word would disappear to prevent using extra time to develop artificial encoding strategies. However, participants could still respond. If participants failed to respond after a total of 4 s from the target word offset, then the trial would be marked as incorrect and the next trial within the set would begin. At the end of each set, participants were cued to recall each of the words in the order in which they were presented. The cued recall screen consisted of a set of empty text boxes that participants could press and then type their responses via an on-screen keyboard. Participants had no time limit to enter their recall responses at the prompt. Categories and exemplars were drawn from the Van Overschelde et al. (2004) category norms. The final stimulus set included a total of 69 unique categories and over 1500 unique words. Items were drawn randomly such that, within a set, each word had an equal probability of belonging to the presented category or not. Across training sessions, items were rotated through such that all categories had to be selected at least once before a particular category could be repeated again.

In *Lexical Decision Span*, participants were presented with a set of letter strings constituting words (e.g., seek) or non-words (e.g., ceek) and were cued to decide whether or not each string formed a word or not. The letter string was presented for 4 s. At any point within this interval, participants could decide if the letter string was a word or non-word by pressing a "Yes" button or "No" button at the bottom of the screen. Once participants made a decision, the letter string would disappear, and participants were presented with accuracy feedback (a green check mark if correct, or a red cross if incorrect) for 1 s. If participants took longer than 4 s to respond, then the letter string would disappear, but participants could still respond. However, if participants failed to respond after a total of 4 s from offset of the letter string, then the trial would be marked as incorrect and the next trial within the set would begin. Following each lexical decision, an unrelated single letter was presented for 1500 ms for participants to recall at the end of the set. At the end of each set, participants were cued to recall each of the letters in the order in which they were presented. The cued recall screen consisted of a set of empty text boxes that participants could press and then type their responses via an on-screen keyboard. Participants had no time limit to enter their recall responses at the prompt. A total of 9,000 common and proper nouns and 10,000 phonologically regular and pronounceable non-words were generated from the English Lexicon Project database (Balota et al., 2007). Word/non-word strings ranged in length between 4 and 9 characters (for word stimuli: log word frequency range: 5–13.67).

Finally, in *Sentence Span,* participants read a series of either semantically congruent sentences or "syntactic prose" sentences (e.g., *As the ship gets better, your child needs to develop this oven*) for which they made sentence acceptability judgments on each sentence (cf. Waters and Caplan, 1996, 2003). Participants had 15 s to read each sentence and make an acceptability judgment by pressing a "Yes" button or "No" button at the bottom of the screen. Once participants made a decision, the sentence would disappear, and participants were then presented with accuracy feedback (a green check mark if correct, or a red cross if incorrect) for 1 s. If participants took longer than 15 s to respond, then the sentence would disappear. If participants failed to respond after a total of 5 s from the offset of the sentence, then the trial would be marked as incorrect and the next trial within the set would begin. At the end of the set, participants were cued to recall the last word of each sentence in the order in which they were presented. The cued recall screen consisted of a set of empty text boxes that participants could press and then type their responses via an on-screen keyboard. Participants had no time limit to enter their recall responses at the prompt. Acceptable sentences were adapted from two sources. The Nelson and Narens (1980) general information question norms provided 244 sentences. The other source was the Manually Annotated Sub-Corpus (MASC) of the Open American National Corpus (Ide et al., 2013), which provided 301 sentences that ranged widely in topic, length, and syntactic structure. In addition, 346 unacceptable sentences were adapted from the "syntactic prose" conditions in earlier studies by Lee and Federmeier (2011) and Payne et al. (2015). Unacceptable sentences have syntactically well-formed sentence frames, but contain no coherent message-level semantics. All sentences ranged between 60 and 90 characters, and all sentence final words were between 4 and 9 characters.

The training was designed to be individually adaptive (cf. Lustig et al., 2009; Karbach et al., 2015), such that for all three tasks, the set size (number of items to recall within a trial) adaptively changed according to current performance. In this way, each participant was always engaging in the task at a level that was matched to his or her current ability. Task difficulty was programmed to follow a step function, such that when recall was perfect on set size n, the set size for the next set was increased to $n+1$. If perfect recall was not achieved at set size n, the set size was reduced to n-1. At the end of each set, feedback was presented to participants on both the accuracy of the judgment task (proportion correctly judged) and the proportion of items correctly recalled. The presentation order of the three tasks was randomized across session. The memory set size on the first session began at $n = 2$ for all tasks and subjects. The memory set size at the end of each training session was saved so that participants began the following session at the memory set level from their prior training session. All timing and set size parameters were based on extensive norming and testing of the iTrain software during its development. The source code for the training can be viewed and downloaded in full at: https://github.com/TALL1532/itrain.

Active Component-Control Group

A component-control design (Mohr et al., 2009; Boot et al., 2013) was adopted in designing the active control group. In a component-control design, a multi-component intervention serves as the focal treatment and an active control group is created by administering the same treatment absent a single component of the focal training. By matching the two groups on the surface level aspects of the tasks, along with presenting the same stimuli, this process reduces the likelihood of placebo effects or differential expectancies for change (Boot et al., 2013).

Participants in the active control group completed the same three tasks as in the treatment group without the recall component. Thus, in the *Category Task*, participants practiced making speeded category judgments; in the *Lexical Decision Task*, participants practiced making speeded lexical decision judgments; and in the *Sentence Task*, participants practiced making speeded semantic acceptability judgments. The items were identical to the WM training. Importantly, both the treatment and control groups were matched in their exposure to stimuli, the absolute magnitude of time allocated to training (15 30-min sessions over 3 weeks), and the amount and type of linguistic exposure. Thus, findings comparing the treatment and active control groups are controlled for exposure to linguistic stimuli, an important factor given the putative relationship between verbal WM and language experience (cf. MacDonald and Christiansen, 2002; Wells et al., 2009; Payne et al., 2012a, 2014a). Because removing the memory load from the WM training makes the task less demanding and potentially less engaging, an individually adaptive speed threshold was added in order to maintain continued interest in the task, de-confound memory load from task adaptivity, and reduce the potential for differences in expectancy for training benefits in the two groups (Boot et al., 2013).

In the control training, participants were presented with stimuli in blocks of 15 items and told to make their judgments (lexical decision, category, sentence acceptability) as quickly as possible. The starting presentations times for each task were identical to the presentation times in the WM training task (described above). However, as participants improved in accuracy in the judgment decisions, presentation rates were increased at a rate of 5% across blocks. When accuracy fell below 80%, the presentation rate was decreased, so that task adaptivity followed a similar step function as in the WM training. Participants were encouraged to practice speeded decisions in each of the linguistic tasks while maintaining high accuracy. A "speed level" score, derived from change in presentation rate from the initial training block, was provided after each block, so that participants could monitor their progress from the first block of the first session to the end of the training, as in the WM training protocol.

Assessment Battery

The cognitive battery, administered at pre-test and post-test, was chosen to target both complex WM performance as well as measures of off-line language performance. Language outcome measures included assessments of sentence processing and discourse memory, which were themselves graded in terms of their reliance on WM (Stine and Wingfield, 1990; Jefferies et al., 2004; Stine-Morrow et al., 2008), as well as a measure of verbal fluency. At post-test only, a survey to gauge group differences in expectations for cognitive change was administered based on a survey designed by Boot et al. (2013).

Complex Verbal Working Memory

Four complex WM tasks were administered using the Psychophysics Toolbox in MATLAB (Brainard, 1997), adapted from the CogToolbox (Fraundorf et al., 2014). In all four tasks, participants made a series of judgments about each item in a set of verbal stimuli and then, after the set, recalled information related to each item within that set. Alternate forms of each task were administered at pre-test and post-test. In the (1) *reading span* and (2) *listening span* tasks (Daneman and Carpenter, 1980; Stine and Hindman, 1994), participants read or listened to a set of simple declarative sentences (e.g., "A book is often found in a library"), and judged whether the sentence was true or false. Additionally, participants were asked to recall the sentence-final words (e.g., library) after each set. The number of sentences per set increased with progress through the task (until eight sentences per set or when the participant could no longer recall each of the target words in a set successfully). If the participant could not recall all items at a particular set size, a second trial was administered. If the participant could not recall all items within the second trial within that set, the test would terminate (cf. Stine-Morrow et al., 2001; Waters and Caplan, 2003; Payne et al., 2014a). The score was the number of target words recalled from the highest set with no errors, plus a fraction reflecting the proportion of correctly recalled words on the set with an error. The listening span used the same administration and scoring, except that the sentences were presented in the auditory modality. For the reading span task, the minimum sentence presentation was 1s and the maximum was 7s. In both the sentence and reading span tasks, the maximum time to make true/false judgments was 2 s. In the (3) *operation span* task (Turner and Engle, 1989; Conway et al., 2005), the participant was cued with a series of three-term math problems (e.g., is [8/2] – 1 = 3; True), followed by a letter (e.g., c) to hold in memory after each problem. Following each problem-item set, the participant recalled the set of letters in the order in which they were presented. Fifteen sets were presented randomly, with set size ranging between 3 and 7. Because there are individual differences in the amount of time participants take to solve arithmetic problems, the presentation rate during the memory test was set on a subject-by-subject basis by using a baseline calibration period (see Unsworth et al., 2005). Prior to the onset of the memory task, participants completed a practice block solving math problems without the memory task. The average time it took to solve each problem was calculated separately for each subject, and the maximum presentation rate was calculated as the subjects mean calibration time plus 2.5 *SD*. The total score was the total proportion of correct items in the correct position across all sets (Unsworth et al., 2005). In the (4) *Minus-2 span task* (Waters and Caplan, 2003), participants were presented with a string of digits one at a time with an SOA of 1 s and cued to produce the series with two subtracted from each digit (e.g., [8, 4,

3, 9] to [6, 2, 1, 7]). The total score was the total proportion of correct items in the correct positions across all trials (Waters and Caplan, 2003). Each span task was preceded by practice at the lowest set size. Note that the selected WM span measures vary with respect to their overlap with surface features (e.g., secondary judgment task, source of elements to recall, scoring criteria, set size order, cf. Was et al., 2011).

Sentence Memory

An immediate recall task (Zelinski and Lewis, 2003; Stine-Morrow et al., 2008) was administered in which participants read eight 18-word sentences with presentation time self-paced, and immediately recalled each sentence for later transcription and scoring. Recall was scored as the proportion of individual words correctly recalled (e.g., Potter and Lombardi, 1998; Gilchrist et al., 2008), which for these brief single sentences, was found to correlate very strongly with propositional recall scoring ($r = 0.91$) (Kintsch and van Dijk, 1978; Stine-Morrow et al., 2008). Alternate sentence sets of equivalent difficulty were presented at pre-test and post-test.

Syntactic Comprehension

Participants read a series of sentences and answered a simple a yes/no comprehension question after each sentence. Comprehension was assessed for three different types of syntactic complexity that are known to cause comprehension difficulty among older adults, and have been suggested to increase load on WM capacity: (1) *garden-path* syntactic ambiguities, (2) long-distance relative-clause dependencies (Bartek et al., 2011), and (3) object-relative clauses (see **Table 2** for examples)[1]. Sentences were counterbalanced across conditions at each testing occasion, so that each sentence was equally represented in the high- and low-demand conditions. At pre-test and post-test, participants read 20 items from each sentence set (10 low complexity, 10 high complexity), resulting in a total of 60 sentence-question pairs at each measurement occasion.

[1]Participants read these sentences while having their eye-movements monitored to examine changes in on-line language processing. The eye-tracking data showed no reliable changes over time nor effects of the intervention.

TABLE 2 | Example items in sentence comprehension test as a function of syntactic demand.

Sentence set	Complexity	Sentence
GP	Low	While the man hunted, the deer that was brown and graceful ran into the woods.
GP	High	While the man hunted the deer that was brown and graceful ran into the woods.
SR/OR	Low	The farmer that knew the barber asked for a loan.
SR/OR	High	The farmer that the barber knew asked for a loan.
LDD	Low	The administrator who the nurse supervised scolded the medic for being late.
LDD	High	The administrator who the nurse who was from the clinic supervised scolded the medic for being late.

GP, garden path; SR/OR, subject/object relative clause; LDD, long distance dependency.

Discourse Comprehension and Memory

The Nelson-Denny Standardized Reading Comprehension subtest, to assess general reading comprehension ability, consists of eight prose passages and 36 multiple-choice questions. Participants were given 20 min to read the passages and answer the questions. Alternate forms were administered at pre-test and post-test. In the Rivermead Behavioral Memory Task Paragraph recall subtest (Wilson et al., 2003), participants listened to a short narrative for immediate recall. Production was coded and scored for the number propositions correctly recalled.

Verbal Fluency

Verbal fluency was assessed with the FAS phonemic fluency task (Benton and Hamsher, 1978). In this task, participants were given a letter (at pre-test "F", "A", and "S") and asked to produce as many words that they could think of that begin with that letter for 60 s. A total score is calculated as the sum of unique words correctly produced across the three trials. This task has been shown to be highly predictive of general cognitive status (Kemper and McDowd, 2008) as well as predictive language comprehension (Federmeier, 2007) in older adults. An alternate form, the BDT, was used at post-test (Strauss et al., 2006).

Perceptions of Training Benefits

A 14-item survey to assess individuals' expectations for the effects of training (cf. Boot et al., 2013) was administered at the end of the post-test session. Items probed whether (1) they perceived general improvement in cognition as a function of training (e.g., "I believe that iTrain helped improve my cognition"), and (2) they improved on specific tasks (e.g., for the Listening Span task, "You completed a task called Listening Memory. In this task, you heard a series of sentences and you were asked to judge if the sentences were true or not. You were also asked to remember the last word of each of the sentences in that section in order. Do you believe that iTrain helped lead to better performance on this task?"). Participant's read each statement and then were asked to endorse those statements on a Likert scale from 1 (Strongly Disagree) to 5 (Strongly Agree).

Procedure

At the onset of the study, all participants completed the cognitive battery in a single 3-h laboratory session. Following the pre-test battery, participants were given an iPad 2 tablet computer containing either the complex WM training software (treatment group) or the active control training software, based on random assignment. Testers instructed participants on procedures for completing each of the tasks in the training program, and participants were given the opportunity to practice the tasks in the lab until they understood each task completely. Participants returned to the lab at the end of the training for post-test. The testing was single blind, as testers were aware of the random assignment condition. However, testing sessions were designed to minimize the amount of contact with the participant, and testers were instructed to provide no

identifying information regarding the training program or the study hypotheses.

RESULTS

A series of linear mixed effects models were used to test for the effects of the intervention on each outcome measure. Analyses focused on effect size estimation and quantification of the precision of these effects via confidence intervals (Kelley and Preacher, 2012; Lakens, 2013; Cumming, 2014). Effect sizes and 95% profile confidence intervals of the critical Training Group (Control vs. Training) × Time (Pre-test vs. Post-test) interactions were estimated via restricted maximum likelihood estimation, with random intercepts specified for subjects, and by-subject random slopes for the within-subject Time factor. For the syntactic comprehension data, the critical interaction was a Group × Time × Sentence Type effect and, for these models, the Time × Sentence Type interaction was additionally modeled as a random slope (see Barr et al., 2013; Bates, under review for discussions on the treatment of random slopes). Note that, following an intention-to-treat protocol, all participants were invited back for post-testing and included in all analyses, regardless of the number of sessions that were completed. Thus, models were fit to all available data for each outcome. Treatment coding was used for all fixed-effects factors and statistical inference was limited to the critical interactions that would provide statistical support for group differences in the change in each outcome from pre-test to post-test. Because sample sizes are small, supplemental non-parametric analyses were conducted using a robust bootstrapping approach as described by Kirby and Gerlanc (2013), to estimate the standardized effect size and precision of group differences in change in the outcome measures.

Perceptions of Training Benefit

Table 3 presents mean rating endorsements for both general improvement in cognitive ability, as well as improvement across specific tasks. Overall, average endorsement rates ranged from neutral to positive. Importantly, there was no difference between the treatment and control groups in expectations that they improved in overall cognition following training ($b = 0.13$; 95% CI [−0.15, 0.41]). There was a trend for the WM tasks to show self-reports of greater improvement in the treatment group relative to the control. However, only for one task—the minus-2 span task— did the group difference reach statistical significance, though this effect was quite small ($b = 0.65$; 95% CI [0.004, 1.29]). Importantly, the language tasks showed no evidence of differential expectation for improvement between the control and training groups, with the trend going in the direction of greater perceived improvement in language tasks in the control group (see **Table 3**). Thus, it is unlikely that the effects of training on language outcomes reported below could be attributed to differential expectations for improvement in the training group relative to the active control group.

Training-Related Changes in WM Performance

Trial-level performance was collected by the iPad over the course of training, enabling us to compute the average span score for individuals at each session for each span task. Based on participants who completed at least 80% of the training ($n = 21$), **Figure 2** plots the session-to-session effects of WM training on performance gains for each of the three verbal WM tasks. Raw scores on the span tasks were converted to a metric of percent change from baseline assessment (i.e., their average score on the first day of training) in order to assess the relative degree of improvement from baseline on a similar scale for each span task (e.g., Chein and Morrison, 2010). On average, training gains followed a non-linear trajectory, with larger improvements in early sessions. Indeed, the largest improvements across the three tasks occurred from session 1 to session 2. Over the 15 sessions, trainees showed an approximate 60% peak training improvement from baseline on the category and sentence span tasks and more than doubled their span performance on the lexical decision span task relative to their performance on the first day of training.

To examine individual differences in performance, we calculated subject-specific learning curves, expressed as the percent of change from baseline performance. To accommodate the non-linearity in training gains, a natural cubic smoothing spline was fit to the training data for each participant. Following this, the area under the cubic spline curve was estimated over the training period separately for each participant (using an adaptive quadrature algorithm via the MESS package in R; Venables and Ripley, 2002) as a summary index of non-linear training gains in each task for each individual across the 15 sessions. **Figure 3** plots the bivariate scatterplot matrix among training gains for the three span tasks. With correlations above 0.85, it is apparent that training-related improvements on the trained memory span tasks clustered together tightly, suggesting that training-related improvements occurred broadly and to a similar degree across all tasks, and were thus not likely due to isolated to task-specific strategy development (which would attenuate the correlation among the training-related improvements).

Transfer to Working Memory and Language

Table 4 presents pre-test and post-test mean scores and difference scores for the WM and language tasks administered in the cognitive test battery separately for the control group and treatment groups. Note that, following an intention-to-treat approach, these results reflect all available data at pre-test and post-test, regardless of participants' training adherence. **Figure 4** presents summary bootstrapped effect sizes of the group differences in change in each of the tasks (e.g., the Group × Time interaction) in units of standard deviation change (Cohen's d) separately for the WM and language tasks. Larger values indicate a positive change from pre-test to post-test that was larger for the treatment group than the control group. Appendix A presents correlations between the WM measures and language tasks at baseline.

TABLE 3 | Results from post-test expectation survey.

	Control		Training		Group difference	
	M	*SE*	*M*	*SE*	*Diff*	*95% CI*
Reading span	3.23	0.21	3.55	0.21	0.31	[−0.22, 0.84]
Listening span	3.15	0.18	3.5	0.18	0.35	[−0.11, 0.81]
Minus-2 span	3.23	0.21	3.89	0.21	0.65	[0.004, 1.29]
Operation span	2.91	0.16	3.47	0.16	0.56	[−0.03, 1.15]
Syntactic comprehension	3.38	0.16	3.23	0.16	−0.16	[−0.69, 0.27]
Text memory	3.23	0.23	3.00	0.23	−0.23	[−0.23, 0.36]
Reading comprehension	3.62	0.29	3.27	0.29	−0.34	[−1.06, 0.38]
Overall cognition	3.34	0.12	3.47	0.10	0.13	[−0.15, 0.41]

Items on a Likert scale with 1 indicating low endorsement of training benefit and 5 indicating high endorsement of training benefit. Both groups rated expectations of improvement slightly above neutral (3) across nearly all survey items. 95% confidence intervals containing 0 indicate differences than are not statistically significant at $p < 0.05$. The only item that reached a significant difference was for the Minus-2 span task.

Working Memory

There were no reliable baseline differences in any WM task between treatment and control groups (all *t*'s < 1, see **Table 4**). As can be seen in **Table 4** and **Figure 4**, there was evidence for training-related improvements in verbal WM. All four WM tasks showed effect sizes larger than $d = 0.50$, indicating at least an approximate half standard deviation difference between the treatment and control groups in change in WM. The average effect size of training collapsing across the four tasks was $d = 0.87$. However, 95% confidence intervals were quite large for all of the tasks, suggesting substantial individual differences in responsiveness to the intervention (cf. Payne et al., 2012b). Results from linear mixed-effects models fit to each task showed reliable Group × Time interactions for Listening Span ($b = 1.32$, 95% CI [0.54, 2.12]), Operation Span ($b = 0.24$, 95% CI [0.08, 0.40]), and Minus-2 Span ($b = 0.10$, 95% CI [0.02, 0.18]), indicating greater improvement in span for the training group relative to the control group. Of the four tasks, Reading Span showed the weakest effects, with a negative lower-bound on the bootstrapped 95% confidence interval. Consistent with the bootstrapped effect sizes, the linear mixed-effects model revealed a non-significant Group × Time interaction ($b = 0.61$, 95% CI [−0.12, 1.34]) for reading span only.

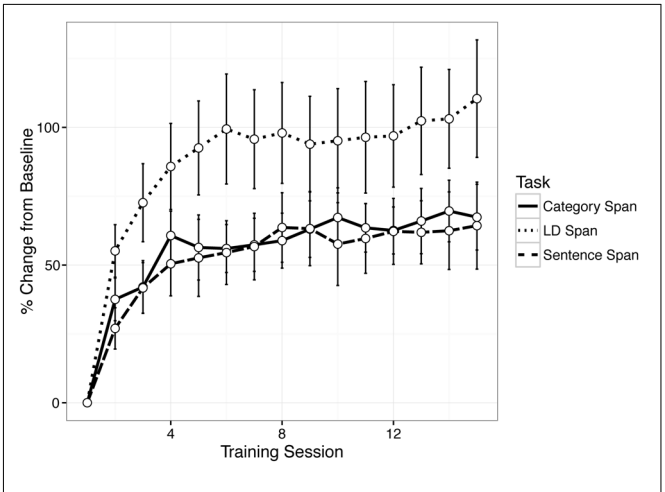

FIGURE 2 | Training group percent change from baseline in working memory (WM) span on three training tasks over 15 sessions.

Language Outcomes

There were no reliable baseline differences between treatment and control groups on any measure (all *t*'s < 1.3, see **Table 4**). As shown in **Table 4** and **Figure 4**, verbal fluency and sentence memory showed evidence of improvement from WM training relative to the control group. The Group × Time interaction was significant for verbal fluency ($b = 6.57$, 95% CI [1.30, 11.79]) and sentence memory ($b = 0.08$, 95% CI [0.02, 0.14]), such that the WM training group showed a larger increase compared to the control group. In contrast, the two tasks assessing discourse understanding and memory, the Rivermead and the Nelson-Denny tasks, showed no evidence of training-related improvements as the Group × Time interaction was not reliable for either the Nelson-Denny ($b = 0.002$, 95% CI [−0.11, 0.12]) or the Rivermead discourse memory task ($b = -2.85$, 95% CI [−11.61, 5.91]).

Finally, WM training showed isolated effects in improving comprehension of ambiguous syntactic forms. **Table 5** presents pre-test and post-test mean scores for the low- and high-demand conditions of each of the three syntactic comprehension sets separately for the control group and treatment groups. For the garden-path sentences, a reliable ambiguity effect was observed at baseline ($b = 0.14$, 95% CI [0.06, 0.23]), such that ambiguous sentences had poorer accuracy than unambiguous sentences. In the model testing training effects on ambiguity resolution, a reliable Syntactic Demand × Time × Treatment interaction was found ($b = -0.18$; 95% CI [−0.34, −0.01]), indicating that there were training group differences in the change in accuracy from pre-test to post-test that differed for the ambiguous sentences compared to the unambiguous sentences. This interaction is depicted in **Figure 5**. As can be seen, accuracy was high across both training groups for syntactically unambiguous sentences at pre-test and post-test. For the ambiguous sentences, however, sentence comprehension is poorer at baseline and only the WM training group showed improvement in accuracy from pre-test to post-test.

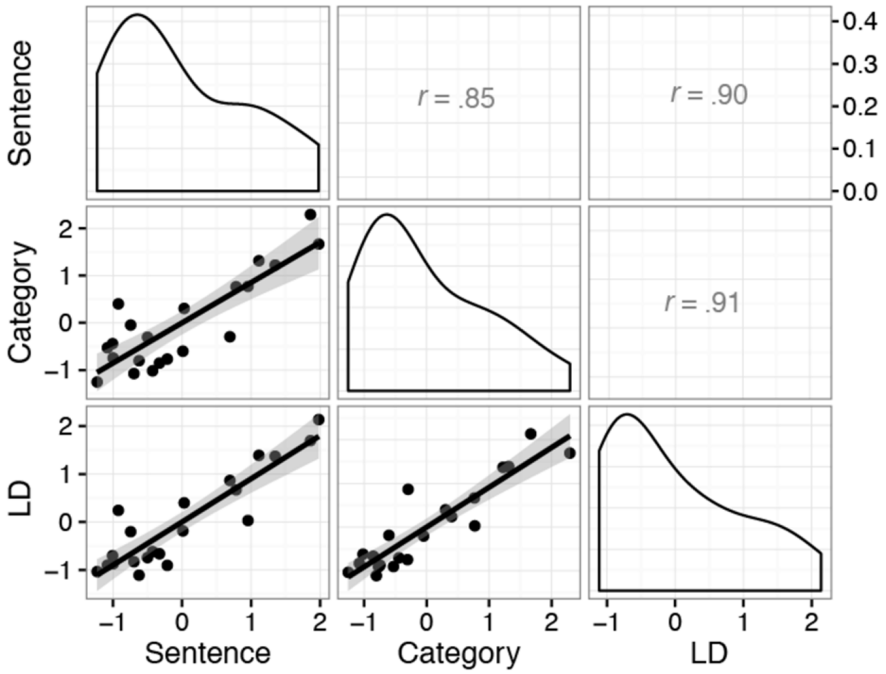

FIGURE 3 | Scatterplot matrix of the relationship between training improvements over 15 training sessions across each of the three WM training tasks. The lower diagonal cells are bivariate scatterplots and best-fit linear functions of the relationship between WM training gains across each pair of tasks. The upper diagonal presents the corresponding Pearson correlation coefficient for each pair of training tasks. The diagonal cells plots the estimated probability density functions of the individual training improvements in each task. Note that training improvements were *z*-score standardized, so that 0 represents average training improvement, and a 1 unit increase represents an approximate 1 *SD* improvement.

TABLE 4 | Pre-test, post-test, and change in working memory and language measures in control and treatment groups.

	Control						Treatment					
	Pre-test		Post-test		Δ		Pre-test		Post-test		Δ	
	M	*SE*	*M*	*SE*	*M*	95% CI	*M*	*SE*	*M*	*SE*	*M*	95% CI
Verbal working memory												
(1) Reading span	2.74	0.25	2.98	0.34	0.22	[−0.20, 0.65]	2.85	0.20	3.70	0.22	0.84	[0.28, 1.40]
(2) Listening span	3.50	0.37	2.88	0.31	−0.64	[−1.31, 0.03]	3.68	0.16	4.40	0.19	0.72	[0.24, 1.18]
(3) Operation span	0.40	0.07	0.44	0.06	0.02	[−0.04, 0.09]	0.39	0.05	0.63	0.05	0.30	[0.19, 0.41]
(4) Minus-2 span	0.58	0.05	0.63	0.06	0.01	[−0.03, 0.05]	0.63	0.04	0.76	0.02	0.12	[0.03, 0.21]
Language transfer												
(5) Nelson-Denny	0.87	0.02	0.82	0.04	−0.06	[−0.13, 0.01]	0.86	0.02	0.81	0.05	−0.05	[−0.11, 0.02]
(6) Verbal fluency	41.00	2.47	42.71	2.07	0.71	[−3.15, 4.56]	43.82	2.22	51.36	3.00	7.55	[3.96, 11.13]
(7) Sentence memory	0.66	0.04	0.71	0.03	0.04	[−0.01, 0.07]	0.65	0.02	0.77	0.02	0.12	[0.08, 0.16]
(8) Discourse memory	0.46	0.04	0.44	0.04	−0.02	[−0.86, 0.43]	0.52	0.03	0.47	0.03	−0.05	[−0.11, 0.01]

Reading span and listening span scores are the number of target words recalled from the highest set with no errors, plus a fraction reflecting the proportion of correctly recalled words on the set with an error. Operation span, Minus-2 span, Nelson-Denny, sentence memory, and discourse memory are scored as proportion correct. Verbal fluency is total number of words produced. Δ *is the difference between pre-test and post-test. 95% Confidence Intervals containing 0 indicate differences than are not statistically significant at* $p < 0.05$*. There were no significant differences between Control and Treatment groups on any measure at baseline.*

For the subject and object relative sentences, a reliable OR-cost effect was observed at baseline, such that object-relative sentences had poorer accuracy than subject-relative sentences ($b = 0.13$; 0.04, 0.22). In the model testing training effects on SR/OR comprehension, a small Syntactic Demand × Time × Treatment interaction was observed ($b = -0.18$; 95% CI [−0.35, −0.007]). However, the nature of this interaction was difficult to attribute strictly to training-related improvements in the costs associated with object-relative processing, as the interaction was driven by the WM training group showing a relative improvement in object-relative comprehension from pre-test to post-test (as predicted), but a corresponding decline in improvement in the

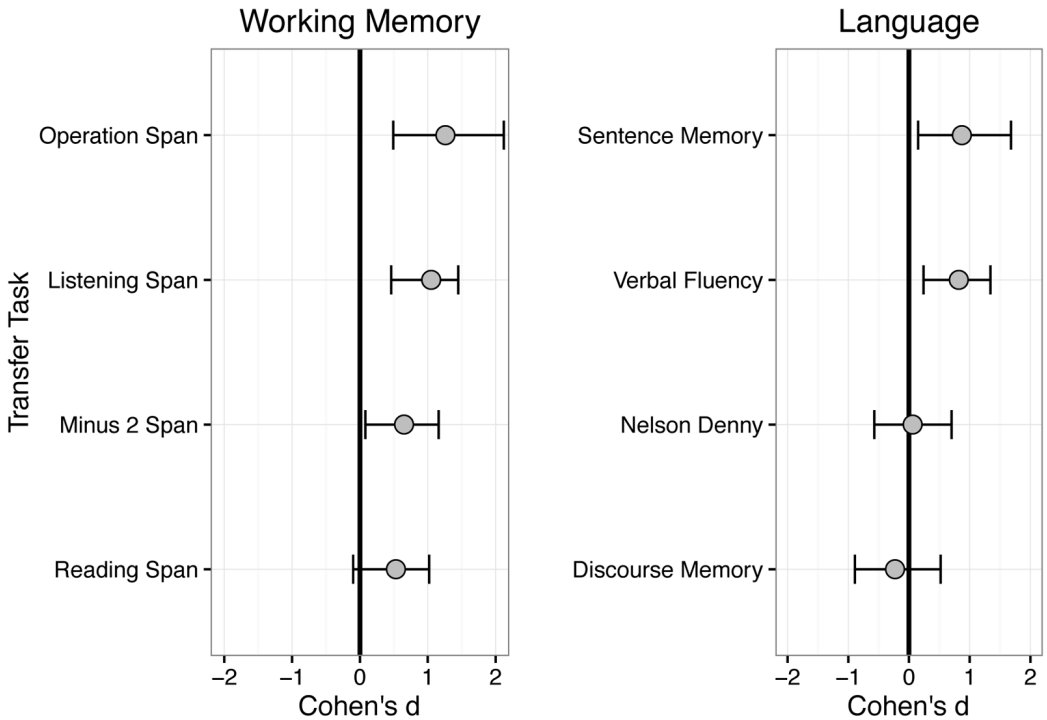

FIGURE 4 | Effect sizes (Cohen's *d*) and 95% bootstrapped confidence intervals of the training group × time interaction for WM **(Left)** and language **(Right)** measures from the neuropsychological test battery. More positive values indicate a greater change from pre-test to post-test for the training group relative to the control group.

TABLE 5 | Syntactic comprehension in control and treatment groups at pre-test and post-test.

	Control				Treatment			
	Pre-test		Post-test		Pre-test		Post-test	
	M	*SE*	*M*	*SE*	*M*	*SE*	*M*	*SE*
Garden path								
Unambiguous	0.82	0.02	0.83	0.03	0.85	0.02	0.84	0.02
Ambiguous	0.67	0.03	0.66	0.03	0.65	0.04	0.81	0.03
Subject-object relative								
Subject-relative	0.81	0.04	0.79	0.03	0.87	0.03	0.76	0.03
Object-relative	0.68	0.04	0.68	0.04	0.65	0.04	0.74	0.04
Long-distance dependency								
Short-distance RC	0.68	0.03	0.71	0.03	0.70	0.04	0.71	0.03
Long-distance RC	0.69	0.05	0.58	0.04	0.73	0.04	0.70	0.02

simpler subject-relative sentences, which is not the expected pattern following WM training.

For the long-distance dependency sentences, surprisingly, there was no reliable LDD-cost observed at baseline ($b = -0.007$; 95% CI [−0.11, 0.10]), as accuracy was approximately equivalent between relative clauses with and without a long-distance dependency introduced between the head noun and the relative-clause verb. Although there was a trend for a Syntactic Demand × Time × Treatment interaction ($b = -0.21$; 95% CI [−0.41, 0.005]) that did not reach statistical significance, like the SR/OR sentences, the nature of the interaction was difficult to attribute to training-related improvements accuracy for the more complex long-distance dependency case (see **Table 5**).

DISCUSSION

It is often assumed that normative age-related changes in basic cognitive functions such as WM capacity compromise the ability to comprehend language and learn from complex texts. However, nearly all of the evidence for a role of the WM system in language comprehension is derived from correlational studies, which are

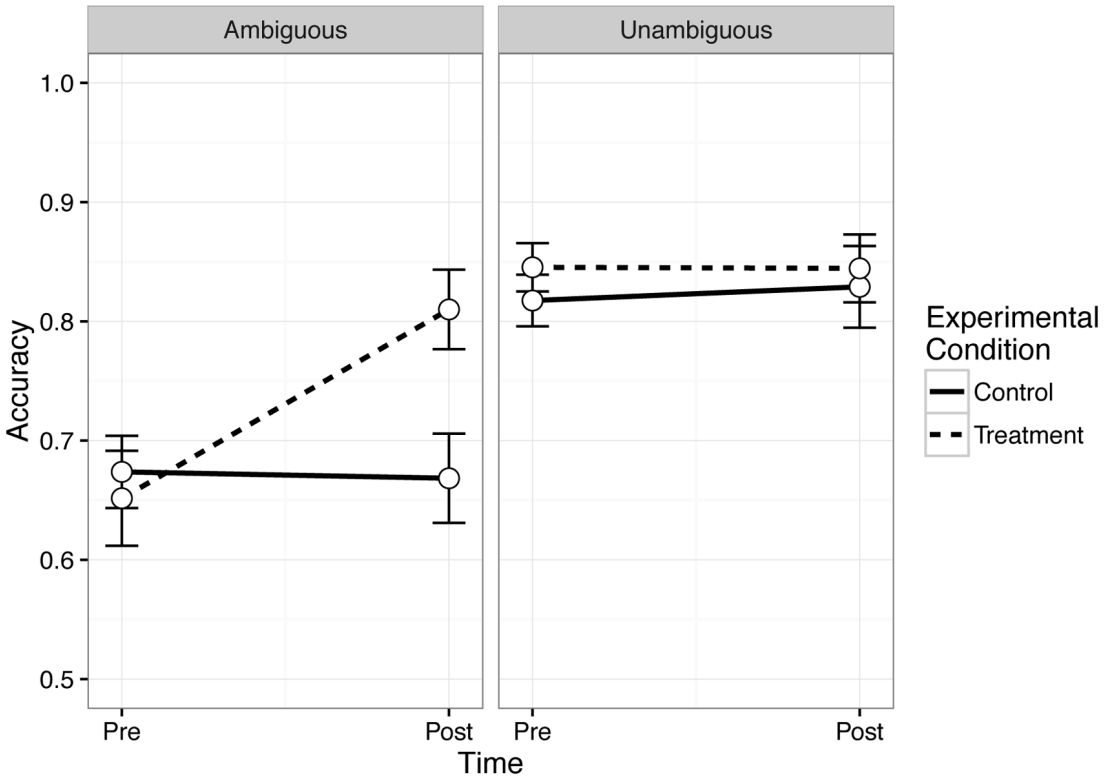

FIGURE 5 | Effects of training on syntactic ambiguity resolution accuracy.

inherently limited. In order to resolve this causal ambiguity, the current study exploited an experimental design to examine the degree to which cognitive training in verbal WM could transfer to aspects of language comprehension among older adults using a novel home-based cognitive training program.

The data presented in the current study yield important insights into both the nature of the verbal WM system and the degree of plasticity in language comprehension among older adults. Specifically, our results indicated that verbal WM is capable of short-term change in adults over the age of 60 through less than 10 h of home-based training over the course of 3 weeks, and that this training showed some evidence of transfer to untrained verbal memory measures as well as measures of language fluency, language memory, and syntactic comprehension. In summary, our findings suggest that WM is plastic in later adulthood, at least in the short-term. These data, while preliminary in nature, are among the first to indicate that selective aspects of WM-dependent language performance can be modified through targeted practice in WM in older adulthood.

Home-Based Working Memory Training

The benefits of home-based training via tablet computers include convenience for the participant and a reduction of resources devoted to weekly testing sessions in the lab. Moreover, lab-based training may lead to biased sampling of study participants who are highly mobile, healthy, and able to allocate substantial amounts of time each week to participating in laboratory sessions. In contrast, home-based training is likely to lead to more heterogeneous sampling at both ends of the ability distribution (i.e., high-ability adults with substantial time and scheduling constraints that prevent participating, as well as lower ability and lower-mobility adults), as it reduces the burden on the participant to complete daily lab visits over several sessions.

However, a major component of home-based training is that it requires the trainees to self-administer and self-monitor their training progress throughout the course of the intervention, which may impact training responsiveness. Very few studies have examined the effects of home-based cognitive training in older adults. In two experiments, Wadley et al. (2006) directly compared training gains in a useful-field-of-view training program among healthy older adults in laboratory and home settings. Both groups showed significant improvements in processing speed relative to a control group that underwent no training. However, gains in the home-based group were 74% that of those in a lab-based training condition. These data suggest that self-administration of cognitive training is indeed feasible, though effect sizes may be smaller and more heterogeneous (see Payne et al., 2012b for similar evidence in a home-based reasoning training). Such home-based training is likely to be more sensitive to individual differences in motivational factors, which may directly influence the amount of effort allocated to the training (e.g., Payne et al., 2012b). Note however, that Wadley et al.'s (2006) findings could also be attributed to the adaptive nature of the in-lab training, which was not replicated in the

home version. Nevertheless, the data from the current study indicate that self-administration of the WM training is feasible.

A key test of the effectiveness of the training program was the assessment of the degree to which training led to improvements in untrained complex verbal WM span. There was positive evidence for improvement across the complex span tasks measured in the current study, with all four tasks showing at least a half standard deviation improvement in WM for the training group relative to the control, three of the four tasks reaching statistical significance, and a pooled effect size of $d = 0.87$. Thus, the evidence from the current study suggests that home-based training of WM can be effective in improving both trained and untrained complex verbal WM span in the short-term. Note however, that the effects of training on the reading span task did not reach statistical significance despite the fact that this measure appeared to have the highest overlap in surface features to one of the training tasks (the sentence span task) while the same outcome in the auditory modality (listening span) did show reliable evidence for near transfer. One reason for the reduced effect size of training on reading span relative to listening span may be due to the self-paced nature of the reading span measure. Prior studies have found that self-paced administration influences estimated WM capacity, as well as the validity of the measure for predicting higher-order cognition (Friedman and Miyake, 2004; Lépine et al., 2005; Clair-Thompson, 2007; Barrouillet et al., 2008). It may be the case that self-pacing in the processing component of the task influences the magnitude of transfer as well.

Working Memory and Language Understanding

The primary aim of the current study was to test the degree to which training-related improvements in WM led to improvements in language comprehension in older adults. Adults in the WM training group showed differentially larger improvements in both sentence memory and verbal fluency relative to the active control group. It is perhaps unsurprising that short-term sentence memory showed transfer, as sentence memory performance is highly related to WM (Stine-Morrow et al., 2008; Lewis and Zelinski, 2010; Payne et al., 2012a), and, at least for the reading span task, overlaps to some degree in task demands (MacDonald and Christiansen, 2002; cf. Roberts and Gibson, 2002). However, demonstrating training-related transfer to sentence memory in older adults is critical for at least two reasons. First, although verbal WM and sentence memory share a substantial amount of variance in older adults, this does not necessarily imply that training should result in transfer. Indeed, individual differences in WM and fluid intelligence share upward of 50% of the same variance (Engle, 2010), and yet evidence for transfer of WM training to fluid intelligence has been inconsistent (see Shipstead et al., 2012; Melby-Lervåg and Hulme, 2013, 2016, for reviews). Second, sentence memory shows some of the largest effect sizes for age-related declines among measures of language comprehension and episodic memory (Johnson, 2003; Stine-Morrow et al., 2008). Demonstrating reductions in age-related deficits in language memory is thus quite valuable for future applications in memory remediation in older adulthood.

The demonstration that WM training transferred to verbal fluency indicates that training can lead to transfer to tasks that share very little overlap with the tasks involved in the training. At the same time, interpreting training effects on verbal fluency are complicated by the fact that tasks such as the *FAS* are used in both research and clinical settings to index a range of theoretically different cognitive functions including executive functioning (Mayr and Kliegl, 2000), semantic processing efficiency (Troyer et al., 1997), frontal-lobe mediated generative language production (Federmeier, 2007), and lexical knowledge (Nagels et al., 2012). Future work should focus on the role that WM training plays in improving executive control components related to aspects of language production and semantic processing. Nevertheless, given the strong relationship between fluency and language comprehension and production in older adulthood (Federmeier et al., 2002, 2010; Federmeier, 2007; Wlotko et al., 2012), such findings are promising from both applied and basic perspectives.

Two tasks tapping discourse comprehension showed no evidence of transfer of training gains: the Nelson-Denny reading comprehension task and the Rivermead behavioral memory task, a measure of discourse memory (see Payne et al., 2014b). While this may be surprising given that prior work has shown that reading comprehension and discourse recall are correlated with WM, one explanation is that age-related declines in discourse understanding are actually quite rare (Stine and Wingfield, 1990; Radvansky, 1999; Radvansky and Dijkstra, 2007). To some extent, this may be due to the reliance of discourse comprehension on the establishment of a situation model, a level of understanding that is robust to cognitive aging (Radvansky and Dijkstra, 2007; Stine-Morrow and Radvansky, in press). Under this account, older adults can rely on situational representations as a compensatory mechanism in order to maintain comprehension despite reduced memory resources. However, for the context-independent sentence memory task, where it is less likely that a situational representation can be established, WM effects are larger, and effects of training are found.

Finally, we tested the degree to which syntactic comprehension accuracy was modulated by WM training. Results were mixed. Sentences that were unambiguous but more syntactically complex (e.g., SR/OR and LDD sentence sets) did not produce the expected pattern of training-related improvements. Only in syntactically ambiguous garden path sentences was there positive evidence for WM-specific-improvements in comprehension of more syntactically difficult sentences. Both the treatment and control groups showed the canonical garden-path ambiguity effect in comprehension (Christianson et al., 2001, 2006) at baseline. At post-test, only the WM training group showed evidence for reduced ambiguity effects on comprehension. This effect was driven by a selective increase in comprehension for the more demanding syntactically ambiguous items. Note that these findings are similar to those of Novick et al. (2013) and Hussey et al. (2016) who have found evidence that younger adults trained on the *n*-back task

with lures showed improvements in comprehension of similar garden-path ambiguities.

One explanation is that WM affords the capacity to maintain multiple alternative syntactic representations of ambiguous phrases, which can be directly accessed at the point of disambiguation. Low-span readers are unable to maintain multiple syntactic representations, and therefore commit to one interpretation, causing subsequent difficulties when they must revise their incorrect interpretation (MacDonald et al., 1992; Kemper et al., 2004). Consistent with this account, Christianson et al. (2006) showed evidence for a robust negative correlation between verbal WM span and the probability of incorrectly interpreting garden path sentences in older adults. These findings suggest that older adults with low WM have particular difficulties in revising an initially incorrect interpretation (see also Payne et al., 2014a for similar evidence in syntactic attachment ambiguities). The training data presented here corroborate prior correlational results and extend these by suggesting that the WM system subserving ambiguity resolution is plastic and is responsive to memory training.

Limitations and Future Research

The primary limitation in the current study is that the small sample size limited our power to detect small-to-moderate effect sizes. The issue of small sample sizes is widespread in the WM training literature. This issue is largely driven by the severe resource constraints associated with conducting adequately powered cognitive training studies in special populations due to issues with staffing, recruitment, retention, maintenance of intention-to-treat protocols, and additional costs of conducting longitudinal randomized controlled trials with large sample sizes. One way in which sample sizes may be increased without substantially increasing costs and resources is through home-based training and assessments, as these approaches require fewer resources to be allocated to each individual subject for daily laboratory visits. Thus, one goal of this work is to illustrate that home-based training is a feasible and valid option for future studies and may be able to help move toward scaling up studies to optimally powered sample sizes to detect more nuanced and reproducible effects of training. Because the current study is our first attempt at targeting language comprehension in older adults using home-based WM training, the results should be interpreted with caution. Future planned work will aim to replicate these results with larger and more diverse samples and continue to follow best practices for cognitive intervention, including pre-registration and examining follow-up and maintenance effects (cf. Simons et al., 2016).

Despite our limited sample size, several advances were made in the current study to meet the criteria of a randomized controlled trial, as laid out in the CONSORT statement. Great care was taken to evaluate the effects of iTrain against an appropriate control group in the context of a literature in which inadequate control groups negatively impact many studies. Because treatment and no-contact control groups are not matched on their expectancies to improve, differential change can be attributed to Hawthorne effects, in which task-related expectancy to improve drives motivational factors to improve performance at post-test. Even in studies with so-called "active" control groups, different groups may vary substantially in their expectations for improvement generally as well as on specific tasks (Boot et al., 2013). In this study, we adopted a "component control" design to keep control and treatment groups as well matched as possible. Indeed, post testing surveys revealed that individuals in both groups had similar endorsement of perceived training improvements. That only moderate perceived change was found in the presence of observable improvement suggests that these effects are not likely attributable to so-called "Hawthorne" effects. In addition, an intention-to-treat approach was used, in order to downwardly bias effect sizes with differential drop from the training (Hollis and Campbell, 1999). However, because the home-based training resulted in such high retention, the issue of differential drop-out causing the observed training benefits is not plausible.

Despite the relative breadth of the measurement battery for assessing language, it was designed to primarily tap into comprehension processes and not language production. However, there is a growing literature posing a strong relationship between WM, WM limitations (e.g., through aging and brain damage), and language production mechanisms (Acheson and MacDonald, 2009; Martin and Slevc, 2014). Indeed, two tasks in the neuropsychological battery—the verbal fluency and the sentence memory tasks—involved verbal production and also showed the strongest evidence of training benefits, despite production *per se* not being the critical theoretical component of these measures. Thus, future work may benefit from more thoroughly targeting language production outcomes.

CONCLUSION

The contributions of this study are two-fold. First, based on a research design that minimized the role of expectancy effects (Boot et al., 2013), our results suggest that verbal WM among older adults is responsive to home-based training, at least in the short-term. With fewer than 10 h of home-based practice with tasks exercising the simultaneous management of verbal operations and storage over the course of 3 weeks, training effects transferred to untrained verbal WM measures. Second and most importantly, WM training lead to selective improvements in measures of language fluency, sentence memory, and syntactic ambiguity resolution, implying that WM may be a critical resource for these aspects of language performance in older adulthood. These findings are among the first to indicate that selective aspects of language performance can be modified through targeted home-based practice in WM in older adulthood. This is not only of theoretical import in defining the cognitive architecture of language processing across the lifespan (e.g., Just and Carpenter, 1992; Stine-Morrow and Payne, 2016), but also suggests applications for improving cognitive functioning among older adults in significant ways (Stine-Morrow and Basak, 2011). Because age-related declines in language comprehension and memory can have far-reaching effects as adults navigate the ordinary demands of work, family, and health (e.g., Morrow et al., 2006; Chin et al., 2015), the development of pathways to mitigate such deficits offers promise for promoting late-life well-being.

This study is motivated by a specific model of vertical transfer in which a skill (language comprehension) was improved by exercise of a component theorized to be a core process constraining this skill (verbal WM). As described above, the cognitive training literature has generally shown relatively narrow transfer of cognitive training across cognitive domains in near transfer tasks. Yet, it is common for training programs to adopt a very broad cognitive battery and predict broad-based changes in cognition, under the rationale of "use it or lose it," without a specific model of what is exactly is being used or what capability will not be lost by using it. Given what is known from existing literature (cf. Simons et al., 2016), it is plausible that training programs will lead to very specific improvements across cognitive domains in transfer tasks that are subserved by the core mechanisms being exercised in the training tasks. A goal of future work must be to develop sound theories of the cognitive architecture of meaningful activities, as well as credible training and transfer tasks to operationalize those theories. Only in this way can cognitive training be used as a method to target specific mechanisms and test mechanistic accounts of theoretical models (Baltes and Kliegl, 1992; Hussey and Novick, 2012; Lindenberger et al., 2017). Thus, although transfer of cognitive training is a controversial area (see open-letter statements by A Consensus on the Brain Training Industry from the Scientific Community, 2014 and cognitivetrainingdata.org), our view is that the current study contributes to a literature aimed at using training-related cognitive plasticity as a tool for examining basic questions about cognitive architectures and functions rather than as a tool to reverse or slow generalized cognitive decline or substantially alter intellectual functioning (Simons et al., 2016; National Academies of Sciences, Engineering, and Medicine, 2017).

ETHICS STATEMENT

University of Illinois Institutional Review Board. Participants had completely voluntary participation and chose to sign up for the study of their own volition. All appropriate procedures were followed to ensure subject confidentiality and privacy, including voluntary participation, freedom to withdraw, and informed consent. Prior to participation in the study, informed consent was obtained from participants, which involved verbally explaining the research, risks and benefits, and confidentiality. Risk level for this study was deemed to be no more than minimal risk, meaning that the probability and magnitude of harm or discomfort were not greater than those ordinarily encountered in daily life.

AUTHOR CONTRIBUTIONS

BP and ES-M designed the research. BP performed the research and analyzed the data. BP and ES-M wrote the paper.

FUNDING

This research was funded by the University of Illinois Campus Research Board. The first author was supported by a National Institutes of Health training grant (T32-HD055272) and a Beckman Institute Graduate Fellowship at the University of Illinois at Urbana-Champaign, with funding provided by the Arnold and Mabel Beckman Foundation. Portions of this research were completed by BP in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the University of Illinois and were presented at the Cognitive Aging Conference, 2014. We would like to thank Thomas Deegan and Andy Battles for their programming assistance, and Kyle Payne and Sneha Gummuluri for their recruitment and data collection efforts. We'd like to thank Kiel Christianson, Duane Watson, and Kara Federmeier for their helpful comments on previous versions of this manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnagi.2017.00256/full#supplementary-material

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 10 August 2017
doi: 10.3389/fnagi.2017.00265

Age-Related Shift in Neuro-Activation during a Word-Matching Task

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Growing evidence from the neuroscience of aging suggests that executive function plays a pivotal role in maintaining semantic processing performance. However, the presumed age-related activation changes that sustain executive semantic processing remain poorly understood. The aim of this study was to explore the executive aspects of semantic processing during a word-matching task with regard to age-related neuro-functional reorganization, as well as to identify factors that influence executive control profiles. Twenty younger and 20 older participants underwent fMRI scanning. The experimental task was based on word-matching, wherein visual feedback was used to instruct participants to either maintain or switch a semantic-matching rule. Response time and correct responses were assessed for each group. A battery of cognitive tests was administrated to all participants and the older group was divided into two subgroups based on their cognitive control profiles. Even though the percentage of correct responses was equivalent in the task performance between both groups and within the older groups, neuro-functional activation differed in frontoparietal regions with regards to age and cognitive control profiles. A correlation between behavioral measures (correct responses and response times) and brain signal changes was found in the left inferior parietal region in older participants. Results indicate that the shift in age-related activation from frontal to parietal regions can be viewed as another form of neuro-functional reorganization. The greater reliance on inferior parietal regions in the older compared to the younger group suggests that the executive control system is still efficient and sustains semantic processing in the healthy aging brain. Additionally, cognitive control profiles underlie executive ability differences in healthy aging appear to be associated with specific neuro-functional reorganization throughout frontal and parietal regions. These findings demonstrate that changes in neural support for executive semantic processing during a word-matching task are not only influenced by age, but also by cognitive control profile.

Keywords: fMRI, word-matching task, executive processes, healthy aging, cognitive control profile, neuro-functional reorganization

OPEN ACCESS

Edited by:
Pamela M. Greenwood, George Mason University, United States

Reviewed by:
Didac Vidal Piñeiro, University of Oslo, Norway
Verónica Expósito De Mäki-Marttunen, Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia, Argentina

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Received: *12 September 2016*
Accepted: *24 July 2017*
Published: *10 August 2017*

Citation:
Methqal I, Provost J-S, Wilson MA, Monchi O, Amiri M, Pinsard B, Ansado J and Joanette Y (2017) Age-Related Shift in Neuro-Activation during a Word-Matching Task. Front. Aging Neurosci. 9:265. doi: 10.3389/fnagi.2017.00265

INTRODUCTION

Healthy aging is accompanied by changes in numerous cognitive abilities, with performance differences noted within and between cognitive domains (Valdois et al., 1990; Goh et al., 2012). For instance, slight age-related changes have been reported for cognitive abilities that involve semantic processing, which remains relatively stable across the lifespan (Burke and Shafto, 2004), unlike those abilities that have been shown to decline with age such as episodic memory, visual attention and inhibition (e.g., Park et al., 2002). However, these age-related cognitive changes are less extensive than one would expect, given age-related structural brain changes.

The preservation of cognitive performance in healthy aging is usually associated with adaptive changes in brain activity (Reuter-Lorenz and Cappell, 2008). One such neuro-functional change is the presence of more widespread activation involving both hemispheres in older adults, a phenomenon formalized in the HAROLD model (Hemispheric Asymmetry Reduction in Older Adults; Cabeza, 2002). In addition to inter-hemispheric neuro-functional symmetry, intra-hemispheric changes have been also described, such as the PASA phenomenon (Posterior–Anterior Shift with Aging; Davis et al., 2008). Interestingly, convergent findings from our laboratory and from other studies reflect that there is often an age-related activation shift from anterior to posterior regions to support cognitive performance (Ansado et al., 2013b; Lacombe et al., 2015). For instance, Ansado et al. (2013a) have reported an age-related additional parietal recruitment to cope with increasing cognitive demands during a load-dependent judgment task. Similarly, Oedekoven et al. (2013) have found a greater parietal activity contribution, which resulted in successful episodic memory retrieval among older individuals. Thus, the engagement of parietal regions at high-demanding tasks tends to reflect the neuro-functional reorganization within fronto-parietal networks that supports cognitive performance in healthy cognitive aging.

It is well known that one of the most important age-related changes in brain activation takes place in frontal regions that are known to be involved in executive (or cognitive) control processes (Paxton et al., 2008; Grady, 2012). Although one could assume, from the findings mentioned above, that these regions are not sufficient to explain all age-related differences in executive resources involved in maintaining task performance (Bouazzaoui et al., 2014; Collette and Salmon, 2014). Based on the most neuroimaging findings, changes in executive control functioning could be the first indicator of the brain's adaptation strategy to insufficient neural resources in healthy aging by flexible neural reallocation (Reuter-Lorenz and Cappell, 2008; Adrover-Roig and Barceló, 2010). In one relevant neuroimaging study, Peelle et al. (2013) showed that older adults with better semantic processing tended to rely more on the prefrontal and inferior parietal regions for word-meaning judgment than younger adults or older adults with poorer semantic performance. These findings suggest that the executive control regions (i.e., frontal and parietal regions) constitute the neuro-functional basis for semantic performance maintenance in healthy aging.

From a cognitive perspective, cognitive control supports a variety of executive processes defined as the ability to maintain and update information in working memory and to switch from current information to the adoption of new information, which involve a higher level of executive control (Miyake et al., 2000; Braver et al., 2003; Adrover-Roig et al., 2012). There has been, however, relatively little investigation on age-related neuro-functional changes of neural patterns relevant to executive control processes in semantic tasks.

The relative preservation of semantic processing can be defined by the degree of control over maintaining and/or switching among different types of semantic word relationships (Nagel et al., 2008; Noonan et al., 2010; Maintenant et al., 2011; Whitney et al., 2012). Growing evidence is emerging from functional neuroimaging studies that have considered the interactions between the executive control and language networks (Whitney et al., 2011; Noonan et al., 2013; Lambon Ralph et al., 2016). Consistent findings from these studies reveal the extent of executive control network activation for semantic performance in language comprehension tasks. These large neural networks underpinning semantic and executive processes consist of inferior prefrontal, anterior cingulate, inferior parietal and posterior temporal cortices, as well as the cerebellum (Bookheimer, 2002; Noppeney et al., 2004; Binder et al., 2009). For instance, prefrontal regions supporting executive control processes are specifically active for the effective use of relevant semantic knowledge as well as when manipulation of semantic relationships is required during retrieval and selection among semantically related competitor words (Thompson-Schill et al., 1997; Wagner et al., 2001; Badre and Wagner, 2007; Maintenant et al., 2013). In addition to this prefrontal involvement, inferior parietal regions were also consistently activated across semantic tasks with high level of executive control (Noonan et al., 2010; Whitney et al., 2012). However, it is unclear whether these age-related changes in the activation of cognitive control networks sustain the semantic processing of words or if such activation reveals some dynamic processes. Overall, we could claim that studying executive aspects of semantic words processing is particularly appropriate for exploring possible neuro-functional reorganization with age.

Considering the fronto-parietal network involvement in semantic tasks requiring executive control processes (Binder and Desai, 2011; Noonan et al., 2013; Peelle et al., 2013), the first goal of this study was to explore, behaviorally and neuro-functionally, the age-related activation changes in fronto-parietal regions that underlie executive aspects of semantic processing. More specifically, an original word-matching task was developed based on the executive requirements of the Wisconsin Card Sorting Test (WCST) and was adapted for use in fMRI protocols (Monchi et al., 2001). This task requires the flexible use of semantic relationship (or rules) supported by two executive processes: (a) maintain rule; and (b) switch rule. The first process requires participants to maintain a given semantic rule through working memory updates, while the second one requires a shift from one rule to another. The latter is related to higher-level of executive control relative to the former.

Given the neuro-functional changes that occur concomitantly with the relative preservation of semantic ability in healthy aging (Ansado et al., 2013a; Peelle et al., 2013; Lacombe et al., 2015), we expected that older adults show greater activation in the inferior parietal regions, relative to younger adults. More precisely, these age-related neuro-functional changes were expected at the higher-level of executive control process necessary for the switch rule rather than for the maintain rule. Finally, it was expected that behavioral performance differences, measured by response times and correct responses, would be correlated with brain activation changes for both groups.

A current issue in cognitive aging studies is the reorganization of executive processes that occurs in contribution to age-related changes performance in complex executive tasks. In the past decade of cognitive aging studies, many researchers have supported the idea of the non-unitary nature of executive functions in healthy aging (Hull et al., 2008; Adrover-Roig et al., 2012), unlike those who have focused on a single and common executive system in aging (de Frias et al., 2006). These claims might further be viewed as extending work of Miyake et al. (2000) by supporting the notion that age-related changes in executive performance could be better explained by diversity in executive functions represented by at least two distinct executive subcomponents, though they are not completely independent. These executive processes consist of updating and maintaining information in working memory, and shifting between mental sets. Such distinction has also been found at the level of the neuro-functional organizations between updating and shifting processes, the former process supported by the activation of prefrontal regions, while the latter being mainly associated with parietal regions engagement (e.g., Collette et al., 2006; Braver et al., 2009; Herd et al., 2014; Kopp et al., 2014).

These executive processes are defined as distinct executive subcomponents that are differentially used by older adults. Some findings have further highlighted that higher level of global cognitive functioning would be associated with largely separable executive control processes (Adrover-Roig and Barceló, 2010; Collette and Salmon, 2014). In this context, de Frias et al. (2006) have reported that high cognitive functioning in older adults is related to highly differentiated executive control processes rather than unitary process. Moreover, Adrover-Roig et al. (2012) have found neuro-functional changes that are associated with the level of cognitive control in older adults. In that study, older adults with low level of cognitive control showed less activation in frontal regions indicating inefficiency in updating/maintaining processing compared to older adults with high level of cognitive control. As the existence of changes in executive function among older adults is supported by distinct executive control processes underpinned by neurally distributed networks, the second goal of this study was to explore whether different cognitive control profiles in aging would correspond to specific neuro-functional reorganization patterns.

Based on different cognitive measures that encompass executive (or cognitive) control processes, we aimed to identify if (a) at a behavioral level, individual differences in executive performance could be triggered by different cognitive control profile (updating-specific and shifting-specific) among older adults; and (b) at a neuro-functional level, neuro-functional reorganization patterns are associated to specific cognitive control profiles. More specifically, the possibility that central cognitive control processes may be linked to specific cognitive profiles was examined in elderly people. It was expected that older adults with a shifting-specific profile would rely more extensively on parietal regions, while the updating-specific profile would recruit more frontal regions to maintain the performance to a given task. Finally, it was also expected that there would be a correlation between behavioral performance (response times and correct responses) and task-induced brain activation changes in each cognitive profile within an elderly group.

MATERIALS AND METHODS

Participants

Twenty healthy older adults aged between 63 and 80 and 20 younger adults whose ages ranged from 19 to 35 were recruited from a pool of volunteers at the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal (CRIUGM). All participants were native French speakers and all were right-handed (scores greater than +95) as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). All had normal or corrected-to-normal vision; none had any history of major neurological disease, psychiatric illness, head injury, stroke, substance abuse, learning disabilities, or any problems that could interfere with behavior testing. Prior to the neuro-imaging session, all participants were also given a battery of neuro-psychological tests during a single 90-min session which included: screening of global cognitive function (The Montreal Cognitive Assessment, MoCA; Nasreddine et al., 2005); the inhibition measure (Stroop Test; Stroop, 1935); the flexibility measure (Trail Making Test, TMT A and B; Reitan, 1955); working memory measure (forward and backward Digit Span, WAIS III; Wechsler, 1981); several measures of ability to select a rule, maintain it, and switch to a new rule are from Burgess and Shallice (1997), for the Brixton test and Nelson (1976), for the Wisconsin Card Sorting Test (WCST); and semantic fluency as represented by the total number of words produced in 2 min for the category Animals (Cardebat et al., 1990). **Table 1** provides a detailed description of the raw cognitive measures as well as a statistical comparison of group means. Furthermore, the older adults' cognitive scores (not shown in **Table 1**) were within the average range according to all psychometric standardized data, suggesting normal cognitive functioning within the older adult group. All participants gave written informed consent to the protocol, which was approved by the Institut universitaire de gériatrie de Montréal Human Ethics Committee and by the Regroupement Neuroimagerie/Québec (RNQ). This committee follows the guidelines of the Civil Code of Quebec, the Tri-Council Policy Statement of Canada, the Declaration of Helsinki, and the code of Nuremberg. Finally, in order to clearly identify subgroups of older

participants according to their cognitive control profile, classification was based on their *z*-score for neuropsychological tests.

Characterization of Older Subgroups

Five executive *z*-scores for each older participant were entered into hierarchical cluster analysis with CLUSTAN (Aldenderfer and Blashfield, 1984). Using the Clustan Graphics program (version 5.27), case classification was based on the squared Euclidean distance as a coefficient of similarity, and on the Ward method of classification (Ward, 1963). The *k*-means clustering procedure of relocation was then applied to ensure that the two-cluster solution was stable. This procedure allowed for the identification of two possible natural older subgroups of participants, based on their performances on five executive measures (TMT B/A, digits backward, number of errors on the Brixton test, number of errors on the WCST, number of words produced correctly for the semantic fluency task). This grouping was confirmed *a posteriori* using an independent-samples *t*-test, which revealed that the two subgroups (henceforward referred to as the updating-profile and shifting-profile groups) differed significantly on five neuro-psychological tests (see part B).

The updating-profile group scored significantly higher on the backward digit span and Trail Making Test (Part B) than on the WCST, Brixton, and semantic fluency tests. Conversely, the shifting-profile group scored significantly higher on the WCST, Brixton, and semantic fluency tests than on the backward digit span and Trail Making Test (Part B). Thus, the latter group's executive performance relied more on their shifting ability than on updating/working memory, which the former group depended on more.

A cluster analysis approach was also performed on the group of younger participants. However, the results provided no clear indication of a given cognitive profile associated with a sub-group of participants. Thus, for younger participants, behavioral data were analyzed as a group.

Experimental Procedure

The word-matching task used in this study was based on the computerized WCST developed and adapted to fMRI by Monchi et al. (2001) and Simard et al. (2011). The word-matching task was administered using stimulus presentation software (Media Control Function; Digivox, Montréal, QC, Canada). Throughout the task, three reference cards based on three semantic rules were presented in a row at the bottom of the screen, displaying moderately, atypical, and functionally related words (see **Figure 1** for example). In each trial, a new target card was presented in the middle of the screen above the reference cards; it displayed a highly typical word. Participants must then match the target card with one of the reference cards based on moderately typical, atypical, or functional relatedness. Participants used a joystick to select among the three reference words, pressing left, right, or upward to select the reference word on the left, on the right, or in the middle, respectively (the description of selection stimuli is reported in Supplementary Data Sheet 1).

The word-matching task trials contained two periods: matching and feedback.

- The matching period started with the presentation of a new target card (highly typical word). The participant then chose one of the three reference words by using one of the three joystick directions. The length of each matching period depended on the participant's response times, which varied between 1470 and 4690 milli-seconds (ms) for this task. The period ended when the participant provided a selection response.
- The feedback period was indicated by a blue screen, which lasted for 500 ms and started as soon as a first correct match was made. Feedback was conveyed through a specific cue lasting for 2000 ms. An incorrect match was indicated by a

TABLE 1 | Means (M) and standard deviations (SD) of the demographic and neuropsychological variables of all participants ($n = 40$).

	Younger ($n = 20$)	Older ($n = 20$)		
	M (*SD*)	*M* (*SD*)	*F*(1,38)	*p*-values
Age	24.85 (3.85)	69.45 (4.54)	1129.02	0.001
Gender (F: M)	16:4	17:3	0.603	0.714
Education (years)	17.95 (2.52)	18.85 (2.88)	1.01	0.301
Edinburgh inventory	95%	96%	0.89	0.122
MoCA	28.6 (1.53)	28.7 (1.03)	0.058	0.81
Stroop C	49.95 (6.88)	62.2 (9.12)	22.95	0.001
Stroop W	39.25 (4.02)	45.30 (5.82)	14.61	0.001
Stroop C–W	83.05 (13.42)	114.65 (22.29)	29.5	0.001
TMT A	17.40 (4.35)	27.60 (8.22)	23.98	0.001
TMT B	41.60 (11.77)	62.82 (16.29)	22.24	0.001
Digits forward	10.5 (1.67)	9.65 (1.75)	2.46	0.125
Digits backward	8.45 (2.03)	6.8 (1.73)	7.6	0.009
Brixton (errors)	1.15 (1.03)	1.45 (1.05)	0.82	0.37
WCST (errors)	0.88 (1.19)	1.05 (1.27)	0.41	0.527
Semantic Fluency	39.70 (8.27)	28.85 (8.1)	17.55	0.001

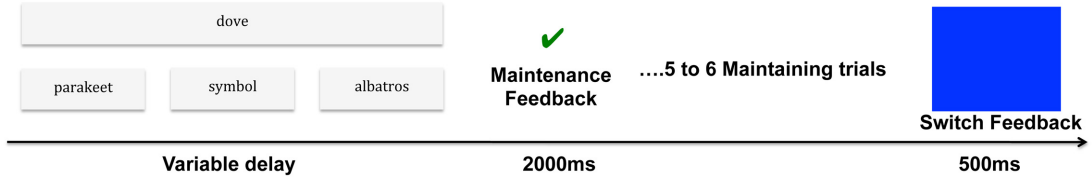

FIGURE 1 | Experimental procedure of the word-matching task. In this example, each participant performed a task in which a target word presented at the top of the screen, dove ('*colombe*') had to be paired with one of three reference words, presented at the bottom, according to three possible semantic relationships: (a) typically related word (co-hyponyms) parakeet ('*perruche*'); (b) atypically related word (co-hyponyms) albatross ('*albatros*'); and (c) functionally related words (F) symbol ('*symbole*'). The sorting period was followed by a maintenance feedback signal (green check mark displayed for 2000 ms) indicating that participants should maintain the same semantic rule as in the previous trial. After 5 or 6 maintaining trials, the rule changed (blue screen displayed for 500 ms) and participants had to discover the new classification rule and maintain it. As a control condition, a target card (e.g., AAAA) would be matched with the same sequence (e.g., aaaa) among three reference cards: aaaa, bbbb, cccc.

red cross, whereas a correct match was indicated by a green check mark, which informed participants that the current matching rule was the correct one and that they should maintain the same rule as in the previous trial (see **Figure 1** for experimental procedure).

- In addition, there were control trials during which the target card was represented by a series of letters (e.g., AAAA), which was identical with one of the three reference cards (e.g., aaaa, bbbb, cccc). These trials involved pairing a target with an identical reference card (alphabetic association: AAAA with aaaa). No rule changes occurred in the control condition and control feedback indicated a correct or incorrect match.

All participants had one fMRI session, which consisted of four runs. Blocks of each of the four trials (the three semantic rule trials and the control trial) were presented in pseudo-random order four times per run. The rules changed without warning and the new correct rule would be applied and maintained until the participant achieved five to six consecutive correct matching trials (maintaining a rule if shown a green check mark) or had to switch it (if presented with a blue screen as feedback). It is worth mentioning that no participant reported learning the sequence regularity or having deduced the frequency of the changing rule. The control block consisted of eight trials. For each participant, the total number of trials per run changed according to performance, which depended on the number of errors. The participants were fully trained on the word-matching task by performing a block of conditions outside the scanner. Each participant needed to reach a performance level of 90% correct matching trials and have less than 5% of set-loss and perseverative errors before moving on to the scanning session.

The stimuli were presented via an LCD projector onto a mirror placed in front of the participant in the MRI scanner. Stimuli were outlined in black against a white background to improve visual contrast. All words were displayed horizontally at the top of the screen and were centered on a computer screen placed 50 cm away from the participant. The target word was placed in a larger rectangle and subtended a visual angle of 26.6° horizontally and 13.8° vertically. All words were presented in 28-point Arial font, and reference words were placed in three small rectangles 1.3 cm apart from each other.

For this study, we explored, exclusively, executive processing during the word-matching task. All correct (5–6) consecutive matching trials, after the maintenance feedback period and the correct trial after switch feedback, were taken into account for behavioral and imaging analysis, as were the correct control matching trials. To ensure that the rule was successfully acquired after rule-matching change (related to the search for a correct rule), we removed the first correct trial after switch feedback.

DATA ANALYSIS

Behavioral Data

Two behavioral measures were also collected: response times and correct responses (defined as 5 or 6 consecutive correct matching trials after maintenance and switch feedback). Intergroup analyses were performed using SPSS 18.0 software for Mac (IBM SPSS Statistics 18). A comparison ANOVA was done between the two groups (younger and older) for each executive component (henceforth, matching after maintenance feedback is referred to as *maintain rule* and matching after switch feedback as *switch rule*) and between these executive components for each group (younger and older). For these analyses, the response times for control matching trials were subtracted from those for matching trials after maintain rule in order to account for age-related decline in motor speed (Fristoe et al., 1997; Martins et al., 2014). In addition, errors were analyzed for each group (younger vs. older) and a one-way ANOVA was carried out.

Results for response times and correct responses were divided into two parts; the first part (A) was based on a comparison between groups (younger vs. older), and the second part (B) was based on a comparison within the older group. This latter part of the study was exploratory.

fMRI Scanning

Image Acquisition

Participants were scanned at the Unité de Neuroimagerie Fonctionnelle of the Institut de Gériatrie de Montréal using a 3T Siemens Trio Magnetom MRI scanner (Siemens AG,

Erlangen, Germany). The structural scan was a high-resolution T1-weighted 3D-MPRAGE, sagittal plane acquisition, field of view (FOV) = 256 mm, and matrix size = 256 × 256. In addition, we acquired functional images [T2* weighted, TR = 2500 ms, TE = 30 ms, 36 slices parallel to the anterior and posterior commissure (AC-PC) line, slice thickness = 3.5 mm with 3.5 mm^3 isotropic voxels, distance factor 0% (gap = 0 mm), Flip-angle = 90°, matrix = 64 × 64]. Each 252-volume functional run lasted 10.30 min; four such runs were acquired for each participant. The stimulus presentation and the scanning were synchronized at the beginning of each run. To minimize head movement during scanning, cushions were placed between the subject's head and the coil.

fMRI Data Analysis

FMRI Expert Analysis Tool (FEAT) Version 5.98, part of the FSL analysis package (FMRIB's Software Library, Version 4.1.4[1]), was used to conduct image pre-processing procedures. We corrected for head motion using MCFLIRT (FMRIB's motion correction linear image registration tool; Jenkinson et al., 2002), and also used the fsl_motion_outliers script to detect and remove any volumes with excessive head motion. Non-brain tissue was removed using BET (Brain Extraction Tool; Smith, 2002). Grand-mean intensity normalization was applied to the 4D dataset from each run based on multiplicative scaling factor. We applied a Gaussian kernel of 6 mm FWHM for spatial smoothing, and for temporal filtering, a high-pass filter was applied to remove low-frequency noise using Gaussian-weighted least-squares straight-line fitting (1/60 Hz). Temporal auto-correlation was corrected by using pre-whitening as implemented by FILM (FMRIB's improved linear model). Functional images of each participant were co-registered to structural images in native space, and structural images were normalized to Montreal Neurological Institute (MNI) standard space using FSL's MNI Avg 152 T1 2 mm × 2 mm × 2 mm. The same transformation matrices used for structural-to-standard transformations were then used for functional-to-standard space transformations of co-registered functional images.

The FEAT module in FSL was used for first level analysis. An event-related design was used to model the fMRI data, allowing for inference based on contrast. We included five different event types in the design matrix: typical, functional, and atypical maintain rules; switch rules; and control trials. The maintain rule period was defined on the basis of the time period, for which each length varied between trials depending on the participant's response time. This period started with the presentation of a new trial and ended only when the participant provided a selection response. The maintain rule period was convolved with a double-gamma hemodynamic response function (HRF). The switch rule period was defined as a shift event based on the second correct trial after switch feedback, during which the participant had to discover and apply the new matching rule, convolved with a double-gamma HRF. The aim was to separate correct maintain and switch-rule periods as well as control trials. Motion regressors generated by MCFLIRT were then included as confound covariates. A first-level GLM analysis was carried out separately for each run, followed by a second-level fixed-effects analysis. We then combined these analyses across all participants in group-level analysis (Higher-level) using a mixed effects analysis controlling for variation within and between participant groups, using FLAME (FMRIB's Local Analysis of Mixed Effects). For age-group comparison (younger vs. older), statistical results were at a threshold voxel significance level of $Z > 2.3$, and a whole-brain-corrected cluster significance threshold of $p < 0.05$. To explore the effect of cognitive control profile on activation changes in the older group, an exploratory study was conducted. For the older subgroup's exploratory study, all the steps in the analysis were as described above. However, Flames 1 and 2 were added at a higher level of analysis due to the small sample size of the older subgroups. For the same reason, the statistical results were at a threshold voxel significance level of $Z > 1.96$ and a whole-brain-corrected cluster significance threshold of $p < 0.05$ for the main-effect of each subgroup. For subgroup difference analysis, due to a limited sample size, a more liberal threshold at $p < 0.001$ was set. In this manner, a literature-guided hypothesis was tested for activity differences specifically located in frontoparietal regions, while ensuring that no other significant clusters were found in the brain.

To investigate regional differences of BOLD (blood-oxygen-level dependent) signal changes in the areas that showed significant activation, we used a region of interest (ROI) approach. Each ROI centered on a peak level of significant activation produced by a group average of the statistical maps. For the between-group comparison (younger vs. older), these ROIs were in the right posterior prefrontal cortex [BA 6/8/44; $x = 37$; $y = 18$; $z = 52$] and in the left inferior parietal cortex [BA 39/40; $x = -33$; $y = -61$; $z = 39$]. For between older subgroups (updating-profile vs. shifting-profile): within the left dorsolateral prefrontal cortex [BA 9/46; $x = -42$; $y = 10$; $z = 35$] and the left inferior parietal cortex [BA 39/40; $x = -33$; $y = -61$; $z = 39$] were considered as ROIs. These ROIs (identified in our participants) have been widely reported in cognitive control tasks in previous studies (Rypma et al., 2006; Badre and D'Esposito, 2007; Nagel et al., 2008; Niendam et al., 2012; Whitney et al., 2012; Noonan et al., 2013). ROI masks were generated with a 4 mm-radius sphere centered on the peak voxel coordinate within each significant cluster. The mean BOLD signal change of the ROIs was extracted separately for each participant from the maintain rule and switch rule. Finally, we conducted a correlation analysis for each age group and also for each older subgroup to investigate potential patterns of relation between behavioral performance (response times, correct responses) and BOLD signal changes during the word-matching task. Additionally, the Fisher r-to-z transformation was also applied to calculate a value of z that can be applied to assess the significance of the difference between two correlation coefficients found, in one case, between younger and older groups and, in the other, older subgroups separated by cognitive profile.

[1] www.fmrib.ox.ac.uk/fsl

RESULTS

Part A: Age-Related Neuro-Functional Reorganization

Behavioral Performance

Response times in maintain rule proved to be significantly longer in the older adult group than in the younger group [M_{older} = 2741 ms, SD = 481; $M_{younger}$ = 2265 ms, SD = 705; $F(1,38) = 6.219$, $p = 0.017$]. The same was true in the switch rule [M_{older} = 2974 ms, SD = 793; $M_{younger}$ = 2365 ms, SD = 965; $F(1,38) = 4.74$, $p = 0.036$] and control condition [M_{older} = 1330 ms, SD = 166; $M_{younger}$ = 1048 ms, SD = 207; $F(1,38) = 22.44$, $p = 0.001$]. For the maintain rule condition, when control response times were taken into account, older adults showed no significant difference in response times compared to younger adults [$F(1,38) = 1.704$, $p = 0.20$] (**Table 2**).

A 2 × 2 ANOVA was performed to explore the effects of age group (younger vs. older) and executive component (maintain rule vs. switch rule) on response times. There was a marginal effect of age group [$F(1,38) = 3.64$, $p = 0.064$], with response times slower in the older adults than in the younger adults. The interaction between age and executive component was also significant [$F(2,38) = 7.32$, $p = 0.010$]. The main effect analysis revealed a significant effect of the executive component [$F(1,38) = 313.25$, $p = 0.001$], showing that maintain rule took less time than switch rule. More specifically, for the maintain rule, planned comparisons did not reveal any significant effect of age [M_{older} = 1411 ms, SD = 383; $M_{younger}$ = 1217 ms, SD = 542; $F(1,38) = 1.704$, $p = 0.20$], whereas the older adults showed significantly longer response times in the switch rule condition than the younger adults. It is worth noting that there was no difference between older and younger participants in total correct responses or in the word-matching task [$F(1,38) = 0.693$, $p = 0.41$] regardless of feedback type, indicating that both younger and older adults performed well.

Imaging Results

The aim of this study was to investigate the impact of age on neuroimaging patterns during a word-matching task. The brain activation pattern was described for maintain rule and switch feedback compared to the control condition. Given the relevance of executive aspects in the word-matching task used in this study, we combined the three semantic relationships. We compared the average BOLD signal obtained during maintain rule and switch rule with the control matching condition. Intergroup analyses were also performed.

Maintain rule vs. control matching

As predicted, neuroimaging analyses revealed the involvement of cognitive control networks during the word-matching task in both groups (younger and older). The younger group showed significant activation in the right dorsolateral prefrontal cortex (BA 9/46), the left ventrolateral prefrontal cortex (BA 44/45), the bilateral insula (BA 41), the left lateral premotor cortex (BA 6), the left posterior prefrontal cortex (junction of BAs 6, 8, and 44), the bilateral superior parietal cortex (BA 7), and the left inferior parietal cortex (BA 39).

The older adults showed significant activation in the left ventrolateral prefrontal cortex (BA 44/45), the bilateral insula (BA 41), the bilateral posterior prefrontal cortex (junction of BAs 6, 8, and 44), the dorsolateral prefrontal cortex (BA 9/46) bilaterally, the left lateral premotor cortex (BA 6), the left inferior temporal cortex (BAs 37 and 20), the bilateral superior parietal cortex (BA 7), the left inferior parietal cortex (BA 39), the left occipital cortex (BA 18), and the right cerebellum.

The comparison between groups showed significantly greater activation in the older adults than in the younger ones in the left and the right hemispheres in the posterior cingulate cortex (BA 31), the right inferior temporal cortex (BA 37), the left inferior

TABLE 2 | Behavioral performance (response times and correct responses) in word-matching task for 20 younger and 20 older adults.

	Younger	Older		
	Mean (*SD*)	**Mean (*SD*)**	***F*(1,38)**	***p*-values**
Response times (in milliseconds)				
Experimental condition				
Maintain rule	1217 (542)	1411 (383)*	1.704	0.20
Switch rule	2365 (965)	2974 (793)	4.74	0.036
Control condition	1048 (207)	1330 (166)	22.44	0.001
Total correct responses (in %)	95.26 (5.30)	93.11 (7.51)	1.093	0.302

*SD, standard deviation. *Control condition response time was subtracted from only maintain rule condition.*

TABLE 3 | Maintain rule minus control matching.

		MNI peak (mm)				
Cluster	**Anatomical areas**	***x***	***y***	***z***	***Z* score**	**Voxel**
	Younger > Older					
	Older > Younger					
1	Left caudate nucleus	−6	18	−6	4.05	20788
	Right caudate nucleus	6	16	−1	4	
2	Left inferior parietal cortex (area 40)	−42	−60	31	4.05	23136
	Right posterior cingulate cortex (area 31)	18	−55	18	3.58	
	Left posterior cingulate cortex (area 31)	−16	−58	21	3.17	
3	Left cerebellum	−27	−83	−31	4	32824
	Right cerebellum	40	−65	−23	3.7	
	Right inferior temporal cortex (area 37)	46	−57	−22	3.69	
	Right occipital cortex (area 18)	11	−98	−11	3.64	

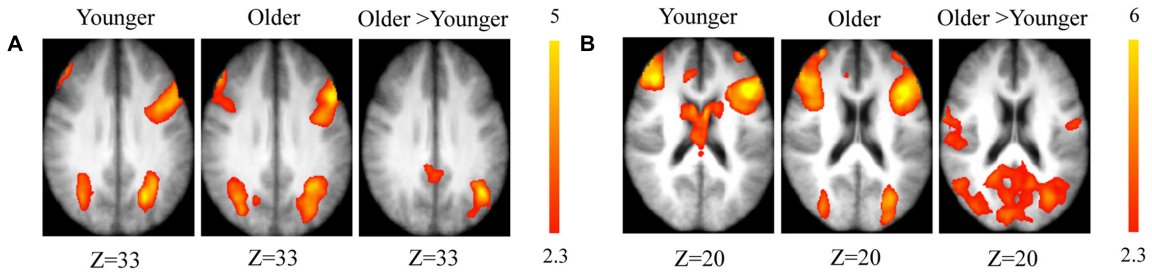

FIGURE 2 | (A) Brain activation for maintain rule minus control condition. The younger group (cf. left). The older group (cf. middle). The comparison between the older adults and the younger adults (cf. right). The color scale represents the *Z* statistic. *Z*-values correspond to the coordinate of the axial plane. **(B)** Brain activation for switch rule minus control condition. The younger group (cf. left). The older group (cf. middle). The comparison between the older adults and the younger adults (cf. right).

cortex (BA 40), the cerebellum bilaterally, the right occipital cortex (BA 18), and in the bilateral caudate nucleus. Comparison of younger minus older adults showed no significant difference (**Table 3** and **Figure 2A**; for younger and older see Supplementary Table S1).

Switch rule vs. control matching

As predicted, stronger activation was found in both groups in the switch rule relative to control matching. The younger group showed significant activation in the right dorsolateral prefrontal cortex (BA 9/46), the left supplementary motor area (BA 6), the left ventrolateral prefrontal cortex (BA 44/45), the right posterior prefrontal cortex (junction of BAs 6, 8, and 44), the right anterior cingulate cortex (BA 32), the bilateral superior parietal cortex (BA 7), the inferior parietal cortex bilaterally (BA 39), the left occipital cortex (BA 18), and the bilateral caudate nucleus.

The older adults showed significant bilateral activation in the frontopolar cortex (BA 10), the right dorsolateral prefrontal cortex (BA 9/46), the left supplementary motor area (BA 6), bilateral insula (BA 41), the left posterior prefrontal cortex (junction of BAs 6, 8, and 44), the bilateral lateral prefrontal cortex (BA 6), the inferior parietal cortex bilaterally (BA 40), and the right superior parietal cortex (BA 7).

The comparison between groups showed significantly greater activation in the older adults than in the younger adults in the left supplementary motor area (BA 6), the left inferior parietal cortex (BA 39/40), and the right cerebellum. Comparison of younger minus older adults showed no significant difference (**Table 4** and **Figure 2B**; for younger and older see Supplementary Table S2).

Switch rule vs. maintain rule

When the switch rule was compared with the maintain rule, the younger group showed significant activation in the left frontopolar cortex (BA 10), the left anterior cingulate (BA 32), the right dorsolateral prefrontal cortex (BA 9/46), the right posterior prefrontal cortex (junction of BAs 6, 8, and 44), the right inferior parietal cortex (BA 40), the bilateral superior parietal cortex (BA 7), and the left occipital cortex (BA 18).

The older adults showed significant activation in the left frontopolar cortex (BA 10), the left dorsolateral prefrontal cortex (BA 9/46), the left supplementary motor area (BA 6), the left inferior parietal cortex (BA 40), the superior parietal cortex bilaterally (BA 7), and the left occipital cortex (BA 18).

The comparison between groups showed significantly more activation in the older adults than in the younger adults in the left posterior cingulate cortex (BA 31), the left inferior parietal

TABLE 4 | Switch rule minus control matching.

Cluster	Anatomical areas	MNI peak (mm)				
		x	*y*	*z*	*Z* score	Voxel
	Younger > Older					
	Older > Younger					
1	Left SMA (area 6)	−1	−5	48	3.41	16016
2	Left inferior parietal cortex (area 39/40)	−59	−28	31	3.33	16065
3	Right cerebellum	30	−68	−40	4.29	28680

TABLE 5 | Switch rule minus maintain rule.

Cluster	Anatomical areas	MNI peak (mm)				
		x	*y*	*z*	*Z* score	Voxel
	Younger > Older					
1	Right SMA (area 6)	1	37	37	3.95	13342
	Right posterior prefrontal cortex (junction of 6, 8, and 44)	37	18	52	3.81	
	Older > Younger					
1	Left occipital cortex (area 19)	−26	−78	26	3.51	11648
	Left occipital cortex (area 18)	−11	−75	28	3.22	
2	Posterior cingulate cortex (area 31)	−12	−51	16	3.24	21623
	Left superior parietal cortex (area 7)	−12	−74	37	3.19	
	Left inferior parietal cortex (area 39)	−47	−67	28	3.13	

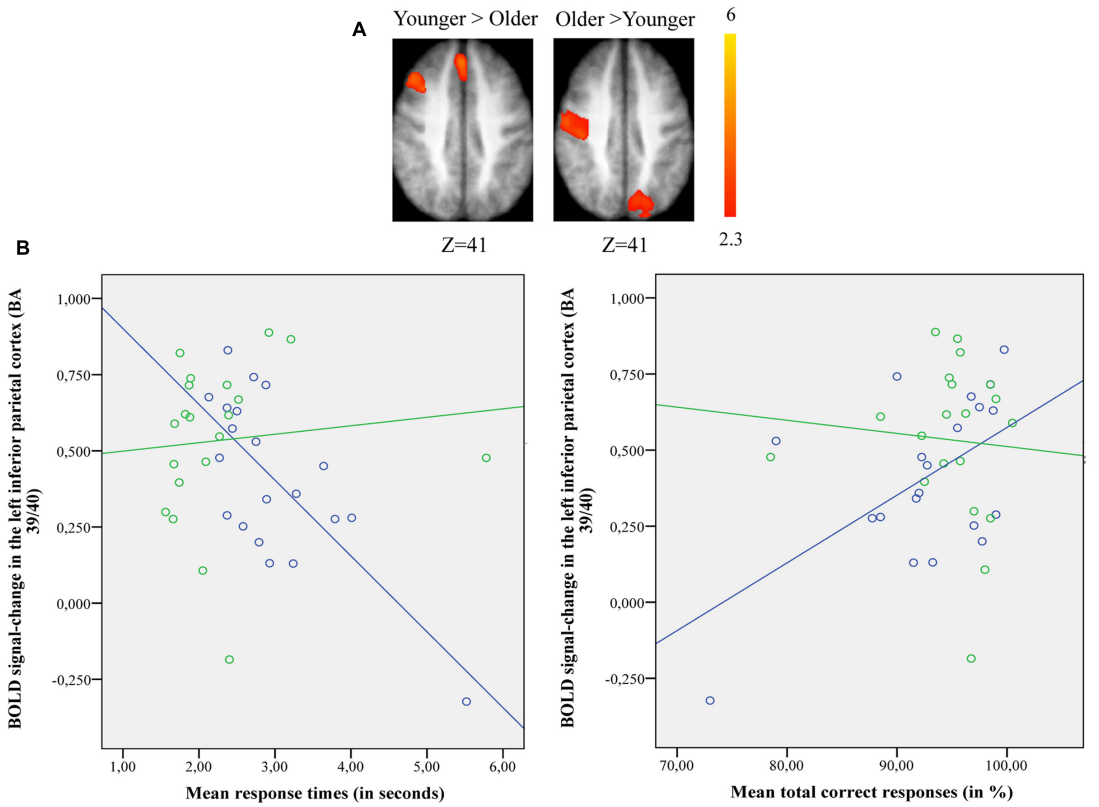

FIGURE 3 | (A) Brain activation for performing switch rule relative to maintain rule for the younger adults compared to the older in the right posterior prefrontal cortex (cf. right) and in the left inferior parietal cortex in the older adults compared to the younger adults (cf. left). The color scale represents the *Z* statistic. *Z*-values correspond to the coordinate of the axial plane. **(B)** Correlation between activation in the left inferior parietal cortex and behavioral measures for younger (blue circles) and older adults (green circles). The left plot represents response times and the right plot the total correct responses for two groups. Note that correlation between behavioral measures and brain activity change in the right posterior prefrontal cortex did not reach any significant difference for two groups (not shown in this figure).

cortex (BA 39), the superior parietal cortex (BA 7), and the left occipital cortex (BAs 18 and 19). The comparison of younger minus older adults showed significantly more activation in the right supplementary motor cortex (BA 6) and the right posterior prefrontal cortex (junction of BAs 6, 8, and 44) in the younger adults (**Table 5** and **Figure 3A**; for younger and older see Supplementary Table S3).

The comparison of brain activity patterns in the two age groups revealed more pronounced activity in the left inferior parietal cortex for the older adults and in the right posterior prefrontal cortex for the younger adults only when the maintain rule was subtracted from the switch rule. To explore the age-related neuro-functional relevance of these regions involved in the executive processes underlying the word-matching task, we first tested for an interaction effect before exploring the simple effects. Finally, we did a correlation analysis between older and younger participants' performance and brain activity within these regions.

ROI BOLD signal and performance in older and younger groups

The results of 2 (group) × 2 (executive component) mixed effects ANOVA on BOLD signal in the left inferior parietal cortex revealed a significant main-effect of group [$F(1,38) = 5.923$, $p = 0.020$] and executive component [$F(1,38) = 32.72$, $p = 0.001$], but no group × executive component interaction [$F(2,38) = 0.478$, $p = 0.49$]. However, planned comparison showed significant differences between younger and older adults. The BOLD signal change in the left inferior parietal cortex was significantly greater for older adults when compared to younger adults only for switch rule [$F(1,38) = 62.88$, $p = 0.001$]. No significant main-effect of group [$F(1,38) = 2.169$, $p = 0.149$] or executive component [$F(1,38) = 0.389$, $p = 0.537$] was observed in the right posterior prefrontal cortex, with no group × executive component interaction [$F(2,38) = 3.140$, $p = 0.073$].

Pearson's correlation analysis conducted between behavioral performance (response times, correct responses) and BOLD signal changes in the left inferior parietal cortex [BA 39/40; $x = -33$; $y = -61$; $z = 39$] for younger and older adults (**Figure 3B**) showed significant negative correlation with response times ($r = -0.72$, $p = 0.001$) and significant positive correlation with correct responses ($r = 0.55$, $p = 0.011$) in the older group. However, the younger adults showed no significant correlation with response times ($r = 0.098$, $p = 0.68$) or correct responses ($r = -0.077$, $p = 0.74$). The difference in correlation

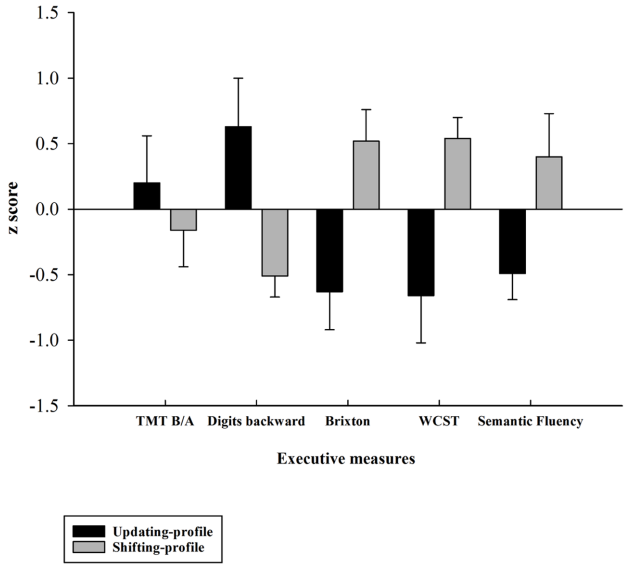

FIGURE 4 | *Z*-executive scores of the two older subgroups (updating-profile vs. shifting-profile) based on five executive measures: TMT B/A, digits backward, number of errors on the Brixton test, number of errors on the WCST, number of words produced correctly on the semantic fluency task). Tests for which increasing values in the original scores indexed lower performance were reversed in sign so that increasing values always reflected higher performance. Errors bars are represented by standard error mean values (SEM).

coefficients between the BOLD signal changes in the left inferior parietal cortex and the response times was statistically significant ($z = -2.94$, $p = 0.0003$) between the two groups (younger vs. older), as well as for the correct responses ($z = 2.03$, $p = 0.042$). There was no significant correlation between BOLD signal changes in the right posterior prefrontal cortex [BA 6/8/44; $x = 37$; $y = 18$; $z = 52$] and behavioral performance for younger (response times: $r = 0.028$, $p = 0.90$; correct responses: $r = 0.04$, $p = 0.85$) and older adults (response times: $r = -0.43$, $p = 0.06$; correct responses: $r = 0.19$, $p = 0.40$) (not shown in **Figure 3B**). The statistical difference between the two correlation coefficients for the two groups (younger vs. older) was not significant for response times ($z = 1.42$, $p = 0.15$) or for correct responses ($z = -0.44$, $p = 0.65$).

Part B: Cognitive Control Profiles and Neuro-Functional Reorganization in Older Adults

Behavioral Performance

The two older subgroups' (**Figure 4**) behavioral performance (correct responses and response times) on the word-matching task was equivalent. A comparison between the two older subgroups (updating-profile vs. shifting-profile) for maintain rule and switch rule was performed using an independent-group *t*-test. The difference between the two older subgroups was not significant for maintain rule [$t(18) = -0.641$, $p = 0.52$] or for switch rule [$t(18) = -0.440$, $p = 0.66$] (**Tables 6**, **7**).

Imaging Results

Maintain rule vs. control matching

The updating-profile group showed significant activation in the left ventrolateral prefrontal cortex (BA 47/12), left dorsolateral prefrontal cortex (BA 9/46), the left posterior prefrontal cortex (junction of BAs 6, 8, and 44), the left lateral premotor cortex (BA 6), and the cerebellum bilaterally. The shifting-profile group showed significant activation in the left inferior parietal cortex (BA 40), the left superior parietal cortex (BA 7), and the left inferior temporal cortex (BA 20). The comparison between the two groups showed more activation in the updating-profile group than in the shifting-profile group within the left dorsolateral prefrontal cortex (BA 9/46). The reverse inter-group comparison showed no significant difference (**Table 8** and **Figure 5A**; for each older subgroups see Supplementary Table S4).

Switch rule vs. control matching

The updating-profile group showed significant activation in the right dorsolateral prefrontal cortex (BA 9/46), the left posterior prefrontal cortex (junction of BAs 6, 8, and 44), the right lateral premotor cortex (BA 6), the left superior parietal cortex (BA 7), the occipital cortex (BAs 18 and 19), and the cerebellum bilaterally. The shifting-profile group showed significant activation in the left frontopolar cortex (BA 10), the bilateral posterior prefrontal cortex (junction of BAs 6, 8, and 44), the right dorsolateral prefrontal cortex (BA 9/46), the left ventrolateral prefrontal cortex (BA 44/45), the right lateral premotor cortex (BA 6), the right superior parietal cortex (BA 7), the left inferior parietal cortex (BA 39/40), and the right cerebellum (**Table 9** and **Figure 6A**; for each older subgroup see Supplementary Table S5). The comparison between the two subgroups showed more activation in the shifting-profile group than the updating-profile group within the left inferior parietal cortex (BA 39/40). The reverse inter-group comparison showed no significant difference.

The comparison of brain activity patterns of the two older subgroups revealed more pronounced activity in the left dorsolateral prefrontal cortex for the updating-profile group, only during maintain rule. However, the shifting-profile group showed more pronounced activity in the left inferior parietal cortex (BA 39/40), only during switch rule. To explore the functional changes and age-related differences in cognitive control profiles, an interaction effect was tested before exploring simple effects. Finally, a correlation analysis was performed between the updating-profile group and the shifting-profile group's behavioral performance and BOLD signal, within functionally relevant regions.

ROI BOLD signal and performance in the two older subgroups

The results of 2 (cognitive profiles) × 2 (executive component) mixed effects ANOVA on BOLD signal in the left dorsolateral prefrontal cortex revealed a significant main-effect of cognitive profile [$F(1,18) = 4.41$, $p = 0.051$] and executive component [$F(1,18) = 9.129$, $p = 0.008$], but no cognitive profile × executive component interaction [$F(2,18) = 0.172$, $p = 0.68$]. Similarly,

TABLE 6 | Means (*M*) and standard deviation (*SD*) on the demographic and neuropsychological variables of the sample of older adults ($n = 20$) divided into two subgroups: updating-profile ($n = 9$) and shifting-profile ($n = 11$).

	Updating-profile	Shifting-profile		
	***M* (*SD*)**	***M* (*SD*)**	***t*(1.18)**	***p*-values**
Age	70.77 (4.96)	68.36 (4.08)	1.194	0.248
Education (years)	18.44 (2.12)	19.18 (3.45)	−0.558	0.584
MoCA	28.77 (0.97)	28.63 (1.12)	0.298	0.769
Stroop C	65 (3.1)	59.90 (2.63)	−1.262	0.223
Stroop W	46.33 (1.99)	44.45 (1.75)	−0.705	0.490
Stroop C–W	112.88 (7.04)	116.09 (7.27)	0.314	0.757
TMT A	24.55 (1.76)	30.09 (2.87)	1.552	0.138
TMT B	52.11 (4.04)	71.54 (4.26)	3.259	0.004
TMT B/A	2.25 (0.30)	2.55 (0.23)	0.799	0.435
Digits forward	9.88 (0.58)	9.45 (0.54)	0.539	0.596
Digits backward	7.88 (0.63)	5.99 (0.28)	3.039	0.007
Brixton (errors)	2.11 (0.30)	0.90 (0.25)	−3.057	0.007
WCST (errors)	1.88 (0.45)	0.36 (0.20)	−3.267	0.004
Semantic fluency	24.88 (1.65)	32.09 (2.68)	−2.161	0.044

TABLE 7 | Behavioral performance (response times and correct responses) on the word-matching task for two older subgroups: updating-profile ($n = 9$) vs. shifting-profile ($n = 11$).

	Updating-profile	Shifting-profile		
	Mean (*SD*)	**Mean (*SD*)**	***t*(1.18)**	***p*-values**
Response times (in milliseconds)				
Experimental condition				
Maintain rule	2677 (453)	2818 (529)	−0.641	0.529
Switch rule	3062 (994)	2901 (625)	−0.440	0.665
Control condition	1341 (163)	1315 (178)	0.344	0.735
Total correct responses (in %)	92.25 (7.67)	93.11 (6.37)	0.271	0.789

significant main-effects of cognitive profile [$F(1,18) = 6.151$, $p = 0.023$] and executive component [$F(1,18) = 25.48$, $p = 0.001$] were observed in the left inferior parietal cortex in the absence of a cognitive profile × executive component interaction [$F(2,18) = 1.27$, $p = 0.275$]. However, planned comparison of BOLD signal change in the left dorsolateral prefrontal cortex showed significant difference between updating-profile and shifting-profile. The BOLD signal change in the left dorsolateral prefrontal cortex was significantly greater for the updating-profile when compared to the shifting-profile, only for the maintain rule ($p = 0.028$). Conversely, the BOLD signal changes in the left inferior parietal cortex were significantly greater for the shifting-profile when compared to the updating-profile, only for the switch rule ($p = 0.038$).

Spearman's correlation analysis was conducted between behavioral performance (response times, correct responses) and BOLD signal changes in the left dorsolateral prefrontal cortex [BA 9/46; $x = -42$; $y = 10$; $z = 35$] and in the left inferior parietal cortex [BA 39/40; $x = -33$; $y = -61$; $z = 39$] for both older subgroups (updating-profile and shifting-profile).

During maintain rule, relative to control matching (**Figure 5B**), the correlation between BOLD signal changes in the left dorsolateral prefrontal cortex and correct responses was significantly positive for the updating-profile group ($r = 0.83$, $p = 0.005$), while for the shifting-profile group there was no significant correlation ($r = -0.25$, $p = 0.486$). The difference in correlation coefficients between BOLD signal changes in the left dorsolateral prefrontal cortex and correct responses was significant ($z = 2.63$, $p = 0.008$) between updating-profile and shifting-profile groups. Furthermore, there was no significant correlation between the BOLD signal change in the

TABLE 8 | Maintain rule minus control matching.

		MNI peak (mm)				
Cluster	**Anatomical areas**	***x***	***y***	***z***	***Z* score**	**Voxel**
1	Updating-profile > Shifting-profile					
	Left dorsolateral prefrontal cortex (area 9/46)	−45	14	45	2.86	96
	Shifting-profile > Updating-profile					

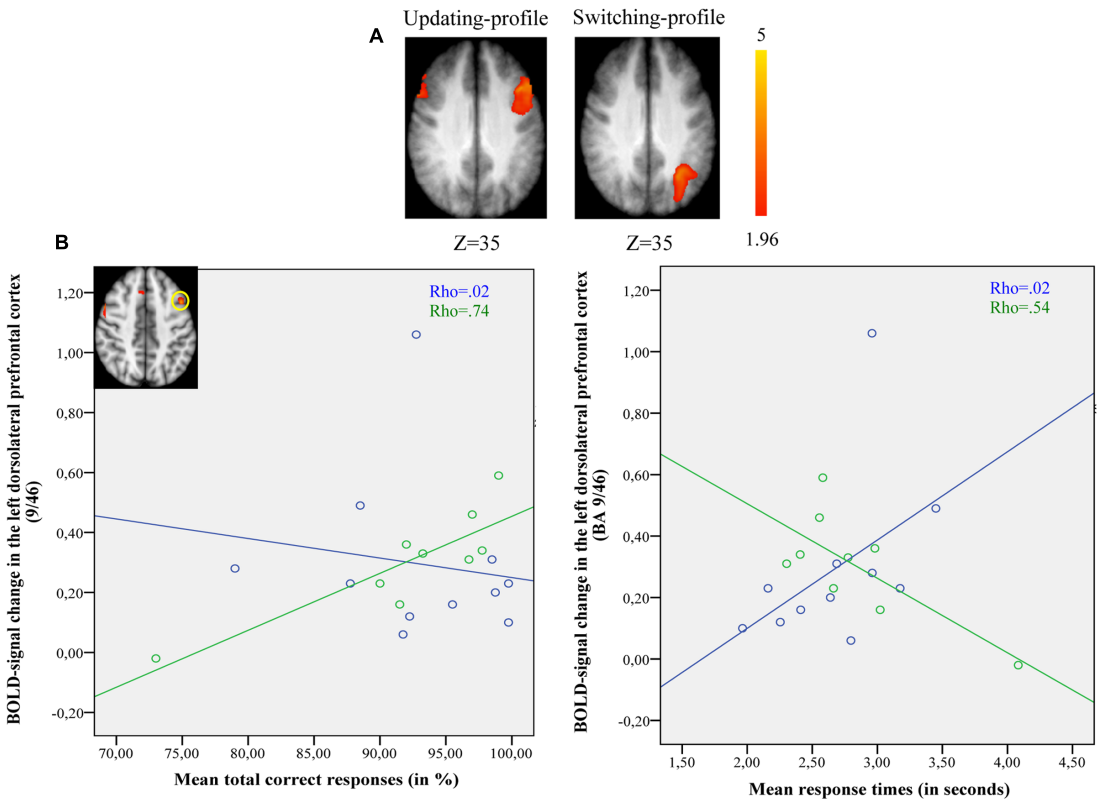

FIGURE 5 | (A) Brain activation for maintain rule minus control matching. The updating-profile group (cf. left). The shifting-profile group (cf. right). The color scale represents the *Z* statistic. *Z*-values correspond to the coordinate of the axial plane. **(B)** Correlation the left dorsolateral prefrontal cortex [BA 9/46; *x* = –42; *y* = 10; *z* = 35] and behavioral measures for the updating-profile group (green circles) and shifting-profile group (blue circles). The left plot represents the total correct responses and the right plot mean response times. On the upper left, the updating-profile group shows significant activation in the left dorsolateral prefrontal cortex (BA 9/46) compared to shifting-profile group.

left dorsolateral prefrontal cortex and response times in either of the two older subgroups (updating-profile: $r = -0.50$, $p = 0.055$; shifting-profile: $r = 0.60$, $p = 0.085$). The difference between correlation coefficients was significant for updating-profile and shifting-profile groups ($z = -2.18$, $p = 0.002$).

Comparing switch rule to control matching (**Figure 6B**), there was no correlation between BOLD signal changes in the left inferior parietal cortex and correct responses ($r = -0.14$, $p = 0.736$) for the updating-profile, while positive correlation was observed for the shifting-profile group ($r = 0.82$, $p = 0.002$). Note: one outlier participant from the updating-profile group (extremely long response time) was removed from correlation analysis. The difference between the two correlation coefficients was significant for updating-profile and shifting-profile groups ($z = -2.28$, $p = 0.022$).

Furthermore, there was no correlation between the BOLD signal change in the left inferior parietal cortex and response times ($r = -0.48$, $p = 0.22$) for the updating-profile group, while a negative correlation was observed for the shifting-profile group ($r = -0.72$, $p = 0.023$). The difference between the two correlation coefficients was not significant for the updating-profile or the shifting-profile groups ($z = 0.71$, $p = 0.47$).

DISCUSSION

The aim of this study was to explore the age-related, neuro-functional basis for executive semantic processing of words. It is known that healthy aging is associated with neuro-functional reorganization that maintains cognitive performance. Herein, this investigation evaluated the effects of healthy aging and cognitive changes on executive function, neuro-functional activation, and behavioral measures during

TABLE 9 | Switch rule minus control matching.

		MNI peak (mm)				
Cluster	**Anatomical areas**	***x***	***y***	***z***	***Z* score**	**Voxel**
	Updating-profile > Shifting-profile					
1	Shifting-profile > Updating-profile					
	Left inferior parietal cortex (area 39/40)	−45	−57	35	2.36	104

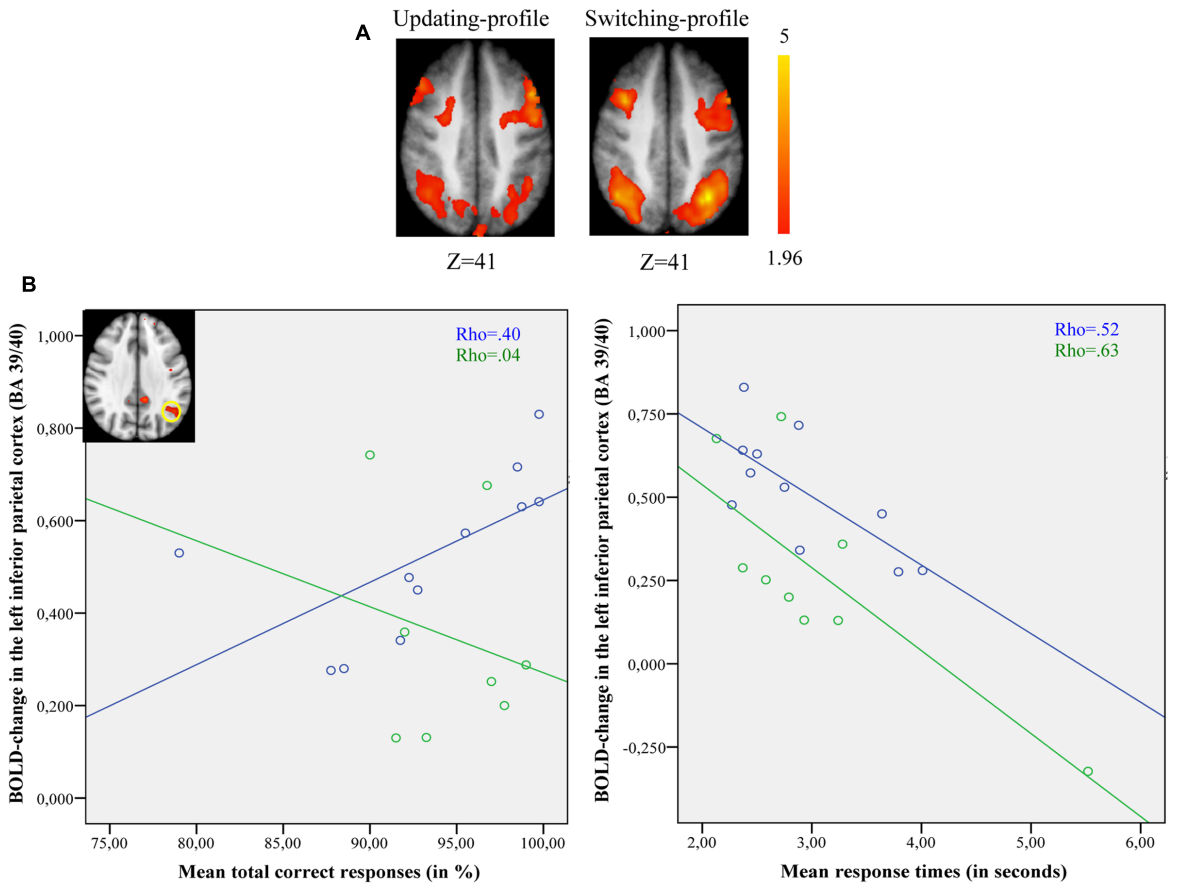

FIGURE 6 | (A) Brain activation for switch rule minus control matching. The updating-profile group (cf. left). The shifting-profile group (cf. right). **(B)** Correlation between the left inferior parietal cortex [BA 39/40; $x = -33$; $y = -61$; $z = 39$] and behavioral measures for the updating-profile group (green circles) and shifting-profile group (blue circles). The left plot represents the total correct responses and the right plot the mean response times. On the upper left, the shifting-profile group shows significant activation in the left inferior parietal cortex (BA 39/40) compared to updating-profile group.

a word-matching task. To do so, a new word-matching task was employed that was based on the WCST and was adapted for fMRI by Monchi et al. (2001) and Simard et al. (2011). Results demonstrated that the shift in age-related brain activation from frontal to parietal regions is another form of neuro-functional reorganization, which sustains executive processes during a word-matching task. In addition, differences in cognitive control profile during aging appeared to be mediated by specific neuro-functional reorganization, which maintains task performance. Taken together, these results demonstrate functional changes during a word-matching task related to age and cognitive control profile. Further, correlations were identified between behavioral task performance and changes in brain activity within the relevant frontoparietal regions. These findings are discussed below.

Age-Related Neuro-Functional Reorganization

As predicted, and consistent with the literature (Jefferies and Lambon Ralph, 2006; Whitney et al., 2011; Noonan et al., 2013), the cognitive control network was found to be involved in executive aspects of semantic processing, including the lateral prefrontal cortex, the anterior cingulate cortex, the parietal and temporal cortices, which are responsible for executive processing in the semantic domain that overlaps general executive processing. These findings are consistent with the recent neurobiology of language model, which proposes that successful language processing is based on the interaction between the neural mechanisms underlying cognitive control and the semantic system (Badre et al., 2005; Nagel et al., 2008). The brain activity patterns that emerged during the word-matching task revealed some age-related changes that appear to support better performance, even though the response time of older adults (compared to younger adults) was significantly longer after switch than maintenance feedback. It should be noted that differences in age-related response times were not systematically observed when control-matching performance was taken into account through a motor-speed measure. There was an age-related decline in performance of complex executive tasks such as the WCST, but controlling for a decrease in perceptual-motor speed in a task involving perception of stimuli

followed by a simple motor response – the control condition (i.e., alphabet pairing in our study) – significantly reduced this performance decline (Fristoe et al., 1997; Martins et al., 2014). Taken together, our findings along with evidence from cognitive aging studies suggest that age-related differences in the reliance on high-level executive control processes, as it related to switching process (i.e., switch rule) during a word-matching task, may undergo greater age-related neuro-functional changes than the maintenance processes (i.e., maintain rule).

Regarding the maintain rule, bilateral frontal activation (**Table 3**) observed in older adults, compared to more lateralized activations in younger adults, suggests that the posterior prefrontal cortex (junction of BAs 6, 8, and 44) and the dorsolateral prefrontal cortex (BA 9/46) were recruited more when older participants maintained and updated rule classifications in working memory. The presence of posterior prefrontal involvement during different cognitive control tasks has been attributed to flexible cognitive performance (Brass and Von Cramon, 2004; Derrfuss et al., 2005). However, regarding these neuro-functional patterns, the differential involvement of the two lateral prefrontal regions (dorsal and ventral parts) in cognitive control may mediate different kinds of control. Indeed, Spreng et al. (2010) have suggested that older adults show reduced maintenance of information mediated by the left ventrolateral prefrontal cortex when compared to greater activation in the dorsolateral prefrontal cortex, which is more involved in strategic control.

When older adults were compared with younger ones, activations were noted in the posterior cingulate cortex, inferior parietal cortex, inferior temporal cortex, occipital cortex, and the superior and inferior portions of the cerebellum. Such activations are consistent with the pattern of activity seen during a set of semantic tasks, thought to require activation of specific conceptual knowledge features (Cristescu et al., 2006). The activations reported in the cerebellum are compatible with studies that have shown such activation in cases where high-level language processing is required in the context of tasks that require frontal areas to support lexico-semantic strategies (Walter and Joanette, 2007; Murdoch, 2010), as well as the storing and maintenance of information in working memory (Bellebaum and Daum, 2007). Overall, these changes in neuro-functional patterns support the hypothesis that older adults rely more on posterior regions in order to efficiently process semantic rules during word matching. The more demands are placed on their semantic knowledge, the more their strategic semantic processes involve the posterior regions, that underlie successful cognitive performance (Hazlett et al., 1998; Wierenga et al., 2008; Ansado et al., 2013b; Lacombe et al., 2015).

As predicted, switch rule compared to control matching was associated with bilateral frontal and parietal activations in both younger and older adults, although activation was greater in older adults (**Figure 2B**). These regions have been found to be consistently related to cognitive switching within a WCST paradigm (Monchi et al., 2001; Simard et al., 2011). Greater activity was displayed in cognitive-control-related frontoparietal regions that support higher-level executive processing. However, these networks may be differentially engaged during executive tasks (Braver et al., 2009). To improve cognitive performance, the brain activation pattern in older adults showed involvement of the frontopolar cortex and insula, possibly recruited to support processing task demands thought to be sub-served by primary neural resources.

Increased frontal activation during word-matching confirms the frontal cortex's contribution to semantic retrieval, selection, and control demands. It remains to be determined whether semantic executive functions are primarily sustained by the frontal cortex or by other regions. Within cognitive control networks, frontoparietal regions may be differentially engaged depending on executive control demands. For example, maintaining information over a period of time and selecting responses have been associated with more frontal than parietal engagement (Braver et al., 2003). Furthermore, the parietal regions seem to represent a convergence zone for many executive domains (Duncan, 2006). Many neuroimaging studies have emphasized the parietal cortex's contribution to a wide range of tasks, including working memory (Derrfuss et al., 2005; Riis et al., 2008) and interference resolution (Zysset et al., 2007; Campbell et al., 2012). Conceivably, involvement of parietal regions may mechanistically underlie task performance maintenance in healthy aging.

The most relevant neural pattern was observed for intergroup comparisons when maintain rule was subtracted from switch rule (**Figure 3A**). Indeed, older adults recruited the inferior parietal region (BA 39/40), while younger adults recruited the posterior prefrontal region (junction of BAs 6, 8, and 44). This age-related shift in activation from anterior (frontal) to posterior (parietal) region reflects different patterns of activation in the two age groups, indicating the use of different brain networks to mediate task performance. An integrative theory of aging proposed by Park and Reuter-Lorenz (2009) suggests that a dynamic-adaptive, neuro-functional reorganization takes place in which the older brain builds neural scaffolds to engage more functional resources and to compensate for the insufficiency of available basic-neural resources. Based on the results of this study, older adults tend to recruit parietal regions as an alternate strategy to ensure successful behavioral performance avoiding limited frontal resources. Furthermore in older adults, activity in the left inferior parietal region increased with a correct response and with a decreased response speed, whereas younger adults showed an inverse behavioral pattern (**Figure 3B**). This region-dependent pattern of activation and performance suggests that involvement of the inferior parietal region is necessary for older adults as another form of neuro-functional reorganization to maintain processing efficiency during a word-matching task.

In this context, activation in parietal regions can be considered as a more straightforward form of older-brain neural scaffold in response to neural insult and to age-related changes in frontal regions (Reuter-Lorenz and Cappell, 2008; Peelle et al., 2013). According to recent studies (Harding et al., 2015; Grady et al., 2016), the age-related changes in functional connectivity between frontal and parietal nodes are relevant in task performance, since greater neural recruitment in this cognitive control network co-occurs with greater improvements in executive

processing. Those studies described patterns reflecting the neuro-functional adaptability of neural resources in healthy aging within the frontoparietal network, with a decrease in age-related parietal structural changes. This suggests that one of many mediating factors for neural resource reallocation is a cognitive control ability that enhances the development of dynamic neuro-functional reorganization trajectories that compensate for changes in the aging brain (Reuter-Lorenz and Cappell, 2008). These results provide some evidence for the HAROLD phenomenon in parietal regions (Cabeza, 2002; Grady et al., 2002; Angel et al., 2010). More interestingly, despite a decline in cognitive control processing in healthy aging, increasing reliance on parietal regions may be a means by which to functionally and cognitively cope with limited frontal resources. This possibility is supported by a recent observation that the aging brain is widely involved in executive control of resources during highly process-dependent tasks (Bouazzaoui et al., 2014). Nevertheless, the lack of correlation between behavioral performance and the right posterior prefrontal cortex implies that this region is less critical to successful executive processing in semantic tasks than is the inferior parietal region, which is associated with executive semantic processing (Noonan et al., 2013; Peelle et al., 2013).

In summary, executive functions have been found to support semantic performance, with increased reliance on neural substrates that sustain the demand for higher executive control; these substrates include the inferior parietal region, which is correlated with age-related performance maintenance in older age. However, it seems reasonable that changes in executive functional organization in healthy aging underlie very different executive abilities, and by extension, might predict distinct cognitive profiles preferentially sustained by distinct neural substrates as suggested by Hull et al. (2008). This may also explain why inter-individual variability in executive performance is more evident among older adults than younger ones (Logan et al., 2002; Braver and West, 2008). These possibilities are explored in the next section.

Cognitive Control Profiles and Neuro-Functional Reorganization in Older Adults

A common finding on cognitive aging is that changes in cognitive function tend to be accompanied by changes in cognitive control processes in healthy elderly adults (Braver et al., 2001; Velanova et al., 2007; Mudar et al., 2015). Age-related executive function is supported by at least two executive components (updating and shifting), which make different contributions to task performance and probably depend on different neural patterns in healthy aging. The existence of different components within executive function (updating and shifting) indicates that executive functioning is organized in a non-unitary, multifaceted way in normal aging – and throughout the lifespan (Hull et al., 2008).

In accordance with our second prediction, we found two subgroups of older adults (updating-profile and shifting-profile) who showed different neuro-functional patterns depending on their executive abilities while performing equally well on the word-matching task (response times and correct responses). According to the flexible hub theory (Cole et al., 2013), a cognitive control network including the lateral prefrontal cortex, posterior parietal cortex and insula (which is known as the frontoparietal network) supports functional adaptation changes in healthy aging. Moreover, data supporting the theory indicates that age-related neuro-functional ability consists in flexibly coordinating cooperation between the cognitive control and language regions, to maintain task performance. Regarding the relevant functional regions and age-related executive changes, the findings reported herein support the hypothesis that older adults have developed a cognitive style that makes greater use of neural resources that mediate cognitive control of task performance.

Furthermore, several prior studies have highlighted activity changes in the frontoparietal network based on inter-individual differences in task performance. For example, Rypma et al. (2002) analyzed specific ROIs (dorsolateral, ventrolateral, posterior prefrontal cortex, and parietal cortex) and found that the frontoparietal network was associated with maintenance performance. In that study, older participants with slow response times showed bilateral activation in the dorsolateral prefrontal cortex, whereas older participants who responded faster showed widespread bilateral parietal cortex activation. Moreover, Gevins and Smith (2000) found differences in the involvement of frontal and parietal regions based on their participants' cognitive ability. In their study, older adults with higher verbal ability showed greater activation in parietal regions, while those with lower verbal ability exhibited more activation in frontal regions.

These findings suggest that individual differences in performance may be due to distinct functional changes. In the same vein, Peelle et al. (2013) found differences in the involvement of frontal and parietal regions depending on older participants' cognitive ability. They reported that older adults with higher cognitive function showed greater activation in parietal regions, while those with lower function exhibited more activation in frontal regions. These group differences suggest that older participants with more cognitive resources are able to adopt a strategy that involves larger, more distributed brain areas, while those with fewer resources use a strategy based on specific frontal regions.

Similarly, our results support this assumption since different patterns of neuro-functional reorganization in the frontoparietal network were found to relate to the elderly participant's cognitive control profile. The updating-profile group improved their behavioral performance during maintain rule with more reliance on the dorsolateral prefrontal region (**Figure 5B**), which the shifting-profile group did not. Conversely, the inferior parietal region was more relevant for successful performance in the shifting-profile participants than for the updating-profile group's performance during switch rule (**Figure 6B**). This result is of considerable importance, since it provides evidence for changes in executive process organization in healthy aging. As proposed by Noonan et al. (2013), the executive control over semantic processing underlies a flexible neural network including the bilateral posterior prefrontal cortex and the left inferior parietal cortex. Disruption of one region results in shift activation in other

parts of the network. Hence, a healthy aging brain recruits more than one pathway to preserve cognitive performance.

CONCLUSION

Age-differences in fronto-parietal region involvement during executive processing in a word-matching task are associated with behavioral performance maintenance by recruiting the inferior parietal region when executive frontal resources are in high demand. This greater reliance on the inferior parietal region by older adults could be interpreted as a neuro-functional change reflecting age-associated mechanistic differences in the executive control system, which are known to be dynamic in healthy aging. A distinction between frontal and parietal regions was also observed in older adults, which was related to cognitive control profile. This finding appears to be consistent with changes in executive process organization in healthy aging as proposed by Hull et al. (2008) and Adrover-Roig and Barceló (2010). Thus, diversity in executive control system serves to adapt older brain to different functional changes. This characterizes older people in terms of frontal and parietal network utilization for more proficient executive semantic processing, as assessed by a word-matching task. The relationships between changes in brain activity and in executive ability in healthy aging are relevant to future cognitive aging studies and more specifically to brain-injured individuals with semantic aphasia as well as executive dysfunction. We acknowledge that the relatively small number of elderly participants included in our second study represents a limitation; the study should be replicated with a larger sample. Even so, as discussed, our findings are in accordance with various previous studies.

AUTHOR CONTRIBUTIONS

Study conception and design: IM, MW, OM, J-SP, and YJ. Acquisition of Data: IM and YJ. Analysis and interpretation of data: IM, MA, BP, J-SP, and YJ. Drafting of manuscript: IM and YJ. Critical revision: IM, MA, BP, MW, JA, and YJ.

FUNDING

This research was supported by grants from the Canadian Institutes of Health Research MOP-93542 to YJ and Bernadette Ska and IOP-118608 to YJ.

ACKNOWLEDGMENT

The authors are grateful to Dr. Thomas Espeseth for his relevant critical revision of this manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnagi.2017.00265/full#supplementary-material

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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