THE INTERSECTION OF COGNITIVE, MOTOR, AND SENSORY PROCESSING IN AGING: LINKS TO FUNCTIONAL OUTCOMES

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THE INTERSECTION OF COGNITIVE, MOTOR, AND SENSORY PROCESSING IN AGING: LINKS TO FUNCTIONAL OUTCOMES

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Editorial: The intersection of cognitive, motor, and sensory processing in aging: Links to functional outcomes, Volume I

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Editorial on the Research Topic
The intersection of cognitive, motor, and sensory processing in aging: Links to functional outcomes, Volume I

Integral to the ability to carry out everyday tasks is the successful coordination of cognitive, motor, and sensory processing in the brain. However, age-related changes alter cognitive, motor, and sensory functioning, as well as their interactions, which can affect daily functioning in older adults. Investigations of the interplay across these three systems has been somewhat limited in the aging literature, though research examining relationships across various combinations (e.g., cognitive & motor, motor & sensory, sensory & cognitive, and multisensory) has been plentiful.

For instance, there is extensive research on the link between unisensory impairments and motor decline in aging (Center for Disease Control, 2010). That is, unisensory impairments have been linked to slower gait speed (Kaye et al., 1994), worse functional decline (Laforge et al., 1992), increased risks of falls (Lord and Ward, 1994; Judge et al., 1995; Camicioli et al., 1997; Lord et al., 1999) and poorer quality of life (Carabellese et al., 1993). Age-related hearing loss has also been associated with a greater risk of mobility problems, including a three-fold increased risk of falls (Lin and Ferrucci, 2012; Jiam et al., 2016; Campos et al., 2018). Impairments in balance have also been associated with inefficient interactions between musculoskeletal and sensory systems (Shumway-Cook and Woollacott, 2012), which are often compromised in aging (Lord et al., 2007). Furthermore, deficits in multisensory integration processes, specifically visual-somatosensory and auditory-visual interactions, have been associated with impairments in gait (Mahoney and Verghese, 2018), balance (Mahoney et al., 2014, 2019), falls (Setti et al., 2011; Lupo and Barnett-Cowan, 2018; Mahoney et al., 2019) and individuals with hearing loss have poorer vestibular functioning (Gabriel et al., 2022).

Mobility declines are common in aging, especially in older adults with mild cognitive impairment and dementia (Beauchet et al., 2008; Verghese et al., 2008). The association of executive functioning with balance (Woollacott and Shumway-Cook, 2002; Zettel-Watson et al., 2017), gait (Verghese et al., 2007, 2008; Holtzer et al., 2012), and falls (Hausdorff and Yogev, 2006; Holtzer et al., 2007) in aging is well-established. The link between cognitive and motor function in aging reveals that the prefrontal cortex plays a critical role in successful gait and cognition (Beauchet et al., 2016). In fact, evidence of combined slow gait and subjective cognitive complaints are indicators for Motoric Cognitive Risk syndrome [MCR]—a pre-dementia syndrome first proposed by Verghese et al. (2013, 2014) almost a decade ago.

Age-related sensory loss is also associated with cognitive decline and dementia (Baltes and Lindenberger, 1997; Albers et al., 2015; Livingston et al., 2017, 2020; Lin, 2011). For example, hearing loss has been identified as the top potentially-modifiable risk factor for dementia (Livingston et al., 2017, 2020). Links between impairments in multisensory integration and cognition have also been observed, and highlight the need for increased development of clinical translational multisensory integration investigations (Mahoney and Barnett-Cowan, 2019) and tools. Multisensory integration has been associated with attention-based performance (Poliakoff et al., 2006; Hugenschmidt et al., 2009; Mahoney et al., 2012; Mahoney and Verghese, 2020) and individuals with mild cognitive impairment demonstrate differences in multisensory integration compared to those with normal cognition (Chan et al., 2015). Further, the mediating effect of cognitive impairment on the association between poor visual-somatosensory integration and slow gait, as well as worse balance, has recently been documented (Mahoney and Verghese, 2020) and investigations establishing visual-somatosensory integration as a novel marker for Alzheimer's disease are currently underway.

Greater understanding of the neural connections between and across (multi)sensory, motor, and cognitive processing in both healthy and pathological aging is clearly warranted. The express purpose of this compilation is to collectively consider the existing inter-relationships between sensory, motor, and cognitive functioning, as well as to promote novel lines of research examining the intersection of these systems in aging. For this special issue, it was expected that contributions would consider age-related functionality of more than one system (e.g., sensory, motor, and/or cognitive) and the implications of these systematic interactions on important functional outcomes, including but not limited to clinical, motor, and social outcomes to name a few. Gaining further knowledge about the successful (or unsuccessful) intersection of these systems could prove valuable for older adults, especially with regard to refining and restructuring multimodal interventions aimed at preventing declines, reducing disability, and maintaining functional independence, in an effort to enhance quality of life.

In terms of sensory and motor interactions, Marusic, Peskar, et al. set out to determine the root cause of age-related sensorimotor slowing using electrophysiological measures and a simple visual reaction time test. Their results reveal that age-related slowing of sensorimotor activity originating in motor cortex is relatively uninfluenced by early-visual stimulus processing but related to later-visual processes linked to higher-order cognitive function like attention and working memory. In a study examining the effectiveness of multisensory training for improving self-motion perception, Gabriel et al. found that visual-vestibular training improves visual heading perception, particularly in older adults. Results reveal the potential beneficial effects of multisensory training in aging and provide clues that multisensory training could enhance future rehabilitation programs that target age-related mobility declines. Scurry et al. present preliminary support of drastic reductions in multisensory integration (*via* top-down inhibitory control mechanisms) in older adults with a history of falling. In addition, Wunderlich et al. define a Mobile Brain/Body Imaging (MoBI) approach to gain deeper insights into the neural dynamics underlying cognitive and motor interactions during several dual-task conditions in young and old adults with hearing impairment.

In a novel dual-task paradigm, Ward et al. demonstrates cognitive-motor dual-task interference effects on balance (i.e., postural control) irrespective of age and cognitive task load. In an exercise study, Tsai et al. investigated the acute effect of high-intensity interval *vs.* moderate-intensity continuous exercise on executive-related oculomotor performance in aging and found that high-intensity interval exercise appears to be more effective in terms of modulating oculomotor control. Li N. et al. examined the effect of age on visuomotor adaptation and found that compared to the younger adults, older adults had less adaptation to visual feedback perturbation in a reaching task. However, the authors further that while the effect of aging on visuomotor adaptation was not associated with chronological age, it was correlated with the declines in cognitive performance. Di Tella et al. examined functional and structural neural changes in old vs. young adults and found reduced cortical thickness of the mirror neuron system, coupled with increased activation in premotor and prefrontal areas indicative of age-related changes in both cognitive and motor neural systems.

Using sophisticated structural equation modeling, Xue et al. reveal that cognitive function significantly interacts with frailty and urge that both should be considered when developing tailored interventions so as to further improve overall health outcomes and quality of life for older adults. Marusic, Verghese et al. examined the effect of cognitive training using computerized brain games on mobility measures in healthy, active older adults and found that cognitive training had both near- (executive function & processing speed enhancements) and far- (dual-task gait speed enhancement) transfer effects concurrently related to increased activation over sensorimotor regions important for cognitive, motor, and sensory processes. In another intervention study, Merriman et al. found that cognitive training focused on spatial navigation and obstacle avoidance training with balance control was successful in improving egocentric spatial processing and executive function in older adults. In terms of pathological aging, Li X. et al. compared older adults with and without cerebral microbleeds and found that cerebral microbleeds were closely associated with worse cognitive and motor performance on dual-task performance-based tests. Beauchet et al. reveal an overlap between late-life depressive symptomatology and motoric cognitive risk syndrome (MCR) suggesting a complex interplay between depressive symptoms and MCR that could prove useful for prevention of dementia.

Lastly, we include a series of review studies that highlight interactions between sensory, cognitive, and motor processes. Basharat et al. and Gray et al. report on sensory interactions and links to cognition in aging. In a two-pronged review, Basharat et al. sought to investigate the rigor with which researchers studying audiovisual sensory integration account for age-abnormal declines in sensory acuity and cognitive decline. Gray et al. aimed to contribute to the field of cognitive aging by proposing a framework that details the impact of musical training on speech perception. Lastly, Bai et al. review a series of neuroimaging and electrophysiological studies that highlight both visuospatial and sensorimotor functions of the posterior parietal cortex in drawing tasks.

In summary, this unique collection expands knowledge regarding the associations among cognitive, motor, and sensory processing in aging and the implications for everyday function and application. We believe that further investigations aimed at unraveling the interwoven neural circuitry of cognitive, motor and (multi)sensory functioning in aging will promote future lines of research that will potentially guide the development of novel prognostic tools, environmental adaptations, and novel technologies, and/or aid in the development of new research-driven therapeutic interventions giving rise to solutions aimed at improving the quality of life of older adults.

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

Author JRM has a financial interest in JET Worldwide Enterprises Inc., a digital health startup spun out of research conducted at Albert Einstein College of Medicine.

The remaining 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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References

Albers, M. W., Gilmore, G. C., Kaye, J., Murphy, C., Wingfield, A., Bennett, D. A., et al. (2015). At the interface of sensory and motor dysfunctions and Alzheimer's disease. *Alzheimer's Dement.* 11, 70–98. doi: 10.1016/j.jalz.2014.04.514

Baltes, P. B., and Lindenberger, U. (1997). Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging? *Psychol. Aging.* 12, 12–21. doi: 10.1037//0882-7974.12.1.12

Beauchet, O., Allali, G., Annweiler, C., and Verghese, J. (2016). Association of motoric cognitive risk syndrome with brain volumes: results from the GAIT study. *J. Gerontol. A Biol. Sci. Med. Sci.* 71, 1081–1088. doi: 10.1093/gerona/glw012

Beauchet, O., Allali, G., Berrut, G., Hommet, C., Dubost, V., and Assal, F. (2008). Gait analysis in demented subjects: interests and perspectives. *Neuropsychiatr. Dis. Treat.* 4, 155–160. doi: 10.2147/NDT.S2070

Camicioli, R., Panzer, V. P., and Kaye, J. (1997). Balance in the healthy elderly: posturography and clinical assessment. *Arch. Neurol.* 54, 976–981. doi: 10.1001/archneur.1997.00550200040008

Campos, J., Ramkhalawansingh, R., Pichora-Fuller, M. K. (2018). Hearing, self-motion perception, mobility, and aging. *Hear Res.* 369, 42–55.

Carabellese, C., Appollonio, I., Rozzini, R., Bianchetti, A., Frisoni, G. B., Frattola, L., et al. (1993). Sensory impairment and quality of life in a community elderly population. *J. Am. Geriatr. Soc.* 41, 401–407. doi: 10.1111/j.1532-5415.1993.tb06948.x

Center for Disease Control (2010). *Vision, Hearing, Balance, and Sensory Impairment in Americans Aged 70 Years and Over: United States, 1999-2006.* Center for Disease Control. Available online at: http://www.cdc.gov/nchs/products/databriefs/db31.htm (accessed April 2, 2022).

Chan, J., Kaiser, J., Brandl, M., Matura, S., Prvulovic, D., Hogan, M. J., et al. (2015). Expanded temporal binding windows in people with mild cognitive impairment. *Curr. Alzheimer Res.* 12, 61–68. doi: 10.2174/1567205012666141218124744

Gabriel, G. A., Harris, L. R., Gnanasegaram, J. J., Cushing, S. L., Gordon, K. A., Haycock, B. C., et al. (2022). Vestibular perceptual thresholds in older adults with and without age-related hearing loss. *Ear Hear.* 43, 420–435. doi: 10.1097/AUD.0000000000001118

Hausdorff, J. M., and Yogev, G. (2006). Cognitive function may be important for fall injury prevention trials. *J. Am. Geriatr. Soc.* 54, 865; author reply 865–866. doi: 10.1111/j.1532-5415.2006.00718.x

Holtzer, R., Friedman, R., Lipton, R. B., Katz, M., Xue, X., and Verghese, J. (2007). The relationship between specific cognitive functions and falls in aging. *Neuropsychology* 21, 540–548. doi: 10.1037/0894-4105.21.5.540

Holtzer, R., Wang, C., and Verghese, J. (2012). The relationship between attention and gait in aging: facts and fallacies. *Motor Control* 16, 64–80. doi: 10.1123/mcj.16.1.64

Hugenschmidt, C. E., Mozolic, J. L., and Laurienti, P. J. (2009). Suppression of multisensory integration by modality-specific attention in aging. *Neuroreport* 20, 349–353. doi: 10.1097/WNR.0b013e328323ab07

Jiam, N. T., Li, C., and Agrawal, Y. (2016). Hearing loss and falls: a systematic review and meta-analysis. *Laryngoscope.* 126, 2587–2596. doi: 10.1002/lary.25927

Judge, J. O., King, M. B., Whipple, R., Clive, J., and Wolfson, L. I. (1995). Dynamic balance in older persons: effects of reduced visual and proprioceptive input. *J. Gerontol. A Biol. Sci. Med. Sci.* 50, M263–270. doi: 10.1093/gerona/50A.5.M263

Kaye, J. A., Oken, B. S., Howieson, D. B., Howieson, J., Holm, L. A., and Dennison, K. (1994). Neurologic evaluation of the optimally healthy oldest old. *Arch. Neurol.* 51, 1205–1211. doi: 10.1001/archneur.1994.00540240049015

Laforge, R. G., Spector, W. D., and Sternberg, J. (1992). The relationship of vision and hearing impairment to one-year mortality and functional decline. *J. Aging Health* 4, 126–148. doi: 10.1177/089826439200400108

Lin, F. R. (2011). Hearing loss and cognition among older adults in the United States. *J. Gerontol. A Biol. Sci. Med. Sci.* 66, 1131–1136. doi: 10.1093/gerona/glr115

Lin, F. R., and Ferrucci, L. (2012). Hearing loss and falls among older adults in the United States. *Arch. Intern. Med.* 172, 369–371.

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., et al. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet.* 396, 413–446.

Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S. G., Huntley, J., Ames, D., et al. (2017). The lancet international commission on dementia prevention and care. *Lancet.* 390, 2673–2734.

Lord, S., Sherrington, C., Menz, H., and Close, J. C. (2007). *Falls in Older People: Risk facTors and Strategies for Prevention.* Cambridge: Cambridge University Press. doi: 10.1017/CBO9780511722233

Lord, S. R., Rogers, M. W., Howland, A., and Fitzpatrick, R. (1999). Lateral stability, sensorimotor function and falls in older people. *J. Am. Geriatr. Soc.* 47, 1077–1081. doi: 10.1111/j.1532-5415.1999.tb05230.x

Lord, S. R., and Ward, J. A. (1994). Age-associated differences in sensori-motor function and balance in community dwelling women. *Age Ageing* 23, 452–460. doi: 10.1093/ageing/23.6.452

Lupo, J., and Barnett-Cowan, M. (2018). Impaired perceived timing of falls in the elderly. *Gait Posture* 59, 40–45. doi: 10.1016/j.gaitpost.2017.09.037

Mahoney, J. R., and Barnett-Cowan, M. (2019). Introduction to the special issue on multisensory processing and aging (part II): links to clinically meaningful outcomes. *Multisens. Res.* 32, 665–670. doi: 10.1163/22134808-20191509

Mahoney, J. R., Cotton, K., and Verghese, J. (2019). Multisensory integration predicts balance and falls in older adults. *J. Gerontol. A Biol. Sci. Med. Sci.* 74, 1429–1435. doi: 10.1093/gerona/gly245

Mahoney, J. R., Holtzer, R., and Verghese, J. (2014). Visual-somatosensory integration and balance: evidence for psychophysical integrative differences in aging. *Multisens. Res.* 27, 17–42. doi: 10.1163/22134808-00002444

Mahoney, J. R., and Verghese, J. (2018). Visual-somatosensory integration and quantitative gait performance in aging. *Front Aging Neurosci.* 10, 377. doi: 10.3389/fnagi.2018.00377

Mahoney, J. R., and Verghese, J. (2020). Does cognitive impairment influence visual-somatosensory integration and mobility in older adults? *J. Gerontol. A Biol. Sci. Med. Sci.* 75, 581–588. doi: 10.1093/gerona/glz117

Mahoney, J. R., Verghese, J., Dumas, K., Wang, C., and Holtzer, R. (2012). The effect of multisensory cues on attention in aging. *Brain Res.* 1472, 63–73. doi: 10.1016/j.brainres.2012.07.014

Poliakoff, E., Ashworth, S., Lowe, C., and Spence, C. (2006). Vision and touch in ageing: crossmodal selective attention and visuotactile spatial interactions. *Neuropsychologia* 44, 507–517. doi: 10.1016/j.neuropsychologia.2005.07.004

Setti, A., Burke, K. E., Kenny, R. A., and Newell, F. N. (2011). Is inefficient multisensory processing associated with falls in older people? *Exp. Brain Res.* 209, 375–384. doi: 10.1007/s00221-011-2560-z

Shumway-Cook, A., and Woollacott, M. (2012). *Motor Control.* New York, NY: Lippincott, Williams, & Wilkins.

Verghese, J., Ayers, E., Barzilai, N., Bennett, D. A., Buchman, A. S., Holtzer, R., et al. (2014). Motoric cognitive risk syndrome: multicenter incidence study. *Neurology* 83, 2278–2284. doi: 10.1212/WNL.0000000000001084

Verghese, J., Robbins, M., Holtzer, R., Zimmerman, M., Wang, C., Xue, X., et al. (2008). Gait dysfunction in mild cognitive impairment syndromes. *J. Am. Geriatr. Soc.* 56, 1244–1251. doi: 10.1111/j.1532-5415.2008.01758.x

Verghese, J., Wang, C., Lipton, R. B., and Holtzer, R. (2013). Motoric cognitive risk syndrome and the risk of dementia. *J. Gerontol. A Biol. Sci. Med. Sci.* 68, 412–418. doi: 10.1093/gerona/gls191

Verghese, J., Wang, C., Lipton, R. B., Holtzer, R., and Xue, X. (2007). Quantitative gait dysfunction and risk of cognitive decline and dementia. *J. Neurol. Neurosurg. Psychiatry* 78, 929–935. doi: 10.1136/jnnp.2006.106914

Woollacott, M., and Shumway-Cook, A. (2002). Attention and the control of posture and gait: a review of an emerging area of research. *Gait Posture* 16, 1–14. doi: 10.1016/S0966-6362(01)00156-4

Zettel-Watson, L., Suen, M., Wehbe, L., Rutledge, D. N., and Cherry, B. J. (2017). Aging well: processing speed inhibition and working memory related to balance and aerobic endurance. *Geriatr. Gerontol. Int.* 17, 108–115. doi: 10.1111/ggi.12682

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ORIGINAL RESEARCH
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How Do We Motorically Resonate in Aging? A Compensatory Role of Prefrontal Cortex

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Aging is the major risk factor for chronic age-related neurological diseases such as neurodegenerative disorders and neurovascular injuries. Exploiting the multimodal nature of the Mirror Neuron System (MNS), rehabilitative interventions have been proposed based on motor-resonance mechanisms in recent years. Despite the considerable evidence of the MNS' functionality in young adults, further investigation of the action-observation matching system is required in aging, where well-known structural and functional brain changes occur. Twenty-one healthy young adults (mean age 26.66y) and 19 healthy elderly participants (mean age 71.47y) underwent a single MRI evaluation including a T1-3D high-resolution and functional MRI (fMRI) with mirror task. Morphological and functional BOLD data were derived from MRI images to highlight cortical activations associated with the task; to detect differences between the two groups (Young, Elderly) in the two MRI indexes (BOLD and thickness z-scores) using mixed factorial ANOVA (Group*Index analyses); and to investigate the presence of different cortical lateralization of the BOLD signal in the two groups. In the entire sample, the activation of a bilateral MNS fronto-parietal network was highlighted. The mixed ANOVA (pFDR-corr < 0.05) revealed significant interactions between BOLD signal and cortical thickness in left dorsal premotor cortex, right ventral premotor and prefrontal cortices. A different cortical lateralization of the BOLD signal in frontal lobe activity between groups was also found. Data herein reported suggest that age-related cortical thinning of the MNS is coupled with increased interhemispheric symmetry along with premotor and prefrontal cortex recruitment. These physiological changes of MNS resemble the aging of the motor and cognitive neural systems, suggesting specific but also common aging and compensatory mechanisms.

Keywords: aging, mirror neuron system, magnetic resonance image, rehabilitation, stroke, premotor cortex, prefrontal cortex

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INTRODUCTION

Mirror neurons are a neural population discovered in the ventral premotor cortex of the monkey (di Pellegrino et al., 1992; Gallese et al., 1996; Rizzolatti et al., 1996a) discharging not only during action execution but also during action observation, configuring a movement observation-execution matching system. Functional magnetic resonance imaging (fMRI) studies provided several evidences for the existence of a Mirror Neuron System (MNS) in humans as well (Hardwick et al., 2018). Specifically, the premotor cortex, particularly the lower part of the precentral gyrus (BA6), the posterior part of the inferior frontal gyrus (BA44), the inferior parietal lobule (BA40), and the superior temporal sulcus (BA22/42) are implicated in human motor resonance and hence can be regarded as part of the human MNS (Rizzolatti et al., 1996b; Grèzes et al., 2001). The MNS is involved in higher motor/cognitive processes, such as the understanding of the meaning of an action and the intentionality of the person executing it, motor learning (Buccino and Riggio, 2006), learning and imitation processes (Jeannerod, 1994; Gallese and Goldman, 1998; Iacoboni et al., 1999; Rizzolatti et al., 2002; Buccino et al., 2004; Vogt et al., 2007; Gallese, 2009), language, and empathy (Antonietti and Corradini, 2013; Oztop et al., 2013; Cook et al., 2014; Rizzolatti and Fogassi, 2014; Buccino et al., 2016). In particular, the MNS operates through a motor resonance mechanism that implies the understanding of the meaning of a gesture through an internal reproduction of the same action in the observer (Fadiga et al., 1995; Strafella and Paus, 2000; Borroni et al., 2005; Borroni and Baldissera, 2008).

Despite the considerable evidence of the MNS' functionality, further investigation is required to explore its role in aging. Aging is the major non-modifiable risk factor for chronic age-related diseases (Kennedy et al., 2014) associated with mental and physical disabilities for which it is crucial to develop effective rehabilitative interventions. Recently, new rehabilitative interventions for age-related pathologies such as stroke and Parkinson's disease have been proposed based on the motor resonance mechanism activated by the MNS (Ertelt et al., 2007; Buccino, 2014; Farina et al., 2020). Thus, the comprehension of the mechanisms involved in aging of the MNS is relevant to implement effective rehabilitation programs for age-related pathologies.

Aging is accompanied by structural (for a review see: Vinke et al., 2018) and functional (Cabeza et al., 2002) neural substrate changes and reorganization affecting predominantly the frontal cortex (Raz et al., 1997; Good et al., 2001; Jernigan et al., 2001; Resnick et al., 2003). Functional changes have been observed for both motor and cognitive domains, showing increased activity in contralateral and ipsilateral premotor areas (Calautti et al., 2001; Mattay et al., 2002; Ward and Frackowiak, 2003; Heuninckx et al., 2005, 2008) and bilateralization of activity in prefrontal cortices (Cabeza, 2002). However, relatively little is known regarding physiological changes associated with aging and neurodegeneration within the MNS. Nedelko et al. (2010) reported no age dependent changes in the activity of the MNS, while Farina et al. (2017) found a posterior to anterior shift in activity associated with neurodegenerative decline.

To date however, there is no evidence for a comparison with young people integrating the brain reserve data such as cortical thickness and brain activity within the MNS, defined as the action execution and observation matching system. The purpose of the present study was to investigate these changes in normal aging. We hypothesized that due to the involvement of the MNS in several complex behaviors, ranging from sensory-motor to cognitive and learning processes, the aging of this system would likely involve several brain regions implicated in the aging of both the motor and cognitive systems such as premotor and prefrontal cortices at both the functional and structural level. Specifically, according to literature we expected to find within the MNS of aged subjects cortical thinning, coupled with increased activation and reduced lateralization in the premotor cortices and in the more cognitive-related prefrontal cortices.

MATERIALS AND METHODS

Experimental Design and Statistical Analyses

We employed functional and structural MRI to compare young and elderly participants (between factor) with functional BOLD measures of MNS activity and cortical thickness (within factor). Functional measures for each participant consisted in a conjunction analysis of two conditions, action observation and execution (Price and Friston, 1997; Cabinio et al., 2010; Cerri et al., 2015) to select MNS areas. The functional BOLD signal related to the conjunction analysis derived from regions of interest (ROIs) within the MNS was then extracted and related to the cortical thickness of each ROI. A 2 by 2 ANOVA was used to compare the two groups (between factor) and the two MRI indices, BOLD signal and cortical thickness (within factor).

Sample size was determined based on generally accepted and validated sample size minimums for fMRI studies (Desmond and Glover, 2002) and is in agreement with previous studies from our group (Cabinio et al., 2010).

Participants

Forty healthy individuals were recruited, consisting of twenty-one young adults [age range 23.20–35.10 years, mean (SD) age 26.66 (3.30) years; 9 females] and 19 elderly participants [age range 57.20–87.60 years, mean (SD) age 71.47 (8.52) years; 11 females]. All participants were preliminarily screened to exclude those with major systemic, psychiatric and neurological illnesses. In elderly participants, conditions associated with cognitive impairment were carefully investigated with the administration of a neuropsychological battery to evaluate general cognitive efficiency: Mini Mental State Examination—MMSE (Measso et al., 1993) (inclusion criteria $\geq$ 24); language (phonological and semantic fluency) (Novelli et al., 1986); memory (Free and Cued Selective Reminding Test—FCSRT) (Frasson et al., 2011); and attention and executive abilities (Trail Making Test—TMT, part A and B) (Giovagnoli et al., 1996).

All the participants were right-handed as assessed by the Edinburgh inventory (Oldfield, 1971) and were free from psychotropic medications. The study conformed to the ethical principles of the Helsinki Declaration and approved by the Ethics Committee section of "IRCCS Fondazione Don Carlo Gnocchi," part of the IRCCS Ethics Committee of Regione Lombardia. Informed written consent was obtained from all the included subjects before study initiation. Once included in the study, each participant underwent a single MRI examination, which included structural and functional sequences (see below for details).

MRI Acquisition

Structural and functional MRI data were acquired during a single session using a 1.5 Tesla Siemens Magnetom Avanto scanner, at Santa Maria Nascente Institute IRCCS, Don Carlo Gnocchi Foundation. Functional images were collected by a gradient echo echo-planar (EPI) T2* sequence (TR = 3,000 ms; TE = 50 ms; flip angle = 90°; voxel size = $2.8125 \times 2.8125 \times 4$ mm^3; matrix size = 64×64; number of slices = 38; thickness = 4 mm) to detect Blood Oxygenation Level Dependent (BOLD) contrast. Each fMRI session included two runs of 122 volumes. A 3D T1-weighted scan (TR = 1,900 ms; TE = 3.37 ms; voxel size = $1 \times 1 \times 1$ mm^3; matrix size = 192×256; slice thickness = 1 mm; number of slices = 176) was also acquired, to perform volumetric measurements and for anatomical reference in fMRI analysis.

A conventional T2-weighted scan (TR = 2,920 ms; TE = 108 ms; voxel size = $0.75 \times 0.75 \times 5.2$ mm^3; matrix size = 320×320; slice thickness = 4 mm; number of slices = 25) was collected as well, to exclude participants with brain abnormalities. Conventional anatomical sequences (PD-T2, FLAIR) were also executed in order to exclude participants with macroscopic brain lesions and/or more than five white matter hyperintensities (Vale et al., 2015).

fMRI Experimental Design

In the course of the fMRI session, subjects were requested to complete 2 block-design runs (i.e., Observation - O- run and Execution - E - run) with an A-B structure (task vs. rest), according to the paradigm described in Cabinio et al. (2010), Farina et al. (2017). In the first run all participants were asked to observe film clips of a right hand executing several grasping movements (O) while in second run participants were asked to execute grasping actions with their right hand according to the object that they viewed on the screen (E). In the O-runs, participants viewed 12 precision-grip movements (e.g., grip a coffee cup from the handle, a key, a pencil) and 12 whole-hand movements (e.g., grasp a torch, a glass, a kitchen sponge). In the E-runs, subjects viewed the pictures of the same 24 objects (see **Figure 1**). In both the O and the E runs the rest condition was to watch the picture of a right hand at rest. The design was fully randomized (both blocks and runs). Before the fMRI experiment, the participants had a short training session outside the scanner for 15 min. During the training session, participants were also instructed to keep their gaze on the fixation point for the entire duration of the experiment, and to execute grasping actions about once every second. See our previous works for further details (Cabinio et al., 2010; Cerri et al., 2015; Farina et al., 2017). We used an MR-compatible visual system to present the stimuli which included digital goggles (VisuaStim Digital system, Resonance Technology Inc.). The use of E-Prime software (E-Prime 2.0 Psychology Software tool)[1] ensured exact timing of prompts during MR acquisition. The performance was visually checked by the examiner, who controlled the accuracy and the number of repetitions of the grasping actions during the task execution.

fMRI Analysis

fMRI data were analyzed according to the General Linear Model with SPM12[2] running on MATLAB 8.1.0 (MathWork, Natick, MA). Images were first realigned and movement parameters were estimated. Anatomical and functional images were then spatially normalized to the MNI template using a $2 \times 2 \times 2$ mm^3 voxel size with trilinear interpolation. The normalized functional images were spatially smoothed using an 8-mm full-width at half-maximum isotropic Gaussian kernel. Plots of linear and rotational indices of in-scanner motion were visually inspected to rule out the presence of major artifacts. A threshold of 3 mm or 3 degrees was chosen as limit of acceptable in-scanner motion. Bad volumes were detected and repaired just before estimation using the ArtRepair toolbox[3]. Outlier volumes were first repaired by interpolation to avoid side-effects in the high-pass filtering stage. These volumes were then deweighted in General Linear Model estimation to maintain unbiased estimates.

For first-level statistical analyses, we modeled the expected hemodynamic response function of the software package with a block design. The six parameters related to head movement were included as regressors of no interest. For each participant, we estimated two t-contrasts: observation of a hand grasping (O) and execution of grasping movements (E).

A second level paired *t*-test with both Observation and Execution contrasts was then run. To identify the contour of the MNS, a conjunction ("E" and "O") analysis, in which the null hypothesis (Nichols et al., 2005) concerns the probability that each voxel is equally activated in both conditions, was performed at the group level using an inclusive mask with both conditions ($p < 0.001_{unc}$). To perform group level statistics on the conjunction data, the whole group conjunction activation map was used to define frontal, parietal and temporo-occipital regions of interest (ROIs). Functional ROIs (BOLD-ROIs) were defined as spheres with a 10 mm radius and centered on the peak of activation (see **Figure 2**).

Conjunction probabilistic maps were then extracted from each participant (single-subject level) considering an inclusive mask with "O" and "E" conditions. The mean signal derived from single-subject level conjunction maps was then calculated for each BOLD-ROI using MARSBAR[4] (see **Figure 2**).

The mean signal of each BOLD-ROI was converted into a z-score using the mean and standard deviation of the group and then z-scores were included in statistical ANOVA analyses (see **Figure 2**).

[1] http://www.pstnet.com
[2] http://www.fil.ion.ucl.ac.uk/spm
[3] http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html
[4] http://marsbar.sourceforge.net

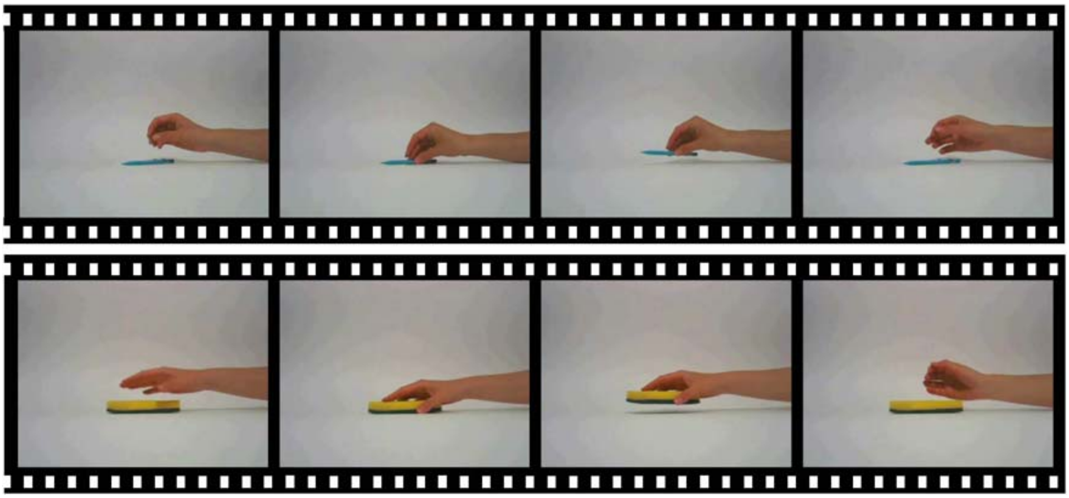

FIGURE 1 | fMRI task stimuli. Sample frames taken from movie clips of a precision grip (upper line): a whole-hand grasp (lower line) used in the observation condition of the fMRI task.

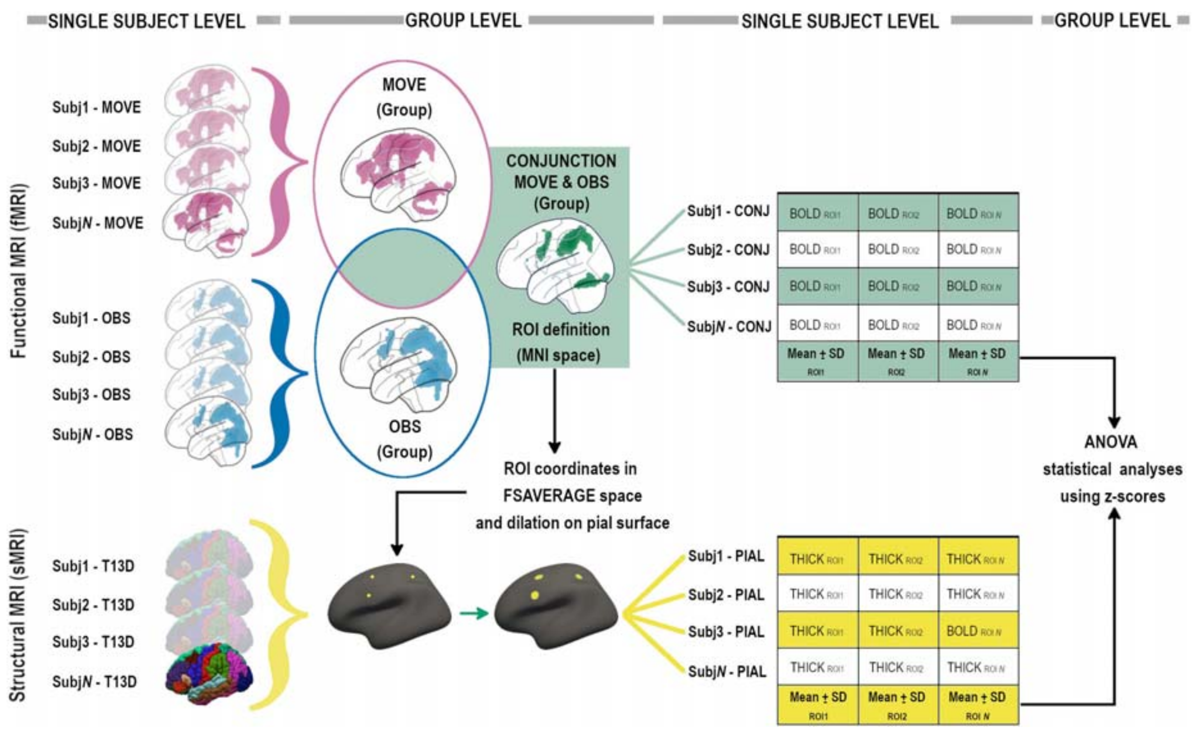

FIGURE 2 | Analysis pipeline, graphical flow-chart representation (see "Materials and Methods" sections for details).

Lastly, the Juelich Histological Atlas (Eickhoff et al., 2007; Amunts and Mohlberg, 2020), the Harvard-Oxford Cortical Structural Atlas (Desikan et al., 2006), and the Talairach Atlas, non-linearly transformed to convert coordinates from the MNI space to Talairach space[5] (Lancaster et al., 2007), were used for interpretative purposes.

T13D MRI Data Analysis—ROIs' Cortical Thickness

High resolution 3D T1-weighted images were parcellated using the standard recon-all pipeline in FreeSurfer v. 5.3[6]. Quality checks were performed according to ENIGMA guidelines and manual corrections were done when required.

[5]http://imaging.mrccbu.cam.ac.uk/downloads/MNI2tal/mni2tal-m

[6]http://www.freesurfer.net/

Mean thickness was then computed in subject space within selected morphological ROIs (Thick-ROIs), created around the coordinates of the peak of activation of each BOLD-ROI derived from the Conjunction group-level contrast. In order to create circular ROIs in subject space, a multi-step procedure was used (see **Figure 2**). For each ROI, after conversion of the coordinates from MNI to fsaverage space and the creation of a single-point label, the coordinate was projected on the nearest point on the pial surface and then dilated 10 times forming a circular shape onto the pial surface. Each circular Thick-ROI was then back-projected in subject space and thickness measurements computed creating the Thick-ROIs. Each Thick-ROI measure was converted into a z-score using mean and standard deviation of the group and then z-scores were included in statistical ANOVA analyses (see **Figure 2**).

Statistical Analyses

To detect differences between groups for each ROI in the BOLD signal and the cortical thickness, a mixed factorial ANOVA Group*Index was designed. Both Group and Index consisted of 2 levels (Group: Young and Elderly; Index: BOLD z-scores and Thickness z-scores). The statistical analyses were carried out using IBM SPSS version 24. Main effects of Group and Index and interaction effects Group*Index were tested and considered as statistically significant at $p < 0.05$ after applying the Benjamini–Hochberg procedure to control the False Discovery Rate (FDR) (Benjamini and Hochberg, 1995). Simple effects were performed to explore the effect of the independent variable Group within each level of the second independent variable Index.

Moreover, to quantify the degree of lateralization in every subject (see also Cabinio et al., 2010), we used LI-Toolbox software[7], a toolbox for SPM able to compute the laterality index (LI) (Wilke and Lidzba, 2007). LI was calculated on the basis of the number of voxels surviving the $p < 0.001$ 50K threshold, in the right and in the left frontal and parietal lobes separately. LI values ranged between + 1(completely left lateralized) and −1 (completely right lateralized).

RESULTS

Sample and Neuropsychological Assessment

Demographics of the study sample are summarized in **Table 1**. The neuropsychological examination of elderly participants confirmed the absence of cognitive deficits in any explored domain (mean values are above the cut-off scores in all tests as detailed in **Table 1**).

TABLE 1 | Demographic data and neuropsychological evaluation of elderly group.

	Elderly	Young	Group comparison	
N	19	21		
Sex (M:F)	8:11	12:9	0.342[a]	
Age (years, mean ± SD)	71.47 ± 8.52	26.66 ± 3.30	<0.001[b]	
Neuropsychological assessment of Elderly Group	**Mean**	**SD**	**Minimum–Maximum**	**Cut-off**
MMSE adjusted score (Measso et al., 1993)	27.25	0.99	26.00–29.10	≥23.80
FCSRT—IFR adjusted score (Frasson et al., 2011)	29.30	3.49	22.00–34.40	≥19.60
FCSRT—ITR (Frasson et al., 2011)	35.95	0.23	35.00–36.00	≥35.00
FCSRT—DFR adjusted score (Frasson et al., 2011)	10.09	1.48	7.10–12.00	≥6.32
FCSRT—DTR (Frasson et al., 2011)	11.89	0.46	10.00–12.00	≥11.00
FCSRT—CSI (Frasson et al., 2011)	0.99	0.03	0.85–1.00	≥0.90
Phonemic Fluency adjusted score (Novelli et al., 1986)	38.58	9.11	23.20–57.00	≥17.00
Semantic Fluency adjusted score (Novelli et al., 1986)	41.33	7.80	27.90–58.30	≥25.00
TMT A adjusted score (Giovagnoli et al., 1996)	28.08	19.06	0–66.00	≤93.00
TMT B adjusted score (Giovagnoli et al., 1996)	43.60	41.02	0–145.90	≤282.00
TMT B-A adjusted score (Giovagnoli et al., 1996)	14.97	30.24	0–81.80	≤187.00

[a]*Chi-squared (χ^2) test.*
[b]*Independent samples Student's t-test were performed to compare the two groups.*
MMSE, Mini Mental State Examination; FCSRT, Free and Cued Selective Reminding Test; FCRST-IFR, Immediate Free Recall; FCRST-ITR, Immediate Total Recall; FCRST-DFR, Delayed Free Recall; FCRST-DTR, Delayed Total Recall; FCRST-CSI, Cueing Sensitivity Index; TMT, Trail Making Test; TMT-A, Part A; TMT-B, Part B.

Whole Sample fMRI Conjunction Results

In the whole sample, to detect the activation of the MNS, fMRI results are explored with the conjunction (action observation and execution) contrast (t contrast 3.20; $k = 50$; $p < 0.001_{unc}$) showing activation of a bilateral fronto-parietal network formed by the inferior parietal lobule, intraparietal sulcus, postcentral gyrus, middle and inferior frontal gyri; along with activation of the right inferior temporal gyrus, and the bilateral fusiform gyrus. A bilateral cerebellar activation was also detected. All regions of significant activation are summarized in **Table 2** and illustrated in **Figure 3**.

Twenty-three ROIs were selected from the conjunction contrast in the whole sample corresponding to the peaks of activation clusters and within each cluster to different cortical gyri or Brodmann areas (BAs) (see **Table 3**). After that we extracted the mean BOLD signal from single subject conjunction activation maps in the BOLD-ROIs and the cortical thickness from the Thick-ROIs.

[7] www.fil.ion.ucl.ac.uk/spm/ext/

Between Group Comparison of Functional and Structural Data

A mixed factorial ANOVA to compare Group (Young, Elderly) and Index (BOLD-ROIs z-scores, Thick-ROIs z-scores) was performed (see **Table 3**). Results of ANOVA analysis are also reported in **Table 3** and **Figure 3**. To summarize, no significant main effects of Group and Index were found. All significant Group × Index interactions were explored with *post hoc* analyses. Accordingly, significant Group x Index interaction with significant difference in cortical thickness in *post hoc* comparison was found in the left inferior parietal lobule (ROI 3, IPL, $p_{FDR-corr}$ = 0.009), left fusiform gyrus (ROI 5, FuG, $p_{FDR-corr}$ = 0.020), right inferior temporal gyrus (ROI 8, ITG, $p_{FDR-corr}$ = 0.027), right anterior intraparietal sulcus (ROI 11, aIPS, $p_{FDR-corr}$ = 0.027), left ventral premotor cortex (ROI 12, vPMC, $p_{FDR-corr}$ = 0.008), left ventrolateral prefrontal cortex (ROI 14, vlPFC, p = 0.003), left dorsal premotor cortex (ROI 15, dPMC, $p_{FDR-corr}$ = 0.019), left vlPFC (ROI 16, $p_{FDR-corr}$ = 0.004), right dPMC (ROI 18, $p_{FDR-corr}$ = 0.014), left pars orbitalis (ROI 22, IFG, $p_{FDR-corr}$ < 0.001), left inferior frontal gyrus (ROI 23, IFG, $p_{FDR-corr}$ = 0.005), right medial frontal cortex (ROI 24, preSMA, $p_{FDR-corr}$ < 0.001), left MeFC (ROI 25, $p_{FDR-corr}$ = 0.012). A significant Group x Index interaction with significant difference in both cortical thickness and BOLD signal in *post hoc* comparison was found in left dPMC (ROI 13, p < $0.001_{FDR-corr}$), right vPMC (ROI 17, $p_{FDR-corr}$ < 0.001), right vlPFC (ROI 19, $p_{FDR-corr}$ = 0.003), right vlPFC (ROI 20, $p_{FDR-corr}$ < 0.001), and right vPMC (ROI 21, $p_{FDR-corr}$ < 0.001).

Laterality Index

In the elderly group, the LI in the frontal lobe was –0.262 with a total voxel count 1333 on the left and 2281 on the right, and 0.239 for the parietal lobe with 3248 voxels on the left and 1994 on the right. In the young group, the LI in the frontal lobe was 0.586 with 1488 on the left and 389 on the right, and in the parietal was 0.637 with 5068 on the left and 1123 on the right.

DISCUSSION

Our aim was to explore the functional and structural modifications occurring in the MNS during normal aging. In particular, we found evidence of reduced cortical thickness and increased activation of the premotor cortices bilaterally, areas belonging to the MNS, and an additional involvement of right prefrontal cortices. Finally, unlike the young participants, the elderly group showed evidence of right frontal lateralization.

The whole sample showed an activation within a fronto-parietal network which comprised bilateral parietal areas (aIPS, IPL, SPL, primary sensorimotor cortex), vPMC and dPMC (middle and inferior frontal gyri, BA6, 44 and 45), classically considered MNS areas, and visual areas (BA37, 19), which do not belong to the MNS properly. Finally, right vlPFC (BA44-45) was also found.

The herein data agree with an extensive quantitative meta-analysis (Molenberghs et al., 2012) of fMRI data from 125 studies reporting the localization of the human MNS. The recruitment of the vPMC in the present study is in line with previous studies showing how the ventral sector of the premotor cortex is the most likely human equivalent of macaque mirror area F5 and the brain area where hand actions are represented (Binkofski et al., 1999; Rizzolatti et al., 2001; Rizzolatti and Craighero, 2004; Rizzolatti, 2005). Moreover, we also found the recruitment of dPMC, an area involved in the motor preparation of actions and in the observation of hand movements in association with the IFG (pars opercularis) (Buccino et al., 2001).

In our sample, we observed the recruitment of bilateral parietal areas centered in the IPS. Posterior parietal cortices are involved in the multimodal integration of information to construct a spatial representation of the external world. More specifically, the IPS can be considered a visuo-motor interface in the control of arm and eye movements in space for the object manipulation (Buccino et al., 2004; Grefkes and Fink, 2005; Vogt et al., 2007). Moreover, in agreement with previous reports (Gazzola et al., 2007; Cabinio et al., 2010), the MNS network included activation of the postcentral gyrus. This is in line with the role of the MNS in the mechanism of the internal simulation of the observed action. Thus, when we observe an action, a sensory motor resonance mechanism creates an internal subliminal reproduction of the sensory and kinematic aspects of the observed action.

Outside the strictly-defined MNS areas, we observed recruitment of temporal visual areas, corresponding to extrastriate body area (EBA) as previously described (Cabinio et al., 2010; Molenberghs et al., 2012) a region involved in the visual recognition of the human body (Downing et al., 2001; Urgesi et al., 2004).

The herein presented results confirmed the starting hypothesis of the presence of structural and functional modifications in MNS with normal aging, following the constraints of the age-related brain changes. Specifically, the frontal areas on both the right and left hemispheres were significantly different between the two groups for both fMRI activation and cortical thickness with the left dPMC, the right vPMC and right ventrolateral PFC showing increased activity in the elderly group coupled with a right frontal lateralization and reduced cortical thickness in the same areas. The dorsal and ventral PMC are part of the MNS (Rizzolatti and Craighero, 2004; Molenberghs et al., 2012), with a possible role in facilitating the motor output from the primary motor cortex through the motor resonance mechanism. Increased activation of these areas in the elderlies might suggest the necessity of increased activity by these areas to modulate and affect motor output from the primary motor cortex. Note that this implies that the PMC, as sector of the MNS, maintains its function to observe action, recognize them, and eventually allowing the individual to interact with one another.

Specifically, the observed PFC activation overlaps with the prefrontal area previously observed during a "learning-by-imitation" fMRI experiment in which musically naïve young subjects were asked to observe and then imitate the hand movement of a guitar chord (Buccino et al., 2004; Vogt et al., 2007). Buccino et al. (2004) interpreted the role of this PFC area in the selection of the appropriate motor act for the execution of the new motor acts (playing the guitar chord), to operate

TABLE 2 | fMRI Conjunction analysis results in the whole sample [threshold p_{uncorr} < 0.001 with a k = 50 contiguous voxels].

P-uncorr	Equivk	T	x	y	z	ROI number	Anatomical region	Brodmann area	Side
<0.001	6237	11.45	−38	−42	48	1	aIPS*	40	L
		8.64	−22	−62	54	2	SPL*	7	L
		8.02	−62	−24	30	3	IPL*	40/2	L
		6.16	−24	−70	40	4	SPL*	7	L
<0.001	15458	11.15	32	−58	−20	*	Cerebellar declive		R
		10.70	−36	−56	−22	*	Cerebellar declive		L
		8.93	−36	−70	−20	5	FuG	19	L
		8.80	−32	−70	−18	*	Cerebellar declive		L
		8.10	−30	−96	−16	6	IOG	18	L
		7.92	−26	−62	−16	*	Cerebellar declive		L
		7.15	44	−38	60	7	Postcentral gyrus (SM1*)	2	R
		7.15	58	−60	−14	8	ITG	37	R
		6.96	48	−34	54	9	Postcentral gyrus (SM1*)	2	R
		6.88	−56	−68	−14	10	MOG	37	L
		6.80	40	−48	56	11	aIPS*	40	R
		6.73	8	−78	−22	*	Cerebellar declive		R
<0.001	3041	8.81	−50	6	30	12	IFG (vPMC)	44	L
		7.54	−40	−2	50	13	Precentral Gyrus (dPMC*)	6	L
		6.03	−38	32	16	14	MFG (vlPFC)	46	L
		4.46	−16	6	58	15	MFG (dPMC*)	6	L
		4.21	−42	22	24	16	MFG (vlPFC)	46	L
< 0.001	2617	7.23	46	6	30	17	IFG (vPMC)	9	R
		6.01	40	−2	54	18	MFG (dPMC)	6	R
		4.95	58	18	4	19	IFG (vlPFC)	45	R
		4.44	54	24	−8	20	IFG (vlPFC)	47	R
		3.35	44	22	18	21	IFG (vPMC)	45	R
0.018	245	5.43	−46	46	−4	22	IFG (pars orbitalis)	47	L
		4.12	−30	26	−4	23	IFG	47	L
0.070	171	4.18	10	14	50	24	MFG (preSMA)	6	R
		4.14	−4	24	44	25	MeFG	8	L

*In gray colors the coordinates selected as Regions of Interest (ROIs) in subsequent statistical analyses. *Juelich atlas label.*
*BA, Brodmann area; aIPS, Anterior Intra-parietal Sulcus; SPL, Superior Parietlal Lobule; IPL, Inferior Parietal Lobule; FuG, Fusiform Gyrus; IOG, inferior occipital gyrus; MOG, middle occipital gyrus; SM1, Primary somatosensory cortex; ITG, Inferior temporal gyrus; Middle occipital gyrus; vPMC, Ventral premotor cortex; IFG, Inferior Frontal Gyrus; dPMC, dorsal premotor cortex; MFG, middle frontal gyrus; vlPFC, ventrolateral prefrontal cortex; oPFC, orbital prefrontal cortex; MeFG, medial frontal gyrus; * ROI not included in ANOVA analysis (Group× Index).*

a recombination of the "resonated" motor acts into a new motor sequence. This finding is particularly interesting since participants in the present study the were asked to observe and execute very simple and well-known grasping actions.

The increased ventral PFC activation in the elderly group suggests a higher cognitive/attentive load probably related to a step-by-step planning of the motor action also during simple actions. One might argue that while in young healthy participants these prefrontal areas become active during the acquisition of novel motor tasks (e.g., when naïve participants learn to play some guitar chords following a model; Buccino et al., 2004; Vogt et al., 2007), in healthy elderly participants the recruitment of these areas always occurs also during the observation and recognition of actions that are already part of the participants' motor repertoire. This in turn suggests that, as compared to younger people, the activation of these areas in elderly participants is necessarily a pre-requisite to process even for familiar and well-known actions. In other words, physiological aging is associated with the necessity to recombine simple motor acts *de novo* each time.

From a more cognitive point of view, the PFC is also widely associated with attention and executive-control systems and has been implicated in the allocation of resources (Badre, 2008; Badre and Nee, 2018). This area is typically recruited during cognitive tasks requiring attentional control and manipulation of information in working memory (Goldman-Rakic, 1995; Badre, 2008; Badre and Nee, 2018). Many neuroimaging studies investigating executive control have reported greater frontal cortex activation in older adults compared to younger adults (Nielson et al., 2002; Cabeza et al., 2004; Colcombe et al., 2005; Townsend et al., 2006; Kurth et al., 2016), supporting the hypothesis that this area may be linked to compensatory mechanisms in aging related to cognition (Cabeza et al., 2002). Taken together, these data are also relevant when planning rehabilitative intervention targeted to elderly individuals. Moreover, preliminary evidence showed how an

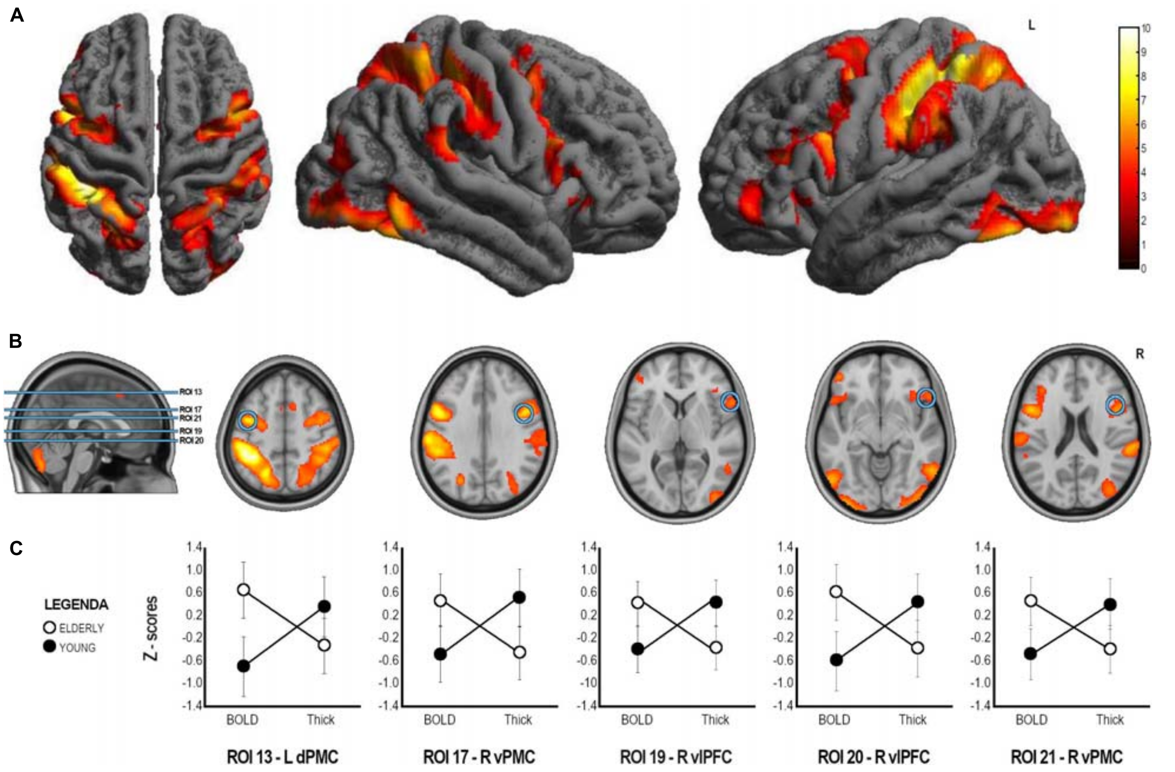

FIGURE 3 | ANOVA analysis results**. (A)** Whole sample fMRI conjunction results (t contrast 3.20; k = 50; p < 0.001$_{unc}$, see **Table 2** for details). **(B)** Brain localization of the ROIs found to have significant Group x Index interaction with significant difference in both cortical thickness and BOLD signal in *post hoc* comparison. **(C)** Graphical representation of BOLD and Thickness Z-scores in the two groups in the statistically significant ROIs. ROI, Region of Interest; L, Left; R, Right; dPMC, dorsal Premotor Cortex; vPFC, ventral premotor cortex; vlPFC, ventrolateral prefrontal cortex.

action observation rehabilitation treatment was associated with improvements in attention and facial recognition in nursing home residents with dementia (Eggermont et al., 2009). Increased activation of premotor cortices with aging has been previously documented in several experiments investigating the motor system (Calautti et al., 2001; Hutchinson et al., 2002; Mattay et al., 2002; Heuninckx et al., 2005; Ward, 2006; Seidler et al., 2010; Wang et al., 2019; Tscherpel et al., 2020). The increased activation in the pre motor cortex can be interpreted as a compensatory mechanism specifically related to the MNS due to its well-established involvement in the MNS. However, considering the specificity of the mirror-task used, it is not possible to rule out a more general compensatory role in aging for this area.

In our study, the increased activation of the bilateral PMC and of the right PFC mentioned was coupled with reduced cortical thickness, a marker of neuronal loss and reduced brain reserve typical of the aging processes (Salat et al., 2004; van Velsen et al., 2013; Cabeza et al., 2018).

Our data are coherent with functional neurocompensatory models in aging such as the HAROLD model (Hemispheric Asymmetry Reduction in Older Adults) (Cabeza, 2002) that supports the reduction of lateralization of brain activity in aging, and the CRUNCH model (Compensation-Related Utilization of Neural Hypothesis Circuits) (Reuter-Lorenz and Cappell, 2008) that captures other aging related mechanisms consisting in the recruitment of additional brain regions to play out compensatory strategies to cope with the reduced brain reserve.

To the best of our knowledge, only one previous study explored aging and the MNS (Nedelko et al., 2010), comparing young versus elderly participants. In that study the seminal areas of the MNS did not show changes between groups. However, methodological differences might explain the discrepant results. Our paradigm, an execution-observation conjunction experimental design, allowed us to selectively define mirror areas, while Nedelko's paradigm (Nedelko et al., 2010) was focused on action observation and imagery. The latter recruits a network only partially overlapping with the MNS (Gerardin et al., 2000).

The strength of our findings consists in this specific coupling of age-related measures obtained using two different MRI techniques (i.e., structural and functional MRI). The differential age effect observed in the brain reserve in frontal regions belonging to the MNS is associated both with an increased activity in the designated MNS (premotor) areas and an additional recruitment of non-specific MNS (prefrontal) areas. In light of this multimodal MRI study, we can hypothesize two possible mechanisms: compensation by up-regulation, if we consider the hyperactivity observed in the areas belonging to the MNS in the bilateral PMC, and compensation by reorganization if we consider the recruitment of right PFC observed in the elderly

TABLE 3 | Results of the ANOVA Group (Young, Elderly) *Index (BOLD, Thickness z-scores).

ROI n.	Region	Z-scores	Young Mean	Young SD	Elderly Mean	Elderly SD	Group F (1,37) pFDR	Index F (1,37) pFDR	Group * Index F (1,37) pFDR	Young vs. Elderly Thickness *p*-value	Young vs. Elderly BOLD *p*-value
ROI 1	aIPS	Thickness	0.27	0.90	−0.28	1.04	2.662	0.000	0.615	0.086	0.534
		BOLD	0.10	1.01	−0.11	1.00	0.253	0.998	0.456		
ROI 2	SPL	Thickness	0.41	0.78	−0.43	1.04	2.880	0.000	4.569	0.007*	0.841
		BOLD	−0.02	0.91	0.02	1.11	0.253	0.998	0.052		
ROI 3	IPL	Thickness	0.51	0.74	−0.53	0.97	3.799	0.020	9.221	0.001*	0.698
		BOLD	−0.07	0.84	0.08	1.17	0.245	0.998	0.009*		
ROI 4	SPL	Thickness	0.22	0.97	−0.23	1.00	0.167	0.020	3.373	0.158	0.437
		BOLD	−0.08	0.84	0.09	1.17	0.779	0.998	0.089		
ROI 5	FuG	Thickness	0.50	0.81	−0.53	0.92	4.968	0.003	6.877	0.001*	0.874
		BOLD	0.03	0.90	−0.03	1.13	0.245	0.998	0.020*		
ROI 6	IOG	Thickness	0.07	1.13	−0.07	0.86	1.167	0.001	0.208	0.656	0.283
		BOLD	0.17	0.91	−0.19	1.09	0.399	0.998	0.651		
ROI 7	SM1	Thickness	0.32	0.82	−0.34	1.08	1.671	0.022	2.805	0.037*	0.829
		BOLD	−0.05	0.88	0.06	1.14	0.365	0.998	0.111		
ROI 8	ITG	Thickness	0.35	0.79	−0.37	1.08	0.804	0.030	5.941	0.022*	0.278
		BOLD	−0.11	0.85	0.12	1.16	0.470	0.998	0.027*		
ROI 9	SM1	Thickness	0.32	0.76	−0.34	1.13	1.381	0.013	3.224	0.037*	0.718
		BOLD	−0.04	0.91	0.08	1.13	0.399	0.998	0.092		
ROI 10	MOG	Thickness	0.38	0.78	−0.40	1.06	2.794	0.012	3.594	0.012*	0.872
		BOLD	−0.04	0.90	0.04	1.13	0.253	0.998	0.082		
ROI 11	aIPS	T Thickness	0.54	0.64	−0.56	1.02	7.301	0.004	6.054	<0.001*	0.794
		BOLD	0.04	1.09	−0.04	0.95	0.245	0.998	0.027*		
ROI 12	IFG (vPMC)	Thickness	0.53	0.74	−0.55	0.95	4.030	0.016	9.703	<0.001*	0.540
		BOLD	−0.10	0.78	0.11	1.21	0.245	0.998	0.008*		
ROI 13	Precentral Gyrus (dPMC)	Thickness	0.65	0.58	−0.69	0.89	2.467	0.006	28.819	<0.001*	0.024*
		BOLD	−0.32	0.88	0.36	1.03	0.260	0.998	<0.001*		
ROI 14	MFG (vlPFC)	Thickness	0.46	0.78	−0.49	0.99	1.189	0.037	13.230	0.002*	0.167
		BOLD	−0.23	0.91	0.25	1.06	0.399	0.998	0.003*		
ROI 15	MFG (dPMC)	Thickness	0.48	0.71	−0.50	1.03	3.816	0.030	7.152	0.001*	0.825
		BOLD	−0.05	1.16	0.06	0.82	0.245	0.998	0.019*		
ROI 16	MFG (vlPFC)	Thickness	0.54	0.82	−0.57	0.85	3.977	0.006	12.168	<0.001*	0.606
		BOLD	−0.08	1.09	0.08	0.92	0.245	0.998	0.004*		
ROI 17	IFG (vPMC)	Thickness	0.46	0.94	−0.49	0.83	0.011	0.020	25.073	0.002*	0.001*
		BOLD	−0.46	0.51	0.51	1.17	0.955	0.998	<0.001*		
ROI 18	MFG (dPMC)	Thickness	0.47	0.86	−0.45	0.93	1.796	0.000	7.948	0.004*	0.356
		BOLD	−0.15	0.95	0.17	1.05	0.189	0.998	0.014*		
ROI 19	vlPFC/IFG	Thickness	0.40	0.85	−0.40	0.99	0.000	0.100	12.849	0.013*	0.016*
		BOLD	−0.37	0.58	0.41	1.21	0.998	0.998	0.003*		
ROI 20	IFG (vlPFC)	Thickness	0.61	0.70	−0.61	0.89	0.482	0.051	36.452	<0.001*	0.007*
		BOLD	−0.38	0.58	0.42	1.20	0.586	0.998	<0.001*		
ROI 21	IFG (vPMC)	Thickness	0.47	0.90	−0.47	0.89	0.090	0.007	17.186	0.003*	0.012*
		BOLD	−0.38	0.54	0.42	1.22	0.833	0.998	<0.001		
ROI 22	IFG pars orbitalis	Thickness	0.62	0.68	−0.66	0.86	2.675	0.000	31.249	<0.001*	0.109
		BOLD	−0.22	0.63	0.24	1.27	0.253	0.998	<0.001		
ROI 23	IFG	Thickness	0.46	0.77	−0.48	1.00	1.207	0.007	10.979	0.002*	0.162
		BOLD	−0.21	0.72	0.23	1.21	0.399	0.998	0.005*		
ROI 24	MFG (preSMA)	Thickness	0.50	0.72	−0.55	0.99	1.020	0.009	17.639	0.001*	0.060
		BOLD	−0.32	0.63	0.35	1.21	0.420	0.998	<0.001*		
ROI 25	MeFG	Thickness	0.47	0.71	−0.50	1.03	2.930	0.001	8.382	0.001*	0.595
		BOLD	−0.07	1.10	0.08	0.90	0.253	0.998	0.012*		

BA, Brodmann area; aIPS, Anterior Intra-parietal Sulcus; SPL, Superior Parietal Lobule; IPL Inferior Parietal Lobule; FuG, Fusiform Gyrus; SM1, Primary somatosensory cortex; ITG, Inferior temporal gyrus; Middle occipital gyrus; vPMC, Ventral premotor cortex; IFG, Inferior Frontal Gyrus; dPMC, dorsal premotor cortex; MFG, middle frontal gyrus; vlPFC, ventrolateral prefrontal cortex; oPFC, orbital prefrontal cortex; MeFC, medial frontal cortex.
**Statistically significant results.*

(Cabeza et al., 2018). More generally, according to the CRUNCH model, our data can be considered as evidence for an important role of this area as a brain reserve hub, thus involved in the aging process of several domains.

A final remark concerns the characteristics of the elderly participants included in the study. Results from the neuropsychological assessment showed that they performed within the normal range on all the neuropsychological tests, confirming that they were globally preserved in cognitive functioning and thus representative of the normal aging population.

Although the findings of the current investigation provided deeper understanding of the functional organization and structural brain reserve of the MNS in healthy older adults, there are some limitations that need to be considered. First, we selected participants that underwent a single session study, but we did not include longitudinal evaluations. A future study should provide further evidence with a longitudinal design and explore the age-related monitoring changes during normal aging. Second, the lack of reserve measures in these participants can limit the comprehension of aging process. Future studies investigating the correlation between neuroimaging data and aspects of reserve (such as cognitive reserve) will be necessary to account for inter-individual variability in aging.

CONCLUSION

In conclusion, our data suggest that during aging, the MNS is subject to both structural and functional modifications resembling what occurs in the neuromotor and neurocognitive aging. At a structural level, the MNS undergoes cortical thinning; whereas from a functional level, its activation increases bilaterally in the premotor cortices with additional recruitment of right prefrontal cortex.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee section of "IRCCS Fondazione Don Carlo Gnocchi," part of the IRCCS Ethics Committee of Regione Lombardia. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SD, VB, MC, GB, and FB contributed to conception and design of the study. SD, VB, NB, and MC performed the statistical analysis and wrote the first draft of the manuscript. SD, VB, MC, NB, and GB contributed to manuscript revision, read, and approved the submitted version. All authors contributed to the article and approved the submitted version.

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REFERENCES

Amunts, K., and Mohlberg, H. (2020). Julich-Brain: A 3D probabilistic atlas of the human brain's cytoarchitecture. *Science* 369, 988–992. doi: 10.1126/science.abb4588

Antonietti, A., and Corradini, A. (2013). Mirroring mirror neurons in an interdisciplinary debate. *Conscious Cogn.* 22, 1092–1094. doi: 10.1016/j.concog.2013.04.007

Badre, D. (2008). Cognitive control, hierarchy, and the rostro-caudal organization of the frontal lobes. *Trends Cogn. Sci.* 12, 193–200. doi: 10.1016/j.tics.2008.02.004

Badre, D., and Nee, D. E. (2018). Frontal cortex and the hierarchical control of behavior. *Trends Cogn. Sci.* 22, 170–188. doi: 10.1016/j.tics.2017.11.005

Benjamini, Y., and Hochberg, Y. (1995). Controlling the false discovery rate - a practical and powerful approach to multiple testing. *J. R. Stat. Soc. Ser. B* 57, 289–300. doi: 10.2307/2346101

Binkofski, F., Buccino, G., Posse, S., Seitz, R. J., Rizzolatti, G., and Freund, H. (1999). A fronto-parietal circuit for object manipulation in man: evidence from an fMRI-study. *Eur. J. Neurosci.* 11, 3276–3286. doi: 10.1046/j.1460-9568.1999.00753.x

Borroni, P., and Baldissera, F. (2008). Activation of motor pathways during observation and execution of hand movements. *Soc. Neurosci.* 3, 276–288. doi: 10.1080/17470910701515269

Borroni, P., Montagna, M., Cerri, G., and Baldissera, F. (2005). Cyclic time course of motor excitability modulation during the observation of a cyclic hand movement. *Brain Res.* 1065, 115–124. doi: 10.1016/j.brainres.2005.10.034

Buccino, G. (2014). Action observation treatment: a novel tool in neurorehabilitation. *Philos. Trans. R. Soc. Lond B Biol. Sci.* 369:20130185. doi: 10.1098/rstb.2013.0185

Buccino, G., Binkofski, F., Fink, G. R., Fadiga, L., Fogassi, L., Gallese, V., et al. (2001). Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. *Eur. J. Neurosci.* 13, 400–404.

Buccino, G., Colagè, I., Gobbi, N., and Bonaccorso, G. (2016). Grounding meaning in experience: A broad perspective on embodied language. *Neurosci. Biobehav. Rev.* 69, 69–78. doi: 10.1016/j.neubiorev.2016.07.033

Buccino, G., and Riggio, L. (2006). The role of the mirror neuron system in motor learning. *Kinesiology* 38, 1–13.

Buccino, G., Vogt, S., Ritzl, A., Fink, G. R., Zilles, K., Freund, H. J., et al. (2004). Neural circuits underlying imitation learning of hand actions: an event-related fMRI study. *Neuron* 42, 323–334. doi: 10.1016/s0896-6273(04)00181-3

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol. Aging* 17, 85–100. doi: 10.1037//0882-7974.17.1.85

Cabeza, R., Albert, M., Belleville, S., Craik, F. I. M., Duarte, A., Grady, C. L., et al. (2018). Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. *Nat. Rev. Neurosci.* 19, 701–710. doi: 10.1038/s41583-018-0068-2

Cabeza, R., Anderson, N. D., Locantore, J. K., and McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage* 17, 1394–1402. doi: 10.1006/nimg.2002.1280

Cabeza, R., Daselaar, S. M., Dolcos, F., Prince, S. E., Budde, M., and Nyberg, L. (2004). Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. *Cereb. Cortex* 14, 364–375. doi: 10.1093/cercor/bhg133

Cabinio, M., Blasi, V., Borroni, P., Montagna, M., Iadanza, A., Falini, A., et al. (2010). The shape of motor resonance: right- or left-handed? *Neuroimage* 51, 313–323. doi: 10.1016/j.neuroimage.2010.01.103

Calautti, C., Serrati, C., and Baron, J. C. (2001). Effects of age on brain activation during auditory-cued thumb-to-index opposition: A positron emission tomography study. *Stroke* 32, 139–146. doi: 10.1161/01.str.32.1.139

Cerri, G., Cabinio, M., Blasi, V., Borroni, P., Iadanza, A., Fava, E., et al. (2015). The mirror neuron system and the strange case of Broca's area. *Hum. Brain Mapp.* 36, 1010–1027. doi: 10.1002/hbm.22682

Colcombe, S. J., Kramer, A. F., Erickson, K. I., and Scalf, P. (2005). The implications of cortical recruitment and brain morphology for individual differences in inhibitory function in aging humans. *Psychol. Aging* 20, 363–375. doi: 10.1037/0882-7974.20.3.363

Cook, R., Bird, G., Catmur, C., Press, C., and Heyes, C. (2014). Mirror neurons: from origin to function. *Behav. Brain Sci.* 37, 177–192. doi: 10.1017/s0140525x13000903

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., et al. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 31, 968–980. doi: 10.1016/j.neuroimage.2006.01.021

Desmond, J. E., and Glover, G. H. (2002). Estimating sample size in functional MRI (fMRI) neuroimaging studies: Statistical power analyses. *J. Neurosci. Methods* 118, 115–128. doi: 10.1016/S0165-0270(02)00121-8

di Pellegrino, G., Fadiga, L., Fogassi, L., Gallese, V., and Rizzolatti, G. (1992). Understanding motor events: a neurophysiological study. *Exp. Brain Res.* 91, 176–180. doi: 10.1007/bf00230027

Downing, P. E., Jiang, Y., Shuman, M., and Kanwisher, N. (2001). A cortical area selective for visual processing of the human body. *Science* 293, 2470–2473. doi: 10.1126/science.1063414

Eggermont, L. H., Swaab, D. F., Hol, E. M., and Scherder, E. J. (2009). Observation of hand movements by older persons with dementia: effects on cognition: a pilot study. *Dement. Geriatr. Cogn. Disord.* 27, 366–374. doi: 10.1159/000209311

Eickhoff, S. B., Paus, T., Caspers, S., Grosbras, M. H., Evans, A. C., Zilles, K., et al. (2007). Assignment of functional activations to probabilistic cytoarchitectonic areas revisited. *Neuroimage* 36, 511–521. doi: 10.1016/j.neuroimage.2007.03.060

Ertelt, D., Small, S., Solodkin, A., Dettmers, C., McNamara, A., Binkofski, F., et al. (2007). Action observation has a positive impact on rehabilitation of motor deficits after stroke. *NeuroImage* 36, T164–T173. doi: 10.1016/j.neuroimage.2007.03.043

Fadiga, L., Fogassi, L., Pavesi, G., and Rizzolatti, G. (1995). Motor facilitation during action observation: a magnetic stimulation study. *J. Neurophysiol.* 73, 2608–2611. doi: 10.1152/jn.1995.73.6.2608

Farina, E., Baglio, F., Pomati, S., D'Amico, A., Campini, I. C., Di Tella, S., et al. (2017). The mirror neurons network in aging, mild cognitive impairment, and Alzheimer Disease: A functional MRI study. *Front. Aging Neurosci.* 9:371. doi: 10.3389/fnagi.2017.00371

Farina, E., Borgnis, F., and Pozzo, T. (2020). Mirror neurons and their relationship with neurodegenerative disorders. *J. Neurosci. Res.* 98, 1070–1094. doi: 10.1002/jnr.24579

Frasson, P., Ghiretti, R., Catricalà, E., Pomati, S., Marcone, A., Parisi, L., et al. (2011). Free and cued selective reminding test: an Italian normative study. *Neurol. Sci.* 32, 1057–1062. doi: 10.1007/s10072-011-0607-3

Gallese, V. (2009). Motor abstraction: a neuroscientific account of how action goals and intentions are mapped and understood. *Psychol. Res.* 73, 486–498. doi: 10.1007/s00426-009-0232-4

Gallese, V., Fadiga, L., Fogassi, L., and Rizzolatti, G. (1996). Action recognition in the premotor cortex. *Brain* 119, 593–609. doi: 10.1093/brain/119.2.593

Gallese, V., and Goldman, A. (1998). Mirror neurons and the simulation theory of mind-reading. *Trends Cogn. Sci.* 2, 493–501. doi: 10.1016/s1364-6613(98)01262-5

Gazzola, V., Rizzolatti, G., Wicker, B., and Keysers, C. (2007). The anthropomorphic brain: the mirror neuron system responds to human and robotic actions. *Neuroimage* 35, 1674–1684. doi: 10.1016/j.neuroimage.2007.02.003

Gerardin, E., Sirigu, A., Lehéricy, S., Poline, J. B., Gaymard, B., Marsault, C., et al. (2000). Partially overlapping neural networks for real and imagined hand movements. *Cereb. Cortex* 10, 1093–1104. doi: 10.1093/cercor/10.11.1093

Giovagnoli, A. R., Del Pesce, M., Mascheroni, S., Simoncelli, M., Laiacona, M., and Capitani, E. (1996). Trail making test: normative values from 287 normal adult controls. *Italian J. Neurol. Sci.* 17, 305–309.

Goldman-Rakic, P. S. (1995). Cellular basis of working memory. *Neuron* 14, 477–485. doi: 10.1016/0896-6273(95)90304-6

Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N., Friston, K. J., and Frackowiak, R. S. (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 14, 21–36. doi: 10.1006/nimg.2001.0786

Grefkes, C., and Fink, G. R. (2005). The functional organization of the intraparietal sulcus in humans and monkeys. *J. Anat.* 207, 3–17. doi: 10.1111/j.1469-7580.2005.00426.x

Grèzes, J., Fonlupt, P., Bertenthal, B., Delon-Martin, C., Segebarth, C., and Decety, J. (2001). Does perception of biological motion rely on specific brain regions? *Neuroimage* 13, 775–785. doi: 10.1006/nimg.2000.0740

Hardwick, R. M., Caspers, S., Eickhoff, S. B., and Swinnen, S. P. (2018). Neural correlates of action: Comparing meta-analyses of imagery, observation, and execution. *Neurosci. Biobehav. Rev.* 94, 31–44. doi: 10.1016/j.neubiorev.2018.08.003

Heuninckx, S., Wenderoth, N., Debaere, F., Peeters, R., and Swinnen, S. P. (2005). Neural basis of aging: the penetration of cognition into action control. *J. Neurosci.* 25, 6787–6796. doi: 10.1523/jneurosci.1263-05.2005

Heuninckx, S., Wenderoth, N., and Swinnen, S. P. (2008). Systems neuroplasticity in the aging brain: recruiting additional neural resources for successful motor performance in elderly persons. *J. Neurosci.* 28, 91–99. doi: 10.1523/jneurosci.3300-07.2008

Hutchinson, S., Kobayashi, M., Horkan, C. M., Pascual-Leone, A., Alexander, M. P., and Schlaug, G. (2002). Age-related differences in movement representation. *Neuroimage* 17, 1720–1728. doi: 10.1006/nimg.2002.1309

Iacoboni, M., Woods, R. P., Brass, M., Bekkering, H., Mazziotta, J. C., and Rizzolatti, G. (1999). Cortical mechanisms of human imitation. *Science* 286, 2526–2528. doi: 10.1126/science.286.5449.2526

Jeannerod, M. (1994). The representing brain: Neural correlates of motor intention and imagery. *Behav. Brain Sci.* 17, 187–202.

Jernigan, T. L., Archibald, S. L., Fennema-Notestine, C., Gamst, A. C., Stout, J. C., Bonner, J., et al. (2001). Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiol. Aging* 22, 581–594. doi: 10.1016/s0197-4580(01)00217-2

Kennedy, B. K., Berger, S. L., Brunet, A., Campisi, J., Cuervo, A. M., Epel, E. S., et al. (2014). Geroscience: linking aging to chronic disease. *Cell* 159, 709–713. doi: 10.1016/j.cell.2014.10.039

Kurth, S., Majerus, S., Bastin, C., Collette, F., Jaspar, M., Bahri, M. A., et al. (2016). Effects of aging on task- and stimulus-related cerebral attention networks. *Neurobiol. Aging* 44, 85–95. doi: 10.1016/j.neurobiolaging.2016.04.015

Lancaster, J. L., Tordesillas-Gutiérrez, D., Martinez, M., Salinas, F., Evans, A., Zilles, K., et al. (2007). Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. *Hum. Brain Mapp.* 28, 1194–1205. doi: 10.1002/hbm.20345

Mattay, V. S., Fera, F., Tessitore, A., Hariri, A. R., Das, S., Callicott, J. H., et al. (2002). Neurophysiological correlates of age-related changes in human motor function. *Neurology* 58, 630–635. doi: 10.1212/wnl.58.4.630

Measso, G., Cavarzeran, F., Zappalà, G., Lebowitz, B., Crook, T., Pirozzolo, F., et al. (1993). The mini-mental state examination: normative study of an Italian random sample. *Dev. Neuropsychol.* 9, 77–85. doi: 10.1080/87565649109540545

Molenberghs, P., Cunnington, R., and Mattingley, J. B. (2012). Brain regions with mirror properties: a meta-analysis of 125 human fMRI studies. *Neurosci. Biobehav. Rev.* 36, 341–349. doi: 10.1016/j.neubiorev.2011.07.004

Nedelko, V., Hassa, T., Hamzei, F., Weiller, C., Binkofski, F., Schoenfeld, M. A., et al. (2010). Age-independent activation in areas of the mirror neuron system during action observation and action imagery. A fMRI study. *Restor. Neurol. Neurosci.* 28, 737–747. doi: 10.3233/rnn-2010-0542

Nichols, T., Brett, M., Andersson, J., Wager, T., and Poline, J. B. (2005). Valid conjunction inference with the minimum statistic. *Neuroimage* 25, 653–660. doi: 10.1016/j.neuroimage.2004.12.005

Nielson, K. A., Langenecker, S. A., and Garavan, H. (2002). Differences in the functional neuroanatomy of inhibitory control across the adult life span. *Psychol. Aging* 17, 56–71. doi: 10.1037//0882-7974.17.1.56

Novelli, G., Papagno, C., Capitani, E., and Laiacona, M. (1986). Tre test clinici di ricerca e produzione lessicale. Taratura su sogetti normali. *Archivio di psicologia neurologia e psichiatria* 47, 477–506.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113. doi: 10.1016/0028-3932(71)90067-4

Oztop, E., Kawato, M., and Arbib, M. A. (2013). Mirror neurons: functions, mechanisms and models. *Neurosci. Lett.* 540, 43–55. doi: 10.1016/j.neulet.2012.10.005

Price, C. J., and Friston, K. J. (1997). Cognitive conjunction: a new approach to brain activation experiments. *Neuroimage* 5, 261–270. doi: 10.1006/nimg.1997.0269

Raz, N., Gunning, F. M., Head, D., Dupuis, J. H., McQuain, J., Briggs, S. D., et al. (1997). Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. *Cereb. Cortex* 7, 268–282. doi: 10.1093/cercor/7.3.268

Resnick, S. M., Pham, D. L., Kraut, M. A., Zonderman, A. B., and Davatzikos, C. (2003). Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. *J. Neurosci.* 23, 3295–3301. doi: 10.1523/jneurosci.23-08-03295.2003

Reuter-Lorenz, P. A., and Cappell, K. A. (2008). Neurocognitive aging and the compensation hypothesis. *Curr. Direc. Psychol. Sci.* 17, 177–182. doi: 10.1111/j.1467-8721.2008.00570.x

Rizzolatti, G. (2005). The mirror neuron system and its function in humans. *Anat. Embryol. (Berl)* 210, 419–421. doi: 10.1007/s00429-005-0039-z

Rizzolatti, G., and Craighero, L. (2004). The mirror-neuron system. *Annu. Rev. Neurosci.* 27, 169–192. doi: 10.1146/annurev.neuro.27.070203.144230

Rizzolatti, G., Fadiga, L., Gallese, V., and Fogassi, L. (1996a). Premotor cortex and the recognition of motor actions. *Brain Res. Cogn. Brain Res.* 3, 131–141. doi: 10.1016/0926-6410(95)00038-0

Rizzolatti, G., Fadiga, L., Matelli, M., Bettinardi, V., Paulesu, E., Perani, D., et al. (1996b). Localization of grasp representations in humans by PET: 1. Observation versus execution. *Exp. Brain Res.* 111, 246–252. doi: 10.1007/bf00227301

Rizzolatti, G., and Fogassi, L. (2014). The mirror mechanism: recent findings and perspectives. *Philos. Trans. R Soc. Lond B Biol. Sci.* 369:20130420. doi: 10.1098/rstb.2013.0420

Rizzolatti, G., Fogassi, L., and Gallese, V. (2001). Neurophysiological mechanisms underlying the understanding and imitation of action. *Nat. Rev. Neurosci.* 2, 661–670. doi: 10.1038/35090060

Rizzolatti, G., Fogassi, L., and Gallese, V. (2002). Motor and cognitive functions of the ventral premotor cortex. *Curr. Opin. Neurobiol.* 12, 149–154. doi: 10.1016/s0959-4388(02)00308-2

Salat, D. H., Buckner, R. L., Snyder, A. Z., Greve, D. N., Desikan, R. S., Busa, E., et al. (2004). Thinning of the cerebral cortex in aging. *Cereb. Cortex* 14, 721–730. doi: 10.1093/cercor/bhh032

Seidler, R. D., Bernard, J. A., Burutolu, T. B., Fling, B. W., Gordon, M. T., Gwin, J. T., et al. (2010). Motor control and aging: links to age-related brain structural, functional, and biochemical effects. *Neurosci. Biobehav. Rev.* 34, 721–733. doi: 10.1016/j.neubiorev.2009.10.005

Strafella, A. P., and Paus, T. (2000). Modulation of cortical excitability during action observation: a transcranial magnetic stimulation study. *Neuroreport* 11, 2289–2292. doi: 10.1097/00001756-200007140-00044

Townsend, J., Adamo, M., and Haist, F. (2006). Changing channels: an fMRI study of aging and cross-modal attention shifts. *Neuroimage* 31, 1682–1692. doi: 10.1016/j.neuroimage.2006.01.045

Tscherpel, C., Hensel, L., Lemberg, K., Freytag, J., Michely, J., Volz, L. J., et al. (2020). Age affects the contribution of ipsilateral brain regions to movement kinematics. *Hum. Brain Mapp.* 41, 640–655. doi: 10.1002/hbm.24829

Urgesi, C., Berlucchi, G., and Aglioti, S. M. (2004). Magnetic stimulation of extrastriate body area impairs visual processing of nonfacial body parts. *Curr. Biol.* 14, 2130–2134. doi: 10.1016/j.cub.2004.11.031

Vale, T. C., Caramelli, P., and Cardoso, F. (2015). Clinicoradiological comparison between vascular parkinsonism and Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* 86, 547–553. doi: 10.1136/jnnp-2014-307867

van Velsen, E. F., Vernooij, M. W., Vrooman, H. A., van der Lugt, A., Breteler, M. M., Hofman, A., et al. (2013). Brain cortical thickness in the general elderly population: the Rotterdam Scan Study. *Neurosci. Lett.* 550, 189–194. doi: 10.1016/j.neulet.2013.06.063

Vinke, E. J., de Groot, M., Venkatraghavan, V., Klein, S., Niessen, W. J., Ikram, M. A., et al. (2018). Trajectories of imaging markers in brain aging: the Rotterdam Study. *Neurobiol. Aging* 71, 32–40. doi: 10.1016/j.neurobiolaging.2018.07.001

Vogt, S., Buccino, G., Wohlschläger, A. M., Canessa, N., Shah, N. J., Zilles, K., et al. (2007). Prefrontal involvement in imitation learning of hand actions: effects of practice and expertise. *Neuroimage* 37, 1371–1383. doi: 10.1016/j.neuroimage.2007.07.005

Wang, L., Zhang, Y., Zhang, J., Sang, L., Li, P., Yan, R., et al. (2019). Aging changes effective connectivity of motor networks during motor execution and motor imagery. *Front. Aging Neurosci.* 11:312. doi: 10.3389/fnagi.2019.00312

Ward, N. S. (2006). Compensatory mechanisms in the aging motor system. *Ageing Res. Rev.* 5, 239–254. doi: 10.1016/j.arr.2006.04.003

Ward, N. S., and Frackowiak, R. S. (2003). Age-related changes in the neural correlates of motor performance. *Brain* 126, 873–888. doi: 10.1093/brain/awg071

Wilke, M., and Lidzba, K. (2007). LI-tool: a new toolbox to assess lateralization in functional MR-data. *J. Neurosci. Methods* 163, 128–136. doi: 10.1016/j.jneumeth.2007.01.026

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Impoverished Inhibitory Control Exacerbates Multisensory Impairments in Older Fallers

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Impaired temporal perception of multisensory cues is a common phenomenon observed in older adults that can lead to unreliable percepts of the external world. For instance, the sound induced flash illusion (SIFI) can induce an illusory percept of a second flash by presenting a beep close in time to an initial flash-beep pair. Older adults that have enhanced susceptibility to a fall demonstrate significantly stronger illusion percepts during the SIFI task compared to those older adults without any history of falling. We hypothesize that a global inhibitory deficit may be driving the impairments across both postural stability and multisensory function in older adults with a fall history (FH). We investigated oscillatory activity and perceptual performance during the SIFI task, to understand how active sensory processing, measured by gamma (30–80 Hz) power, was regulated by alpha activity (8–13 Hz), oscillations that reflect inhibitory control. Compared to young adults (YA), the FH and non-faller (NF) groups demonstrated enhanced susceptibility to the SIFI. Further, the FH group had significantly greater illusion strength compared to the NF group. The FH group also showed significantly impaired performance relative to YA during congruent trials (2 flash-beep pairs resulting in veridical perception of 2 flashes). In illusion compared to non-illusion trials, the NF group demonstrated reduced alpha power (or diminished inhibitory control). Relative to YA and NF, the FH group showed reduced phase-amplitude coupling between alpha and gamma activity in non-illusion trials. This loss of inhibitory capacity over sensory processing in FH compared to NF suggests a more severe change than that consequent of natural aging.

Keywords: inhibition, multisensory processing, sound-induced flash illusion, fall-risk, aging

INTRODUCTION

An individual's experience of the natural world is largely dictated by innate biases and sensitivities toward external stimuli. For instance, as light is propagated at a rapidly faster speed relative to sound, the brain learns this relationship over development and becomes extremely sensitive to auditory-leading signals, as compared to visual-leading. This asymmetry has been continuously observed and reported, particularly in the case of the temporal binding window (TBW) (Powers et al., 2009; Stevenson and Wallace, 2013), an estimate that quantifies the likelihood of perceptually binding two stimuli that are separated by variable temporal delays. Learned temporal relationships of naturally occurring stimuli drive the flexibility of this window (Murray et al., 2016). For instance, TBWs estimated using simple audiovisual stimuli (e.g., a flash and a beep) are much narrower compared to TBWs derived from using more complex audiovisual stimuli (e.g., the visual and auditory cues from speech) (Van Atteveldt et al., 2007; Stevenson and Wallace, 2013). The broader TBW observed in this more ethologically relevant context is not surprising. The brain requires additional flexibility, or increased processing time, to decode the unitary signals and perceive them as either a single, coherent source or as two separate and distinct sources. The temporal relationship between the constituent unimodal parts of a multisensory event is the major driver in dictating this coherent versus segregated perception. Reductions in sensitivity toward audiovisual temporal differences would therefore result in incoherent perceptions and difficulties in experiencing and navigating the environment.

In the healthy older adult, changes in temporal thresholds do occur as a natural consequence of the aging process and thus, deficits in unisensory and multisensory processing are observed (Allison et al., 1984; Schmolesky et al., 2000; Stephen et al., 2010; Ng and Recanzone, 2018). However, explicitly controlling for differences in unisensory processing thresholds cannot completely explain multisensory impairments reported in older adults (Chan et al., 2014). Therefore, additional age-related cortical modifications that affect multisensory-specific functionality are likely at fault. In the auditory region of senescent rhesus macaques, neurons displayed increased spontaneous activity, reduced selectivity in coding patterns and broader-tuned neurons relative to young controls (Ng and Recanzone, 2018). Similar age-related alterations were observed in visual cortex of older macaques with increased responsiveness and broader-tuning curves toward the orientation and direction of visual stimuli (Schmolesky et al., 2000). In addition, the proportion of audiovisual neurons exhibiting tuning toward low spatial frequencies was reduced in the aged rat model while those audiovisual neurons exhibiting band-pass tuning was increased suggesting compensation for this reduction in sensitivity (Costa et al., 2016). In both multisensory and primary sensory regions, the aged cortex displays heightened excitability accompanied by broader-tuning neuronal profiles responsible for impaired precision and reduced reliability in sensory processing. This suggests diminished signal to noise and a loss of inhibitory control on the processing and decoding strategies necessary for precise representations of sensory inputs. In fact, visual cortex neurons of older macaques that were treated with a GABA agonist demonstrated recovered response profiles similar to young monkeys (Leventhal et al., 2003).

The loss of inhibition hypothesis supported by these findings is a feasible explanation for the impaired multisensory processing reported in older adults. While performing an auditory target detection task, older adults demonstrated altered evoked responses consistent with reduced top-down inhibition via frontal areas (Stothart and Kazanina, 2016). In addition, when incongruent visual information was presented with auditory, older adults demonstrated less efficient and more distributed cortical processing to retain perceptual constancy (Stothart and Kazanina, 2016). Older adults also have reduced ability to ignore irrelevant, distracting information, likely due to the reduced signal to noise present in the aging brain (Tun et al., 2002; Van Gerven and Guerreiro, 2016). Indeed, older adults demonstrated poor suppression of visually distracting, task-irrelevant information in a working memory task (Borghini et al., 2018). However, the ability to filter irrelevant visual cues was recovered by the application of alpha *trans*-alternating current stimulation over the parietal lobe indicating that reduced power in the alpha band is related to the poor inhibitory control found in the aging population (Borghini et al., 2018). This is not a surprising finding given the known functional role of top-down inhibitory control reflected by cortical oscillatory activity in the alpha range (7–13 Hz) (Klimesch et al., 2007).

Intact, coordinated alpha activity provides dynamic and specific control of processing in other areas of the brain by (1) controlling the amount of cognitive resources applied to the task at hand and (2) providing discrete temporal windows for processing to occur (Klimesch et al., 2007; Jensen and Mazaheri, 2010; Klimesch, 2012). For instance, feed-forward processing of sensory information is modulated by the phase of alpha activity so that bursts of activity occur during the troughs of the alpha cycle while suppression of active processing occurs at alpha peaks (Bonnefond and Jensen, 2015). Indeed, this sensory gating via inhibition during multisensory tasks is necessary to filter irrelevant sensory information and promote processing in relevant areas (Jensen and Mazaheri, 2010; Keller et al., 2017). Therefore, proper inhibitory control via alpha activity enables robust synchronization of activity between cortical regions most relevant for the present, required function.

Synchronization of oscillations across cortical regions is particularly relevant for multisensory processing as it enables the transfer and integration of information from multiple modalities. One mechanism involved in cross-modal influence is phase resetting where congruent audiovisual signals induce stronger phase coherence and results in faster behavioral response times to a congruent multisensory stimulus compared to an incongruent multisensory cue or single unisensory cues (Keil and Senkowski, 2018). Furthermore, congruent visual-tactile motion as well as temporally aligned audiovisual stimuli induced stronger gamma band (30–70 Hz) power within the respective primary sensory areas, indicative of enhanced low-level processing that is synchronized across these cortical regions (Senkowski et al., 2007; Krebber et al., 2015). These findings are in line with the known function of gamma oscillations in the active, bottom-up processing of low-level inputs.

In addition to enhanced and synchronized gamma power, the involvement of alpha activity regulating this feed-forward processing is also an integral mechanism. A commonly reported coupling between alpha and gamma demonstrates pulsed gating by inhibition induced by alpha activity wherein gamma power is lowest at peaks in the alpha band and highest at troughs in the alpha band (Jensen et al., 2014; Bonnefond and Jensen, 2015). This phase-amplitude coupling (PAC) has helped to explain and predict the percepts associated with the sound-induced flash illusion (SIFI) task where a simultaneous flash and beep is followed close in time by a secondary beep in order to induce the illusory perception of 2 flashes, also known as a fission or double-flash illusion (Shams et al., 2002, 2000). A significant increase in gamma power was observed for illusory versus non-illusory trials within occipital area suggesting that gamma activity reflects the low-level perceptual binding of multisensory stimuli (Bhattacharya et al., 2002). In addition, stronger alpha power further limits the length of the duty-cycle by which gamma activity can function providing an additional way of modulating lower-level processing (Jensen and Mazaheri, 2010). Decreased alpha power was associated with higher probabilities of experiencing the illusion, likely because stronger alpha activity inhibits the bottom-up processing reflected by the gamma band within the occipital area (Cecere et al., 2015; Keil and Senkowski, 2017).

The SIFI is an especially intriguing multisensory illusion as the same physical stimulus can elicit two opposing perceptual states. Therefore, it is an excellent task to parse out differences in cortical processes that drive opposing percepts. In addition, the stimulus onset asynchrony (SOA), or temporal difference, between the simultaneous flash/beep pair and the second beep can elucidate perceptual differences driven by altered temporal sensitivity, as observed in young versus older adults performing the fission SIFI task (McGovern et al., 2014). Most intriguingly, the SIFI task has also distinguished multisensory perceptual differences between older adults with a history of falling compared to those older adults without. For instance, older adults with a history of falling had significantly worse accuracy in perceiving the single veridical flash (versus the illusory 2 flashes) compared to older non-fallers and young adults at SOAs ≥110 ms indicating that multisensory temporal sensitivity was severely impaired in the fall history group (Setti et al., 2011). In a separate study, older adults with and without a history of falling performed the SIFI task while maintaining their posture. Variability in postural sway was significantly worse in older fallers while they performed illusory trials of the SIFI task but not control, congruent trials (Stapleton et al., 2014). Following a 5-week balance intervention program, improved postural stability measures were positively correlated with reduced susceptibility to the SIFI in the fall-history group only (Merriman et al., 2015). Taken together, these findings implicate shared deficits within multisensory and postural systems that are present in older adults prone to a fall.

By measuring cortical oscillations in the alpha and gamma band recorded during the SIFI task, the present study sought to examine inhibitory function during multisensory processing and contrast this function between young adults, older adults with a fall history (FH) and those older adults without a fall history (non-fallers; NF). Presuming a global impairment of top-down control in older adults, we expected reduced multisensory function in perceptual measures across older adults and more severe deficits in the FH group. In addition, we hypothesized reduced alpha power, increased gamma power and diminished alpha-gamma PAC during illusion conditions as a consequence of natural aging. While we proposed a more severe deficit of inhibitory capacity in the FH group, we expected more robust deficiencies in these measures of oscillatory activity and coupling for this group.

MATERIALS AND METHODS

Participants

24 young adults (24.16±3.86 years, 15 males), 24 older adults without any history of falling (non-fallers; NF) (69.93 ±3.50 years, 10 males) and 16 older adults with a recent fall history (FH) (73.20 ±3.28 years, 5 males) participated in this study. A fall history was identified as the individual experiencing at least 1 fall in the 18 months preceding experimentation with a fall defined as “unintentionally coming to rest on the ground or lower level” (Tinetti et al., 1988). The average age of the NF group was significantly lower than that of the FH group [$t(38) = -2.96$, $p < 0.05$].

All participants were screened for normal hearing using AudioScope 3,a screening audiometer (Welch Allyn, Skaneateles Falls, NY, United States), and were required to have a pure tone threshold lower than 40 (for older adults) or 25 (for younger adults) dB for 1 and 2 kHz Hearing Level (HL) in both ears. Participants were asked to declare any uncorrected visual deficits and were excluded if they presented with any visual problem such as cataracts or glaucoma. Other exclusion criteria included history of neurological disorders or disease, seizure disorder, brain injury and use of antipsychotic medications. To account for any vestibular or musculoskeletal problems that could contribute to an individual’s risk of falling, all participants were further screened for any chronic pain, use of pain medications, recent musculoskeletal injuries, or any vestibular disorders. Finally, older adults were required to score ≥26 on the Montreal Cognitive Assessment (MoCA) to control for any potential cognitive decline.

Participants provided signed informed consent before any experimentation and were financially compensated for their time. The experimental protocol was reviewed and approved by the Institutional Review Board at the University of Nevada, Reno.

Stimuli and Equipment

Stimuli were generated using MATLAB (MathWorks, Natick, MA, United States) and Psychtoolbox extensions (Brainard, 1997; Pelli, 1997). The visual stimulus was a stationary white circle with a diameter of 3.5° presented on a grey background in the center of the screen. Auditory stimuli were pure tones of 1,000 Hz created in MATLAB and presented binaurally at 70 dB (measured at the auditory source) via a speaker (Fantech HellScream GS 201, Nepal) directly under the center of the display to approximate the same spatial location as the visual signal. Visual and auditory stimuli were delivered through a Display ++ system with a refresh rate of 120 Hz and an AudioFile stimulus processor, respectively (Cambridge Research Systems, Rochester, United Kingdom). For all experiments, participants sat in front of the display 60 cm away from the screen.

Sound-Induced Flash Illusion (SIFI) Task

There were 3 possible trial types that could be presented throughout the experiment. In congruent trials, either a flash and beep pair were followed by a second, synchronous flash and beep pair (2F2B) (top panel of **Figure 1**) or a single flash-beep

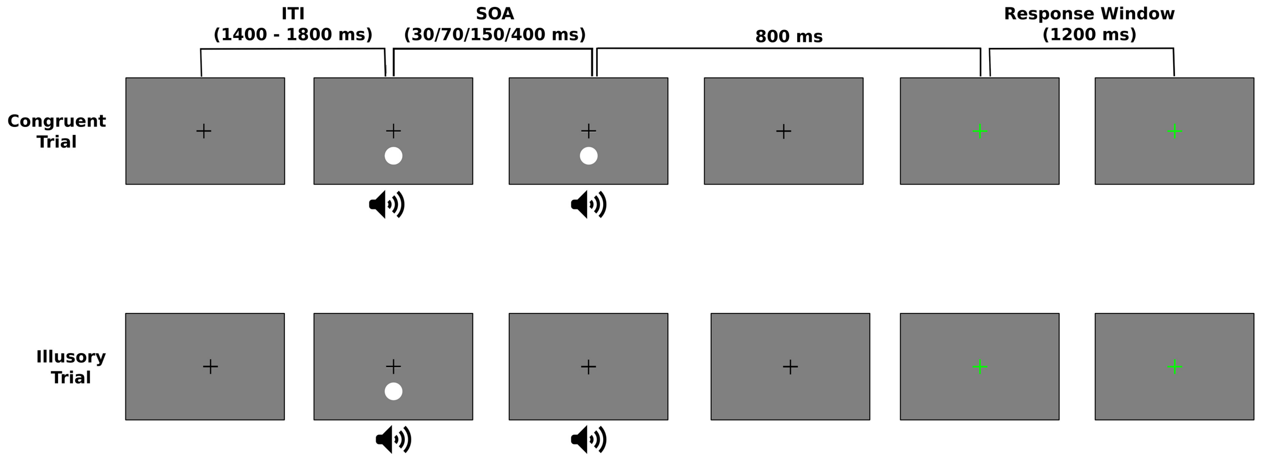

FIGURE 1 | Experimental design of the Sound Induced Flash Illusion (SIFI) task. During a trial, the visual stimulus (white circle) was presented below the fixation cross while the pure tone auditory beep was presented via speakers centered underneath the display. Trials were either a congruent or illusory trial. Congruent trials could either be a single flash-beep pair (1F1B) or two sequential flash-beep pairs (2F2B) that were separated by a variable stimulus onset asynchrony (SOA) (top panel). During the illusory trials, a flash-beep pair was first presented followed by a second auditory beep at some SOA (bottom panel). Regardless of trial type, participants were asked to respond as to how many flashes they perceived during the trial. To prevent motor artifacts, this response was entered 800 ms following the end of the stimulus presentation, indicated by a change in the color of the fixation from black to green. The response window was 1,200 ms and trials were separated by a variably intertrial interval (ITI) between 1,400 and 1,800 ms.

TABLE 1 | Number of participants per group that performed illusory trials for each possible SOA value and were included in the perceptual analysis.

	30 ms	70 ms	150 ms	400 ms
YA	9 (7/5)	4 (2/2)	5 (3/2)	6
NF	5 (5/4)	4 (3/3)	7 (6/5)	8
FH	6 (5/5)	6 (4/3)	2 (2/2)	2

Numbers in parenthesis are the final number of participants in each group included for time-frequency analysis / the final number of participants in each group included for PAC analysis.

pair was presented (1F1B). The 1F1B condition was presented on 30 trials. In the 2F2B condition, the second flash-beep pair was delayed by a variable SOA (30, 70, 150, or 400 ms) with each SOA repeated 30 times. In illusory trials, a flash-beep pair was presented simultaneously followed by a second beep (1F2B) (bottom panel of **Figure 1**). The second beep was delayed by a variable SOA (30, 70, 150, or 400 ms), however, as the temporal limits dictating a person's susceptibility to the illusion can greatly vary (McGovern et al., 2014) and be influenced by the number of SOAs (Chan et al., 2018), each participant was randomly assigned a single, experimental SOA for the 1F2B condition. There were a total of 240 illusory (1F2B) trials. **Table 1** displays the number of participants that performed each of the 4 possible SOA conditions for illusory trials.

Throughout all experimental trials, a central white fixation was present on the screen. The 17 ms visual stimulus was presented at 4.1° below the fixation (see **Figure 1**). The auditory stimulus was a 10 ms 1,000 Hz pure tone presented via speakers centered below the display to approximate the spatial location of the visual stimulus. The experimental trials were separated into 8 experimental blocks and the order of trial type and SOAs (for the 2F2B condition) was randomized. Participants were instructed to wait until the fixation cross turned green before they entered their response to reduce contamination from muscle artifacts (see **Figure 1**). 800 ms following the presentation of the second stimulus in 2F2B or 1F2B trials and of the simultaneous stimulus in 1F1B trials, the fixation turned green for a maximum of a 1,200 ms response window and participants used the number pad on the keyboard to respond as to the number of flashes they perceived during the trial. Trials were separated by an intertrial interval that randomly varied between 1,400 and 1,800 ms.

To ensure participants understood the task and became familiarized with the response procedure and timing, each participant performed a short practice block prior to experimentation that consisted of 9 total trials: 4 illusory, 4 2F2B congruent and 1 1F1B congruent trial. Trial order was randomized, and 2 SOA levels (100 and 500 ms) were used in illusory and 2F2B trials.

Electroencephalography Acquisition and Pre-processing

Participants performed the SIFI task while EEG data were continuously recorded from a Biosemi 128 Channel system. In addition to the standard 10–20 electrode locations, this system included intermediate positions. Default electrode labels were renamed to approximate the more conventional 10–20 system (see **Supplementary Figure 1** in Rossion et al., 2015). 4 additional channels recorded electrooculography (EOG) signals, two channels on the lateral sides of each eye to detect horizontal movement and two channels above and below the right eye to detect vertical movement (e.g., blinks). EEG was sampled at a rate of 512 Hz and processed offline using EEGLAB (v.14_0_0b) and

ERPLAB (v.6.1.3) with MATLAB R2013b (MathWorks, Natick, MA, United States).

Due to the altered experimental design in which participants were randomly presented with only one SOA during the illusory 1F2B condition, some participants did not experience any illusion throughout the experiment and their data was excluded for subsequent analysis. Further, across the older adults who received the 400 ms SOA illusory condition, no individual perceived more than 8 illusion trials. Therefore, the 400 ms was completely excluded from further analysis. A total of 12 datasets from YA group, 14 from NF group and 11 from FH group were retained for subsequent EEG analysis.

EEG data were initially bandpass filtered from 0.5 to 125 Hz with a second order, non-causal Butterworth filter and re-referenced to the common average reference. Channels were identified for rejection using the TrimOutlier plugin (v.0.17) based on a threshold of ±200 μV. Across participants, an average of 1.3 (±2.22) channels were rejected and spherically interpolated. Next, epochs of 2,300 ms, beginning 800 ms before trial onset (defined as onset of the first flash-beep pair), were extracted from continuous data. Epochs corrupted by muscle artifacts were identified by visual inspection and an average of 28.58 (±30.58) trials (<5.7%) were rejected across participants. Blink and eye movement artifacts were corrected in the epoched data using Independent Component Analysis (ICA).

Time-Frequency Analysis

Time-frequency analysis was focused on a region of interest (ROI) based in the occipital area. This ROI was *a priori* selected as it has been implicated for both gamma-mediated processing in the SIFI (Bhattacharya et al., 2002) and alpha activity in occipital sensors has been previously associated with temporal limits of illusory perception (Cecere et al., 2015; Keil and Senkowski, 2017). The occipital ROI was an average of 9 electrodes: PO11, PO1, POO5, POOz, Oz, OIz, POI2, O2, POO6 (McGovern et al., 2014).

Epoched data was categorized into 4 conditions: Illusion trials (illusory 1F2B trials w/2 flash response), non-Illusion trials (illusory 1F2B trials w/1 flash response), 2F2B congruent trials for each of the 4 SOA levels used and 1F1B congruent trials. **Table 2** shows the average number of trials retained for time-frequency analysis for each participant group and presented SOA level. Oscillatory activity was analyzed by convolving the EEG data with a set of complex Morlet wavelets. A total of 35, linearly spaced frequencies were used to create the set of 35 wavelets that ranged from 3 to 90 Hz. The full-width at half-maximum (FWHM) ranged from 42.96 to 652.34 ms with increasing wavelet peak frequency. Subsequent analysis extracted power information from 7 to 14 Hz for the alpha band and from 35 to 70 Hz for the gamma band. Raw amplitudes were decibel (dB) normalized using the average power measured from the −500 to −200 ms pre-stimulus window. **Table 1** displays the number of datasets used in time-frequency analysis for each participant group and illusory SOA.

TABLE 2 | Average number of trials (SD) that survived preprocessing for subsequent time-frequency analysis for each group and illusory SOA level.

	30 ms	70 ms	150 ms
YA	206.57 (27.31)	229.00 (1.41)	222.67 (10.41)
NF	222.20 (8.56)	222.33 (5.03)	224.00 (6.63)
FH	222.83 (5.23)	220.75 (5.74)	220 (0.00)

Phase-Amplitude Coupling (PAC)

A participant's EEG data was selected for PAC analysis if (1) the participant experienced both conditions (illusion and non-illusion) and (2) that participant had a minimum of 10 trials for each condition. This inclusion criteria resulted in a total of 9 YA, 12 NF, and 10 FH datasets. **Table 1** displays the number of datasets for each participant group and illusory SOA used in the PAC analysis. Further, the PAC analysis was focused on a single source, Oz, as this electrode has previously been implicated in coupling between alpha and gamma band (Cecere et al., 2015; Keil and Senkowski, 2017).

Instantaneous phase and amplitude were extracted by convolving the EEG data with complex Morlet wavelets separately for each condition (Samiee and Baillet, 2017; Hirano et al., 2018). A range of linearly spaced frequencies from 7 to 14 Hz and from 34 to 80 Hz were used for phase and amplitude, respectively. To ensure 3 cycles of the lowest phase frequency used, a time window of 36–464 ms, centered around 200 ms post-stimulus (the flash/beep pair), was used within each trial and concatenated across trials. After instantaneous phase and amplitude information was extracted, the PAC values were calculated for each phase-amplitude pair using the following equation:

$$PAC = \left| \frac{1}{n} \sum_{t=1}^{n} a_t e^{i\phi_t} \right|$$

Where t is time point, a is power at time point t, i is the imaginary operator and ϕ is the phase angle at time point t, and n is the total number of timepoints.

Raw PAC values were then converted into z scores using permutation testing. Using the power time series, within each trial, a time point based on the time window of interest was pseudo-randomly chosen as the point to cut the data. This time point was constrained so that at least 45 ms preceded and at most 385 ms followed it. The original second half of the data was then shifted to the front and the original first half of the data was placed after it. A new, permuted PAC value was then computed between this new, shuffled power time series and the original phase time series. A total of 1,500 iterations were performed to create a sampling distribution and a z-score was created using the mean and SE of this sampling distribution.

Alpha Phase-Locked Power Spectra

In order to differentiate and characterize the results from our initial PAC analysis, we followed an approach from Bonnefond and Jensen (2015) and aligned time-frequency representations of low-frequency gamma band (30–60 Hz) to peaks of 10.5 Hz alpha activity. This particular alpha frequency was chosen as it represented the median frequency in the alpha range showing robust coupling with amplitude of the gamma range (as discovered in the PAC analysis). For each epoch, we convolved the fast Fourier transform of EEG data with that of a complex Morlet wavelet defined by the 10.5 Hz alpha phase frequency. Phase values were extracted from a 300 ms time window centered around 200 ms post-stimulus (the flash/beep pair), this ensured 3 cycles of alpha activity. Separately, power values were estimated using the same approach but with complex Morlet wavelets defined using linearly spaced frequencies from 30 to 60 Hz. Then, peaks of the 10.5 Hz activity were detected by ensuring each peak was surrounded by troughs and corresponding timepoints of the peaks were identified. Time-frequency representations were subsequently re-aligned to be phase-locked with the peak of the cycle. This alignment occurred for epochs that we could extract a full cycle of alpha activity before and after each peak. Power values were then averaged across epochs within the illusion and non-illusion trials for each subject and converted to relative power change with respect to the average activity across the pre-defined time window. These individual time-frequency representations were then used to estimate the alpha phase-locked group average power spectrum of the low-gamma band.

Perceptual Analysis

To determine the strength of the fission, SIFI illusion, the difference between the accuracy of illusion trials (1F2B) and the accuracy of 1F1B congruent trials was calculated for each individual (Narinesingh et al., 2017). This was done across all participants, including those whose data was excluded for EEG analysis. In addition, accuracy of determining 2 flashes in the 2F2B congruent trials were computed for each SOA value across all participants.

Statistical Analysis

Mixed ANOVAs were performed to determine effects of group and SOA on illusion rate from the SIFI experiment. To determine statistical differences in alpha and gamma power, an initial, group-level time-frequency window was created. Specifically, a time-frequency plot was created by averaging across all subjects and all conditions. This plot was then visually inspected, and 2 separate time-frequency windows were identified to extract gamma and alpha power. At this group level, the temporal boundaries were 0–120 ms and 30–300 ms while the frequency boundaries were 30–60 Hz and 6–14 Hz for the gamma and alpha bands, respectively (**Figure 2**). Using these group-averaged constraints, individual time-frequency windows were then created for each subject using their time-frequency plots created by averaging across all conditions (**Figure 2**).

Subject-specific time-frequency windows were used to estimate gamma and alpha power for illusion and non-illusion trials. For each individual, all time-frequency points were averaged within the previously defined, subject-specific gamma and alpha time-frequency windows so that a gamma and an alpha estimate were extracted for each condition for each individual. These values were then used in subsequent mixed ANOVAs and follow up *t*-tests with multiple comparison corrections to determine differences between illusion and non-illusion conditions and between groups. In addition, △ alpha (△ alpha = $\text{Illusion}_{\text{Alpha}}$ – $\text{NonIllusion}_{\text{Alpha}}$) and △ gamma (△ gamma = $\text{Illusion}_{\text{Gamma}}$ – $\text{NonIllusion}_{\text{Gamma}}$) values were quantified and used in an ANOVA with *post hoc* tests to understand the effect of group on the difference in alpha/gamma power between illusion and non-illusion trials. Because there were significant effects of group across all illusory SOA levels, illusory trials were combined within each group for statistical analysis. This statistical approach provides a non-biased, hypothesis-driven approach to determine the temporal and frequency range of interest at the group level while allowing for a wider range of frequencies across subjects, as is commonly observed in young versus older adults in the alpha range (Grandy et al., 2013). The subject-specific time-frequency windows increases sensitivity and accounts for individual differences across peak frequencies (Cohen, 2014).

In order to account for the lack of independence, avoid circular inference, and solve the issue of multiple comparisons, we followed a statistical approach similar to Hirano et al. (2018). We initially identified clusters of interest using unrestricted permutation mixed ANOVAs using the between-subjects factor, group (YA; NF; FH), and the within-subjects factor condition (Illusion; No Illusion) applied to PACz maps pooled across groups and conditions for 1,000 permutations (Manly, 2007). The estimated alpha value was the proportion of permuted *F* values that exceeded the original F statistic and clusters were defined using a threshold of $p < 0.05$ with *p* values adjusted by the positive False Discovery Rate (FDR) using the method outlined by Hirano et al. (2018).

Pearson correlations with a Bonferroni corrected alpha value of 0.005 (0.05/10) were conducted to examine the relationships between illusory strength and EEG measures (△ alpha, △ gamma, PACz) using R statistical software.

RESULTS

A two-way ANOVA was conducted on the perceptual data extracted from the SIFI EEG experiment (shown in **Figure 3**) to assess the significance of group and SOA on illusory strength. There was a significant effect of both group [$F(2,183) = 11.98$, $p < 0.001$] and SOA [$F(2,183) = 4.52$, $p = 0.012$] but no significant interaction [$F(4,183) = 1.57$, $p = 0.18$]. A *post hoc* Tukey HSD test showed that FH group had significantly greater illusion rates than both YA and NF (both adjusted $p < 0.05$) and NF had significantly greater illusion rates than YA (adjusted $p = 0.037$). A separate Tukey HSD test revealed significantly stronger illusion rates at the 70 ms SOA relative to the 150 ms SOA (adjusted $p = 0.016$) but illusory strength was not significantly different between 70 and 30 ms SOAs (adjusted $p = 0.06$) or between 150 and 30 ms SOAs (adjusted $p = 0.74$).

In addition, we examined participant's accuracy during 2F2B congruent trials (**Figure 4**). A mixed ANOVA was performed and revealed a significant effect of both group [$F(2,60) = 5.13$, $p = 0.009$] and SOA [$F(2,120) = 54.13$, $p < 0.001$] but no significant interaction [$F(4,120) = 1.62$, $p = 0.17$]. A *post hoc* Tukey HSD test revealed that there was no difference in accuracy

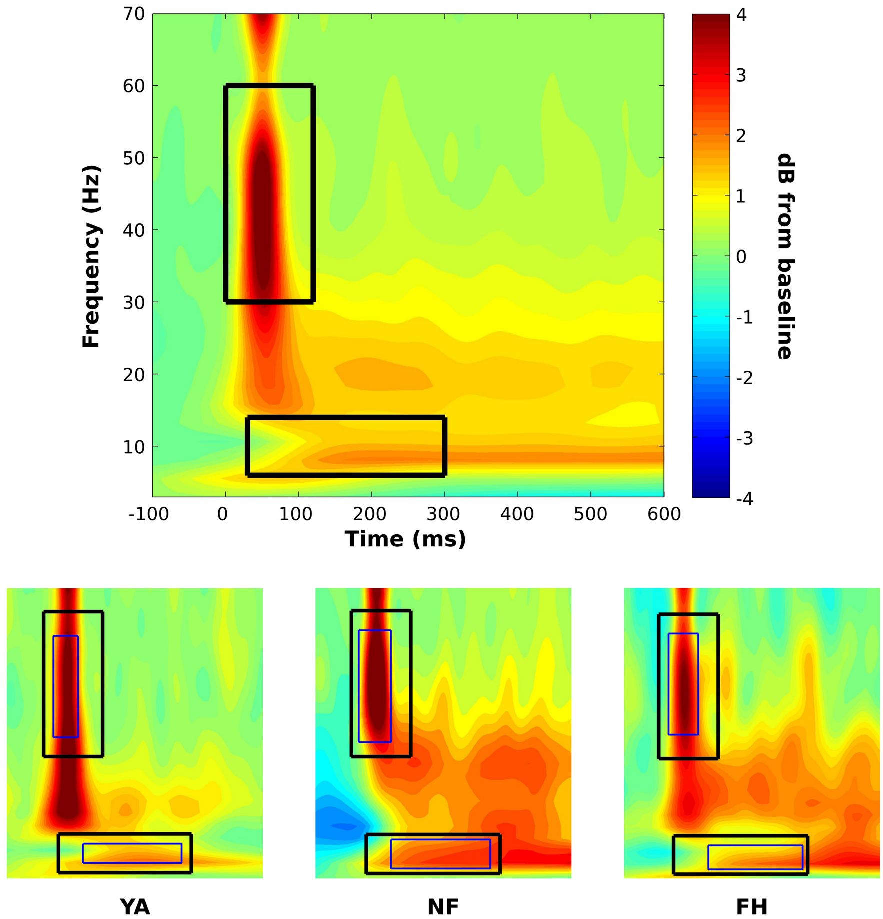

FIGURE 2 | Time-frequency windows for statistical analysis on power spectra. A time-frequency plot that was constructed across groups and conditions (top panel) was visually inspected to identify initial time-frequency windows to extract average alpha (lower box) and gamma power (higher box). Using these pre-defined constraints, subject specific time-frequency windows (bottom panel; thin box within group-defined box) were identified for alpha and gamma using time-frequency plots that were averaged across conditions within each subject. Representative subject-specific time-frequency windows are displayed on time-frequency plots of the respective YA (bottom panel, left plot), NF (bottom panel, middle plot), and FH (bottom panel, right plot) participants. Power values are displayed in dB.

between the NF group and the YA or the FH group (both adjusted $p > 0.06$) while the FH group did have significantly worse accuracy than the YA group (adjusted $p < 0.001$). Another *post hoc* Tukey HSD test showed that at both the 70 and 150 ms SOAs, accuracy was significantly better than the 30 ms SOA (both adjusted $p < 0.001$) while there was no significant difference in accuracy between the 70 and 150 ms SOAs (adjusted $p = 0.10$).

Next, we wanted to examine differences in alpha and gamma power between illusion and non-illusion trials (combined across SOAs) while participants performed the 1F2B illusion trials in the SIFI task. Time-frequency plots are shown in **Figure 5** for each group and condition combined across SOA levels (**Supplementary Figures 1–3** show time-frequency plots for each group and condition segregated by SOA level). Within occipital ROI, a mixed ANOVA was performed to examine the effect of group and condition (illusion versus non-illusion) on alpha power. There was a significant effect of group [$F(2,34) = 180.7$, $p < 0.001$] but not condition [$F(1,34) = 0.04$, $p = 0.85$] as well as a significant interaction [$F(2,34) = 54.17$, $p < 0.001$]. *Post hoc* *t*-tests with multiple comparisons (0.05/3 = 0.0167) were performed to examine the difference between condition within each group. There was no significant difference between conditions for YA adults [$t(22) = 2.12$, *uncorrected* $p = 0.05$] or for FH group [$t(20) = 0.50$, *uncorrected* $p = 0.62$] while NF group had significantly reduced alpha in illusion versus non-illusion conditions [$t(26) = 10.50$, *uncorrected* $p < 0.001$]. To further understand the significant interaction, we calculated the difference in alpha power between illusion and non-illusion trials ($\triangle$ alpha = $\text{Illusion}_{\text{Alpha}} - \text{NonIllusion}_{\text{Alpha}}$) for each individual and then conducted an ANOVA with a *post hoc* Tukey HSD test to understand the effect of group on this difference in alpha power. NF group had a significantly larger $\triangle$ alpha compared to YA (adjusted $p < 0.001$) and compared to FH group (adjusted $p < 0.001$) but there was no difference in $\triangle$ alpha between FH and YA (adjusted $p = 0.66$).

A similar analysis conducted for the gamma band demonstrated a significant effect of group [$F(2,34) = 223.3$, $p < 0.001$], of condition [$F(1,34) = 6.96$, $p = 0.013$], and a

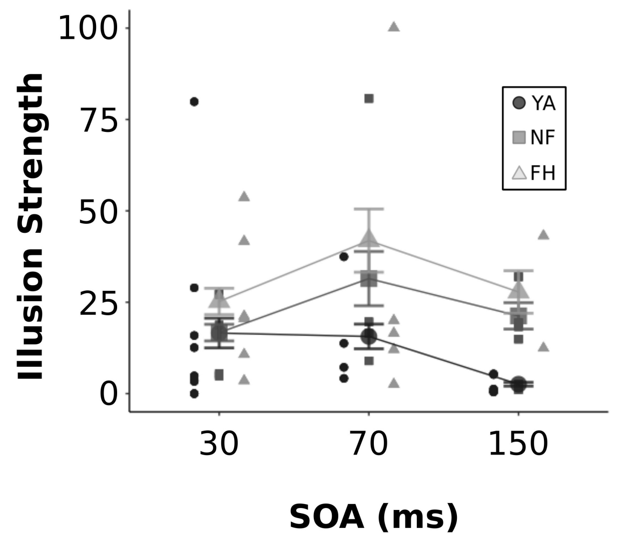

FIGURE 3 | Illusion strength across SOA levels. Individual and group-averaged estimates of illusion strength are displayed for each SOA value. YA adults are represented by black circles, NF by dark gray squares, FH by light gray triangles. Error bars reflect standard error.

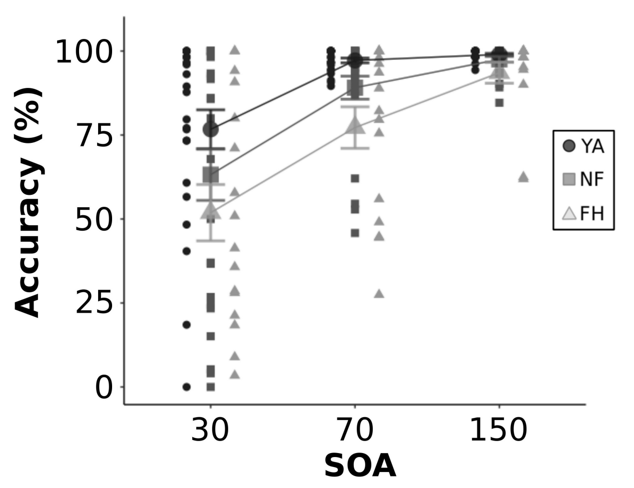

FIGURE 4 | Accuracy during 2F2B congruent trials. Individual and group-averaged values for perceptual accuracy in discriminating 2 veridical flashes during congruent trials are displayed for each SOA level. YA adults are represented by black circles, NF by dark gray squares, FH by light gray triangles. Error bars reflect standard error.

significant interaction [$F(1,34) = 1479.24$, $p < 0.001$]. Further t-tests adjusted for multiple comparisons revealed that the condition type did not induce significant differences in gamma power within YA [$t(22) = 1.87$, *uncorrected* $p = 0.08$] or NF group [$t(26) = -2.2$, *uncorrected* $p = 0.04$]. However, in FH group gamma power was significantly enhanced in illusory compared to non-illusory trials [$t(20) = 6.22$, *uncorrected* $p < 0.001$]. Again, we computed the difference in gamma power by subtracting non-illusion from illusion trials (△ gamma) for each individual and ran an ANOVA to examine the effect of group. The *post hoc* Tukey HSD test revealed that FH had a significantly larger △ gamma than NF and YA and that NF had a significantly larger △ gamma than YA (all adjusted $p < 0.001$).

Next, we examined the effect of trial type (illusory vs. non-illusory) and group on PACz. **Figure 6** displays the PACz plots for each group (columns) across the non-illusion (top row) and illusion (bottom row) conditions. Significant clusters on these plots (shown in **Figure 7**) were identified by F values that exceeded those F values obtained from permutation ANOVAS (reported below) and had FDR-adjusted p values that passed a 0.05 threshold (see section "Materials and Methods"; Hirano et al., 2018). However, only the statistical map displaying the interaction [all $F(2,28) > 3.43$, all $p < 0.047$] is shown as the main effects of group and condition were not significant. As expected from the group PACz maps (**Figure 6**), this significant interaction occurred in Cluster 1 spanning a phase frequency between 8 and 10 Hz and an amplitude frequency between 40 and 46 Hz; Cluster 2 spanning a phase frequency between 10 and 12 Hz and an amplitude frequency between 42 and 48 Hz; Cluster 3 with a phase frequency ranging from 11 to 13 Hz and an amplitude frequency from 46 to 52 Hz; Cluster 4 with a phase frequency between 9 and 12 Hz and an amplitude frequency between 42 and 56 Hz. However, no statistically significant simple effects survived in follow up one-way ANOVAs that examined the effect of group on mean PACz in both non-illusion [all $F(2,28) \leq 2.23$, all $p > 0.13$] and illusion conditions [all $F(2,28) \leq 0.76$, all $p > 0.48$].

To characterize the PAC within these clusters, time-frequency representations of the low-gamma band was aligned to the peaks of 10.5 Hz alpha activity. **Figure 8** depicts the power spectra from the non-illusion condition (top row) and illusion condition (bottom row) aligned to the peaks of the alpha cycle (depicted in the middle row) in YA (left column), NF (middle column), and FH (right column). As is most evident in the YA group, bursts of gamma activity were aligned to troughs of the alpha band ($\sim \pm$ 50 ms) during non-illusion trials but to peaks of the alpha band ($\sim$ 0 ms) during illusion trials. While the NF group demonstrates an equivalent pattern in both conditions, there is also gamma activity present during peak alpha activity in non-illusion trials ($\sim$ 0 ms). Finally, the FH group doesn't show substantial patterns of gamma activity during non-illusion conditions and altered pattern of gamma activity during illusion conditions with a burst around the alpha peak ($\sim$0 ms) and at the alpha troughs ($\sim \pm$ 50 ms).

Finally, we investigated the correlations between the various electrophysiological measures (△ gamma, △ alpha, PACz) and the perceptual measure of illusion strength. In addition, we examined any correlation between age and these different variables. Although not significant at the Bonferroni corrected alpha value of 0.005 (0.05/10), weak relationships were found between illusion strength and PACz ($r = -0.28$, uncorrected $p = 0.12$) and between illusion strength and age ($r = 0.33$, uncorrected $p = 0.02$). There were not significant correlations between illusion strength and △ alpha ($r = 0.15$, uncorrected $p = 0.39$), between illusion strength and △ gamma ($r = 0.01$, uncorrected $p = 0.94$), between age and △ gamma ($r = -0.09$,

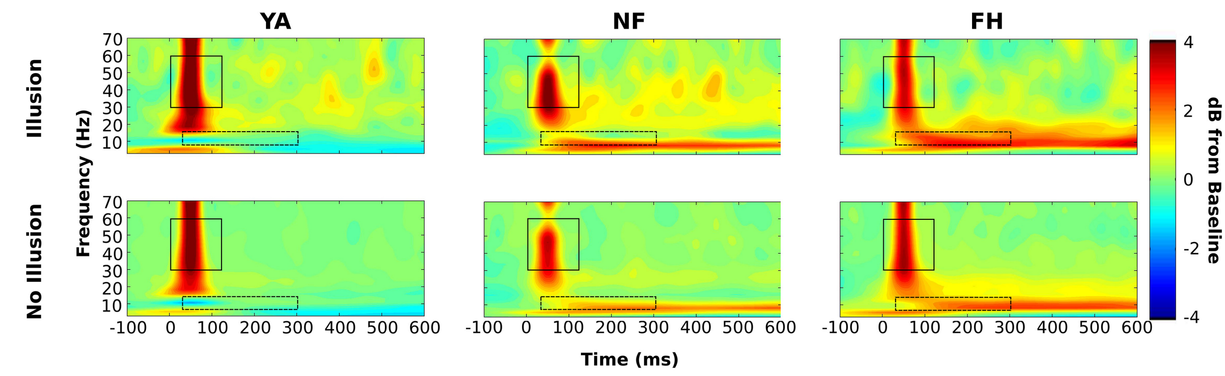

FIGURE 5 | Time-frequency plots combined across SOA type. Group-averaged time-frequency representations are displayed for illusion (top row) and no illusion (bottom row) conditions combined across the 30, 70, and 150 ms SOA levels. Timepoint 0 ms represents the onset of the flash-beep pair and power spectra are displayed as the decibel (dB) change from the average –500 to –200 baseline period. Group level time frequency windows are shown for gamma (solid boxes) and alpha (dashed boxes). Power values are displayed in dB.

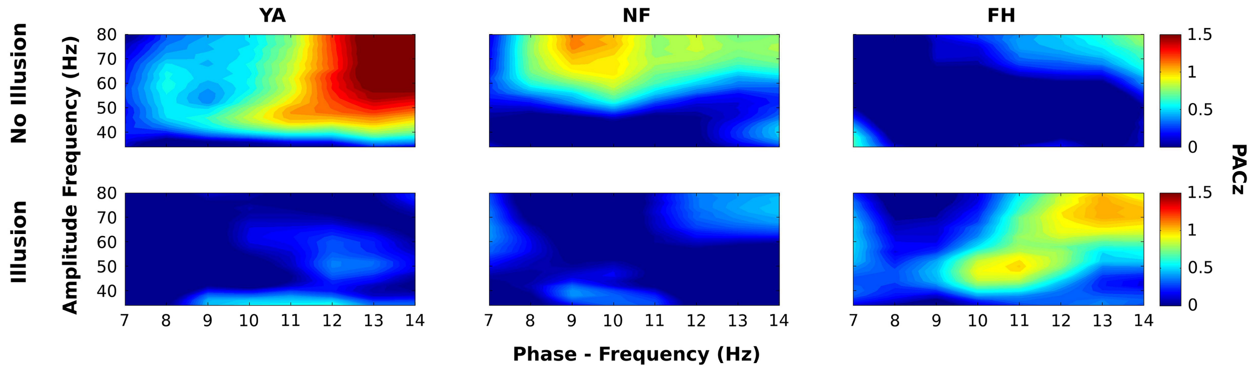

FIGURE 6 | Group average maps of phase-amplitude coupling (PAC) within electrode Oz. Average PAC z scores across groups (YA: left column; NF: middle column; FH: right column) are displayed for each phase-amplitude pair during non-illusion (top row) and illusion (bottom row) conditions. For all maps, the phase frequency (7–14 Hz) is displayed along the *x*-axis while the amplitude frequency (30–80 Hz) is displayed along the *y*-axis.

uncorrected $p = 0.61$) or between age and △ alpha ($r = 0.38$, uncorrected $p = 0.02$). The full correlation matrix is reported in **Table 3**.

DISCUSSION

The purpose of this study was to examine differences in multisensory processing between YA, NF, and FH adults at both the perceptual and cortical levels. Prior studies have shown more severe impairments to multisensory temporal perception in older adults with a history of falls (Setti et al., 2011; Stapleton et al., 2014; Merriman et al., 2015) suggesting that more global cognitive deficits increasing an older individual's susceptibility to a fall may also result in the deficits associated with multisensory processing. Using a combination of perceptual and EEG measures, the current findings help parse the specific differences in cortical processing during multisensory stimulation between the three groups.

Previous findings reporting more robust multisensory deficits in older adults with a fall history have used the SIFI task wherein increased susceptibility to the illusion reflects reduced precision in multisensory temporal perception. In line with prior findings, the current study found significant increases in illusion strength for the FH group compared to the YA and NF group and increased illusion strength for NF relative to YA group (McGovern et al., 2014; Stapleton et al., 2014; Merriman et al., 2015). It has been well established that natural aging results in reduced temporal precision and enhanced susceptibility to multisensory illusions (Setti et al., 2011; McGovern et al., 2014; Bedard and Barnett-Cowan, 2016; Baum and Stevenson, 2017; Scurry et al., 2019a,b). The present results show an exacerbated deficit in FH group, similar to prior findings (Setti et al., 2011; Merriman et al., 2015), possibly due to an altered ability of effective management of cortical resources during ambiguous or challenging information processing. Indeed, older fallers show significantly worse postural control than non-fallers when performing a challenging cognitive task while maintaining posture (Piirtola and Era, 2006; Stapleton et al., 2014). The

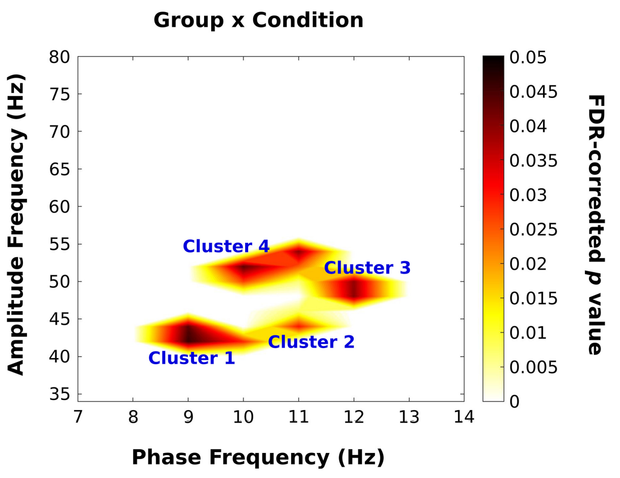

FIGURE 7 | Results of permutation ANOVA analysis on PACz scores. A *p* value map with false discovery rate (FDR) corrected *ps* is displayed for the group × condition interaction. Any *p* value greater than 0.05 was converted to zero. There were 4 alpha/low-gamma clusters that revealed a significant interaction between group and condition. The main effects of group and condition did not retain any significant coupling following statistical analysis and are thus excluded.

increased illusion strength in FH may be due to central deficits in employing cognitive resources during the more difficult and conflicting illusory trials. In addition, degraded unisensory information is a normal consequence of the natural aging process leading to sensory reweighting (Ostroff et al., 2003; Humes et al., 2009; Werner et al., 2010; Alberts et al., 2019). This is enhanced in older adults prone to falls, often manifesting in greater reliance on visual cues (Jeka et al., 2010), which in the case of the SIFI may contribute to conflicting perceptual information and greater illusion susceptibility.

The FH group, but not NF, had significantly worse accuracy than YA in the congruent 2F2B trials. Along with sensory reweighting, differences in multisensory processing strategies may contribute to the impaired performance of FH. To compensate for age-related unisensory decline, older adults more heavily weight prior perceptual information in their predictive coding strategy, contributing to their increased illusion rate (Chan et al., 2021). This enhanced reliability on prior information is also seen in stronger rapid audiovisual recalibration effects in older compared to young adults, where the perception of audiovisual synchrony in a current trial is influenced by the temporal alignment of the preceding trial (Noel et al., 2016). As age-related declines in unisensory processing is enhanced in older fallers (Horak, 2006; Manor et al., 2010), it is plausible that FH group not only reweights sensory information but also relies more heavily on these internal perceptual templates leading to greater illusion rates. Future investigation of beta activity, thought to reflect predictive cortical processing (Bastos et al., 2012; Chan et al., 2021) may help pinpoint the contribution of perceptual priors in NF and FH groups processing and perception of the illusion versus non-illusion.

The current design used a single SOA for illusory trials but multiple SOAs for congruent trials. Recently, Chan et al. (2018) showed that both young and older adults perceived greater illusions with a reduced number of SOAs (3) compared to a larger number of SOAs (5). Presumably, more SOA levels provide additional information allowing for a more informed prediction strategy by the participant. Therefore, the single SOA used in the illusory trials may have affected illusion susceptibility across groups. Future studies manipulating this factor would be needed to understand this particular influence on FH versus NF and YA. Finally, a consistent and smaller step size in SOAs may allow for a better understanding of the temporal flexibility for the illusion in these different participant groups. For instance, prior studies show enhanced illusion susceptibility in older fallers at longer SOAs (110–270 ms w/40 ms step size) but not at shorter SOAs (30 and 70 ms) compared to older non-fallers and young adults (Setti et al., 2011). Setting the illusory SOA at the individual's SIFI temporal threshold may be a more fruitful approach in future experiments to understand the temporal limits and the cortical mechanisms driving illusory vs. non-illusory percepts. This would also address the current limitation of having a small number of participants at the various illusory SOA levels by enhancing the statistical robustness of between group comparisons. In addition, this would reduce the likelihood of floor or ceiling performance by participants, a possible occurrence in the present study (i.e., some young adults had 0% susceptibility at 30 and 150 ms SOAs – see **Figure 3**).

In addition to altered illusory strength between groups, some interesting differences in gamma and alpha power within the current ROI were observed at the cortical level when contrasting illusion with non-illusion conditions. In the NF group only, alpha power was greater in non-illusion versus illusion trials and this △ alpha was significantly larger compared to FH and YA. However, when examining differences in gamma power, only the FH group demonstrated significantly greater gamma amplitude in the illusion compared to the non-illusion trials and this △ gamma was significantly larger compared to NF and YA, in line with our hypothesis.

In the young adults, the lack of any difference between illusory and non-illusory conditions in alpha and gamma power suggests they don't require inhibitory control via alpha power modulating gamma power to detect the veridical single flash. More specifically, the low-level sensory processing, reflected in the gamma band, is dictated by temporal sensitivity and the population tuning profiles of early sensory areas (Meredith and Stein, 1983; Kayser et al., 2008; Schormans et al., 2017a). Therefore, young adults that demonstrate precise temporal sensitivity will process the physical visual signals accurately, without the need to filter or regulate this bottom up processing by higher-order controls, reflected in alpha activity (Bonnefond and Jensen, 2015).

In contrast, as shown in **Figure 5**, the NF group had a different pattern of gamma and alpha activity. The decreased alpha in illusion compared to non-illusion trials may indicate a faulty top-down mechanism that would lead to the enhanced illusion strength found in NF relative to YA. Increased gamma power with reduced alpha power has been specifically linked to the

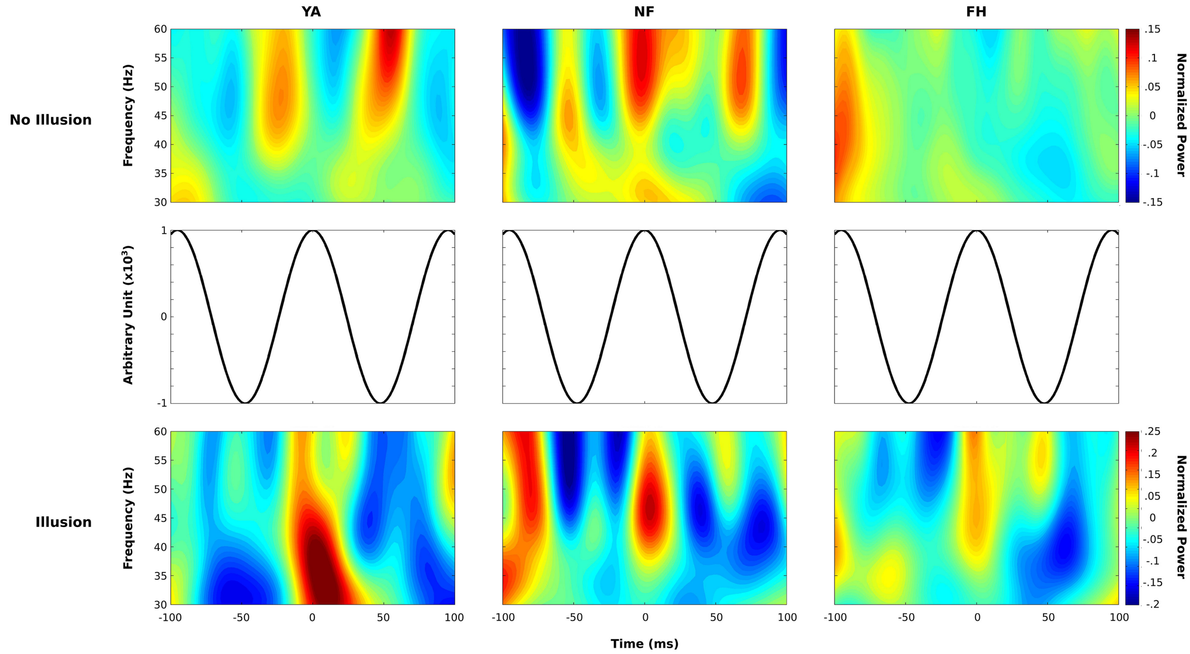

FIGURE 8 | Phase-locked power spectrum of the gamma band. Normalized time-frequency maps are displayed for non-illusion (top row) and illusion (bottom row) conditions within each group (YA: left column; NF: middle column; FH: right column). Power estimates in the low gamma range were extracted within a 200 ms time window time-locked to the peak of 10. 5 Hz alpha activity (middle row) and averaged over epochs. This methodology revealed bursts of gamma activity coupled to the troughs of alpha activity during no-illusion conditions in YA and NF group. Power values are displayed in dB.

TABLE 3 | Pearson r and associated uncorrected *p* values (in parentheses) from correlations between illusory strength and EEG measures (△ Alpha, △ Gamma, PACz) and age.

	Illusory strength	△ Alpha	△ Gamma	PACz	Age
Illusory strength	1.00	0.145 (.39)	0.013 (.94)	−0.282 (0.12)	0.33 (0.02)
△ Alpha		1.00	0.813 (<0.001)	−0.127 (0.50)	−0.38 (0.02)
△ Gamma			1.00	0.091 (0.63)	−0.09 (0.61)
PACz				1.00	0.11 (0.56)
Age					1.00

SIFI percept, presumably reflecting an increased readiness to integrate signals without proper top-down influence of signal processing (Bhattacharya et al., 2002; Cecere et al., 2015; for review see Keil, 2020). While there is a visible pattern of increased gamma activity for illusion compared to non-illusion (middle panel of **Figure 5**), this wasn't significant limiting the current interpretation. Future studies that increase sample size, particularly for the PAC analysis, would be needed to identify any relationship between PACz and illusory strength and strengthen this interpretation. An increased sample size would also allow these correlations to be done separately within each group, possibly identifying a PACz-illusory strength relationship in some but not all groups furthering our understanding of this top-down control over SIFI percepts.

Finally, in the FH group, the significant increase in gamma power for illusion compared to non-illusion trials without concomitant modification in alpha power suggests a likely mechanism driving the increased susceptibility in this population. Enhanced low-level processing (i.e., increased gamma) of the sensory information without specific regulation by top-down processes (i.e., no change in alpha) would certainly lead to an illusory percept (Bhattacharya et al., 2002; Cecere et al., 2015; Keil and Senkowski, 2017). Synchronization of gamma activity across multiple networks increases feature integration and induces congruent multisensory percepts (Yuval-Greenberg and Deouell, 2007; Senkowski et al., 2008; Keil and Senkowski, 2018). Enhanced low-level sensory processing is consistent with what is known of neuronal responsiveness in sensory regions of aged animal models. For instance, the level of spontaneous activity is increased in the primary and secondary visual and auditory regions of aged animal cortices while tuning bandwidths become wider (Schmolesky et al., 2000; Leventhal et al., 2003; Fu et al., 2010; Gray et al., 2013; Ng and Recanzone, 2018). Therefore, the precision of bottom-up processing gets attenuated and top-down mechanisms would be required to filter out irrelevant sensory information from these initial processing stages. It should be noted that while typically alpha activity reflects top-down processes, as discussed, it can also represent bottom-up processing when generated from occipital region and feeding-forward to frontal areas (Wang et al., 2016). Therefore, the current interpretations based on changes in alpha power should be taken with some caution.

In addition, in the rat model of adult-onset hearing loss, firing rates were retained within multisensory and unisensory cortices, while the proportion of multisensory neurons decreased in the multisensory area but increased in primary auditory cortex (Schormans et al., 2017b). Therefore, it is likely that as age-related deterioration of sensory systems occurs, compensation ensues by altering the responsiveness of neurons in earlier, low-level stages of sensory processing. This theoretical framework would suggest that in the healthy older adult group (NF), increased alpha power is used to adjust for reductions in sensory processing precision. However, absence of such recruitment and increased low-level processing in the FH group suggests that this population suffers from global deficits in top-down control mechanisms enabling precision throughout the various functional, cognitive networks. In other words, FH group may suffer from deficits in top-down functionality (i.e., alpha activity) which is necessary to compensate for noisier and imprecise bottom-up processing (i.e., gamma activity).

Along with changes in the strength of oscillatory activity, coupling between lower frequency alpha and the higher frequency gamma has previously been shown to control sensory processing via "gating by inhibition" (Bonnefond and Jensen, 2015, 2013). As observed in **Figure 6**, YA and NF groups show an absence of PAC during illusion trials with more robust PAC in non-illusion trials. Presumably, sensory gating was present in YA (and to a lesser extent in NF) leading to a more accurate perception of the single, veridical flash. Curiously, the FH group shows weak PAC during illusion trials and a near absence during non-illusion trials, possibly contributing to the significantly worse accuracy during congruent trials.

Follow up analysis that aligned gamma power to peaks of alpha activity confirm that weak or absent PAC confers illusion susceptibility. In non-illusion trials, the bursts of gamma activity during troughs of the alpha cycle were clearly defined in the YA group while the NF group also exhibited gamma activity during the alpha peaks (**Figure 8**) suggesting a reduced, albeit relatively intact, capacity of sensory gating in this group. As preferred phase can influence the strength of PAC (Bonnefond and Jensen, 2015), the wider spread of gamma activity in NF (**Figure 8**) could help explain the weaker PAC found in this group (**Figure 6**). Regardless, the distinct shift in timing of gamma activity found in illusion compared to non-illusion trials in the YA groups suggests that gating by inhibition is a necessary mechanism that promotes veridical perception in young adults.

Indeed the alpha-phase locked power spectra analysis revealed that during the illusion percept, all three groups demonstrated gamma activity at peaks of the alpha cycle. This is expected as absence of sensory gating via the alpha band would lead to increased low-level sensory processing and subsequent perception of an illusory second flash. Interestingly, the FH group also showed some gamma activity during the troughs of the alpha cycle during the illusion condition which likely explain the PAC observed in this group, and not in YA or NF, during illusory trials (see **Figure 6**). However, the stronger increase in gamma activity found at the peak of the alpha cycle, and common across all three groups, likely drove the illusory percept. Overall, there appears to be a reduced capacity to effectively suppress processing of irrelevant or less reliable sensory information by the FH individuals as there was no robust pattern in PAC from illusion relative to non-illusion trials, unlike the clear distinctions found in the NF and YA groups.

The presented findings suggest that while perceptual measures of multisensory temporal processing are relatively intact in the FH group compared to NF, robust differences are present in the cortical processing driving these perceptual estimates. The increased gamma power in illusion trials for the FH group without any difference in alpha power in non-illusion trials implicate increased likelihood of multisensory integration, and thus the illusion, without proper top-down regulation of this bottom-up process. In contrast, the healthy NF group demonstrated increased alpha power in non-illusion compared to illusion trials indicative of more robust top-down gating on sensory processing enabling more precise and accurate perceptual representations. In addition, sensory gating by inhibition appears to be generally affected by the aging process as the NF group also exhibited weaker PAC and decreased suppression of gamma activity during peaks of the alpha cycle as compared to YA. Reduced PAC between alpha phase and gamma amplitude in non-illusion trials for the FH group suggest that top-down control of sensory processing is significantly impaired.

These various interpretations do need to be taken with some caution. Increasing the number of participants in the FH group to attain a balanced design would increase the statistical power and would likely improve the robustness of these preliminary findings. Further, the current experimental design that randomly assigned participants to a single SOA for illusory trials but multiple SOAs for congruent trials may have affected participant's performance, as previously discussed. Future experiments can address these design issues and further examine how the number of SOAs and step-size of SOA may differentially affect FH from NF and YA groups. In addition, the potential contribution of predictive coding strategies may further explain the present results. Examining beta activity may show group differences and relationships with illusory rate confirming the proposed hypothesis of increased reliance on perceptual priors in FH and NF. Final limitations worth noting address the time-frequency and PAC analytical methods. The selection of group-level time-frequency windows could have induced experimenter bias and may benefit from future analyses that conduct random field test of time-frequency windows (Kilner et al., 2005). While wavelet transformation prior to extracting phase and amplitude is a common approach and shows enhanced PAC performance relative to other filtering methods (Caiola et al., 2019), bandpass filtering the data (i.e., wavelet transformations) can induce spurious phase-amplitude coupling and alternative methods may be useful in identifying PAC (Aru et al., 2015; Hülsemann et al., 2019; Munia and Aviyente, 2019). Nevertheless, the present results provide preliminary support for our hypothesis of a more drastic reduction in sensory gating via top-down inhibitory mechanisms in older adults with a history of falls.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board at the University of Nevada, Reno. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AS and FJ designed the experiment. AS, ZL, and DL collected the data. AS performed data and statistical analysis with assistance on approach and interpretation from ZL, DL, and FJ. AS wrote the manuscript. FJ critically evaluated the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

Alberts, B. B. G. T., Selen, L. P. J., and Medendorp, W. P. (2019). Age-related reweighting of visual and vestibular cues for vertical perception. *J. Neurophysiol.* 121, 1279–1288. doi: 10.1152/jn.00481.2018

Allison, T., Hume, A. L., Wood, C. C., and Goff, W. R. (1984). Developmental and aging changes in somatosensory, auditory and visual evoked potentials. *Electroencephalogr. Clin. Neurophysiol.* 58, 14–24. doi: 10.1016/0013-4694(84)90196-2

Aru, J., Aru, J., Priesemann, V., Wibral, M., Lana, L., Pipa, G., et al. (2015). Untangling cross-frequency coupling in neuroscience. *Curr. Opin. Neurobiol.* 31, 51–61. doi: 10.1016/j.conb.2014.08.002

Bastos, A. M., Usrey, W. M., Adams, R. A., Mangun, G. R., Fries, P., and Friston, K. J. (2012). Canonical microcircuits for predictive coding. *Neuron* 76, 695–711. doi: 10.1016/j.neuron.2012.10.038

Baum, S. H., and Stevenson, R. A. (2017). Shifts in audiovisual processing in healthy aging. *Curr. Behav. Neurosci. Rep.* 4, 198–208. doi: 10.1007/s40473-017-0124-7

Bedard, G., and Barnett-Cowan, M. (2016). Impaired timing of audiovisual events in the elderly. *Exp. Brain Res.* 234, 331–340. doi: 10.1007/s00221-015-4466-7

Bhattacharya, J., Shams, L., and Shimojo, S. (2002). Sound-induced illusory flash perception: role of gamma band responses. *Neuroreport* 13, 1727–1730. doi: 10.1097/00001756-200210070-00007

Bonnefond, M., and Jensen, O. (2013). The role of gamma and alpha oscillations for blocking out distraction. *Commun. Integr. Biol.* 6:e22702. doi: 10.4161/cib.22702

Bonnefond, M., and Jensen, O. (2015). Gamma activity coupled to alpha phase as a mechanism for top-down controlled gating. *PLoS One* 10:e0128667. doi: 10.1371/journal.pone.0128667

Borghini, G., Candini, M., Filannino, C., Hussain, M., Walsh, V., Romei, V., et al. (2018). Alpha oscillations are causally linked to inhibitory abilities in ageing. *J. Neurosci.* 38, 4418–4429. doi: 10.1523/JNEUROSCI.1285-17.2018

Brainard, D. H. (1997). The Psychophysics Toolbox. *Spat. Vis.* 10, 433–436.

Caiola, M., Devergnas, A., Holmes, M. H., and Wichmann, T. (2019). Empirical analysis of phase-amplitude coupling approaches. *PLoS One* 14:e0219264. doi: 10.1371/journal.pone.0219264

Cecere, R., Rees, G., and Romei, V. (2015). Individual differences in alpha frequency drive crossmodal illusory perception. *Curr. Biol.* 25, 231–235. doi: 10.1016/J.CUB.2014.11.034

Chan, J. S., Connolly, S. K., and Setti, A. (2018). The number of stimulus-onset asynchronies affects the perception of the sound-induced flash illusion in young and older adults. *Multisens. Res.* 31, 175–190. doi: 10.1163/22134808-00002605

Chan, J. S., Wibral, M., Stawowsky, C., Brandl, M., Helbling, S., Naumer, M. J., et al. (2021). Predictive coding over the lifespan: increased reliance on perceptual priors in older adults—A magnetoencephalography and dynamic causal modeling study. *Front. Aging Neurosci.* 13:631599. doi: 10.3389/fnagi.2021.631599

Chan, Y. M., Pianta, M. J., and McKendrick, A. M. (2014). Older age results in difficulties separating auditory and visual signals in time. *J. Vis.* 14:13. doi: 10.1167/14.11.13

Cohen, M. X. (2014). *Analyzing Neural Time Series data: Theory and Practice.* Cambridge, MA: The MIT Press, doi: 10.1017/CBO9781107415324.004

Costa, M., Piché, M., Lepore, F., and Guillemot, J. P. (2016). Age-related audiovisual interactions in the superior colliculus of the rat. *Neuroscience* 320, 19–29. doi: 10.1016/j.neuroscience.2016.01.058

Fu, Y., Wang, X. S., Wang, Y. C., Zhang, J., Liang, Z., Zhou, Y. F., et al. (2010). The effects of aging on the strength of surround suppression of receptive field of V1 cells in monkeys. *Neuroscience* 169, 874–881. doi: 10.1016/j.neuroscience.2010.05.015

Grandy, T. H., Werkle-Bergner, M., Chicherio, C., Schmiedek, F., Lövdén, M., and Lindenberger, U. (2013). Peak individual alpha frequency qualifies as a stable neurophysiological trait marker in healthy younger and older adults. *Psychophysiology* 50, 570–582. doi: 10.1111/psyp.12043

Gray, D. T., Engle, J. R., and Recanzone, G. H. (2013). Age-related neurochemical changes in the rhesus macaque superior olivary complex. *J. Comp. Neurol.* 522, 573–591. doi: 10.1002/cne.23427

Hirano, S., Nakhnikian, A., Hirano, Y., Oribe, N., Kanba, S., Onitsuka, T., et al. (2018). Phase-amplitude coupling of the electroencephalogram in the auditory cortex in schizophrenia. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* 3, 69–76. doi: 10.1016/j.bpsc.2017.09.001

Horak, F. B. (2006). Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? *Age Ageing* 35(Suppl. 2), ii7–ii11. doi: 10.1093/ageing/afl077

Hülsemann, M. J., Naumann, E., and Rasch, B. (2019). Quantification of phase-amplitude coupling in neuronal oscillations:comparison of phase-locking value, mean vector length, modulation index, and generalized-linear-modeling-cross-frequency-coupling. *Front. Neurosci.* 13:573. doi: 10.3389/fnins.2019.00573

Humes, L. E., Busey, T. A., Craig, J. C., and Kewley-port, D. (2009). The effects of age on sensory thresholds and temporal gap detection in hearing, vision, and touch. *Atten. Percept. Psychophys.* 71, 860–871. doi: 10.3758/APP.71.4.860.The

Jeka, J. J., Allison, L. K., and Kiemel, T. (2010). The dynamics of visual reweighting in healthy and fall-prone older adults. *J. Mot. Behav.* 42, 197–208. doi: 10.1080/00222895.2010.481693

Jensen, O., and Mazaheri, A. (2010). Shaping functional architecture by oscillatory alpha activity: gating by inhibition. *Front. Hum. Neurosci.* 4:186. doi: 10.3389/fnhum.2010.00186

Jensen, O., Gips, B., Bergmann, T. O., and Bonnefond, M. (2014). Temporal coding organized by coupled alpha and gamma oscillations prioritize visual processing. *Trends Neurosci.* 37, 357–369. doi: 10.1016/J.TINS.2014.04.001

Kayser, C., Petkov, C. I., and Logothetis, N. K. (2008). Visual modulation of neurons in auditory cortex. *Cereb. Cortex* 18, 1560–1574. doi: 10.1093/cercor/bhm187

Keil, J. (2020). Double flash illusions: current findings and future directions. *Front. Neurosci.* 14:298. doi: 10.3389/fnins.2020.00298

Keil, J., and Senkowski, D. (2017). Individual alpha frequency relates to the sound-induced flash illusion. *Multisens. Res.* 30, 565–578. doi: 10.1163/22134808-00002572

Keil, J., and Senkowski, D. (2018). Neural oscillations orchestrate multisensory processing. *Neuroscientist* 24, 609–626. doi: 10.1177/1073858418755352

Keller, A. S., Payne, L., and Sekuler, R. (2017). Characterizing the roles of alpha and theta oscillations in multisensory attention. *Neuropsychologia* 99, 48–63. doi: 10.1016/j.neuropsychologia.2017.02.021

Kilner, J. M., Kiebel, S. J., and Friston, K. J. (2005). Applications of random field theory to electrophysiology. *Neurosci. Lett.* 374, 174–178. doi: 10.1016/j.neulet.2004.10.052

Klimesch, W. (2012). Alpha-band oscillations, attention, and controlled access to stored information. *Trends Cogn. Sci.* 16, 606–617. doi: 10.1016/j.tics.2012.10.007

Klimesch, W., Sauseng, P., and Hanslmayr, S. (2007). EEG alpha oscillations: the inhibition–timing hypothesis. *Brain Res. Rev.* 53, 63–88. doi: 10.1016/J.BRAINRESREV.2006.06.003

Krebber, M., Harwood, J., Spitzer, B., Keil, J., and Senkowski, D. (2015). Visuotactile motion congruence enhances gamma-band activity in visual and somatosensory cortices. *Neuroimage* 117, 160–169. doi: 10.1016/J.NEUROIMAGE.2015.05.056

Leventhal, A. G., Wang, Y., Pu, M., Zhou, Y., and Ma, Y. (2003). GABA and its agonists improved visual cortical function in senescent monkeys. *Science* 300, 812–815. doi: 10.1126/science.1082874

Manly, F. J. B. (2007). *Randomization, Bootstrap and Monte Carlo Methods in Biology*. Boca Raton, FL: CRC Press.

Manor, B., Costa, M. D., Hu, K., Newton, E., Starobinets, O., Kang, H. G., et al. (2010). Physiological complexity and system adaptability: evidence from postural control dynamics of older adults. *J. Appl. Physiol.* 109, 1786–1791. doi: 10.1152/japplphysiol.00390.2010

McGovern, D. P., Roudaia, E., Stapleton, J., McGinnity, T. M., and Newell, F. N. (2014). The sound-induced flash illusion reveals dissociable age-related effects in multisensory integration. *Front. Aging Neurosci.* 6:250. doi: 10.3389/fnagi.2014.00250

Meredith, M. A., and Stein, B. E. (1983). Interactions among converging sensory inputs in the superior colliculus. *Science* 221, 389–391. doi: 10.1126/science.6867718

Merriman, N. A., Whyatt, C., Setti, A., Craig, C., and Newell, F. N. (2015). Successful balance training is associated with improved multisensory function in fall-prone older adults. *Comput. Human Behav.* 45, 192–203. doi: 10.1016/j.chb.2014.12.017

Munia, T. T. K., and Aviyente, S. (2019). Time-frequency based phase-amplitude coupling measure for neuronal oscillations. *Sci. Rep.* 9:12441. doi: 10.1038/s41598-019-48870-2

Murray, M. M., Lewkowicz, D. J., Amedi, A., and Wallace, M. T. (2016). Multisensory processes: a balancing act across the lifespan. *Trends Neurosci.* 39, 567–579. doi: 10.1016/j.tins.2016.05.003

Narinesingh, C., Goltz, H. C., and Wong, A. M. F. (2017). Temporal binding window of the sound-induced flash illusion in amblyopia. *Investig. Ophthalmol. Vis. Sci.* 58, 1442–1448. doi: 10.1167/iovs.16-21258

Ng, C. W., and Recanzone, G. H. (2018). Age-related changes in temporal processing of rapidly-presented sound sequences in the macaque auditory cortex. *Cereb. Cortex* 28, 3775–3796. doi: 10.1093/cercor/bhx240

Noel, J.-P., De Niear, M., Van der Burg, E., and Wallace, M. T. (2016). Audiovisual simultaneity judgment and rapid recalibration throughout the lifespan. *PLoS One* 11:e0161698. doi: 10.1371/journal.pone.0161698

Ostroff, J. M., McDonald, K. L., Schneider, B. A., and Alain, C. (2003). Aging and the processing of sound duration in human auditory cortex. *Hear. Res.* 181, 1–7. doi: 10.1016/S0378-5955(03)00113-8

Pelli, D. G. (1997). The Video Toolbox software for visual psychophysics: transforming numbers into movies. *Spat. Vis.* 10, 437–442.

Piirtola, M., and Era, P. (2006). Force platform measurements as predictors of falls among older people – A review. *Gerontology* 52, 1–16. doi: 10.1159/000089820

Powers, A. R., Hillock, A. R., and Wallace, M. T. (2009). Perceptual training narrows the temporal window of multisensory binding. *J. Neurosci.* 29, 12265–12274. doi: 10.1523/JNEUROSCI.3501-09.2009

Rossion, B., Torfs, K., Jacques, C., and Liu-Shuang, J. (2015). Fast periodic presentation of natural images reveals a robust face-selective electrophysiological response in the human brain. *J. Vis.* 15, 1–18. doi: 10.1167/15.1.18

Samiee, S., and Baillet, S. (2017). Time-resolved phase-amplitude coupling in neural oscillations. *Neuroimage* 159, 270–279. doi: 10.1016/J.NEUROIMAGE.2017.07.051

Schmolesky, M. T., Wang, Y., Pu, M., and Leventhal, A. G. (2000). Degradation of stimulus selectivity of visual cortical cells in senescent rhesus monkeys. *Nat. Neurosci.* 3, 384–390. doi: 10.1038/73957

Schormans, A. L., Scott, K. E., Vo, A. M., Tyker, A., Typlt, M., Stolzberg, D., et al. (2017a). Audiovisual temporal processing and synchrony perception in the rat. *Front. Behav. Neurosci.* 10:246. doi: 10.3389/fnbeh.2016.00246

Schormans, A. L., Typlt, M., and Allman, B. L. (2017b). Crossmodal plasticity in auditory, visual and multisensory cortical areas following noise-induced hearing loss in adulthood. *Hear. Res.* 343, 92–107. doi: 10.1016/j.heares.2016.06.017

Scurry, A. N., Dutcher, D., Werner, J. S., and Jiang, F. (2019a). Age-related effects on cross-modal duration perception. *Multisens. Res.* 32, 693–714. doi: 10.1163/22134808-20191461

Scurry, A. N., Vercillo, T., Nicholson, A., Webster, M., and Jiang, F. (2019b). Aging impairs temporal sensitivity, but not perceptual synchrony, across modalities. *Multisens. Res.* 32, 671–692. doi: 10.1163/22134808-20191343

Senkowski, D., Schneider, T. R., Foxe, J. J., and Engel, A. K. (2008). Crossmodal binding through neural coherence: implications for multisensory processing. *Trends Neurosci.* 31, 401–409. doi: 10.1016/J.TINS.2008.05.002

Senkowski, D., Talsma, D., Grigutsch, M., Herrmann, C. S., and Woldorff, M. G. (2007). Good times for multisensory integration: effects of the precision of temporal synchrony as revealed by gamma-band oscillations. *Neuropsychologia* 45, 561–571. doi: 10.1016/J.NEUROPSYCHOLOGIA.2006.01.013

Setti, A., Burke, K. E., Kenny, R. A., and Newell, F. N. (2011). Is inefficient multisensory processing associated with falls in older people? *Exp. Brain Res.* 209, 375–384. doi: 10.1007/s00221-011-2560-z

Shams, L., Kamitani, Y., and Shimojo, S. (2000). What you see is what you hear. *Nature* 408, 788–788. doi: 10.1038/35048669

Shams, L., Kamitani, Y., and Shimojo, S. (2002). Visual illusion induced by sound. *Cogn. Brain Res.* 14, 147–152. doi: 10.1016/S0926-6410(02)00069-1

Stapleton, J., Setti, A., Doheny, E. P., Kenny, R. A., and Newell, F. N. (2014). A standing posture is associated with increased susceptibility to the sound-induced flash illusion in fall-prone older adults. *Exp. Brain Res.* 232, 423–434. doi: 10.1007/s00221-013-3750-7

Stephen, J. M., Knoefel, J. E., Adair, J., Hart, B., and Aine, C. J. (2010). Aging-related changes in auditory and visual integration measured with MEG. *Neurosci. Lett.* 484, 76–80. doi: 10.1016/j.neulet.2010.08.023

Stevenson, R. A., and Wallace, M. T. (2013). Multisensory temporal integration: task and stimulus dependencies. *Exp. Brain Res.* 227, 249–261. doi: 10.1007/s00221-013-3507-3

Stothart, G., and Kazanina, N. (2016). Auditory perception in the aging brain: the role of inhibition and facilitation in early processing. *Neurobiol. Aging* 47, 23–34. doi: 10.1016/j.neurobiolaging.2016.06.022

Tinetti, M. E., Speechley, M., and Ginter, S. F. (1988). Risk factors for falls among elderly persons living in the community. *N. Engl. J. Med.* 319, 1701–1707. doi: 10.1056/NEJM198812293192604

Tun, P. A., O'Kane, G., and Wingfield, A. (2002). Distraction by competing speech in young and older adult listeners. *Psychol. Aging* 17, 453–467. doi: 10.1037/0882-7974.17.3.453

Van Atteveldt, N. M., Formisano, E., Blomert, L., and Goebel, R. (2007). The effect of temporal asynchrony on the multisensory integration of letters and speech sounds. *Cereb. Cortex* 17, 962–974. doi: 10.1093/cercor/bhl007

Van Gerven, P. W. M., and Guerreiro, M. J. S. (2016). Selective attention and sensory modality in aging: curses and blessings. *Front. Hum. Neurosci.* 10:147. doi: 10.3389/fnhum.2016.00147

Wang, C., Rajagovindan, R., Han, S.-M., and Ding, M. (2016). Top-down control of visual alpha oscillations: sources of control signals and their mechanisms of action. *Front. Hum. Neurosci.* 10:15. doi: 10.3389/FNHUM.2016.00015

Werner, J. S., Schefrin, B. E., and Bradley, A. (2010). "Optics and vision of the aging eye," in *Handbook of Optics*, 3rd Edn, ed. M. Bass (New York, NY: The McGraw-Hill Companies, Inc.), 14.11–14.38.

Yuval-Greenberg, S., and Deouell, L. Y. (2007). What you see is not (always) what you hear: induced gamma band responses reflect cross-modal interactions in familiar object recognition. *J. Neurosci.* 27, 1090–1096. doi: 10.1523/jneurosci.4828-06.2007

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Late-Life Depressive Symptomatology, Motoric Cognitive Risk Syndrome, and Incident Dementia: The "NuAge" Study Results

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Background: Late-life depressive symptomatology and motoric cognitive risk syndrome (MCR) have independently been associated with an increased risk for incident dementia. This study aimed to examine the association of late-life depressive symptomatology, MCR, and their combination on incident dementia in community-dwelling older adults living in Quebec (Canada).

Methods: The study was carried out in a subset of 1,098 community dwellers aged $\geq$65 years recruited in the "*Nutrition as a determinant of successful aging: The Quebec longitudinal study*" (NuAge), an observational prospective cohort study with 3 years follow-up. At baseline, MCR was defined by the association of subjective cognitive complaint with slow walking speed, and late-life depressive symptomatology with a 30-item Geriatric Depression Scale (GDS) score >5/30. Incident dementia, defined as a Modified Mini-Mental State score $\leq$79/100 test and Instrumental Activity Daily Living score <4/4, was assessed at each annual visit.

Results: The prevalence of late-life depressive symptomatology only was 31.1%, of MCR only 1.8%, and the combination of late-life depressive symptomatology and MCR 2.4%. The combination of late-life depressive symptomatology and MCR at baseline was associated with significant overall incident dementia (odds ratio (OR) = 2.31 with $P \leq 0.001$) but not for MCR only ($OR = 3.75$ with $P = 0.186$) or late-life depressive symptomatology only ($OR = 1.29$ with $P = 0.276$).

Conclusions: The combination of late-life depressive symptomatology and MCR is associated with incident dementia in older community dwellers. The results suggested an interplay between late-life depressive symptomatology and MCR exposing them to an increased risk for dementia.

Keywords: aging, community dwellers, dementia, depression, motor dysfunction, cohort study, EPI–epidemiology

BACKGROUND

Late-life depressive symptomatology is a common psychiatric condition in older adults with a prevalence ranging from 8 to 16% (Diniz et al., 2013; Bennett and Thomas, 2014; Steffens, 2017). A systematic review and meta-analysis of community-based cohort studies have shown that late-life depressive symptomatology is associated with an increased risk for incident dementia, regardless of its type (i.e., Alzheimer's disease (AD) and non-AD) (Diniz et al., 2013). Older adults with late-life depressive symptomatology frequently have subjective cognitive complaints (SCC) and a slow walking speed compared to their healthy counterparts (Lichtenberg et al., 1995; Bennett and Thomas, 2014). The combination of these two clinical characteristics (i.e., SCC and slow walking speed) defines the motoric cognitive risk syndrome (MCR), which is associated with an increased risk for dementia (Verghese et al., 2013). Recently, it has been reported in the Canadian population that there was a higher prevalence of depressive symptomatology in adults with MCR compared to those without MCR (Sekhon et al., 2019a). We suggested that this overlapping condition influences the risk for incident dementia. More precisely, we hypothesized that the presence of late-life depressive symptomatology with MCR could increase the risk for incident dementia, regardless of its type, compared to each condition alone. We used the data collected in the *"Nutrition as a determinant of successful aging: The Quebec longitudinal study"* (NuAge) to test this hypothesis (Gaudreau et al., 2007). NuAge is a 3-year-follow-up observational prospective cohort study performed in community dwellers aged ≥65 years living in Quebec (Canada). This study aimed to investigate the association of late-life depressive symptomatology, MCR, and their combination with incident dementia in participants of the NuAge study.

METHODS

Population

The subset of NuAge participants selected for this study were participants without mobility disability defined by using a walking aid; with information on walking speed and depressive symptomatology assessed with the 30-item Geriatric Depression Scale (GDS) at the baseline assessment; and with information on their cognitive status performance using the Modified Mini-Mental State (3MS) and the simplified instrumental activity daily living (IADL) scores using items of the Functional Autonomy Measurement System (SMAF) over the 3-year follow-up (Yesavage et al., 1982–1983; Teng and Chui, 1987; Hebert et al., 1988; Pérès et al., 2006; Gaudreau et al., 2007). Participants lost to follow-up and those who withdrew their agreement to use data were also excluded. A total of 1,098 (62.6%) NuAge participants from the full set of 1,754 participants were selected.

Assessment

Age, sex, the number of medications, height (m), weight (kg), history of falls, walking speed (m/s), simplified IADL score, 3MS score, and 30-item GDS score were recorded at the baseline assessment (Yesavage et al., 1982–1983; Teng and Chui, 1987; Hebert et al., 1988; Pérès et al., 2006). The Physical Activity Scale for the Elderly (PASE) was used to determine the level of physical activity at baseline; a low level was defined by being below the lowest tertile (i.e., <69.1 for female and <87.7 for male) (Washburn et al., 1999). The body mass index (BMI; kg/m^2) was also determined at baseline; overweight and/or obese were considered if BMI was ≥25 kg/m^2. Polypharmacy was defined as ≥5 drugs taken daily. The 3MS and simplified IADL scores were recorded annually over the 3 years of follow-up (Yesavage et al., 1982–1983; Hebert et al., 1988; Pérès et al., 2006).

Definition of Late-Life Depressive Symptomatology, MCR, and Dementia

The late-life depressive symptomatology was defined at baseline as a 30-item GDS score >5/30 (Yesavage et al., 1982–1983; Alexopoulos et al., 2005). MCR was defined by the combination of SCC with slow walking speed in the absence of major neurocognitive disorders and motor disability (Verghese et al., 2013). The answer "Yes" to the item "*Do you feel you have more problems with memory that most*?" of 30-item GDS defined SCC. A walking speed of one standard deviation (SD) or more below the age-appropriate mean values in the selected subset of participants defined slow walking speed. Cut-off values for defining slow walking speed were calculated as described by Verghese et al. (2013). Overall, the incident dementia was defined with a 3MS score ≤79/100 and simplified IADL score <4/4 at each annual visit after the baseline assessment over the 3-year follow-up (Teng and Chui, 1987; Hebert et al., 1988; Pérès et al., 2006). Low education was associated with a greater risk for incident dementia (Sharp and Gatz, 2011). The number of years of education has been collected in the NuAge cohort and used as a measure of education. There was no significant difference in the number of years of education between groups (data not shown).

Standard Protocol Approval and Participant Consents

The NuAge protocol was approved by the Research Ethics Board (REB) of the University Institutes of Geriatrics of Sherbrooke and Montreal (Quebec, Canada), and the NuAge Database was approved by the REB of the CIUSSS-de-l'Estrie-CHUS (Quebec, Canada). All the participants signed consent for research. The REB of the Jewish General Hospital (Montreal, Quebec, Canada) approved the present study.

Statistical Analysis

Participants were separated into four groups using the baseline assessment information: (1) no late-life depressive symptomatology and no MCR, this group was used as the reference group; (2) late-life depressive symptomatology only (i.e., being in the group of participants with late-life depressive symptomatology only means that participants with late-life depression and MCR are excluded from this group); (3) MCR only (i.e., being in the group of participants MCR only means that participants with MCR and late-life depression and MCR are excluded from this group); and (4) combination of late-life depressive symptomatology and MCR. The characteristics of the participants were described using means, SD, and percentages.

The ANOVA, Kruskal–Wallis, unpaired t-test, Mann–Whitney, Chi-square test, or Fisher's exact tests were used for group comparisons, as appropriate. Value of $P < 0.01$ was considered statistically significant because of multiple comparisons (Verghese et al., 2013). Multiple logistic regressions examined the association of overall incident dementia (dependent variable) with late-life depressive symptomatology, MCR, and their combination (independent variables in separated models) with adjustment for baseline characteristics of the participants. Cox regression models were not used because only the annual incidence of dementia was collected and not the exact date of diagnosis of dementia. Furthermore, the follow-up period was short and limited to 3 years. Value of $P < 0.05$ were considered statistically significant for logistic regressions. Statistics were performed using SPSS (version 24.0).

RESULTS

At baseline, the prevalence of having only late-life depressive symptomatology, MCR, or the combination of both late-life depressive symptomatology and MCR was 31.1, 1.8, and 2.4%, respectively. Polypharmacy, low level of physical activity, 3MS score, and abnormal IADL score were significantly different between groups ($P \leq 0.003$; **Table 1**). A lower prevalence of polypharmacy, low level of physical activity, and abnormal IADL score were reported in individuals without late-life depressive symptomatology and MCR compared to those with late-life depressive symptomatology only ($P \leq 0.01$). Individuals with MCR had a lower 3MS score and a higher prevalence of abnormal IADL score compared to those without late-life depressive symptomatology and MCR ($P \leq 0.01$). The lowest 3MS score and the highest prevalence of abnormal IADL score were reported in individuals with late-life depressive symptomatology and MCR, the difference was significant compared to those without late-life depressive symptomatology and MCR ($P \leq 0.01$). Individuals with late-life depressive symptomatology and MCR had a higher prevalence of abnormal IADL score compared to those with late-life depressive symptomatology ($P \leq 0.01$).

The overall incidence of dementia was different between groups ($P \leq 0.001$), the highest incidence was shown in individuals exhibiting both late-life depressive symptomatology and MCR. Individuals with MCR only and with late-life depressive symptomatology and MCR had a higher incidence compared to those without late-life depressive symptomatology and MCR ($P \leq 0.01$). Individuals with late-life depressive symptomatology and MCR had a higher incidence of dementia compared to those with late-life depressive symptomatology ($P \leq 0.01$). The combination of late-life depressive symptomatology and MCR at baseline was associated with significant overall incident dementia (odds ratio (OR) = 2.31 with 95% confidence interval (CI) = [1.51–3.52] with $P \leq 0.001$ and R-Square = 0.224) but not for MCR only ($OR = 3.75$ with 95% CI = [0.53–26.56] with $P = 0.186$ and R-Square = 0.285) or late-life depressive symptomatology (OR = 1.29 with 95% CI = [0.82–2.04] with $P = 0.276$ and R-Square = 0.132) only (**Figure 1**).

DISCUSSION

The results showed that the combination of late-life depressive symptomatology and MCR is associated with incident dementia but not late-life depressive symptomatology and MCR only in the NuAge participants.

The risk for incident dementia increased in participants combining late-life depressive symptomatology and MCR in the present study. This increased risk was higher compared to participants who had only one symptomatology (around 2.3-fold), and similar compared to the risk reported in individuals with MCR in previous original studies and a recent meta-analysis (pooled estimated ratio for risk of incident dementia in participants with MCR at baseline compared to those without the MCR = 2.5 with 95% CI = [1.75–2.39]) (Sekhon et al., 2019b). This result highlights that, first, an overlap between late-life depressive symptomatology and MCR is possible and, second, that this overlap does not interfere with the risk for dementia, suggesting a complex interplay between depressive symptomatology and MCR. This effect may be of clinical utility for the prevention of dementia. For instance, over half a million Canadians are living with dementia (Beauchet et al., 2021). The health care system in Canada, like others, is ill-equipped to deal with the resulting staggering costs of dementia. One of the three key objectives of the primary prevention strategy of Canada is to reduce the rate of conversion to dementia. Better understanding the association between late-life depressive symptomatology and MCR is in line with this objective. Indeed, this could improve the detection of individuals at risk for dementia at a population level and, consequently, orient appropriate interventions.

We did not report an association between MCR only and overall incident dementia, whereas we showed that this incidence of dementia was higher in participants with MCR only compared to those without MCR and late-life depressive symptomatology. These mixed results have been reported in a recent meta-analysis (Sekhon et al., 2019b). One study selected in this meta-analysis showed no significant association with incident dementia, similar to our study (Kumai et al., 2016). An explanation for the absence of a significant association between MCR only and overall incident dementia in our study may be the good health condition at the baseline assessment of the NuAge participants. Another explanation may be the classification of individuals. Being in the group of participants with MCR only means that participants with MCR and late-life depression were excluded from this group. Thus, the group of MCR patients has been split into two subgroups (i.e., MCR only and MCR with late-life depressive symptomatology) that may explain the absence of significant association between MCR only and incident dementia. Similar to MCR only, late-life depressive symptomatology only was not associated with an increased risk for dementia. Two reasons may explain this result. First, the 30-item GDS score is a way to identify an individual with depressive symptomatology. The final diagnosis of depression must be performed by a clinician. Second, similar to the inconclusive association between MCR only and the incident dementia, the good health condition of the NuAge participants may influence the association of late-life depressive symptomatology and dementia.

TABLE 1 | Baseline characteristics of participants grouped according to their late-life depressive symptomatology and MCR status ($n = 1,098$).

	Participants				*P*-value[‡]
	No late-life depressive symptomatology[*†] and no MCR ($n = 771$)	**Late-life depressive symptomatology[*†] ($n = 341$)**	**Motoric cognitive risk Syndrome[†] ($n = 20$)**	**Late-life depressive symptomatology plus MCR ($n = 26$)**	
Age (years), mean ± SD	73.6 ± 4.1	74.1 ± 4.1	74.9 ± 4.1	75.1 ± 4.0	0.058
Female, n (%)	354 (49.8)	197 (57.8)	9 (45.0)	13 (50.0)	0.095
Overweight/obesity[¶], *n* (%)	508 (71.4)	245 (71.8)	14 (70.0)	19 (73.1)	0.995
Polypharmacy[§], *n* (%)	282 (39.7)	183 (53.7)[a]	12 (60.0)	16 (61.5)	**≤0.001**
Past history of falls, *n* (%)	117 (16.5)	72 (21.1)	6 (30.0)	4 (15.5)	0.143
Low level of physical activity[#], n (%)	210 (29.5)	138 (40.5)[a]	8 (40.0)	11 (42.3)	**0.003**
3MS score (/100), mean ± SD	94.6 ± 4.0	94.4 ± 4.2	92.3 ± 4.5[b,d]	89.9 ± 4.5[c,e]	**≤0.001**
IADL score <4 (/4), *n* (%)	73 (10.3)	55 (16.1)[a]	5 (25.0)[b]	13 (50.0)[c,e]	**≤0.001**
Incident dementia**, *n* (%)	12 (1.7)	10 (2.9)	2 (10.0)[b]	5 (19.2)[c,e]	**≤0.001**

3MS, modified mini-mental state; SD, standard deviation; IADL, instrumental activity daily living.
**30-item Geriatric Depression Scale score >10/30.*
†Exclusive (i.e., only participants with the condition).
‡Multiple comparisons based on ANOVA Kruskal–Wallis or Chi-square test, as appropriate.
¶Body mass index ≥ 25 kg/m².
§Number of therapeutic drugs daily taken ≥ 5.
#Score of the Physical Activity Scale for Elderly below the lowest tertile (i.e., <69.1 for female and <87.7 for male).
***Overall incident of dementia diagnosed with Modified Mental State score ≤ 79/100 and instrumental activity daily living score < 4/4 at each annual visit after the baseline assessment.*
[a]Comparison of participants without late-life depression and motoric cognitive risk syndrome (MCR) with participants with significant late-life depression (i.e., <0.01).
[b]Comparison of participants without late-life depression and MCR of participants with a significant MCR (i.e., <0.01).
[c]Comparison of participants without late-life depression and MCR of participants with combined late-life depression and significant MCR (i.e., <0.01).
[d]Comparison of participants with late-life depression and participants with significant MCR (i.e., <0.01).
[e]Comparison of participants with late-life depression and participants with combined late-life depression and significant MCR (i.e., <0.01).
Significant values of P (i.e., <0.01) are indicated in bold.

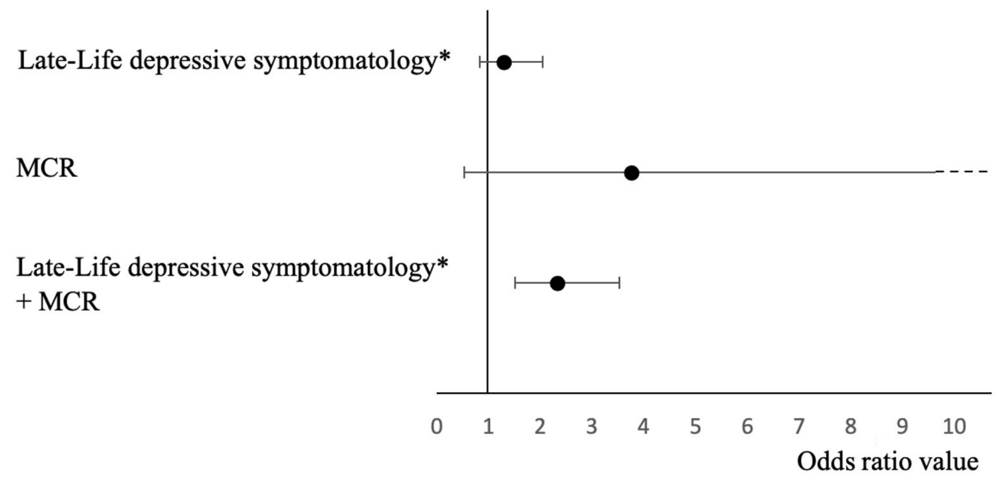

FIGURE 1 | Logistic regressions showing odds ratios and confidence intervals of the association of late-life depressive symptomatology, MCR, and their combination with overall incident dementia adjusted for participant's baseline characteristics ($n = 1,098$). *score >5/30; MCR, motoric cognitive risk syndrome.

Some limitations of the present study need to be underscored. First, the NuAge population was composed of relatively healthy older adults that could prevent the generalization of the results of the present study. Second, the prevalence of MCR (1.8%) and the combination with depressive symptomatology (2.4%) was low, which may lead to a lack of power to show an association with incident dementia in one hand and bringing some degree of uncertainty on their association with incident dementia on the other hand. More studies with a greater variety of health status in older adults are, therefore, required to further confirm this association. Third, although we were able to control for many characteristics likely to modify the association, residual confounding might still be present. As confounding factors can impact both the magnitude and the direction of the association, it is difficult to speculate on the impact of residual confounding factors on the associations found in the study. Fourth, the diagnosis of dementia may be underestimated that may explain its low incidence. Indeed, this diagnosis is usually based on an interdisciplinary meeting and more exhaustive information. In our case, we used only the threshold for dementia of 3MS combined with abnormal simplified IADLs score.

CONCLUSIONS

Our study showed that the combination of late-life depressive symptomatology and MCR, but not its components, is associated with incident dementia in Quebec community-dwelling older adults. The results suggest an interplay between late-life depressive symptomatology and MCR increasing the risk for dementia.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Access to NuAge Database can be obtain by contacting the NuAge team via NuAge-cdrv@usherbrooke.ca. Requests to access these datasets should be directed to the NuAge team, NuAge-cdrv@usherbrooke.ca.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Research Ethics Boards (REB) of the University Institutes of Geriatrics of Sherbrooke and Montreal (Quebec, Canada). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

OB and GA: conceived and designed the experiments. PG and JM: cohort data collection. OB, HS, CL, and GA: analyzed and interpreted the data. OB: contributed reagents, materials, analysis tools, and data. OB, HS, and CL: writing of the manuscript. PG, JM, and GA: revision of the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

Alexopoulos, G. S., Schultz, S. K., and Lebowitz, B. D. (2005). Late-life depression: a model for medical classification. *Biol. Psychiatry* 58, 283–289. doi: 10.1016/j.biopsych.2005.04.055

Beauchet, O., Cooper-Brown, L. A., and Allali, G. (2021). Motoric cognitive risk syndrome: what's new? *Aging (Albany NY)* 13, 7711–7712. doi: 10.18632/aging.202899

Bennett, S., and Thomas, A. J. (2014). Depression and dementia: cause, consequence or coincidence? *Maturitas*. 79, 184–190. doi: 10.1016/j.maturitas.2014.05.009

Diniz, B. S., Butters, M. A., Albert, S. M., Dew, M. A., and Reynolds, C. F. 3rd. (2013). Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *Br. J. Psychiatry* 202, 329–335. doi: 10.1192/bjp.bp.112.118307

Gaudreau, P., Morais, J. A., Shatenstein, B., Gray-Donald, K., Khalil, A., Dionne, I., et al. (2007). Nutrition as a determinant of successful aging: description of the Quebec longitudinal study NuAge and results from cross-sectional pilot studies. *Rejuvenation Res*. 10, 377–386. doi: 10.1089/rej.2007.0596

Hebert, R., Carrier, R., and Bilodeau, A. (1988). The Functional Autonomy Measurement System (SMAF): description and validation of an instrument for the measurement of handicaps. *Age Ageing* 17, 293–302. doi: 10.1093/ageing/17.5.293

Kumai, K., Meguro, K., Kasai, M., Nakamura, K., and Nakatsuka, M. (2016). Neuroepidemiologic and neurobehavioral characteristics of motoric cognitive risk syndrome in an old-old population: the Kurihara project dement. *Geriatr. Cogn. Dis. Extra* 6, 176–182. doi: 10.1159/000445539

Lichtenberg, P. A., Ross, T., Millis, S. R., and Manning, C. A. (1995). The relationship between depression and cognition in older adults: a cross-validation study. *J. Gerontol. B. Psychol. Sci. Soc. Sci*. 50:P25–P32. doi: 10.1093/geronb/50B.1.P25

Pérès, K., Chrysostome, V., Fabrigoule, C., Orgogozo, J. M., Dartigues, J. F., and Barberger-Gateau, P. (2006). Restriction in complex activities of daily living in MCI: impact on outcome. *Neurology* 67, 461–466. doi: 10.1212/01.wnl.0000228228.70065.f1

Sekhon, H., Allali, G., and Beauchet, O. (2019a). The association of anxio-depressive disorders and depression with motoric cognitive risk syndrome: results from the baseline assessment of the Canadian longitudinal study on aging. *Geroscience* 41, 409–418. doi: 10.1007/s11357-019-00093-z

Sekhon, H., Allali, G., Launay, C. P., Barden, J., Szturm, T., Liu-Ambrose, T., et al. (2019b). Motoric cognitive risk syndrome, incident cognitive impairment and morphological brain abnormalities: Systematic review and meta-analysis. *Maturitas* 123, 45–54. doi: 10.1016/j.maturitas.2019.02.006

Sharp, E. S., and Gatz, M. (2011). Relationship between education and dementia: an updated systematic review. *Alzheimer Dis. Assoc. Disord*. 25, 289–304. doi: 10.1097/WAD.0b013e318211c83c

Steffens, D. C. (2017). Late-life depression and the prodromes of dementia. *JAMA Psychiatry* 74, 673–674. doi: 10.1001/jamapsychiatry.2017.0658

Teng, E. L., and Chui, H. C. (1987). The Modified Mini-Mental State (3MS) examination. *J. Clin. Psychiatry* 48, 314–318.

Verghese, J., Wang, C., Lipton, R. B., and Holtzer, R. (2013). Motoric cognitive risk syndrome and the risk of dementia. *J. Gerontol. A. Biol. Sci. Med. Sci*. 68, 412–418. doi: 10.1093/gerona/gls191

Washburn, R. A., McAuley, E., Katula, J., Mihalko, S. L., and Boileau, R. A. (1999). The physical activity scale for the elderly (PASE): evidence for validity. *J. Clin. Epidemiol*. 52, 643–651. doi: 10.1016/S0895-4356(99)00049-9

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., et al. (1982–1983). Development and validation of a geriatric depression screening scale: a preliminary report. *J. Psychiatry Res*. 17, 37–49. doi: 10.1016/0022-3956(82)90033-4

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ORIGINAL RESEARCH
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Acute Effects of Different Exercise Intensities on Executive Function and Oculomotor Performance in Middle-Aged and Older Adults: Moderate-Intensity Continuous Exercise vs. High-Intensity Interval Exercise

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A wealth of evidence has shown that a single bout of aerobic exercise can facilitate executive function. However, none of current studies on this topic have addressed whether the magnitude of the acute-exercise benefit on executive function and oculomotor performance is influenced by different aerobic exercise modes. The present study was thus aimed toward an investigation of the acute effects of high-intensity interval exercise (HIIE) vs. moderate-intensity continuous exercise (MICE) on executive-related oculomotor performance in healthy late middle-aged and older adults. Using a within-subject design, twenty-two participants completed a single bout of 30 min of HIIE, MICE, or a non-exercise-intervention (REST) session in a counterbalanced order. The behavioral [e.g., reaction times (RTs), coefficient of variation (CV) of the RT], and oculomotor (e.g., saccade amplitude, saccade latency, and saccadic peak velocity) indices were measured when participants performed antisaccade and prosaccade tasks prior to and after an intervention mode. The results showed that a 30-min single-bout of HIIE and MICE interventions shortened the RTs in the antisaccade task, with the null effect on the CV of the RT in the late middle-aged and older adults. In terms of oculomotor metrics, although the two exercise modes could not modify the performance in terms of saccade amplitudes and saccade latencies, the participants' saccadic peak velocities while performing the oculomotor paradigm were significantly altered only following an acute HIIE intervention. The present findings suggested that a

30-min single-bout of HIIE and MICE interventions modulated post-exercise antisaccade control on behavioral performance (e.g., RTs). Nevertheless, the HIIE relative MICE mode appears to be a more effective aerobic exercise in terms of oculomotor control (e.g., saccadic peak velocities) in late middle-aged and older adults.

Keywords: eye movement, antisaccade, prosaccade, high-intensity interval exercise, acute exercise

INTRODUCTION

Executive functions, referring to top-down cognitive processes, include three core components: response inhibition, cognitive flexibility, and working memory (Diamond, 2013). Such complex cognitive abilities enable an individual to independently perform complex, goal-directed, and self-serving activities (e.g., problem solving and inhibition of irrelevant processing) (Lezak et al., 2004). Impairment of executive functions is associated with poor functional achievement, lower ability to perform daily living tasks, and a more rapid progression to dementia (Royall et al., 2005; Tsai et al., 2018, 2019a). Therefore, executive dysfunctions affect the individual's functional ability and increase the risk of cognitive decline in cognitively normal elderly individuals (Mirsky et al., 2011; Tsai et al., 2017b). Since the function of the frontostriatal network supporting executive functions decreases as a part of healthy aging (Buckner, 2004), and declines in executive function precede age-related memory loss (Blacker et al., 2007; Tsai et al., 2016a), determining how to circumvent executive dysfunction in individuals who are at increased risk for cognitive decline is an important issue.

It has been well established that a single bout of exercise can enhance executive functions in middle-aged and older adults, with behavioral performance being facilitated [e.g., shorter reaction times (RTs) and higher accuracy rates (AR)] following acute exercise when they perform cognitive tasks involving executive functioning (Kamijo et al., 2009; Barella et al., 2010; Johnson et al., 2016; Tsai et al., 2018; Formenti et al., 2020). In addition, in terms of cognitive electrophysiological performance, Kamijo et al. (2009) found that, as compared to the baseline session, event-related potential (ERP) P3 latency was significantly shorter following a bout of light or moderate aerobic exercise in older adults when performing a Flanker task. Tsai et al. (2018) also found that acute moderate aerobic exercise significantly enlarged ERP P3 amplitudes in middle-aged and older adults with mild cognitive impairment (MCI). However, some studies have found an inverted U-shaped relationship between acute-exercise intensity and cognitive performance (Kamijo et al., 2007) and have reported that the performance of executive function appears to be improved only with a single bout of moderate, not low or high, intensity exercise due to optimal acute-exercise-induced psychological and physiological arousal (Tomporowski, 2003; McMorris et al., 2010; Dietrich and Audiffren, 2011). In contrast, the "drive" hypothesis supports that the most beneficial effects on post-exercise executive improvements are elicited by heavy to near maximal levels of intensity (Chang et al., 2012) since regional cerebral blood flow and circulating neurotrophic factors levels increase with exercise intensity (i.e., engendering larger neurobiological magnitudes when individuals perform exercise with near maximal levels of intensity as compared to moderate intensity) (Knaepen et al., 2012; Tsai et al., 2014b). As a result, exercise intensity could be one of potential moderators of single-bout post-exercise executive benefits.

A robust body of literature has shown that a single bout of moderate intensity continuous exercise (MICE) can produce a transient facilitating effect on executive functions in various populations (Kamijo et al., 2007; Pontifex et al., 2009; Hung et al., 2013; Tsai et al., 2014a, 2016b, 2018; Hakansson et al., 2017; Formenti et al., 2020). High-intensity interval exercise (HIIE) is characterized by brief, intermittent bursts of intensive aerobic exercise interspersed with brief periods of low-intensity exercise or recovery (Laursen and Jenkins, 2002) and has recently proposed as a time-efficient alternative to traditional cardiorespiratory exercise (Alves et al., 2014; Tsai et al., 2021). Previous studies have reported that HIIE is more effective than MICE for increasing cardiovascular/metabolic health and exercise capacity in healthy individuals (Helgerud et al., 2007). The effectiveness of HIIE has also been demonstrated in older adults with various chronic diseases (Puhan et al., 2006; Tjønna et al., 2008; Angadi et al., 2015). Such a physical exercise mode has been promoted as a low-risk, practical, and time-efficient approach to optimizing health and well-being, thereby reducing the burden of chronic diseases associated with physical inactivity (Lucas et al., 2015). Although both of these aerobic exercise modes (i.e., HIIE and MICE) have been reported to modulate the impact on behavioral and cognitive electrophysiological performance, the potential effects are still somewhat equivocal at the moment (Tsukamoto et al., 2016; Schwarck et al., 2019; Tsai et al., 2021).

An antisaccadic task (i.e., looking mirror-symmetrical to a visual stimulus) highly correlates with neuropsychological measures of executive function and is a well-characterized measure of inhibitory control (Mirsky et al., 2011). The performance of antisaccade tasks declines with advancing age in normal elderly individuals (Peltsch et al., 2011). In addition, the antisaccade task is sensitive to frontal lobe processes that increase the risk of cognitive decline in older adults with or without incipient neurodegenerative progress (e.g., Alzheimer's disease) (Mirsky et al., 2011). In contrast to prosaccades mediated *via* direct retinotopic projections within the superior colliculus (Wurtz and Albano, 1980), antisaccades is tightly regulated by frontoparietal executive networks involved in vector inversion and response inhibition (i.e., the suppression of a stimulus-driven prosaccade) that includes the frontal, supplementary, and parietal eye fields (Munoz and Everling, 2004; Everling and Johnston, 2013). As distinct from the prosaccadic task (i.e., saccade to a target's veridical location), longer RTs, less ARs/increased directional errors, and more variable endpoints emerge when individuals perform an antisaccadic task (Gillen and Heath, 2014). Petrella et al. (2019) used prosaccadic and antisaccadic tasks to examine the effects of 10 min of continuous aerobic exercise at different intensities (i.e., moderate, heavy, and very heavy) on executive-related oculomotor performance in elderly adults. They found that antisaccade RTs, but not prosaccade RTs, were reduced across the continuum of moderate to very-heavy exercise intensities, indicating that the post-exercise benefits in antisaccade RTs did not reliably vary with exercise intensity (Petrella et al., 2019). Since cortical regions responsible for antisaccades show improved task-dependent prefrontal cortex activity following an exercise intervention (Colcombe et al., 2004), and impaired performance on the antisaccade task could serve as indices of potentially increased risk of cognitive decline in normal elderly individuals (Mirsky et al., 2011), the antisaccadic task is an ideal tool for detecting subtle changes in executive functions following a single bout of exercise in such a group (Petrella et al., 2019).

The age-associated declines in some cognitive domains (e.g., executive functions, memory, reasoning, and processing speed) have begun from middle age (i.e., 30 years old and onward) (Hedden and Gabrieli, 2004; Park and Reuter-Lorenz, 2009). Thus far, there have been no previous studies comparing the acute effects of different types and intensities of aerobic exercise (e.g., HIIE vs. MICE) on executive-related oculomotor control in individuals at risk for cognitive decline. Accordingly, the main purpose of the present study is to investigate the effects of a single bout of HIIE vs. MICE interventions on executive control in healthy late middle-aged and older adults when performing the saccade paradigm. Since a single-bout of aerobic exercise performed at a moderate-to-vigorous level of intensity produces a small but reliable cognitive benefit (e.g., executive control) (Lambourne and Tomporowski, 2010; Petrella et al., 2019), and the antisaccade task is a cognitive task modulated by the activity of prefrontal cortex, antisaccade planning processes could be facilitated by an exercise intervention (Samani and Heath, 2018). Therefore, it was hypothesized that an acute bout of 30 min of HIIE and MICE intervention would produce beneficial effects with regard to executive-related behavioral and oculomotor parameters in the exercise-intervention (i.e., HIIE and MICE) groups relative to those seen in the non-exercise-intervention (REST) group. In addition, an inverted U hypothesis regarding the acute exercise-and-cognitive performance relationship (i.e., optimal exercise-induced arousal elicited by acute moderate exercise intensity) was reported in a previous study (Kamijo et al., 2007). Accordingly, we also postulated that the facilitating effects on executive-related behavioral performance and oculomotor control induced by acute exercise would be more prominent in the MICE compared to HIIE intervention.

MATERIALS AND METHODS

Participants

Twenty healthy community dwelling participants (10 males, ages 55–73) were recruited using convenience sampling *via* an informative flyer and word of mouth. This sample size was determined based on an *a priori* power analysis (alpha = 0.05, power = 0.80) to detect a medium-to-large effect (d = 0.06 ∼ 0.14) (Cohen, 1988) of acute MICE and HIIE on behavioral and oculomotor performance during the saccadic task as computed using G*Power 3.1.9 (Faul et al., 2007), with the estimate of the minimum required sample size being 18. A health-screening questionnaire and a structured interview on previous medical history confirmed that the participants were free of significant orthopedic conditions, sensory impairment, neurological or psychiatric disorders, cerebrovascular and metabolic diseases, and substance abuse or addiction influencing central nervous system function that would limit the ability to exercise. All participants had normal or corrected-to-normal vision based on the minimum 20/20 standard, and were non-smokers and right-handed according to the Edinburgh Handedness Inventory. None of the participants exhibited any symptoms of depression, as measured by the Beck Depression Inventory II (DBI-II, all scored below 13), and identified objective cognitive impairments, as measured by the Mini-Mental State Examination (MMSE, all scored over 24) and the Montreal Cognitive Assessment (MoCA, all scored over 26). The participants' baseline demographics and clinical characteristics are shown in **Table 1**. The participants gave written informed consent and visited the laboratory on four occasions to participate in the experimental protocol conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of National Cheng Kung University.

TABLE 1 | Demographic data.

Variables	Total (n = 20)
Age (years)	61.15 ± 4.43
Education (years)	13.75 ± 2.15
Height (cm)	162.85 ± 7.94
Weight (kg)	64.30 ± 7.59
BMI (kg/m^2)	24.23 ± 2.27
Systolic BP (mmHg)	127.60 ± 19.54
Diastolic BP (mmHg)	77.35 ± 11.72
Resting heart rates (beats per minute)	69.70 ± 7.41
MMSE (scores)	29.00 ± 1.03
MoCA (scores)	27.85 ± 1.57
BDI-II (scores)	1.95 ± 2.31
IPAQ (MET-min/week)	1428.55 ± 743.66
Physical fitness	
Grip (kg)	30.57 ± 9.32
Arm curl (number)	37.45 ± 9.19
Chair stand (number)	22.20 ± 5.33
8-foot up-and-go (s)	5.13 ± 0.76
Back scratch (cm)	4.03 ± 4.11
Chair sit-and-reach (cm)	7.50 ± 5.57
Estimated VO_{2max} (mL/kg/min)	35.57 ± 5.46

BMI, body mass index; BP, blood pressure; MMSE, Mini-Mental Status Examination; MoCA, Montreal Cognitive Assessment; BDI-II, Beck Depression Inventory, 2nd edition.

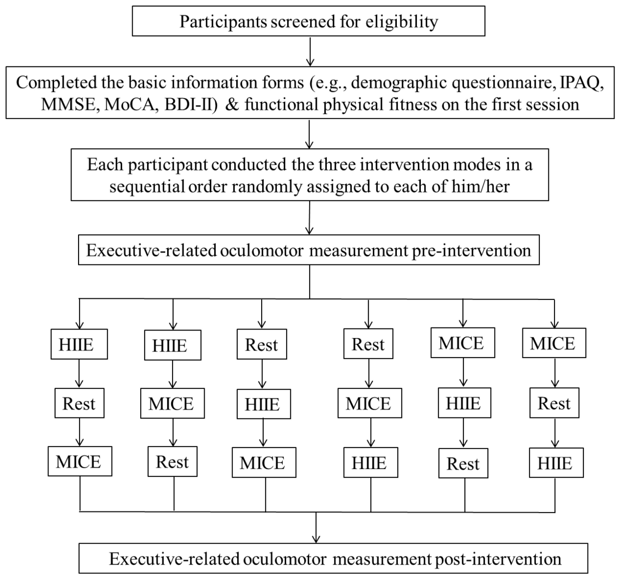

FIGURE 1 | Flowchart of the study.

Experimental Procedure

As illustrated in **Figure 1**, all participants visited the cognitive neurophysiology laboratory four times since a balanced within-subject cross-over design was adopted in the present study. On the first session, an informed consent form was signed prior to testing after the participants understood and agreed to participating in the experimental procedure. Then, the DBI-II, MMSE, MoCA, the basic information form (e.g., a medical history and demographic questionnaire), and a handedness inventory were administered. To lower potential exercise risks before the acute HIIE and MICE interventions, previous levels of physical activity, as assessed using the International Physical Activity Questionnaire (IPAQ), were used to calculate overall energy expenditure per week (MET-min/week) and resting heart rate, and a Physical Activity Readiness Questionnaire was also administered. The participants' height and weight were measured to calculate their BMI. A certified fitness instructor then completed all assessments of senior functional physical fitness (Rikli and Jones, 2012) for each participant. The Rockport Fitness Walking Test (Kline et al., 1987) was used to estimate the participants' cardiorespiratory fitness (i.e., VO_{2max}), in which the participant was required to walk one mile as quickly as possible, with the heart rate (HR) being continuously recorded using a Polar HR monitor (RX800CX, Finland).

For each of three (i.e., MICE, HIIE, or REST) intervention sessions, to control for circadian influences, the participants were required to come to the laboratory at about 8:30–9:30 am on three different days with an interval of 7 days between sessions. They were randomly allocated to a sequential order to conduct the three intervention sessions to minimize potential practice and mode of exercise effects (see **Figure 1**). Each participant was asked to get seven or 8 h of sleep before each intervention exercise session and was also asked refrain from participating in strenuous exercise and consuming alcohol for 24 h before their next arrival. All interventions were administered in an acoustically shielded room with a controlled temperature (23–25°C) and dimmed lights. At the beginning of each session, the participants' body temperature (BT) and resting HR (HRrest) were measured, and then they were asked to be fitted with a Polar HR monitor (RX800CX, Finland) and to sit on a height adjustable chair in front of an IBM-compatible computer with their head placed comfortably in a head/chin rest, at a viewing distance of approximately 75 cm. After a practice session, the formal oculomotor test was immediately administered. All participants completed the saccadic tasks prior to and following a 30-min single bout of MICE, HIIE, or Rest intervention.

For the MICE and HIIE sessions, participants were introduced to a stationary adjustable bike and familiarized with the Borg's rating of perceived exertion (RPE) scale (i.e., 6–20) to self-monitor and report individual effort perceptions to the experimenter every 1.5 min during exercise. The participant performed the two exercise modes on the bike for 30 min. MICE began with a 4 min warm-up, followed by 24 min of moderate-intensity exercise [50–55% Heart Rate Reserve (HRR)], and a 2 min cool-down. HIIE began with a 4 min warm-up, followed by 24 min of high-intensity intervals (1 min, 70–75% HRR) alternated with an active recovery period [2 min, target RPE = 9–11], and a 2 min cool-down. During the HIIE and MICE warm-up and cool-down, the participants' RPE was set at levels ranging from 9–11. The exercise intensities of MICE and HIIE were monitored during which verbal encouragement was provided to facilitate exercise effort. After the acute HIIE and MICE interventions, HR was measured to ascertain it had returned to within 10% of the baseline (between 3 and 5 min following the cool-down). Then, the saccadic tasks test was carried out again. For the Rest session, the participants sat for 35 min and read magazines.

The Saccadic Paradigm

The saccadic paradigm employed in the present study was adapted from Petrella et al.'s (2019) and Ranchet et al.'s (2017) studies. It consists of prosaccade and antisaccade tasks and has been shown to effectively assess the neuropsychological performance of executive function among middle-aged and elderly participants (Mirsky et al., 2011; Ranchet et al., 2017; Petrella et al., 2019). Each of the prosaccade and antisaccade tasks contained both gap and overlap trials to maximize task sensitivity (Briand et al., 2001). A trial commenced with a 3-s countdown followed 1,000 ms later by the appearance of a yellow fixation cross (1° in diameter, 135 cd/m^2, 1,000 ms). In the gap condition, there was a gap interval of 200 ms, and then the eccentric white target stimuli (1° in diameter, 127 cd/m^2) appeared randomly either to the left or right side and in the same horizontal meridian, in a proximal (10.5°) or distal (15.5°) position to prevent stereotyped responses (Gillen and Heath, 2014). In the overlap condition, when the eccentric target appeared, the fixation cross remained visible throughout the remainder of the trial. The target stimuli remained visible for 3,000 ms, after which the next trial started. Each of the prosaccade and antisaccade tasks were divided into eight blocks of 192 trials between runs, with the target location (i.e., left and right of fixation)/eccentricity (i.e., proximal and distal) and gap/overlap fixation conditions being randomly interleaved throughout each block of 24 trials. For the prosaccade task, participants were instructed to shift gaze from the central fixation point to a left or right target (i.e., saccade to the veridical target stimuli location). As soon as the participant looked at the target, he/she pressed a button of the computer keyboard to record the reaction time. For the antisaccade task, the same visual presentations were used as in the prosaccade task, in which the participants were asked to look away from the eccentric target to its mirror location (i.e., saccade mirror-symmetrical to the target stimuli location) and press a button of the computer keyboard. Prosaccade and antisaccade tasks were completed at each pre- and post-intervention session in separate, randomly ordered blocks.

Oculomotor Recordings

The Tobii Pro X3-120 Eye Tracker (Tobii Technology, Inc., Stockholm, Sweden) was used to record the participants' saccadic eye movement patterns at a sampling rate of 120 Hz. Saccade onset was determined by velocity values of greater than 30°/s, and saccade offset occurred when the velocity values were less than 30°/s for 20 ms. Given that the saccade metrics were strongly correlated with cognition (MacAskill et al., 2012; Connell et al., 2017), saccade latencies for correct trials were collected and determined as the duration of the interval from the appearance of an eccentric target to the onset of the first eye movement. Only latencies between 90 and 1,000 ms were analyzed (Chan et al., 2005). Saccade amplitude was defined as the angular distance the eye traveled during the movement, representing the saccade accuracy and spatial decision. Saccadic peak velocity was computed as the maximum eye velocity during the initial saccade.

Data Processing and Statistical Analysis

Trials with missing data (e.g., a blink), RTs less than 100 ms (i.e., anticipatory saccades), and an saccadic amplitude less than 2° or greater than 2.5 standard deviations from the mean value, were excluded from the data analyses, thereby ruling out outliers that could skew the group means. Trials involving a directional error were also not included in the data analyses since such responses are mediated *via* planning processes that are distinct from individual's directionally correct counterparts (DeSimone et al., 2014). The dependent variables included the RT (time from stimulus onset to button press of the computer keyboard), the coefficient of variation (CV) of the RT (standard deviation/mean × 100%), saccade amplitude, saccade latency, and saccadic peak velocity. Kolmogorov-Smirnov and Levene's tests were used to confirm normality and homogeneity of variance assumptions, respectively. Since the main purpose in the present study aimed to investigate the acute effects of MICE and HIIE interventions on executive-related oculomotor performance in the participants when performing the prosaccade and antisaccade tasks and, importantly, previous studies demonstrated that acute aerobic exercise with moderate and intense instensities could not produce a significant main effect on the "target eccentricity by intervention mode" interaction in the young and older adults (Samani and Heath, 2018; Petrella et al., 2019), for increasing the statistical power of the analyses, dependent variables were thus submitted separately to a three-way mixed-model ANOVA, with the following factors: 3 (*Intervention mode*: MICE vs. HIIE vs. REST) × 2 (*Time*: pre-intervention vs. post-intervention) × 2 (*Task*: prosaccade vs. antisaccade). Posterior comparisons of the mean values with paired-sample multiple comparisons (adjusted using the Bonferroni correction) were conducted when the RM-ANOVAs revealed significant main effect interactions. Analyses employing the Greenhouse–Geisser correction with three or more within-subject levels were performed if a major violation of the assumption of sphericity was detected. For complementary use of significance testing, the effect size, partial η^2 ($\eta_p{}^2$), was reported, with the effects of less than 0.08 considered small, 0.08–0.139 considered medium, and greater than 0.14 considered large. An alpha level of.05 was set for statistical significance.

RESULTS

Table 1 presents descriptive data for participants' demographic characteristics. Briefly, the participants had a mean age of 61.15 ± 4.43 years and were free of depressive symptoms (BDI-II scores below 13) and cognitive impairment (MMSE scored over 24 and the MoCA scored over 26). Although the mean BMI values in the late middle-aged and older adults fell into the overweight category based on WHO criteria for Asian populations obtained from the Western Pacific Regional Office (Tsai et al., 2017a, 2019b), they exhibited enough physical activity levels (as seen from IPAQ data) (Sallis et al., 1985) and physical fitness (e.g., cardiorespiratory fitness) (Liskustyawati et al., 2020) to perform the acute HIIE and MICE interventions with lower potential risk factors.

In addition, the average RPE (MICE vs. HIIE: 10.95 ± 0.76 vs. 12.65 ± 0.67) and HRs (MICE vs. HIIE: 112.95 ± 1.50 vs. 129.10 ± 3.60 bpm) during the last 15 s of each minute were significantly lower during MICE than they were during HIIE (both ps < 0.001) in the present study.

Behavioral Performance

Reaction Time

As illustrated in **Figure 2**, the RM-ANOVA on the RTs exhibited significant main effects of *Time* [$F(1, 57) = 10.91$, $p = 0.002$, $\eta_p{}^2 = 0.16$, power = 0.959] and *Task* [$F(1, 57) = 177.55$, $p < 0.001$, $\eta_p{}^2 = 0.76$, power = 1.000]. The *post hoc* analyses showed that the post-intervention RTs (739.83 ms) were shorter than the pre-intervention RTs (776.26 ms) across the three intervention modes and two tasks, and the RTs for the antisaccade task (948.99 ms) were longer than those for the prosaccade tasks (567.09 ms) across the three intervention modes and two time points. These main effects were superseded by the *Time* × *Intervention mode* [$F(2, 57) = 6.82$, $p = 0.002$, $\eta_p{}^2 = 0.19$, power = 0.952], *Time* × *Task* [$F(1, 57) = 16.29$, $p < 0.001$, $\eta_p{}^2 = 0.22$, power = 0.999], and *Time* × *Intervention mode* × *Task*

[$F(2,57) = 3.22$, $p = 0.047$, $\eta_p^2 = 0.10$, power = 0.863] interactions. The *post hoc* analyses for the *Time* × *Intervention mode* × *Task* interaction indicated that the both MICE [$t(19) = 2.20$, $p = 0.040$] and HIIE [$t(19) = 4.77$, $p < 0.001$] modes produced significantly shorter RTs in the antisaccade task, but not in the prosaccade task, post- as compared to pre-intervention.

Coefficient of Variation of Reaction Time

The RM-ANOVA on the CV of the RT exhibited a significant main effect of *Intervention mode* × *Task* [$F(2, 57) = 3.49$, $p = 0.037$, $\eta_p^2 = 0.11$, power = 0.732]. The *post hoc* analyses indicated that only the value for the prosaccade task (31.29) was higher than it was for the antisaccade task (18.99) in the REST intervention mode. Neither significant main effects of *Intervention mode, Task,* and *Time* nor other significant interactions between the three factors ($ps > 0.60$ in all cases), were obtained.

Oculomotor Performance

Saccade Amplitude

As illustrated in **Figure 3**, the RM-ANOVA on the saccade amplitude exhibited significant main effects of *Task* [$F(1, 57) = 5.52$, $p = 0.022$, $\eta_p^2 = 0.09$]. The *post hoc* analyses indicated that saccade amplitudes were less for prosaccades (3.32°) than for antisaccades (3.88°) across the three intervention modes and across two time points. Neither significant main effects of *Intervention mode* and *Time* nor significant interactions between *Intervention mode, Task,* and *Time* ($ps > 0.36$ in all cases) were obtained.

Saccade Latency

The RM-ANOVA on the saccade latency exhibited significant main effects of *Time* [$F(1, 57) = 5.79$, $p = 0.019$, $\eta_p^2 = 0.09$]. The *post hoc* analyses indicated that saccade latencies were faster post- (275.89 ms) as compared to pre-intervention (293.36 ms) across the three intervention modes and across the two tasks. Neither significant main effects of *Intervention mode* and *Time* nor significant interactions between *Intervention mode, Task,* and *Time* ($ps > 0.21$ in all cases) were obtained.

Saccadic Peak Velocity

The RM-ANOVA on the saccadic peak velocity exhibited a significant main effect of *Time* [$F(1, 57) = 9.21$, $p = 0.004$, $\eta_p^2 = 0.14$, power = 0.928]. The *post hoc* analyses showed that the saccadic peak velocities were lower post-intervention (186.19 degree/s) as compared to pre-intervention (200.37 degree/s) across the three intervention modes and the two tasks. The main effect was superseded by the *Time* × *Intervention mode* [$F(2, 57) = 3.24$, $p = 0.047$, $\eta_p^2 = 0.10$, power = 0.683] interaction. The *post hoc* analyses for the *Time* × *Intervention mode* interaction indicated that the HIIE [$t(19) = 4.06$, $p = 0.001$] modes produced significantly shorter saccadic peak velocity across the two saccade tasks post- (174.94 degree/s) as compared to pre-intervention (200.45 degree/s). The MICE [$t(19) = 1.85$, $p = 0.079$] modes only approached significance in the saccadic peak velocity across the two saccade tasks post- (173.33 degree/s) as compared to pre-intervention (192.60 degree/s).

DISCUSSION

The objective of the current study was to examine the effects of acute HIIE and MICE interventions on behavioral and eye-movement performance in healthy late middle-aged and older adults when performing cognitive tasks involving executive-related oculomotor control. The main findings were that a 30-min single-bout of HIIE and MICE intervention modes could

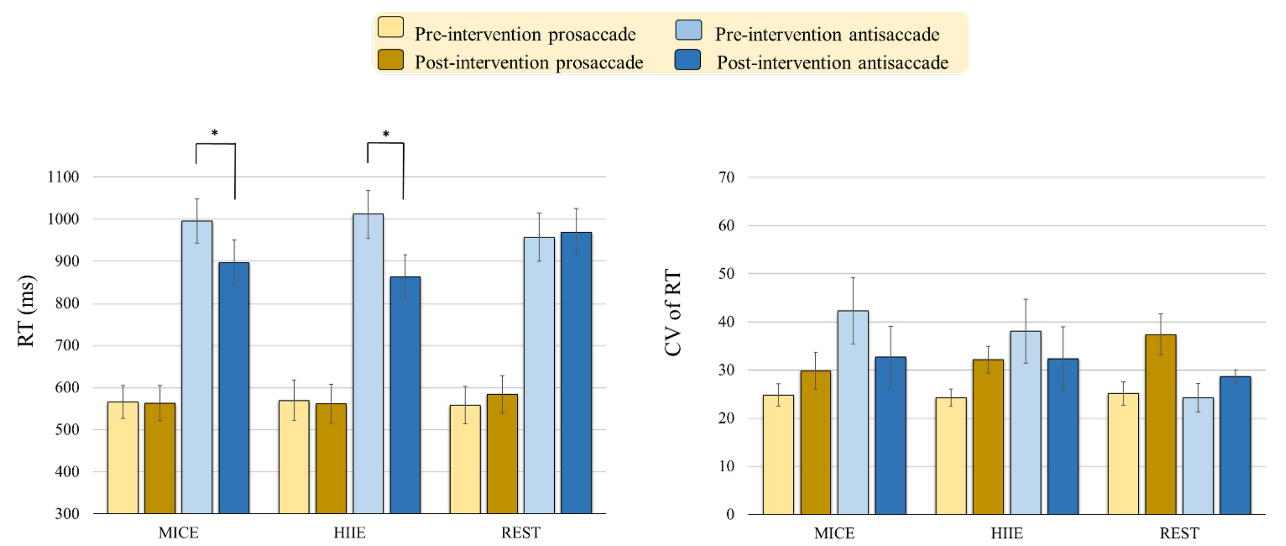

FIGURE 2 | Behavioral performance [i.e., Reaction time (RT) and Coefficient of variation (CV) of RT] (mean ± SE) in the prosaccadic and antisaccadic tasks for the moderate intensity continuous exercise (MICE) and high-intensity interval exercise (HIIE) modes before and after a single bout of exercise, and one non-exercise-intervention (REST) before and after resting (*$p < 0.05$).

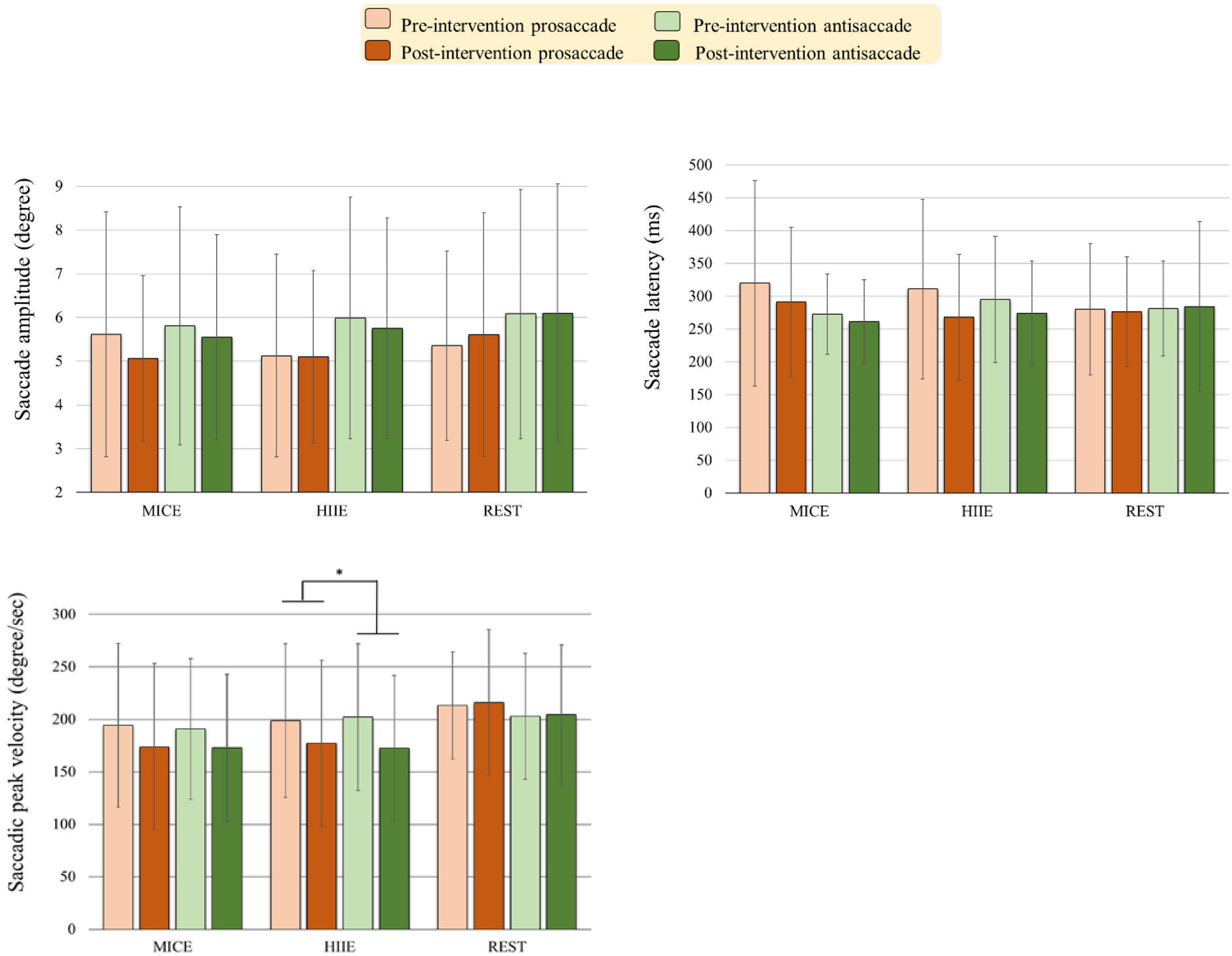

FIGURE 3 | Oculomotor performance [i.e., Saccade amplitude, saccade latency, fixation duration, and saccadic peak velocity] (mean ± SD) in the prosaccadic and antisaccadic tasks for the moderate intensity continuous exercise (MICE) and high-intensity interval exercise (HIIE) modes before and after a single bout of exercise, and one non-exercise-intervention (REST) before and after resting (*$p < 0.05$).

significantly shorten RTs in the antisaccade task in such a group, with the null effect on the CV of the RT. In terms of oculomotor performance, although the two exercise modes did not change the saccade amplitude and saccade latency performance, the saccadic peak velocity during the oculomotor tasks was significantly altered following an acute bout of HIIE, but not MICE, in the late middle-aged and older adults.

Separate parallel descending pathways involving the cerebral frontal and parietal cortex, basal ganglia, superior colliculus, and brainstem saccade generator differently control the generation of saccades, both visually guided (i.e., reflexive) and voluntary (Terao et al., 2013). The planning properties of prosaccades are operated with minimal top-down cortical control (Pierrot-Deseilligny et al., 1995) since spatial relations between stimulus and response are overlapped during the saccadic mode (Wurtz and Albano, 1980). In contrast, the antisaccade task is a task requiring the individual to inhibit a reflexive saccade toward the target (i.e., prosaccade) and instead generate a voluntary-triggered saccade toward a mirror position without a visual target stimulus (Terao et al., 2013). In the present study, longer RTs for the antisaccade task were shown as compared to the prosaccade task when the participants performed the saccadic paradigm, reflecting that such a cognitive task is time-consuming since it is associated with high-level executive demands related to inhibiting a stimulus-driven prosaccade (i.e., pre-potent response), transforming a target's coordinate, and decoupling the spatial relations between the stimulus and the response (i.e., vector inversion) (Samani and Heath, 2018; Petrella et al., 2019). As such, the present findings demonstrated that the oculomotor paradigm adopted in the present study provides a viable framework for investigating acute-exercise-related changes to executive function in late middle-aged and older adults.

Similar to Tsai et al.'s (2014a) study exploring various neurocognitive indices after acute aerobic exercise in young adults with different cardiorespiratory fitness levels when performing a visuospatial attention task and finding the facilitated RTs and cognitive electrophysiological effects (e.g., event-related potential P3 amplitudes and Contingent Negative Variation), the participants in the present study showed significantly shorter RTs following a single bout of HIIE and MICE when performing the executive-related oculomotor paradigm. Both previous and recent studies demonstrate that a reliable post-exercise improvement in executive functions is supported by acute-exercise-based increases in regional cerebral blood flow to executive-related cortical structures and, importantly and specifically, by enhancing arousal, cortical efficiency, and attentional allocation in adults when performing cognitive tasks involving inhibitory control (Dietrich and Audiffren, 2011; Tsai et al., 2014a, 2018, 2021; Verburgh et al., 2014; Formenti et al., 2020). However, it is worth noting that shorter RTs post- as compared to pre-exercise interventions were only found in the antisaccade task, but not in the prosaccade one in the present study. This finding is in line with a previous work by Petrella et al. (2019) reporting that 10-min of single-bout aerobic exercise with different exercise intensities did not alter prosaccade metrics in healthy older adults. There are two plausible mechanisms to account for the pattern in the findings. It is likely that, given the reflexive nature of prosaccades (e.g., humans complete upward of 150,000 prosaccades per day) (Robinson, 1981), neural correlates of prosaccades supported by the midbrain are refractory to a single bout of exercise intervention (Petrella et al., 2019). Another possibility is that prosaccades operate independently of the vector inversion and response suppression executive demands (Pierrot-Deseilligny et al., 1995). However, since the antisaccade task is linked to increased activation of executive-related frontoparietal networks that support maintenance of high-level task rules (Ettinger et al., 2008; Everling and Johnston, 2013; Weiler et al., 2015), the present results support the premise that a single bout of 30 min of HIIE and MICE are effective in terms of improving the brain's executive control in late middle-aged and older adults (Tsai et al., 2021). It is noteworthy that, relative to Petrella et al.'s (2019) study, pre- and post-oculomotor assessments were performed in separate sessions interleaved by a non-exercise (REST) condition in the present study, and non-significant changes in RTs in this intervention mode were observed. The present finding demonstrated that the improved RTs in the antisaccade task after a single bout of HIIE and MICE could not be attributed to practice effects and that executive-control-related performance (e.g., inhibitory control) benefits could be elicited *via* the two exercise modes in late middle-aged and older adults.

Although Petrella et al. (2019) found that a 10-min single bout of continuous aerobic exercise with moderate, heavy, and very heavy-heavy exercise intensities could not alter the oculomotor performance (e.g., eye-movement time, and saccade amplitude, and variability in the horizontal movement direction), and the post-exercise facilitation in antisaccade RTs did not reliably vary with exercise intensity in older adults, changes in the magnitude of the executive-related oculomotor control on saccadic peak velocity influenced by different exercise intensities was observed in the late middle-aged and older adults in the present study, with significant decrements in the peak velocity of saccades emerging following a 30-min single bout of HIIE, but not MICE. One possible explanation for these disparate findings is that the present finding regarding the altered saccadic peak velocity following the acute HIIE in part supports the previous studies reporting that short duration exercise sessions (less than 20 min) produce a null effect on executive control performance, whereas durations greater than 20 min produce a significant effect (Lambourne and Tomporowski, 2010; Chang et al., 2012). In addition, there is a relationship between brain catecholamines (e.g., dopamine and norepinephrine) and saccadic control (Allman et al., 2012). Indeed, the levels of peripheral norepinephrine are linked to saccadic peak velocity (Connell et al., 2017). Acute exercise could cause changes in central neurotransmitters (i.e., increased levels of norepinephrine) (Peake et al., 2014; McMorris, 2016), which could further reduce saccadic peak velocity (Connell et al., 2017). Since the acute HIIE relative to MICE intervention appeared to induce higher levels of norepinephrine (Peake et al., 2014), it is plausible that a significant alteration in saccadic peak velocity was only observed after a single bout of 30 min of HIIE, but not MICE, in the present study. Until now, the acute HIIE relative to MICE effects on executive benefits have appeared to be divergent. For example, Schwarck et al. (2019) found that the null-effect on cognitive response to an acute bout of MICE and HIIE was possibly due to a small sample size. However, a larger improvement in the trail-making task assessing cognitive flexibility was exhibited following MICE as compared to HIIE in the identified responder (Schwarck et al., 2019). In contrast, Tsukamoto et al. (2016) compared the effects of acute HIIE and MICE on executive function in young adults when performing the color-words Stroop task and found that, although the two aerobic exercise modes could improve cognitive performance, the post-exercise executive benefit during 30-min of recovery was sustained in the HIIE but not in the MICE mode. In the present study, although acute HIIE and MICE interventions equally improved the RTs in the antisaccade task, the former relative to the latter exercise mode appears to induce more oculomotor control performance related to saccadic peak velocity. However, it is still worth noting that the alteration in the oculomotor index approached the borderline of significance at 30-min post-exercise following MICE. Future research efforts should continue to address this unclear finding (e.g., exploring what effect aerobic training has on the norepinephrine response to exercise of the different intensities). Importantly, norepinephrine is associated with cognitive function (Holland et al., 2021), with an age-dependent reduction in such a molecular level being exhibited with poor contextual learning and memory (Dang et al., 2014). Also, increasing synaptic norepinephrine activity could improve response inhibition (Liu et al., 2015). It is conceivable that alterations to norepinephrine *via* acute HIIE and MICE interventions could retard age-related declines in executive control. In addition, the saccadic peak velocity seems to be a sensitive non-invasive index by which to observe neurocognitive changes.

Nevertheless, our results did not confirm significant changes in other saccade parameters (e.g., saccade amplitude and latency), which are considered interdependent with saccadic peak velocity.

Saccadic amplitude is reported to be influenced by an interplay of processes in the basal ganglia, frontal cortex, and brainstem (Terao et al., 2016). In addition, the amplitude of the saccade made during visual scanning is associated with the function of basal ganglia (Machado and Rafal, 2004). In accordance with the findings of previous studies (Samani and Heath, 2018; Petrella et al., 2019) reporting that 10-min single-bouts of aerobic exercise at moderate to vigorous intensities did not significantly alter the saccade amplitudes in young and older adults, these oculomotor indices were also not significantly improved following a 30-min single-bout of HIIE and MICE in the late middle-aged and older adults in the present study. One plausible reason for the null effect on this oculomotor metric is that the specification of antisaccade amplitudes is mediated through retinotopic motor maps in the superior colliculus (Wurtz and Albano, 1980) in which the brain subcortical structure is considered to be refractory to exercise-based modulations (Colcombe and Kramer, 2003). However, there was a trend toward lower saccade amplitudes following the acute HIIE and MICE interventions in the present study since the reduced amplitude for the saccade task may be explained by the inhibition of the superior colliculus *via* the basal ganglia (Machado and Rafal, 2004), the two exercise modes could be sufficient to inhibit excessive neural impulses in this brain area.

Similarly, a significant difference in saccade latency was also not exhibited after a single bout of 30 min of HIIE and MICE in the late middle-aged and older adults in this study, which could be attributed to that, as mentioned above, saccade latency is correlated with the magnitude of response in the superior colliculus (Neggers et al., 2005). Until now, there has been no previous study exploring the effect of acute exercise on saccade latency. Nevertheless, Di Russo et al. (2003) found that elite shooters have faster saccadic latency to targets than controls in saccade tasks under standard (i.e., performing a visually guided saccade toward a target as fast as possible as the prosaccade condition in the present study) and distracter (i.e., only saccading toward the red, not the green, stimulus) conditions. In fact, the saccadic latency performance has been found to be associated with attentional levels (Di Russo et al., 2003) when a saccadic program toward a predictable direction is partially or completely prepared before the appearance of eccentric targets (Pare and Munoz, 1996). The facilitating effect that acute exercise has in terms of eliciting more attentional resource allocation (e.g., larger brain event-related potential P3 amplitude following a single bout of 30 min of exercise) has been demonstrated in many previous studies (Tsai et al., 2014a, 2016b, 2018). As such, faster saccade latency following a single bout of HIIE and MICE could be expected when the late middle-aged and older adults performed the oculomotor paradigm. However, there was only a decreasing, but not significant, trend on the saccade latencies observed post-relative to pre-acute-exercise in the present study. How the effect of the saccadic motor preparation coded at the retinotopic level through chronic exercise (Di Russo et al., 2003) could be significantly induced following an acute exercise intervention is worth investigating in further experiment.

There are limitations to the oculomotor approach that must be addressed. First, the posteriori power data of the statistical analyses for the behavioral and oculomotor results were 0.732–1.000 and 0.683–0.928, respectively. Although η_p^2 was also included to provide a measure of effect size in the present study, the small sample size could still be a limitation. A confirmatory study in the future is required to determine whether some null effects translates into significant improvements following a single bout of acute MICE and HIIE protocols in a larger sample. Second, a significant correlation between dynamic saccade latency and visual acuity of saccadic eye movement has been reported (Kohmura et al., 2008). Accordingly, the accurate discrimination of a moving target at high speed could be influenced by the early start of saccadic eye movement. Because of age-related diabetes, macular degeneration, and cataracts, middle-aged and older adults frequently lose visual acuity as they age (Munoz et al., 2000). When performing oculomotor tasks, these individuals have to execute a fast saccade to an eccentric target stimuli. Although normal or corrected-to-normal vision was one of inclusion criteria in the present study, the non-significant finding regarding the saccade latencies after the acute HIIE and MICE interventions could not be avoided due to potential optic nerve degeneration/eye diseases in the middle-aged and older adults. Further investigation of this issue before the oculomotor experiment is warranted. Third, since a lingering inhibition that will elicit the unidirectional prosaccade switch cost (i.e., delayed planning of a subsequent prosaccade) will be engendered by the completion of an antisaccade (Weiler and Heath, 2014), future research efforts using randomly interleaved pro- and antisaccade trials into one block (e.g., a task-switching paradigm) will be necessary to confirm and better understand the specific mechanism contributing to improved executive-related oculomotor control in the antisaccade task elicited by the acute HIIE/MICE intervention, as well as an investigation of the performance benefits/costs following correct and incorrect antisaccade trials (Samani and Heath, 2018).

CONCLUSION AND PERSPECTIVES

Impaired performance on executive function tests precedes cognitive decline in the normal elderly population and conversion to Alzheimer disease in older adults with MCI (Blacker et al., 2007; Tsai et al., 2016a, 2018, 2019a). In the present study, a post-exercise antisaccade, but not prosaccade, benefit on behavioral performance (e.g., RTs) was observed in the late middle-aged and older adults when performing the oculomotor paradigm. In addition, the peak velocity of the first saccadic eye movement was only significantly altered after the HIIE, but not the MICE, intervention. These findings imply that a single bout of HIIE and MICE could produce a short-term "boost" to executive-related cognitive control in late middle-aged and older adults, supporting that the two acute aerobic exercise interventions improved task-specific activity within the frontoparietal networks supporting antisaccades. Nevertheless, the HIIE relative to the MICE mode appears to be a more effective alternative to the alteration of oculomotor control (i.e., saccadic peak velocity) in late middle-aged and older adults, possibly due to acute-exercise-induced in brain neurotransmitters (e.g., norepinephrine). In addition, it is worth noting that, given the deficits in executive functions and saccadic eye movement shown in the patients with neurodegenerative diseases (e.g., Alzheimer's disease and Parkinson's disease) (Tsai et al., 2018, 2019a; Chen et al., 2021; Lage et al., 2021), HIIE could be one of safe and preventive intervention strategies in lowering their declining cognitive functions and oculomotor control in clinical and medical settings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Ethics Committee of National Cheng Kung University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

C-LT designed the study, wrote the protocol and the first draft of the manuscript. Y-CC and T-CW collected and analyzed the data. C-YP, JU, and BU reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

Allman, A. A., Ettinger, U., Joober, R., and O'Driscoll, G. A. (2012). Effects of methylphenidate on basic and higher-order oculomotor functions. *J. Psychopharmacol.* 26, 1471–1479. doi: 10.1177/0269881112446531

Alves, C. R., Tessaro, V. H., Teixeira, L. A., Murakava, K., Roschel, H., Gualano, B., et al. (2014). Influence of acute high-intensity aerobic interval exercise bout on selective attention and short-term memory tasks. *Percep. Mot. Skills* 118, 63–72. doi: 10.2466/22.06.pms.118k10w4

Angadi, S. S., Mookadam, F., Lee, C. D., Tucker, W. J., Haykowsky, M. J., and Gaesser, G. A. (2015). High intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: a pilot study. *J. Appl. Physiol.* 119, 753–758. doi: 10.1152/japplphysiol.00518.2014

Barella, L. A., Etnier, J. L., and Chang, Y. K. (2010). The immediate and delayed effects of an acute bout of exercise on cognitive performance of healthy older adults. *J. Aging Phys. Act.* 18, 87–98. doi: 10.1123/japa.18.1.87

Blacker, D., Lee, H., Muzikansky, A., Martin, E. C., Tanzi, R., McArdle, J. J., et al. (2007). Neuropsychological measures in normal individuals that predict subsequent cognitive decline. *Arch. Neurol.* 64, 862–871. doi: 10.1001/archneur.64.6.862

Briand, K. A., Hening, W., Poizner, H., and Sereno, A. B. (2001). Automatic orienting of visuospatial attention in Parkinson's disease. *Neuropsychologia* 39, 1240–1249. doi: 10.1016/s0028-3932(01)00045-8

Buckner, R. L. (2004). Memory and executive function in aging and AD: Multiple factors that cause decline and reserve factors that compensate. *Neuron* 44, 195–208. doi: 10.1016/j.neuron.2004.09.006

Chan, F., Armstrong, I. T., Pari, G., Riopelle, R. J., and Munoz, D. P. (2005). Deficits in saccadic eye-movement control in Parkinson's disease. *Neuropsychologia* 43, 784–796. doi: 10.1016/j.neuropsychologia.2004.06.026

Chang, Y. K., Labban, J. D., Gapin, J. I., and Etnier, J. L. (2012). The effects of acute exercise on cognitive performance: a meta-analysis. *Brain Res.* 1453, 87–101. doi: 10.1016/j.brainres.2012.02.068

Chen, F., Li, Y., Ye, G., Zhou, L., Bian, X., and Liu, J. (2021). Development and validation of a prognostic model for cognitive impairment in Parkinson's disease with REM sleep behavior disorder. *Front. Aging Neurosci.* 13:703158. doi: 10.3389/fnagi.2021.703158

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*, 2nd Edn. Hillsdale, NJ: Erlbaum.

Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., Cohen, N. J., et al. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proc. Natl. Acad. Sci. U S A.* 101, 3316–3321. doi: 10.1073/pnas.0400266101

Colcombe, S., and Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol. Sci.* 2003, 125–130. doi: 10.1111/1467-9280.t01-1-01430

Connell, C. J. W., Thompson, B., Turuwhenua, J., Srzich, A., and Gant, N. (2017). Effects of dopamine and norepinephrine on exercise-induced oculomotor fatigue. *Med. Sci. Sports Exerc.* 49, 1778–1788. doi: 10.1249/mss.0000000000001307

Dang, V., Medina, B., Das, D., Moghadam, S., Martin, K. J., Lin, B., et al. (2014). Formoterol, a long-acting β2 adrenergic agonist, improves cognitive function and promotes dendritic complexity in a mouse model of Down syndrome. *Biol. Psychiatry* 75, 179–188. doi: 10.1016/j.biopsych.2013.05.024

DeSimone, J. C., Weiler, J., Aber, G. S., and Heath, M. (2014). The unidirectional prosaccade switch-cost: Correct and error antisaccades differentially influence the planning times for subsequent prosaccades. *Vis. Res.* 96, 17–24. doi: 10.1016/j.visres.2013.12.005

Di Russo, F., Pitzalis, S., and Spinelli, D. (2003). Fixation stability and saccadic latency in elite shooters. *Vision Res.* 43, 1837–1845. doi: 10.1016/s0042-6989(03)00299-2

Diamond, A. (2013). Executive functions. *Annu. Rev. Psychol.* 64, 135–168.

Dietrich, A., and Audiffren, M. (2011). The reticular-activating hypofrontality (RAH) model of acute exercise. *Neurosci. Biobehav. Rev.* 35, 1305–1325. doi: 10.1016/j.neubiorev.2011.02.001

Ettinger, U., Ffytche, D. H., Kumari, V., Kathmann, N., Reuter, B., Zelaya, F., et al. (2008). Decomposing the neural correlates of antisaccade eye movements using event-related FMRI. *Cereb. Cortex* 18, 1148–1159. doi: 10.1093/cercor/bhm147

Everling, S., and Johnston, K. (2013). Control of the superior colliculus by the lateral prefrontal cortex. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 368:20130068. doi: 10.1098/rstb.2013.0068

Faul, F., Erdfelder, E., Lang, A. G., and Buchner, A. (2007). G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav. Res. Methods* 39, 175–191. doi: 10.3758/bf03193146

Formenti, D., Cavaggioni, L., Duca, M., Trecroci, A., Rapelli, M., Alberti, G., et al. (2020). Acute effect of exercise on cognitive performance in middle-aged adults: Aerobic versus balance. *J. Phys. Act. Health* 17, 773–780. doi: 10.1123/jpah.2020-0005

Gillen, C., and Heath, M. (2014). Perceptual averaging governs antisaccade endpoint bias. *Exp. Brain Res.* 232, 3201–3210. doi: 10.1007/s00221-014-4010-1

Hakansson, K., Ledreux, A., Daffnerf, K., Terjestama, Y., Bergmang, P., Carlssona, R., et al. (2017). BDNF Responses in healthy older persons to 35 minutes of physical exercise, cognitive training, and mindfulness: Associations with working memory function. *J. Alzheimers Dis.* 55, 645–657. doi: 10.3233/jad-160593

Hedden, T., and Gabrieli, J. D. E. (2004). Insights into the ageing mind: a view from cognitive neuroscience. *Nat. Rev. Neurosci.* 5, 87–96. doi: 10.1038/nrn1323

Helgerud, J., Høydal, K., Wang, E., Karlsen, T., Berg, P., Bjerkaas, M., et al. (2007). Aerobic high intensity intervals improve VO_{2max} more than moderate training. *Med. Sci. Sports Exerc.* 39, 665–671. doi: 10.1249/mss.0b013e3180304570

Holland, N., Robbins, T. W., and Rowe, J. B. (2021). The role of noradrenaline in cognition and cognitive disorders. *Brain* 2021:awab111. doi: 10.1093/brain/awab111

Hung, T. M., Tsai, C. L., Chen, F. T., Wang, C. C., and Chang, Y. K. (2013). The immediate and sustained effects of acute exercise on planning aspect of executive function. *Psychol. Sport Exerc.* 14, 728–736. doi: 10.1016/j.psychsport.2013.05.004

Johnson, L., Addamo, P. K., Selva Raj, I., Borkoles, E., Wyckelsma, V., Cyarto, E., et al. (2016). An acute bout of exercise improves the cognitive performance of older adults. *J. Aging Phys. Act* 24, 591–598. doi: 10.1123/japa.2015-0097

Kamijo, K., Hayashi, Y., Sakai, T., Yahiro, T., Tanaka, K., and Nishihira, Y. (2009). Acute effects of aerobic exercise on cognitive function in older adults. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 64, 356–363.

Kamijo, K., Nishihira, Y., Higashiura, T., and Kuroiwa, K. (2007). The interactive effect of exercise intensity and task difficulty on human cognitive processing. *Int. J. Psychophysiol.* 65, 114–121. doi: 10.1016/j.ijpsycho.2007.04.001

Kline, G. M., Porcari, J. P., Hintermeister, R., Freedson, P. S., Ward, A., McCarron, R. F., et al. (1987). Estimation of VO2max from a one-mile track walk, gender, age, and body weight. *Med. Sci. Sports Exerc.* 19, 253–259.

Knaepen, K., Goekint, M., Heyman, E. M., and Meeusen, R. (2012). Neuroplasticity- Exercise-induced response of peripheral brain-derived neurotrophic factor. *Sports Med.* 40, 765–801. doi: 10.2165/11534530-000000000-00000

Kohmura, Y., Aoki, K., Honda, K., Yoshigi, H., and Sakuraba, K. (2008). The relationship between dynamic visual acuity and saccadic eye movement. *Hum. Perform. Measure.* 5, 23–30.

Lage, C., López-García, S., Bejanin, A., Kazimierczak, M., Aracil-Bolaños, I., Calvo-Córdoba, A., et al. (2021). Distinctive oculomotor behaviors in Alzheimer's disease and frontotemporal dementia. *Front. Aging Neurosci.* 12:603790. doi: 10.3389/fnagi.2020.603790

Lambourne, K., and Tomporowski, P. (2010). The effect of exercise-induced arousal on cognitive task performance: a meta-regression analysis. *Brain Res.* 1341, 12–24. doi: 10.1016/j.brainres.2010.03.091

Laursen, P. B., and Jenkins, D. G. (2002). The scientific basis for high-intensity interval training: Optimising training programmes and maximising performance in highly trained endurance athletes. *Sports Med.* 32, 53–73. doi: 10.2165/00007256-200232010-00003

Lezak, M. D., Howieson, D. B., and Loring, D. W. (2004). *Neuropsychological Assessment*. New York, NY: Oxford University Press.

Liskustyawati, H., Riyadi, S., Sabarini, S. S., Waluyo, and Shidiq, A. A. P. (2020). Level of physical fitness of elderly people from 60 to 80 years old during a pandemic COVID-19. *Health Sport Rehab.* 6, 27–38. doi: 10.34142/hsr.2020.06.04.03

Liu, Y. P., Huang, T. S., Tung, C. S., and Lin, C. C. (2015). Effects of atomoxetine on attention and impulsivity in the five choice serial reaction time task in rats with lesions of dorsal noradrenergic ascending bundle. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 56, 81–90. doi: 10.1016/j.pnpbp.2014.08.007

Lucas, S. J., Cotter, J. D., Brassard, P., and Bailey, D. M. (2015). High-intensity interval exercise and cerebrovascular health: curiosity, cause, and consequence. *J. Cereb. Blood Flow Metab.* 35, 902–911. doi: 10.1038/jcbfm.2015.49

MacAskill, M. R., Graham, C. F., Pitcher, T. L., Myall, D. J., Livingston, L., vanStockum, S., et al. (2012). The influence of motor and cognitive impairment upon visually-guided saccades in Parkinson's disease. *Neuropsychologia* 50, 3338–3347. doi: 10.1016/j.neuropsychologia.2012.09.025

Machado, L., and Rafal, R. D. (2004). Control of fixation and saccades in humans with chronic lesions of oculomotor cortex. *Neuropsychology* 18, 115–123. doi: 10.1037/0894-4105.18.1.115

McMorris, T. (2016). Developing the catecholamines hypothesis for the acute exercise-cognition interaction in humans: Lessons from animal studies. *Physiol. Behav.* 165, 291–299. doi: 10.1016/j.physbeh.2016.08.011

McMorris, T., Myers, S., MacGillvary, W. W., Sexsmith, J. R., Fallowfield, J., Graydon, J. A. N., et al. (2010). Exercise, plasma catecholamine concentrations and decision-making performance of soccer players on a soccer-specific test. *J. Sports Sci.* 17, 667–676. doi: 10.1080/026404199365687

Mirsky, J. B., Heuer, H. W., Jafari, A., Kramer, J. H., Schenk, A. K., Viskontas, I. V., et al. (2011). Anti-saccade performance predicts executive function and brain structure in normal elders. *Cogn. Behav. Neurol.* 24, 50–58. doi: 10.1097/wnn.0b013e318223f6c6

Munoz, B., West, S. K., Rubin, G. S., Schein, D. D., Quigley, H. A., Bressler, S. B., et al. (2000). Causes of blindness and visual impairment in a population of older Americans: the Salisbury Eye Evaluation Study. *Arch. Ophthalmol.* 118, 819–825. doi: 10.1001/archopht.118.6.819

Munoz, D. P., and Everling, S. (2004). Look away: the anti-saccade task and the voluntary control of eye movement. *Nat. Rev. Neurosci.* 5, 218–228. doi: 10.1038/nrn1345

Neggers, S. F. W., Raemaekers, M. A. H., Lampmann, E. E. L., Postma, A., and Ramsey, N. F. (2005). Cortical and subcortical contributions to saccade latency in the human brain. *Eur. J. Neurosci.* 21, 2853–2863. doi: 10.1111/j.1460-9568.2005.04129.x

Pare, M., and Munoz, D. P. (1996). Saccadic reaction time in the monkey: Advanced preparation of oculomotor programs is primarily responsible for express saccade occurrence. *J. Neurophysiol.* 76, 3666–3681. doi: 10.1152/jn.1996.76.6.3666

Park, D. C., and Reuter-Lorenz, P. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annu. Rev. Psychol.* 60, 173–196. doi: 10.1146/annurev.psych.59.103006.093656

Peake, J. M., Tan, S. J., Markworth, J. F., Broadbent, J. A., Skinner, T. L., and Cameron-Smith, D. (2014). Metabolic and hormonal responses to isoenergetic high-intensity interval exercise and continuous moderate-intensity exercise. *Am. J. Physiol. Endocrinol. Metab.* 307, 539–552.

Peltsch, A., Hemraj, A., Garcia, A., and Munoz, D. P. (2011). Age-related trends in saccade characteristics among the elderly. *Neurobiol. Aging* 32, 669–679. doi: 10.1016/j.neurobiolaging.2009.04.001

Petrella, A. F. M., Belfry, G., and Heath, M. (2019). Older adults elicit a single-bout post-exercise executive benefit across a continuum of aerobically supported metabolic intensities. *Brain Res.* 1712, 197–206. doi: 10.1016/j.brainres.2019.02.009

Pierrot-Deseilligny, C., Rivaud, S., Gaymard, B., Müri, R., and Vermersch, A. I. (1995). Cortical control of saccades. *Ann. Neurol.* 37, 557–567. doi: 10.1002/ana.410370504

Pontifex, M. B., Hillman, C. H., Fernhall, B., Thompson, K. M., and Valentini, T. A. (2009). The effect of acute aerobic and resistance exercise on working memory. *Med. Sci. Sports Exerc.* 41, 927–934. doi: 10.1249/mss.0b013e3181907d69

Puhan, M. A., Büsching, G., Schünemann, H. J., VanOort, E., Zaugg, C., and Frey, M. (2006). Interval versus continuous high-intensity exercise in chronic obstructive pulmonary disease: A randomized trial. *Ann. Intern. Med.* 145, 816–825. doi: 10.7326/0003-4819-145-11-200612050-00006

Ranchet, M., Orlosky, J., Morgan, J., Qadir, S., Akinwuntan, A. E., and Devos, H. (2017). Pupillary response to cognitive workload during saccadic tasks in Parkinson's disease. *Behav. Brain Res.* 327, 162–166. doi: 10.1016/j.bbr.2017.03.043

Rikli, R. E., and Jones, C. J. (2012). *Senior Fitness Test Manual*, 2nd Edn. United States: Human Kinetics.

Robinson, D. A. (1981). *Control of eye movements*. Hoboken, NJ: John Wiley & Sons Inc.

Royall, D. R., Palmer, R., Chiodo, L. K., and Polk, J. M. (2005). Executive control mediates memory's association with change in instrumental activities of daily living: the Freedom House Study. *J. Am. Geriatr. Soc.* 53, 11–17. doi: 10.1111/j.1532-5415.2005.53004.x

Sallis, J. F., Haskell, W. L., Wood, P. D., Fortmann, S. P., Rogers, T., Blair, S. N., et al. (1985). Physical activity assessment methodology in the five-city project. *Am. J. Epidemiol.* 121, 91–106. doi: 10.1093/oxfordjournals.aje.a113987

Samani, A., and Heath, M. (2018). Executive-related oculomotor control is improved following a 10-min single bout of aerobic exercise: Evidence from the antisaccade task. *Neuropsychologia* 108, 73–81. doi: 10.1016/j.neuropsychologia.2017.11.029

Schwarck, S., Schmicker, M., Dordevic, M., Rehfeld, M., Müller, N., and Müller, P. (2019). Inter-individual differences in cognitive response to a single bout of physical exercise- A randomized controlled cross-over study. *J. Clin. Med.* 8:1101. doi: 10.3390/jcm8081101

Terao, Y., Fukuda, H., Tokushuge, S., Nomura, Y., Hanajima, R., and Ugawa, Y. (2016). Saccade abnormalities associated with focal cerebral lesions-how cortical and basal ganglia commands shape saccades in humans. *Clin. Neurophysiol.* 127, 2953–2967. doi: 10.1016/j.clinph.2015.07.041

Terao, Y., Fukuda, H., Ugawa, Y., and Hikosaka, O. (2013). New perspectives on the pathophysiology of Parkinson's disease as assessed by saccade performance: A clinical review. *Clin. Neurophysiol.* 124, 1491–1506. doi: 10.1016/j.clinph.2013.01.021

Tjønna, A. E., Lee, S. J., Rognmo, Ø, Stølen, T. O., Bye, A., Haram, P. M., et al. (2008). Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. *Circulation* 118, 346–354.

Tomporowski, P. D. (2003). Effects of acute bouts of exercise on cognition. *Acta Psychol.* 112, 297–324. doi: 10.1016/s0001-6918(02)00134-8

Tsai, C. L., Wang, C. H., Pan, C. Y., Chen, F. C., Huang, T. H., and Chou, F. Y. (2014b). Executive function and endocrinological responses to acute resistance exercise. *Front. Behav. Neurosci.* 8:262. doi: 10.3389/fnbeh.2014.00262

Tsai, C. L., Chen, F. C., Pan, C. Y., Wang, C. H., Huang, T. H., and Chen, T. C. (2014a). Impact of acute aerobic exercise and cardiorespiratory fitness on visuospatial attention performance and serum BDNF levels. *Psychoneuroendocrinology* 41, 121–131. doi: 10.1016/j.psyneuen.2013.12.014

Tsai, C. L., Pan, C. Y., Chen, F. C., and Tseng, Y. T. (2017b). Open- and closed-skill exercise interventions produce different neurocognitive effects on executive functions in the elderly: A 6-month randomized, controlled trial. *Front. Aging Neurosci.* 9:294. doi: 10.3389/fnagi.2017.00294

Tsai, C. L., Huang, T. H., and Tsai, M. C. (2017a). Neurocognitive performances of visuospatial attention and the correlations with metabolic and inflammatory biomarkers in adults with obesity. *Exp. Physiol.* 102, 1683–1699. doi: 10.1113/ep086624

Tsai, C. L., Pai, M. C., Ukropec, J., and Ukropcová, B. (2016a). The role of physical fitness in the neurocognitive performance of task switching in older persons with mild cognitive impairment. *J. Alzheimers Dis.* 53, 143–159. doi: 10.3233/jad-151093

Tsai, C. L., Pan, C. Y., Chen, F. C., Wang, C. H., and Chou, F. Y. (2016b). Effects of acute aerobic exercise on a task-switching protocol and brain-derived neurotrophic factor concentrations in young adults with different levels of cardiorespiratory fitness. *Exp. Physiol.* 101, 836–850. doi: 10.1113/ep085682

Tsai, C. L., Pai, M. C., Ukropec, J., and Ukropcová, B. (2019a). Distinctive effects of aerobic and resistance exercise modes on neurocognitive and biochemical changes in individuals with mild cognitive impairment. *Curr. Alzheimer Res.* 16, 316–332. doi: 10.2174/1567205016666190228125429

Tsai, C. L., Pan, C. Y., Chen, F. C., Huang, T. H., Tsai, M. C., and Chuang, C. Y. (2019b). Differences in neurocognitive performance and metabolic and inflammatory indices in male adults with obesity as a function of regular exercise. *Exp. Physiol.* 104, 1650–1660. doi: 10.1113/ep087862

Tsai, C. L., Pan, C. Y., Tseng, Y. T., Chen, F. C., Chang, Y. C., and Wang, T. C. (2021). Acute effects of high-intensity interval training and moderate-intensity continuous exercise on BDNF and irisin levels and neurocognitive performance in late middle-aged and older adults. *Behav. Brain Res.* 413:113472. doi: 10.1016/j.bbr.2021.113472

Tsai, C. L., Ukropec, J., Ukropcová, B., and Pai, M. C. (2018). An acute bout of aerobic or strength exercise specifically modifies circulating exerkine levels and neurocognitive functions in elderly individuals with mild cognitive impairment. *Neuroimage Clin.* 17, 272–284. doi: 10.1016/j.nicl.2017.10.028

Tsukamoto, H., Suga, T., Takenaka, S., Tanaka, D., Takeuchi, T., Hamaoka, T., et al. (2016). Greater impact of acute high-intensity interval exercise on post-exercise executive function compared to moderate-intensity continuous exercise. *Physiol. Behav.* 155, 224–230. doi: 10.1016/j.physbeh.2015.12.021

Verburgh, L., Königs, M., Scherder, E. J., and Oosterlaan, J. (2014). Physical exercise and executive functions in preadolescent children, adolescents and young adults: a meta analysis. *Br. J. Sports Med.* 48, 973–979. doi: 10.1136/bjsports-2012-091441

Weiler, J., and Heath, M. (2014). Oculomotor task switching: alternating from a nonstandard to a standard response yields the unidirectional prosaccade switch-cost. *J. Neurophysiol.* 112, 2176–2184. doi: 10.1152/jn.00352.2014

Weiler, J., Hassall, C. D., Krigolson, O. E., and Heath, M. (2015). The unidirectional prosaccade switch-cost: electroencephalographic evidence of task-set inertia in oculomotor control. *Behav. Brain Res.* 278, 323–329. doi: 10.1016/j.bbr.2014.10.012

Wurtz, R. H., and Albano, J. E. (1980). Visual-motor function of the primate superior colliculus. *Ann. Rev. Neurosci.* 3, 189–226. doi: 10.1146/annurev.ne.03.030180.001201

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The Visuospatial and Sensorimotor Functions of Posterior Parietal Cortex in Drawing Tasks: A Review

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Drawing is a comprehensive skill that primarily involves visuospatial processing, eye-hand coordination, and other higher-order cognitive functions. Various drawing tasks are widely used to assess brain function. The neuropsychological basis of drawing is extremely sophisticated. Previous work has addressed the critical role of the posterior parietal cortex (PPC) in drawing, but the specific functions of the PPC in drawing remain unclear. Functional magnetic resonance imaging and electrophysiological studies found that drawing activates the PPC. Lesion-symptom mapping studies have shown an association between PPC injury and drawing deficits in patients with global and focal cerebral pathology. These findings depicted a core framework of the fronto-parietal network in drawing tasks. Here, we review neuroimaging and electrophysiological studies applying drawing paradigms and discuss the specific functions of the PPC in visuospatial and sensorimotor aspects. Ultimately, we proposed a hypothetical model based on the dorsal stream. It demonstrates the organization of a PPC-centered network for drawing and provides systematic insights into drawing for future neuropsychological research.

Keywords: drawing, posterior parietal cortex, sensorimotor integration, visuospatial abilities, dementia, constructional apraxia

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DRAWING TASKS

Drawing is a unique high-order human ability that transforms mental representations into fine hand movements (La Femina et al., 2009; McCrea, 2014). Drawing tasks are widely used in the clinical assessment of brain function for their easy availability and high efficiency. Performing drawing tests requires only a pen and a piece of paper, but the drawing performance yields a wealth of information on the cognitive abilities of the drawer. By evaluating the drawing performance of patients, neurologists detect cerebral injuries (Gainotti and Trojano, 2018; Rusconi, 2018), make the diagnosis of dementia (Tan et al., 2015; Salimi et al., 2018), discriminate easily confused diseases (Tan et al., 2015; Salimi et al., 2019), and predict the development of cognitive decline (Youn et al., 2021). Recently, the value of drawing tasks has attracted much attention for their sensitivity in detecting visuospatial symptoms, which are identified as early diagnostic biomarkers for Alzheimer's disease (AD) and Parkinson's disease (PD; Mandal et al., 2012; Zhu et al., 2020; Aarsland et al., 2021; Robinson et al., 2021).

Drawing tasks can be classified into externally-cued (e.g., copying from an existing model) and internally-cued drawings (e.g., drawing from memory and imagery) according to the stimuli (Yuan and Brown, 2014, 2015; Griffith and Bingman, 2020). Moreover, drawing a familiar object (objective drawing) is distinguished from drawing unfamiliar or meaningless stimuli (nonobjective drawing; Yuan and Brown, 2015; Griffith and Bingman, 2020; Raimo et al., 2021). In addition, the need for creativity, complexity of stimuli, and other attributes should also be considered when performing drawing tasks (see **Table 1**, **Figure 1A**; Saggar et al., 2017).

To interpret the neural substrates of drawing, several theoretical neuropsychological models have been developed (Roncato et al., 1987; Sommers, 1989; Grossi, 1991; La Femina et al., 2009; McCrea, 2014). One of the most accepted cognitive models of drawing proposed by Sommers et al. posited that drawing mainly relies on visual perception and graphic production systems (Sommers, 1989; Guérin et al., 1999). Additionally, Roncato et al. (1987) presumed four stages in the externally-cued drawing: exploring the model, preparing the drawing plane, executing the drawing plan, and comparing the drawing to the model. La Femina et al. (2009) organized the drawing procedure into preliminary analysis, preparation of drawing plan, execution, and control processes. From the above theories, it can be concluded that visuospatial encoding of visual representations (visuospatial function) and execution of sensory-guided movements (sensorimotor function) are two fundamental components involved in drawing (McCrea, 2014). Certainly, other cognitive domains such as lexical semantics, visual imagination, and memory processes, may be engaged under specific drawing circumstances (Roncato et al., 1987; Trojano et al., 2009; Paula et al., 2013; Senese et al., 2015; Trojano and Gainotti, 2016).

Visuospatial abilities include the intelligence to specify the parts and overall configuration of a percept, appreciate its position in space, integrate a coherent spatial framework, and perform mental operations on spatial concepts (Salimi et al., 2018). In drawing situations, visuospatial processing produces mental images drawn from the stimuli, which are subsequently transformed into limb movements. Sensorimotor integration is the ability to incorporate sensory inputs from the body and the environment to inform and shape motor output (Edwards et al., 2019). In drawing tasks, sensory inputs provide information about the position of the hand and guide the hand to reach the target loci on canvas. The posterior parietal cortex (PPC) plays a critical role in visuospatial (Whitlock, 2017; Xu, 2018; Hadjidimitrakis et al., 2019) and sensorimotor functions (Chivukula et al., 2019; Edwards et al., 2019). Under the grand frame of the drawing model, here we endeavor to depict the visuospatial and sensorimotor aspects which are specified to be highly associated with the PPC in drawing tasks (Averbeck et al., 2009; Raimo et al., 2021). To better understand the functions of PPC in drawing tasks, we reviewed neuroimaging and electrophysiological studies investigating the anatomic-clinical correlates.

THE ANATOMY OF THE PPC

The PPC comprises the superior parietal lobule (SPL), inferior parietal lobule (IPL), and intraparietal sulcus (IPS). This anatomical region can be approximately equal to the Brodmann Area 5 (BA5), BA7, BA39, and BA40 (Whitlock, 2017; Caspers and Zilles, 2018). The medial portion of the parietal lobe is the precuneus (preCun). The IPL consists of the supramarginal gyrus (SMG, BA40) and the angular gyrus (AG, BA39). The SPL and IPL are further subdivided into a mosaic of cytoarchitectonically distinct areas (Caspers and Zilles, 2018).

The PPC is one of the key association cortices in the brain. It is adjacent to the postcentral gyrus, the occipital and temporal lobes connecting the distant frontal lobe and subcortical regions through the superior longitudinal fasciculus, middle longitudinal fasciculus, and arcuate fasciculus (Caspers and Zilles, 2018).

THE ASSOCIATION BETWEEN DRAWING AND PPC

Drawing Activates the PPC

Numerous functional magnetic resonance imaging (fMRI) and electrophysiological studies have shown that drawing tasks activate the PPC (see **Table 2**). Activation likelihood estimation (ALE) research on fMRI has identified the specific role of IPL and preCun in the core fronto-parietal network by drawing (Raimo et al., 2021).

The intended drawing starts with the encoding of mental representations from either externally or internally-cued stimuli (McCrea, 2014). Externally-cued drawing requires the drawer to directly observe and reproduce the existing model (Tchalenko and Chris Miall, 2009; Perdreau and Cavanagh, 2015). Copying from a model activated more visual processing regions, such as the middle occipital gyrus, cuneus, and lingual gyrus, than internally-cued drawing (Ferber et al., 2007; Ogawa and Inui, 2009; Saggar et al., 2015). The information of visual perception

TABLE 1 | Comparison of common clinical drawing tests.

Drawing tests	Stimuli	Symmetry of the stimuli	Elements of the stimuli
MMSE-PCT (Folstein et al., 1975)	EC, NO	Bilateral	Pentagons
MoCA-CDT (Nasreddine et al., 2005)	IC, O	Central	Circle, lines, and numbers
MoCA-Cube copying (Nasreddine et al., 2005)	EC, O	Central	Squares and parallelogram
ROCFC (Shin et al., 2006)	EC and IC, NO	None	Multiple regular geometric figures
Human face copying (Schaer et al., 2012)	EC, O	Bilateral	Curves and irregular geometric figures
Torrance Tests of Creative Thinking (Torrance, 1972)	IC, NO/O	Unrestricted	Geometrical figures

Abbreviations: CDT, clock drawing test; EC, externally-cued drawing; IC, internally-cued drawing; MMSE, Mini-mental state examination; MoCA, Montreal Cognitive Assessment; NO, nonobjective; O, objective; PCT, pentagon copying test; ROCFC, Rey-Osterrieth complex figure copying.

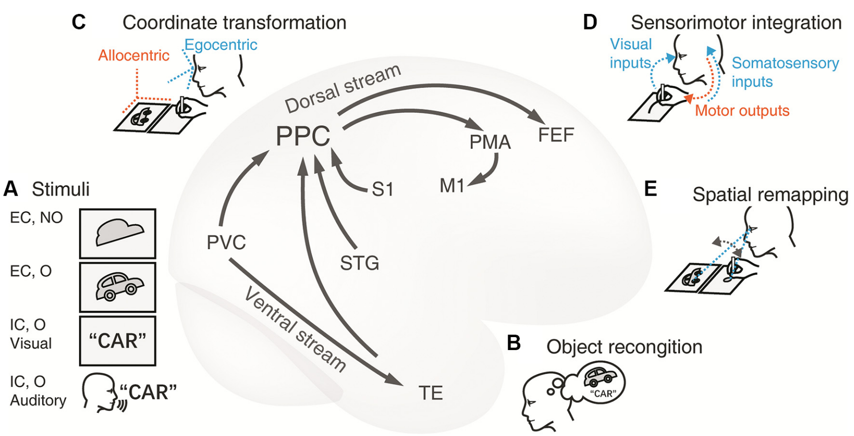

FIGURE 1 | Cortical neural circuitry underlying the visuospatial and sensorimotor functions of PPC in drawing tasks. **(A) Stimuli.** The first card with an irregular shape is an externally-cued nonobject stimulus and the contour of a car in the second card represents an external objective cue. The card with a word and the auditory instructions are instances of the internal cue of familiar objects. The primary visual cortex (PVC) and the superior temporal gyrus (STG) process the visual and auditory stimuli respectively. The information is subsequently conveyed to the adjacent PPC. **(B) Object recognition.** Transfer of object visual information to the temporal lobe through the ventral stream. The inferior temporal lobe is recruited to recognize and name the object presented. This conceptual information is then passed to the PPC through the connections between the dorsal and ventral streams. This extra procedure facilitates the construction of graphical representation to be drawn. **(C) Coordinate transformation.** The movement of limbs is encoded within the egocentric coordination, thus, the visual representation from the allocentric (world-centered) coordinate frame is transformed to an egocentric one (e.g., eye-centered or body-centered) in the PPC. **(D) Sensorimotor integration.** The PPC integrates multidimensional inputs of vision and somatosensory from the PVC and the primary somatosensory cortex (S1) respectively. These sensory inputs together determine the current position of the limb and provide guidance for planning and adjusting the trajectory toward the target on the canvas in the PPC. Then the premotor area (PMA) encodes the motor commands, and the primary motor cortex (M1) programs the motor signals and projects to the limb. As a result, the hand/pen moves to shape the final figure on the paper. **(E) Spatial remapping.** The PPC is communicated to the frontal eye fields (FEE) during saccades, which ensures the consistency of the graphical representations between the model and the copy. Abbreviations: EC, external cue; FEF, frontal eye fields; IC, internal cue; M1, primary motor cortex; MTL, medial temporal lobe; NO, nonobject; O, object; PMA, premotor area; PPC, posterior parietal cortex; PVC, primary visual cortex; S1, primary somatosensory cortex; STG, superior temporal gyrus; TE, rostral inferior temporal cortex.

was conveyed to the PPC, given that drawing activates the projection from the occipital cortex to the IPS (Yuan and Brown, 2014). The activation of the occipito-parietal network reflects the demand for intensive visual perception, visuospatial working memory, and attention remapping components (Ferber et al., 2007; Yuan and Brown, 2014). Given that the PPC and posterior inferior temporal sulcus (pITS, BA37) were activated when the subjects named and drew the object (Makuuchi et al., 2003; Harrington et al., 2009), it was implied that the PPC links the procedure of object recognition to the drawing processes (Ino et al., 2003; Makuuchi et al., 2003; Kravitz et al., 2011; Milner, 2017), by which the information from the ventral "what" pathway is communicated to the dorsal "how" stream.

For most internally-cued drawing tasks, the drawer usually obtains the stimuli by reading or listening to a text instruction instead of viewing graphical stimuli (Ino et al., 2003; Harrington et al., 2007, 2009; Yuan and Brown, 2014; Potgieser et al., 2015; Saggar et al., 2015). These paradigms engage lexical-semantic systems and memory retrieval to generate mental representations of the object (Gainotti et al., 1983; Ellamil et al., 2012; Coslett and Schwartz, 2018). It is supported by the fact that the left fronto-temporo-parietal network, including the temporal lobe, dorsolateral prefrontal cortex, and dorsal anterior cingulate cortex, is activated when the subjects draw a familiar object from memory (Harrington et al., 2009; Ellamil et al., 2012). The left IPL, the reading area, participates in semantic processing in the internally-cued drawing (Ellamil et al., 2012; Saggar et al., 2015; Bzdok et al., 2016; Coslett and Schwartz, 2018). Some tasks require the subjects to create or design novel objects (Chen Q. et al., 2020). Such creative drawing tasks may require elaborate mental imagery and spatial transformation. The PPC plays a causal role in mental rotation ability, which manipulates figural elements and assembles them into a whole (Hawes et al., 2019). Contrastingly, some studies found that parietal activation was relatively suppressed in the creation stage (Kowatari et al., 2009; Saggar et al., 2017) while cerebellar–prefrontal connectivity was activated in improvisation (Saggar et al., 2017). The prefrontal cortex (PFC), especially the dorsolateral prefrontal cortex (dlPFC), is essential for creativity (Chen Q. et al., 2020).

ALE analysis based on fMRI studies supported greater activation including the posterior IPS, right frontal eye field, right fusiform gyrus, and the cerebellum in copying tasks than in memory-based drawing. This indicates the need for more frequent saccades and more intensive visuospatial processing under copying conditions (Yuan and Brown, 2015). In contrast, internally-cued drawings elicit distinct activation of bilateral dlPFC, the occipital-temporal region of the ventral stream (Griffith and Bingman, 2020). The difference in activated patterns is consistent with the involvement of the dorsal and ventral pathways in different drawing paradigms.

TABLE 2 | The activation of the PPC in drawing tests from fMRI studies.

Investigators	Sample size	Drawing tests	Related brain areas (function/process)
Ino (Ino et al., 2003)	18	CDT	SPL, IPS, dPMA, preSMA, vPFC, precentral gyrus, and cerebellum.
Makuuchi (Makuuchi et al., 2003)	17	Object drawing and naming	SPL, IPS, SMG PostITS and vPMA (object recognition).
Ferber (Ferber et al., 2007)	20	Drawing from memory and copying	Cuneus, LG, and ACC (copying vs. drawing from memory).
Gowen and Miall (Gowen and Miall, 2007)	10	Tracing and drawing shapes	Right cerebellar crus I, preSMA, dPMC, right SPL/preCun, and left preCun (drawing vs. tracing).
Harrington (Harrington et al., 2007)	11	Drawing and writing	BA 37 (naming), BA 44 (execution and imagery of movement), BA 7 (spatial processing), BA 40 (motor attention and working memory), FEF (eye movement).
Harrington (Harrington et al., 2009)	8	Objective and nonobjective drawing	ITG, FG, aIFG, and IPL (familiar objects vs. nonobject); IFG and ITG (semantic process).
Kowatari (Kowatari et al., 2009)	20	Designing new pens	PFC-parietal Network (creativity); training exerts a direct effect on the left parietal cortex.
Miall (Miall et al., 2009)	13	Cartoon faces drawing	Lateral occipital lobe and FFA (face processing); PPC and frontal lobe (drawing from memory).
Schaer (Schaer et al., 2012)	20	Portrait drawing	FFA and higher visual cortex (face recognition); PreCun (allocentric coordinate encoding); IPS and cerebellum (feedback during motor feedback).
Ellamil (Ellamil et al., 2012)	15	Book cover designing	MTL, dlPFC, dACC (creative generation); mPFC, PCC/preCun, TPJ (creative evaluation).
Yuan and Brown (Yuan and Brown, 2014)	15	Blind drawing, copying, and visual perception	M1, SMA, cerebellum (hand movement); FEF (eye movement) V5/MT+, V3A, LO (visual motion perception); SPL, IPL, and IPS (visuomotor coupling).
Garbarini (Garbarini et al., 2014)	12	Real and imagery tasks	preSMA, PPC (bimanual coupling); right SPL (mediating spatial interference); left PPC (motor imagery).
Park (Park et al., 2015)	48	Figural Torrance Tests of Creative Thinking	bilateral ITG, left IG, left PL, right AG, PFC (creativity).
Saggar (Saggar et al., 2015)	30	Word-guessing game of Pictionary	Cerebellum, thalamus, left parietal cortex, right SFG, left PFC and paracingulate/cingulate regions.
Saggar (Saggar et al., 2017)	36	Word-guessing game of Pictionary	DLPFC, ACC/PCC, SMA, and parietal regions (executive functioning); cerebellar–frontal connectivity (spontaneous implicit).
Talwar (Talwar et al., 2019)	33	CDT	Fontal, occipital and parietal lobes; DNN negative activation.

Abbreviations: ACC, anterior cingulate cortex; CDT, clock drawing test; dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; dPMC, dorsal premotor cortex; DNN, default neural network; dPMA, dorsal premotor area; FEF, frontal eye field; FFA, fusiform face area; IPS, intraparietal sulcus; ITS, inferior temporal sulcus; LG, lingual gyrus; LO, lateral occipital region; M1, the primary motor cortex; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; PFC, prefrontal cortex; preCun, precuneus; preSMA, pre-supplementary motor area; SFG, superior frontal gyrus; SMA, supplementary motor area; SMG, supramarginal gyrus; SPL, superior parietal lobe; TPJ, temporoparietal junction; V5/MT+, visual area 5/middle temporal complex; V3A, visual area 3; vPFC, ventral prefrontal cortex; vPMA, ventral premotor area.

Visuospatial encoding is followed by the production and output of limb movements. In an fMRI study (Ino et al., 2003), subjects were blindfolded and asked to draw the clock hands at a given time with their index finger. The bilateral SPL, IPS, together with the dorsal premotor area, supplementary motor area, ventral prefrontal cortex, precentral gyrus, and cerebellum were activated in this blind drawing test, suggesting the involvement of the PPC in encoding the movement of drawing. Generally, almost all paradigms that require hand-drawing have reported the activation of bilateral premotor area (BA 6), IPL (BA 40), preCun, and SPL (BA 7; Raimo et al., 2021).

To confirm that activation is associated with the intended drawing, the activation pattern during drawing was compared to that under nonmotor conditions (Harrington et al., 2007, 2009; Schaer et al., 2012; Yuan and Brown, 2014; Talwar et al., 2019; Raimo et al., 2021) and non-drawing hand movements (Ferber et al., 2007; Gowen and Miall, 2007; Ogawa and Inui, 2009; Potgieser et al., 2015; Saggar et al., 2015). Compared with nonmotor tasks, more widespread regions included the IPL (BA 40), precentral gyrus, premotor area (PMA), and supplementary motor area (SMA), and the cerebellum, were activated in drawing. Similarly, in contrast to non-drawing hand tasks, drawing recruits more areas of the PMA, SMA, and SPL (Raimo et al., 2021). These results show that PPC also contributes to planning the limb movements in addition to the frontal motor area and the cerebellum (Chivukula et al., 2019). This aligns with the idea that the IPL constructs the spatial representation while the SPL is connected with visuospatial working memory and sensorimotor processing (McCrea, 2014; Griffith and Bingman, 2020; Raimo et al., 2021). Collectively, these results addressed the core function of the fronto-parietal network in the drawing.

The apparent role of the PPC and the dorsal visual network in drawing was also demonstrated by electrophysiological evidence. High-density electroencephalogram (EEG) showed that the parietal and occipital regions were associated with event-related desynchronization (ERD) activity in the low-frequency theta/alpha range (van der Meer and van der Weel, 2017). This pattern of ERD activity could enhance the involved neurons for visual processing and sensorimotor integration, resulting in cortical activation at the macro level. The desynchronized alpha-range (8–10 Hz) and beta-range (12–30 Hz) activities were more pronounced in drawing than handwriting which may represent the stage of constructing the figure form (Ose Askvik et al., 2020).

PPC Lesions Cause Drawing Deficits

In the early 20th century, researchers noticed connections between parietal lesions and visuospatial impairments (Balint, 1909; Strauss, 1924; Mayer-Gross, 1935). Constructional apraxia (CA) is one of the most common manifestations observed in patients with parietal injury. Noninvasive neuroimaging and electrophysiological techniques facilitate the precise mapping of brain lesions with symptoms and better understand the pathogenesis of CA. Here, we discuss the lesion-symptom relationships in patients with global or bilateral cerebral injury (e.g., AD, frontotemporal dementia, and PD, see **Table 3**), and focal brain injury (e.g., stroke and tumors, see **Table 4**), respectively.

The volume loss of the PPC causes significant visuospatial impairment, leading to CA in drawing tests (Lehmann et al., 2011; Crutch et al., 2012, 2017). Zink et al. reported that the thickness of the left parietal cortex could predict the performance of the patient on the visuospatial memory test. In contrast, the right parietal thickness predicted the performance on a block-design test (Zink et al., 2018), indicating hemispheric dominance for visuospatial working memory and visuospatial construction. The scores of the clock drawing test (CDT) were negatively correlated with the thickness of the right PPC and preCun (Matsuoka et al., 2011), SMG, and bilateral temporal lobes (Hirjak et al., 2017) in the AD population. AD patients with CA show more severe atrophy of the right preCun and AG than those without CA (Serra et al., 2014). Specifically, it is inferred that the preCun is critical for placing the figure, the AG is involved in salient object detection and spatial attention reorientation, and the SMG is the necessity for the control of elaborate reaching movements (Karnath, 2001; Gharabaghi et al., 2006; Xu, 2018).

In addition to structural changes, hypoperfusion and decreased metabolism of PPC undermine the performance of the drawing tests. Decreased regional cerebral glucose metabolism in the right IPL and posterior cingulate cortex is associated with poor performance on the CDT in patients with AD (Lee et al., 2008). Temporal-parietal, occipital, and frontal lobes were correlated with the performance of Rey-Osterrieth complex figure copying (ROCFC; Melrose et al., 2013). Shon et al. (2013) detected metabolic activity in PPC with positron emission tomography under both memory-based drawing and model-based copying. Drawing from memory recruited the left frontal cortex in addition to the PPC, indicating greater demand for the executive ability for the task, highlighting the functional specialization of the visuospatial processing in PPC.

Compared with the neural degeneration disease which generally injures the whole brain, studies in patients with unilateral and focal lesions due to ischemic infarction or tumors can reveal the more precise causal relationship between PPC injury and CA. Voxel-based lesion-symptom mapping (LSM) is usually adopted for such analysis (Bates et al., 2003; Karnath et al., 2018). These studies strongly support the idea that damaging the PPC or interrupting the fibers that pass through the dorsal stream network leads to CA, which indicate the specific role of PPC in visuospatial perceptual and constructional processing (**Table 4**, Vocat et al., 2010; Chechlacz et al., 2014; Chen et al., 2016; Toba et al., 2018).

The different impaired subregions of the PPC exhibited distinct drawing errors. A clock-drawing study found that whether the clock hands were properly oriented was correlated with metabolism in the bilateral PPC, right occipital lobe, right posterior temporal lobe, and right middle frontal gyrus; whether the numbers were correctly arranged and placed on the clock face was influenced by the metabolism of the temporal lobe (Matsuoka et al., 2013). Furthermore, the number loss was attributed to hypometabolism in the right BA40 and the uneven spacing between the numbers of hypometabolism in the right BA40 and BA7 (Nakashima et al., 2016). These results support the dominance of the right PPC in spatial processing by correctly orienting and placing the figure elements. A voxel-based morphology study suggested that injury to the right PPC was associated with visuospatial errors in CDT, and left PPC dysfunction resulted in time-setting errors (Tranel et al., 2008). Biesbroek et al. (2014) compared the anatomic correlates for the complex figure copying and the judgment of line orientation (JLO) test, and found that constructional abilities rely on the integrity of the right SPL, IPL, AG, and middle occipital gyrus (MOG). In another voxel-based LSM study, Chechlacz et al. found that right AG injury was more likely to cause errors in the left part of the figure, while damage to the right AG, IPS, and left preCun were related to inaccuracy in the right part. Furthermore, the left calcarine cortex, temporoparietal junction, and insular gyrus might process detailed local elements, whereas the right MTG organized the overall framework (Chechlacz et al., 2014).

Although these findings emphasized the close correlation between PPC injury and drawing deficits, this does not mean that drawing errors specifically indicate PPC dysfunction. Poor performance in drawing tasks due to the damage of occipital, temporal, frontal lobe, and basal ganglion was also mentioned in most LSM results. Of note, some characteristics of the drawing or specific categories of errors were significantly correlated with the PPC, such as the left part errors in complex figure with the right AG (Chechlacz et al., 2014), and the orientation errors with the SMG (Nakashima et al., 2016; Van der Stigchel et al., 2018).

Electroencephalographic studies have found altered activity in patients with cerebral disease and showing difficulties in drawig. Compared with other structures, EEG slowing of the parietal cortex was associated with visuospatial dysfunction in patients with PD (Eichelberger et al., 2017). The reduction in the alpha/theta ratio of the right posterior region (Jaramillo-

TABLE 3 | Correlations between the PPC and drawing deficits in patients with global brain injury.

Investigators	Drawing tests	Diseases	Imaging method	Related brain areas
Matsuoka (Matsuoka et al., 2011)	CDT	AD, MCI	MRI	Right parietal lobe (general); right posterior ITG, preCun, PTL, left MTG and STG (Shulman criteria); right preCun, posterior ITG (Rouleau criteria); right posterior STG (CLOX1 criteria).
Possin (Possin et al., 2011)	Benson figure copying	AD, bvFTD	MRI	PPC (AD); dlPFC (bvFTD).
Serra (Serra et al., 2014)	Figure drawing, copying	AD	MRI	BA7, BA37, BA21, BA39, BA23/31, BA18.
Barrows (Barrows et al., 2015)	CDT	AD, BvFTD	MRI	Dorsolateral frontal-parietal network (executive hand placement).
Hirjak (Hirjak et al., 2017)	CDT	AD	MRI	Bilateral temporal lobe, IPL, and right SMG.
Van der Stigchel (Van der Stigchel et al., 2018)	PCT	AD	MRI	Right parietal lobe but not frontal lobe (spatial remapping).
Zink (Zink et al., 2018)	BVMT, JoLO, BDT	Dementia, dyskinesia	MRI	Right parietal lobe (BDT); left parietal lobe (BVMT-R); Temporal lobe (JoLO).
Lee (Lee et al., 2008)	CDT	AD	PET	IPL and PCC
Takahashi (Takahashi et al., 2008)	CDT	AD	PET	Left parietal lobe, AG, bilateral hippopotamus.
Shon (Shon et al., 2013)	CDT	AD	PET	Bilateral temporoparietal lobe and left MTG (drawing from memory), bilateral temporoparietal lobe (copying).
Matsuoka (Matsuoka et al., 2013)	CDT	AD	PET	Bilateral parietal lobe, posterior temporal lobe, and right MTG (total score); bilateral parietal lobe, right posterior temporal lobe, occipital lobe, and MFG (clock hands orientation).
Melrose (Melrose et al., 2013)	ROCFC	AD	PET	Bilateral temporal-parietal cortex and occipital lobe, and right frontal lobe.
Nakashima (Nakashima et al., 2016)	CDT	AD	SPECT	BA40 (number loss), BA40, and BA7 (uneven spacing among the numbers).
Yoshii (Yoshii et al., 2018)	ADAS-Jcog	AD	SPECT	Right parietal lobe, STG, MTG, AG, and PCC.

Abbreviations: ACE, Addenbrooke's Cognitive Examination; AD, Alzheimer's disease; ADAS-Jcog, Alzheimer's Disease Assessment Scale, Cognitive Subscale (Japanese version); AG, angular gyrus; BDT, block design test; BVMT, Brief Visuospatial Memory Test-Revised Copying Trial; bvFTD, behavioral variant of frontotemporal dementia; CDT, Clock Drawing Test; CLOX1, Clock Drawing Task 1; dlPFC, dorsolateral prefrontal cortex; IPL, inferior parietal lobe; ITG, inferior temporal gyrus; JoLO, Judgment of Line Orientation test; MCI, mild cognitive impairment; MFG, middle frontal gyrus; MRI, magnet renounce imagination; MTG, middle temporal gyrus; PET, positron emission tomography; PCC, posterior cingulate cortex; PTL, posterior temporal lobe; preCun, precuneus; ROCFC, Rey-Osterrieth complex figure copying; SPECT, single-photon emission computed tomography; STG, superior temporal gyrus; VOSP, Visual Object and Space Perception.

Jimenez et al., 2021) and parietal sigma EEG abnormalities during non-rapid eye movement sleep may be predictors of dementia (Latreille et al., 2016; Jaramillo-Jimenez et al., 2021).

THE FUNCTIONS OF PPC IN DRAWING

Visuospatial Processing

Unerringly encoding the object to be drawn is a prerequisite for drawing accurately. An essential procedure of this step is to transform the spatial representation of the object from an allocentric (world-centered) space to an egocentric (body-centered) space (Buneo and Andersen, 2006; Ekstrom et al., 2017). This process is termed coordinated transformation. With this egocentric reference frame, the individual can manipulate the hand movements to reach the target on canvas (Jackson and Husain, 2006; Filimon, 2015; Edwards et al., 2019).

The PPC plays an important role in egocentric coordinate transformation. In nonhuman primates, the lateral and ventral intraparietal areas are important for egocentric-allocentric transformation (Cohen and Andersen, 2002; Chen et al., 2018). In humans, the PPC, especially the right PPC, encodes egocentric information during the perception and exploration of the peripersonal space (Chokron, 2003; Sherrill et al., 2015). Evidence demonstrated the activation of the IPS in blind drawing (Ino et al., 2003), tracing, and figure copying tasks (Ogawa and Inui, 2009), indicating its involvement in egocentric representation. Damage to the PPC severely disturbs the egocentric coordinate transformation, causing drawing errors (Chechlacz et al., 2014; Kenzie et al., 2015).

Spatial remapping refers to the operation that updates and integrates the selected visual information and spatial changes of objects into stable, successive visual representations during saccades or shifts of attention (Melcher and Colby, 2008; Wurtz, 2008; Pierce and Saj, 2019). In copying tests, spatial remapping is prominent, as the visual attention is frequently shifted between the model and the copy to ensure consistency. After an attentional shift, the newly acquired visual stimuli are seamlessly integrated into those stored before the saccade.

PPC is vital for spatial remapping operations (Melcher and Colby, 2008; Pierce and Saj, 2019). The neurons that encode saccades and coupling previous and current stimuli are located in the lateral IPS (LIP) of primates (Duhamel et al., 1992; Heiser and Colby, 2006; Subramanian and Colby, 2014; Mirpour and Bisley, 2016). The homologous region, SMG in humans, is

TABLE 4 | Correlations between the PPC and drawing deficits in patients with focal brain injury.

Investigators	Drawing tests	Diseases	Hemisphere	Methods	Related brain areas
Vocat (Vocat et al., 2010)	Gainotti–Ogden figure copying	Ischemic stroke	Right	VLSM	dlPFC, PPC (hyperacute phase); dlPFC, PPC and TPJ (subacute phase).
Chechlacz (Chechlacz et al., 2014)	BCoS figure copying	Stroke	Both	VBM	Right BG, Tha (total score); right IPL, MFG (left egocentric neglect); right IG, left LG and calcarine (relative position); right AG, Put, IG (left asymmetry score); right MTG, ITG, AG, IPS, left PreCun (left asymmetry score); left calcarine, Cun, PreCun, IG, cerebellum (local features); right MTG (global features).
Chen (Chen et al., 2016)	BCoS figure copying	Ischemic stroke	Both	VLSM	Right thalamus, MFG, left IPL, postCG (high-level motor control); right MOG extending to FG, left LG, RO (visuo-motor transformation); right LG, preCun, FG, cerebellum, left IFG (interacting with objects and planning).
Toba (Toba et al., 2018)	GEREN battery	Ischemic stroke	Right	VLSM	Right AG and SMG (neglect); right AG, SLF, and IFOF (copying score).
Tranel (Tranel et al., 2008)	CDT	Multiple causes	Both	PM3	Right parietal lobe (visuospatial errors); left frontal lobe (time concept related errors).
Biesbroek (Biesbroek et al., 2014)	ROCFC, JLO	Ischemic stroke	Right	VLSM	Right frontal lobe, SMG, STG (both ROCFC and JLO); right IPL, SPL, AG, MOG (ROCFC only).
Russell (Russell et al., 2010)	ROCFC, BDT	Stroke	Right	LS	Right temporoparietal junction and IG.
Kenzie (Kenzie et al., 2015)	BIT	Stroke	Right	VLSM	SPL, IPL, STG, MTG (allocentric neglect); PreCG, MFG, IG, Cau (egocentric neglect).
Carson (Carson et al., 2019)	Star and cube copying	Stroke	Both	VLSM	Right STG, IG, RO, TP (presence of neglect); right IG, STG, MTG, SMG (left cube face omission).

Abbreviations: AG, angular gyrus; BDT, block design test; BG, basal ganglion; BIT, Behavioral Inattention Test; Cau, caudate nucleus; dlPFC, dorsolateral prefrontal cortex; FG, fusiform gyrus; IFG, insular gyrus; IFOF, inferior fronto-occipital fasciculus; IG, insular gyrus; IPL, inferior parietal lobe; IPS, intraparietal sulcus; ITG, inferior temporal gyrus; JoLO, judgment of line orientation test; LS, lesion subtraction; MOG, middle occipital gyrus; MTG, middle temporal gyrus; PM3, lesion proportion difference map; postCG, postcentral gyrus; PPC, posterior parietal cortex; preCun, precuneus; Put, putamen; RO, rolandic operculum; ROCFC, Rey-osterrieth complex figure copying test; SLF, superior longitudinal fasciculus; SPL, superior parietal lobe; TP, temporal pole; TPJ, temporoparietal junction; VLSM, voxel-based lesion mapping.

specifically sensitive to detect intrasaccade orientation changes in goal-driven movements and is activated in tasks that depend on spatial remapping (Parks and Corballis, 2010; Pierce et al., 2019; Baltaretu et al., 2020). Spatial remapping impairments explain the failure of patients with CA to copy accurately, leading to disorganized, inaccurate images (Pierce and Saj, 2019; Pierce et al., 2019). Right AG atrophy is associated with spatial remapping dysfunction (Serra et al., 2014). SMG lesions lead to spatial remapping dysfunction deficits and cause errors in the shaping and orientation of the pentagons during the pentagons copying task (Van der Stigchel et al., 2018).

Sensorimotor Integration

Intrinsically, drawing can be decomposed into a series of sensory-guided reaching movements. The shape and position of the figure are essentially determined by the location where the hand or pen reaches (Battaglia-Mayer et al., 2003; Huette et al., 2013). With the guidance of multisensory information, the target is set and the movement scheme is planned. In most conditions, visual information is the dominant form of sensory inputs. For blind drawing tests, inputs from the proprioception and the vestibular system instead guide hand movement.

The PPC coordinates the eyes and hands to modulate reaching movement (Jackson and Husain, 2006; Huette et al., 2013). Specifically, the PPC directs hand placement, adjusts velocity, and amends bias along the trajectory to the targeted loci (Buneo and Andersen, 2006; Jackson and Husain, 2006; Averbeck et al., 2009; Archambault et al., 2011; Battaglia-Mayer et al., 2015). In primates, the anterior intraparietal area (AIP) contains neurons for reaching and hand posture (Chivukula et al., 2019). Several areas have been associated with reaching movement, including the preCun, posterior IPS, occipito-parietal conjunction, superior parietal occipital cortex, and lateral IPS (Karnath and Perenin, 2005; Andersen et al., 2014; Xu, 2018).

Besides, damage to other parts of the parieto-frontal network can also affect the PPC's connection, resulting in visuomotor incoordination (Caminiti et al., 2015; Gainotti and Trojano, 2018). Lesions in the frontal motor cortex that receive projections from PPC cause CA (Chen et al., 2016). Damage to the thalamus, caudate nuclei, and putamen, interrupts the connection between the PPC and the motor cortex, resulting in poor visuospatial construction (Chechlacz et al., 2014; Chen et al., 2016).

A HYPOTHETICAL PPC-CENTERED NEURAL CIRCUITRY FOR DRAWING

According to the classic dual-stream theory, drawing is a typical task of the dorsal or "action" stream (Goodale and Milner, 1992; Freud et al., 2016; Milner, 2017). After that, Kravitz et al. (2011) further identified three branches that projected from the PPC for specific visuospatial skills: (1) the parietal-prefrontal pathway, which is related to visuospatial working memory and visual-guided eye movement; (2) the parietal-premotor pathway, which coordinates the position and movement of body parts with the peripheral environment; and (3) the parietal-medial temporal pathway for spatial navigation (Kravitz et al., 2011). Drawing is highly related to the first two branches. Caminiti et al. described a detailed processing frame for the fronto-parietal network. According to the theory, the sensorimotor functions of the PPC in drawing may encompass (1) visual guided hand movement (SPL); (2) visual guided hand-object coordination (ventral parietal-PMC pathway); and (3) direct kinetic and kinematic limb information processing (somatosensory cortex and medial IPS; Caminiti et al., 2015). Interestingly, drawing tasks just perfectly embody the integrated functions of the dorsal stream and concretize the functional organization of the occipital-parietal-frontal network.

With the anatomic-functional corrections, we propose a plausible model of cortical neural circuitry based on the dorsal visual pathway (**Figure 1**). First, the PPC is involved in the visuospatial processing for constructing the mental graphic representations. In drawing tasks, the stimuli can be either from an external or internal cue (**Figure 1A**). Distinct upstream occipital and temporal areas transmit the information to the PPC. Nonobjective visual stimuli (e.g., the first card with the picture of meaningless shape in **Figure 1A**) are directly processed through the occipital-parietal pathway. Objective stimuli (the second card with the picture of a car in **Figure 1A**) are synchronously recognized and conceptualized in the ventral pathway to facilitate visuospatial processing (**Figure 1B**). Non-graphic internally cued stimuli (the third card with the written word of "car" or the auditory instruction of "car" in **Figure 1A**) are initially comprehended by the semantic system; then, the graphic representation is either created out of nothing or retrieved from long-term memory.

Second, the PPC collects perceptual information, constructs the mental representation, and transforms it into an egocentric coordinate (**Figure 1C**), which is essential for producing limb movement. Meanwhile, the IPL also takes part in spatial manipulation in complex drawing tasks.

Third, the PPC encodes the drawing plan and directs the downstream motor cortex to produce and execute the intended movements (**Figure 1D**). Multiple sensory inputs such as visual perception and somatosensory are integrated for eye-hand and hand-object coordination. In this way, continuous visual feedback guides the hand to complete the drawing task. Additionally, the PPC interacts with the frontal eye area and coordinates the saccades, which are especially required for copying tasks (**Figure 1E**). This model may provide new insight into how the PPC works in the occipital-parietal-frontal network and how the PPC communicates between the dorsal and ventral streams.

CONCLUSIONS AND FUTURE PERSPECTIVES

Drawing tasks are powerful neuropsychological assessment tools. The strategic anatomical location of the PPC and its extensive connections make it a bridge between sensory inputs and motor output. Evidence from fMRI and EEG studies has shown that PPC is activated in different drawing tests, and damage in the PPC is associated with various drawing errors, according to LSM research. These findings suggest that the PPC contributes to both visuospatial and sensorimotor processing in drawing.

As the neural mechanism involved in drawing activity is elusive and multifaceted, many unsolved questions remain. Although the PPC is highlighted in drawing activities, its functions are based on the comprehensive degree of association with other parts of the brain. The functional network for drawing may involve a large scale of networks such as the dorsal stream, execution network, attention network, and memory network (Yuan and Brown, 2015; Griffith and Bingman, 2020). How these complex functional networks are organized remains to be explored in future studies.

Recent studies have focused on the value of visuospatial assessment in the early prediction of dementia (Coughlan et al., 2018; Wang et al., 2020; Aarsland et al., 2021). For better diagnostic efficiency, progress has been made by applying artificial intelligence algorithms to evaluate drawing performance (Chen S. et al., 2020; Youn et al., 2021). It is feasible to anticipate the invention of assessing systems with higher accuracy for the diagnosis and differential diagnosis of cerebral disorders. Finally, despite some studies that have shown the benefits of drawing training in cognitive rehabilitation, drawing as a therapeutic method is still controversial in clinical practice. Further investigations are needed to interpret the therapeutic effect of drawing practice and its potential effect on promoting brain plasticity.

AUTHOR CONTRIBUTIONS

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REFERENCES

Aarsland, D., Batzu, L., Halliday, G. M., Geurtsen, G. J., Ballard, C., Ray Chaudhuri, K., et al. (2021). Parkinson disease-associated cognitive impairment. *Nat. Rev. Dis. Primers* 7:47. doi: 10.1038/s41572-021-00280-3

Andersen, R. A., Andersen, K. N., Hwang, E. J., and Hauschild, M. (2014). Optic ataxia: from Balint's syndrome to the parietal reach region. *Neuron* 81, 967–983. doi: 10.1016/j.neuron.2014.02.025

Archambault, P. S., Ferrari-Toniolo, S., and Battaglia-Mayer, A. (2011). Online control of hand trajectory and evolution of motor intention in the parietofrontal system. *J. Neurosci.* 31, 742–752. doi: 10.1523/JNEUROSCI.2623-10.2011

Averbeck, B. B., Crowe, D. A., Chafee, M. V., and Georgopoulos, A. P. (2009). Differential contribution of superior parietal and dorsal-lateral prefrontal cortices in copying. *Cortex* 45, 432–441. doi: 10.1016/j.cortex.2008.02.007

Balint, R. (1909). Seelenlähmung des "schauens", optische ataxie, räumliche störung der aufmerksamkeit. *Eur. Neurol.* 25, 67–81. doi: 10.1159/000210465

Baltaretu, B. R., Monaco, S., Velji-Ibrahim, J., Luabeya, G. N., and Crawford, J. D. (2020). Parietal cortex integrates saccade and object orientation signals to update grasp plans. *J. Neurosci.* 40, 4525–4535. doi: 10.1523/JNEUROSCI.0300-20.2020

Barrows, R. J., Barsuglia, J., Paholpak, P., Eknoyan, D., Sabodash, V., Lee, G. J., et al. (2015). Executive abilities as reflected by clock hand placement: frontotemporal dementia versus early-onset alzheimer disease. *J. Geriatr. Psychiatry Neurol* 28, 239–248. doi: 10.1177/0891988715598228

Bates, E., Wilson, S. M., Saygin, A. P., Dick, F., Sereno, M. I., Knight, R. T., et al. (2003). Voxel-based lesion-symptom mapping. *Nat. Neurosci.* 6, 448–450. doi: 10.1038/nn1050

Battaglia-Mayer, A., Caminiti, R., Lacquaniti, F., and Zago, M. (2003). Multiple levels of representation of reaching in the parieto-frontal network. *Cereb. Cortex* 13, 1009–1022. doi: 10.1093/cercor/13.10.1009

Battaglia-Mayer, A., Ferrari-Toniolo, S., and Visco-Comandini, F. (2015). Timing and communication of parietal cortex for visuomotor control. *Curr. Opin. Neurobiol.* 33, 103–109. doi: 10.1016/j.conb.2015.03.005

Biesbroek, J. M., Van Zandvoort, M. J., Kuijf, H. J., Weaver, N. A., Kappelle, L. J., Vos, P. C., et al. (2014). The anatomy of visuospatial construction revealed by lesion-symptom mapping. *Neuropsychologia* 62, 68–76. doi: 10.1016/j.neuropsychologia.2014.07.013

Buneo, C. A., and Andersen, R. A. (2006). The posterior parietal cortex: sensorimotor interface for the planning and online control of visually guided movements. *Neuropsychologia* 44, 2594–2606. doi: 10.1016/j.neuropsychologia.2005.10.011

Bzdok, D., Hartwigsen, G., Reid, A., Laird, A. R., Fox, P. T., and Eickhoff, S. B. (2016). Left inferior parietal lobe engagement in social cognition and language. *Neurosci. Biobehav. Rev.* 68, 319–334. doi: 10.1016/j.neubiorev.2016.02.024

Caminiti, R., Innocenti, G. M., and Battaglia-Mayer, A. (2015). Organization and evolution of parieto-frontal processing streams in macaque monkeys and humans. *Neurosci. Biobehav. Rev.* 56, 73–96. doi: 10.1016/j.neubiorev.2015.06.014

Carson, L., Filipowicz, A., Anderson, B., and Danckert, J. (2019). Representational drawing following brain injury. *Neuropsychologia* 133:107154. doi: 10.1016/j.neuropsychologia.2019.107154

Caspers, S., and Zilles, K. (2018). Microarchitecture and connectivity of the parietal lobe. *Handb. Clin. Neurol.* 151, 53–72. doi: 10.1016/B978-0-444-63622-5.00003-6

Chechlacz, M., Novick, A., Rotshtein, P., Bickerton, W. L., Humphreys, G. W., and Demeyere, N. (2014). The neural substrates of drawing: a voxel-based morphometry analysis of constructional, hierarchical and spatial representation deficits. *J. Cogn. Neurosci.* 26, 2701–2715. doi: 10.1162/jocn_a_00664

Chen, Q., Beaty, R. E., and Qiu, J. (2020). Mapping the artistic brain: Common and distinct neural activations associated with musical, drawing and literary creativity. *Hum. Brain Mapp.* 41, 3403–3419. doi: 10.1002/hbm.25025

Chen, X., Deangelis, G. C., and Angelaki, D. E. (2018). Flexible egocentric and allocentric representations of heading signals in parietal cortex. *Proc. Natl. Acad. Sci. U S A* 115, E3305–E3312. doi: 10.1073/pnas.1715625115

Chen, H., Pan, X., Lau, J. K. L., Bickerton, W. L., Pradeep, B., Taheri, M., et al. (2016). Lesion-symptom mapping of a complex figure copy task: a large-scale PCA study of the BCoS trial. *Neuroimage Clin.* 11, 622–634. doi: 10.1016/j.nicl.2016.04.007

Chen, S., Stromer, D., Alabdalrahim, H. A., Schwab, S., Weih, M., and Maier, A. (2020). Automatic dementia screening and scoring by applying deep learning on clock-drawing tests. *Sci. Rep.* 10:20854. doi: 10.1038/s41598-020-74710-9

Chivukula, S., Jafari, M., Aflalo, T., Yong, N. A., and Pouratian, N. (2019). Cognition in sensorimotor control: interfacing with the posterior parietal cortex. *Front. Neurosci.* 13:140. doi: 10.3389/fnins.2019.00140

Chokron, S. (2003). Right parietal lesions, unilateral spatial neglect and the egocentric frame of reference. *Neuroimage* 20, S75–S81. doi: 10.1016/j.neuroimage.2003.09.002

Cohen, Y. E., and Andersen, R. A. (2002). A common reference frame for movement plans in the posterior parietal cortex. *Nat. Rev. Neurosci.* 3, 553–562. doi: 10.1038/nrn873

Coslett, H. B., and Schwartz, M. F. (2018). The parietal lobe and language. *Handb. Clin. Neurol.* 151, 365–375. doi: 10.1016/B978-0-444-63622-5.00018-8

Coughlan, G., Laczó, J., Hort, J., Minihane, A. M., and Hornberger, M. (2018). Spatial navigation deficits - overlooked cognitive marker for preclinical Alzheimer disease? *Nat. Rev. Neurol.* 14, 496–506. doi: 10.1038/s41582-018-0031-x

Crutch, S. J., Lehmann, M., Schott, J. M., Rabinovici, G. D., Rossor, M. N., and Fox, N. C. (2012). Posterior cortical atrophy. *Lancet Neurol.* 11, 170–178. doi: 10.1016/S1474-4422(11)70289-7

Crutch, S. J., Schott, J. M., Rabinovici, G. D., Murray, M., Snowden, J. S., Van Der Flier, W. M., et al. (2017). Consensus classification of posterior cortical atrophy. *Alzheimers Dement.* 13, 870–884. doi: 10.1016/j.jalz.2017.01.014

Duhamel, J. R., Colby, C. L., and Goldberg, M. E. (1992). The updating of the representation of visual space in parietal cortex by intended eye movements. *Science* 255, 90–92. doi: 10.1126/science.1553535

Edwards, L. L., King, E. M., Buetefisch, C. M., and Borich, M. R. (2019). Putting the "sensory" into sensorimotor control: the role of sensorimotor integration in goal-directed hand movements after stroke. *Front. Integr. Neurosci.* 13:16. doi: 10.3389/fnint.2019.00016

Eichelberger, D., Calabrese, P., Meyer, A., Chaturvedi, M., Hatz, F., Fuhr, P., et al. (2017). Correlation of visuospatial ability and EEG slowing in patients with Parkinson's disease. *Parkinsons Dis.* 2017:3659784. doi: 10.1155/2017/3659784

Ekstrom, A. D., Huffman, D. J., and Starrett, M. (2017). Interacting networks of brain regions underlie human spatial navigation: a review and novel synthesis of the literature. *J. Neurophysiol.* 118, 3328–3344. doi: 10.1152/jn.00531.2017

Ellamil, M., Dobson, C., Beeman, M., and Christoff, K. (2012). Evaluative and generative modes of thought during the creative process. *Neuroimage* 59, 1783–1794. doi: 10.1016/j.neuroimage.2011.08.008

Ferber, S., Mraz, R., Baker, N., and Graham, S. J. (2007). Shared and differential neural substrates of copying versus drawing: a functional magnetic resonance imaging study. *Neuroreport* 18, 1089–1093. doi: 10.1097/WNR.0b013e3281ac2143

Filimon, F. (2015). Are all spatial reference frames egocentric? reinterpreting evidence for allocentric, object-centered, or world-centered reference frames. *Front. Hum. Neurosci.* 9, 648–648. doi: 10.3389/fnhum.2015.00648

Folstein, M. F., Folstein, S. E., and Mchugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

Freud, E., Plaut, D. C., and Behrmann, M. (2016). 'What' is happening in the dorsal visual pathway. *Trends Cogn. Sci.* 20, 773–784. doi: 10.1016/j.tics.2016.08.003

Gainotti, G., Silveri, M. C., Villa, G., and Caltagirone, C. (1983). Drawing objects from memory in aphasia. *Brain. J. Neurol.* 106, 613–622. doi: 10.1093/brain/106.3.613

Gainotti, G., and Trojano, L. (2018). Constructional apraxia. *Handb. Clin. Neurol.* 151, 331–348. doi: 10.1016/B978-0-444-63622-5.00016-4

Garbarini, F., D'agata, F., Piedimonte, A., Sacco, K., Rabuffetti, M., Tam, F., et al. (2014). Drawing lines while imagining circles: neural basis of the bimanual coupling effect during motor execution and motor imagery. *Neuroimage* 88, 100–112. doi: 10.1016/j.neuroimage.2013.10.061

Gharabaghi, A., Fruhmann Berger, M., Tatagiba, M., and Karnath, H.-O. (2006). The role of the right superior temporal gyrus in visual search—Insights from intraoperative electrical stimulation. *Neuropsychologia* 44, 2578–2581. doi: 10.1016/j.neuropsychologia.2006.04.006

Goodale, M. A., and Milner, A. D. (1992). Separate visual pathways for perception and action. *Trends Neurosci.* 15, 20–25. doi: 10.1016/0166-2236(92)90344-8

Gowen, E., and Miall, R. C. (2007). Differentiation between external and internal cuing: an fMRI study comparing tracing with drawing. *Neuroimage* 36, 396–410. doi: 10.1016/j.neuroimage.2007.03.005

Griffith, F. J., and Bingman, V. P. (2020). Drawing on the brain: an ALE meta-analysis of functional brain activation during drawing. *Arts Psychotherapy* 71:101690. doi: 10.1016/j.aip.2020.101690

Grossi, D. (1991). *La Riabilitazione Dei Disordini Della Cognizione Spaziale*. Milano: Masson.

Guérin, F., Ska, B., and Belleville, S. (1999). Cognitive processing of drawing abilities. *Brain Cogn.* 40, 464–478. doi: 10.1006/brcg.1999.1079

Hadjidimitrakis, K., Bakola, S., Wong, Y. T., and Hagan, M. A. (2019). Mixed spatial and movement representations in the primate posterior parietal cortex. *Front. Neural Circuits* 13:15. doi: 10.3389/fncir.2019.00015

Harrington, G. S., Farias, D., and Davis, C. H. (2009). The neural basis for simulated drawing and the semantic implications. *Cortex* 45, 386–393. doi: 10.1016/j.cortex.2007.10.015

Harrington, G. S., Farias, D., Davis, C. H., and Buonocore, M. H. (2007). Comparison of the neural basis for imagined writing and drawing. *Hum. Brain Mapp.* 28, 450–459. doi: 10.1002/hbm.20286

Hawes, Z., Sokolowski, H. M., Ononye, C. B., and Ansari, D. (2019). Neural underpinnings of numerical and spatial cognition: an fMRI meta-analysis of brain regions associated with symbolic number, arithmetic and mental rotation. *Neurosci. Biobehav. Rev.* 103, 316–336. doi: 10.1016/j.neubiorev.2019.05.007

Heiser, L. M., and Colby, C. L. (2006). Spatial updating in area LIP is independent of saccade direction. *J. Neurophysiol.* 95, 2751–2767. doi: 10.1152/jn.00054.2005

Hirjak, D., Wolf, R. C., Pfeifer, B., Kubera, K. M., Thomann, A. K., Seidl, U., et al. (2017). Cortical signature of clock drawing performance in Alzheimer's disease and mild cognitive impairment. *J. Psychiatr. Res.* 90, 133–142. doi: 10.1016/j.jpsychires.2017.02.019

Huette, S., Kello, C. T., Rhodes, T., and Spivey, M. J. (2013). Drawing from memory: hand-eye coordination at multiple scales. *PLoS One* 8:e58464. doi: 10.1371/journal.pone.0058464

Ino, T., Asada, T., Ito, J., Kimura, T., and Fukuyama, H. (2003). Parieto-frontal networks for clock drawing revealed with fMRI. *Neurosci. Res.* 45, 71–77. doi: 10.1016/s0168-0102(02)00194-3

Jackson, S. R., and Husain, M. (2006). Visuomotor functions of the posterior parietal cortex. *Neuropsychologia* 44, 2589–2593. doi: 10.1016/j.neuropsychologia.2006.08.002

Jaramillo-Jimenez, A., Suarez-Revelo, J. X., Ochoa-Gomez, J. F., Carmona Arroyave, J. A., Bocanegra, Y., Lopera, F., et al. (2021). Resting-state EEG alpha/theta ratio related to neuropsychological test performance in Parkinson's disease. *Clin. Neurophysiol.* 132, 756–764. doi: 10.1016/j.clinph.2021.01.001

Karnath, H. O. (2001). New insights into the functions of the superior temporal cortex. *Nat. Rev. Neurosci.* 2, 568–576. doi: 10.1038/35086057

Karnath, H.-O., and Perenin, M.-T. (2005). Cortical control of visually guided reaching: evidence from patients with optic ataxia. *Cereb. Cortex* 15, 1561–1569. doi: 10.1093/cercor/bhi034

Karnath, H. O., Sperber, C., and Rorden, C. (2018). Mapping human brain lesions and their functional consequences. *Neuroimage* 165, 180–189. doi: 10.1016/j.neuroimage.2017.10.028

Kenzie, J. M., Girgulis, K. A., Semrau, J. A., Findlater, S. E., Desai, J. A., and Dukelow, S. P. (2015). Lesion sites associated with allocentric and egocentric visuospatial neglect in acute stroke. *Brain Connect.* 5, 413–422. doi: 10.1089/brain.2014.0316

Kowatari, Y., Lee, S. H., Yamamura, H., Nagamori, Y., Levy, P., Yamane, S., et al. (2009). Neural networks involved in artistic creativity. *Hum. Brain Mapp.* 30, 1678–1690. doi: 10.1002/hbm.20633

Kravitz, D. J., Saleem, K. S., Baker, C. I., and Mishkin, M. (2011). A new neural framework for visuospatial processing. *Nat. Rev. Neurosci.* 12, 217–230. doi: 10.1038/nrn3008

La Femina, F., Senese, V. P., Grossi, D., and Venuti, P. (2009). A battery for the assessment of visuo-spatial abilities involved in drawing tasks. *Clin. Neuropsychol.* 23, 691–714. doi: 10.1080/13854040802572426

Latreille, V., Carrier, J., Gaudet-Fex, B., Rodrigues-Brazète, J., Panisset, M., Chouinard, S., et al. (2016). Electroencephalographic prodromal markers of dementia across conscious states in Parkinson's disease. *Brain* 139, 1189–1199. doi: 10.1093/brain/aww018

Lee, D. Y., Seo, E. H., Choo, I. H., Kim, S. G., Lee, J. S., Lee, D. S., et al. (2008). Neural correlates of the clock drawing test performance in Alzheimer's disease: a FDG-PET study. *Dement. Geriatr. Cogn. Disord.* 26, 306–313. doi: 10.1159/000161055

Lehmann, M., Crutch, S. J., Ridgway, G. R., Ridha, B. H., Barnes, J., Warrington, E. K., et al. (2011). Cortical thickness and voxel-based morphometry in posterior cortical atrophy and typical Alzheimer's disease. *Neurobiol. Aging* 32, 1466–1476. doi: 10.1016/j.neurobiolaging.2009.08.017

Makuuchi, M., Kaminaga, T., and Sugishita, M. (2003). Both parietal lobes are involved in drawing: a functional MRI study and implications for constructional apraxia. *Brain Res. Cogn. Brain Res.* 16, 338–347. doi: 10.1016/s0926-6410(02)00302-6

Mandal, P. K., Joshi, J., and Saharan, S. (2012). Visuospatial perception: an emerging biomarker for Alzheimer's disease. *J. Alzheimers Dis.* 31, S117–S135. doi: 10.3233/JAD-2012-120901

Matsuoka, T., Narumoto, J., Okamura, A., Taniguchi, S., Kato, Y., Shibata, K., et al. (2013). Neural correlates of the components of the clock drawing test. *Int. Psychogeriatr.* 25, 1317–1323. doi: 10.1017/S1041610213000690

Matsuoka, T., Narumoto, J., Shibata, K., Okamura, A., Nakamura, K., Nakamae, T., et al. (2011). Neural correlates of performance on the different scoring systems of the clock drawing test. *Neurosci. Lett.* 487, 421–425. doi: 10.1016/j.neulet.2010.10.069

Mayer-Gross, W. (1935). Some observations on apraxia: (section of neurology). *Proc. R. Soc. Med.* 28, 1203–1212.

McCrea, S. (2014). A neuropsychological model of free-drawing from memory in constructional apraxia: a theoretical review. *Am. J. Psychiatry Neurosci.* 2, 60–75. doi: 10.11648/j.ajpn.20140205.11

Melcher, D., and Colby, C. L. (2008). Trans-saccadic perception. *Trends Cogn. Sci.* 12, 466–473. doi: 10.1016/j.tics.2008.09.003

Melrose, R. J., Harwood, D., Khoo, T., Mandelkern, M., and Sultzer, D. L. (2013). Association between cerebral metabolism and Rey-Osterrieth Complex Figure Test performance in Alzheimer's disease. *J. Clin. Exp. Neuropsychol.* 35, 246–258. doi: 10.1080/13803395.2012.763113

Miall, R. C., Gowen, E., and Tchalenko, J. (2009). Drawing cartoon faces--a functional imaging study of the cognitive neuroscience of drawing. *Cortex* 45, 394–406. doi: 10.1016/j.cortex.2007.10.013

Milner, A. D. (2017). How do the two visual streams interact with each other? *Exp. Brain Res.* 235, 1297–1308. doi: 10.1007/s00221-017-4917-4

Mirpour, K., and Bisley, J. W. (2016). Remapping, spatial stability and temporal continuity: from the pre-saccadic to postsaccadic representation of visual space in LIP. *Cereb. Cortex* 26, 3183–3195. doi: 10.1093/cercor/bhv153

Nakashima, H., Umegaki, H., Makino, T., Kato, K., Abe, S., Suzuki, Y., et al. (2016). Neuroanatomical correlates of error types on the Clock Drawing Test in Alzheimer's disease patients. *Geriatr. Gerontol. Int.* 16, 777–784. doi: 10.1111/ggi.12550

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., et al. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* 53, 695–699. doi: 10.1111/j.1532-5415.2005.53221.x

Ogawa, K., and Inui, T. (2009). The role of the posterior parietal cortex in drawing by copying. *Neuropsychologia* 47, 1013–1022. doi: 10.1016/j.neuropsychologia.2008.10.022

Ose Askvik, E., Van Der Weel, F. R. R., and Van Der Meer, A. L. H. (2020). The importance of cursive handwriting over typewriting for learning in the classroom: a high-density EEG study of 12-year-old children and young adults. *Front. Psychol.* 11:1810. doi: 10.3389/fpsyg.2020.01810

Park, H. R. P., Kirk, I. J., and Waldie, K. E. (2015). Neural correlates of creative thinking and schizotypy. *Neuropsychologia* 73, 94–107. doi: 10.1016/j.neuropsychologia.2015.05.007

Parks, N. A., and Corballis, P. M. (2010). Human transsaccadic visual processing: presaccadic remapping and postsaccadic updating. *Neuropsychologia* 48, 3451–3458. doi: 10.1016/j.neuropsychologia.2010.07.028

Paula, J. J., Miranda, D. M., Moraes, E. N., and Malloy-Diniz, L. F. (2013). Mapping the clockworks: what does the Clock Drawing Test assess in normal and pathological aging? *Arq. Neuropsiquiatr.* 71, 763–768. doi: 10.1590/0004-282X20130118

Perdreau, F., and Cavanagh, P. (2015). Drawing experts have better visual memory while drawing. *J. Vis.* 15:5. doi: 10.1167/15.5.5

Pierce, J., and Saj, A. (2019). A critical review of the role of impaired spatial remapping processes in spatial neglect. *Clin. Neuropsychol.* 33, 948–970. doi: 10.1080/13854046.2018.1503722

Pierce, J. E., Saj, A., and Vuilleumier, P. (2019). Differential parietal activations for spatial remapping and saccadic control in a visual memory task. *Neuropsychologia* 131, 129–138. doi: 10.1016/j.neuropsychologia.2019.05.010

Possin, K. L., Laluz, V. R., Alcantar, O. Z., Miller, B. L., and Kramer, J. H. (2011). Distinct neuroanatomical substrates and cognitive mechanisms of figure copy performance in Alzheimer's disease and behavioral variant frontotemporal dementia. *Neuropsychologia* 49, 43–48. doi: 10.1016/j.neuropsychologia.2010.10.026

Potgieser, A. R., Van Der Hoorn, A., and De Jong, B. M. (2015). Cerebral activations related to writing and drawing with each hand. *PLoS One* 10:e0126723. doi: 10.1371/journal.pone.0126723

Raimo, S., Santangelo, G., and Trojano, L. (2021). The neural bases of drawing. A meta-analysis and a systematic literature review of neurofunctional studies in healthy individuals. *Neuropsychol. Rev.* doi: 10.1007/s11065-021-09494-4. [Online ahead of print].

Robinson, A. C., Davidson, Y. S., Roncaroli, F., Minshull, J., Tinkler, P., Horan, M. A., et al. (2021). Early changes in visuospatial episodic memory can help distinguish primary age-related tauopathy from Alzheimer's disease. *Neuropathol. Appl. Neurobiol.* doi: 10.1111/nan.12726. [Online ahead of print].

Roncato, S., Sartori, G., Masterson, J., and Rumiati, R. (1987). Constructional apraxia: an information processing analysis. *Cogn. Neuropsychol.* 4, 113–129. doi: 10.1080/02643298708252037

Rusconi, E. (2018). Gerstmann syndrome: historic and current perspectives. *Handb. Clin. Neurol.* 151, 395–411. doi: 10.1016/B978-0-444-63622-5.00020-6

Russell, C., Deidda, C., Malhotra, P., Crinion, J. T., Merola, S., and Husain, M. (2010). A deficit of spatial remapping in constructional apraxia after right-hemisphere stroke. *Brain* 133, 1239–1251. doi: 10.1093/brain/awq052

Saggar, M., Quintin, E. M., Bott, N. T., Kienitz, E., Chien, Y. H., Hong, D. W., et al. (2017). Changes in brain activation associated with spontaneous improvization and figural creativity after design-thinking-based training: a longitudinal fMRI study. *Cereb. Cortex* 27, 3542–3552. doi: 10.1093/cercor/bhw171

Saggar, M., Quintin, E. M., Kienitz, E., Bott, N. T., Sun, Z., Hong, W. C., et al. (2015). Pictionary-based fMRI paradigm to study the neural correlates of spontaneous improvisation and figural creativity. *Sci. Rep.* 5:10894. doi: 10.1038/srep10894

Salimi, S., Irish, M., Foxe, D., Hodges, J. R., Piguet, O., and Burrell, J. R. (2018). Can visuospatial measures improve the diagnosis of Alzheimer's disease? *Alzheimers Dement. (Amst)* 10, 66–74. doi: 10.1016/j.dadm.2017.10.004

Salimi, S., Irish, M., Foxe, D., Hodges, J. R., Piguet, O., and Burrell, J. R. (2019). Visuospatial dysfunction in Alzheimer's disease and behavioural variant frontotemporal dementia. *J. Neurol. Sci.* 402, 74–80. doi: 10.1016/j.jns.2019.04.019

Schaer, K., Jahn, G., and Lotze, M. (2012). fMRI-activation during drawing a naturalistic or sketchy portrait. *Behav. Brain Res.* 233, 209–216. doi: 10.1016/j.bbr.2012.05.009

Senese, V. P., De Lucia, N., and Conson, M. (2015). Cognitive predictors of copying and drawing from memory of the Rey-Osterrieth complex figure in 7- to 10-year-old children. *Clin. Neuropsychol.* 29, 118–132. doi: 10.1080/13854046.2014.995711

Serra, L., Fadda, L., Perri, R., Spano, B., Marra, C., Castelli, D., et al. (2014). Constructional apraxia as a distinctive cognitive and structural brain feature of pre-senile Alzheimer's disease. *J. Alzheimers. Dis.* 38, 391–402. doi: 10.3233/JAD-130656

Sherrill, K. R., Chrastil, E. R., Ross, R. S., Erdem, U. M., Hasselmo, M. E., and Stern, C. E. (2015). Functional connections between optic flow areas and navigationally responsive brain regions during goal-directed navigation. *Neuroimage* 118, 386–396. doi: 10.1016/j.neuroimage.2015.06.009

Shin, M. S., Park, S. Y., Park, S. R., Seol, S. H., and Kwon, J. S. (2006). Clinical and empirical applications of the Rey-Osterrieth Complex Figure Test. *Nat. Protoc.* 1, 892–899. doi: 10.1038/nprot.2006.115

Shon, J. M., Lee, D. Y., Seo, E. H., Sohn, B. K., Kim, J. W., Park, S. Y., et al. (2013). Functional neuroanatomical correlates of the executive clock drawing task (CLOX) performance in Alzheimer's disease: a FDG-PET study. *Neuroscience* 246, 271–280. doi: 10.1016/j.neuroscience.2013.05.008

Sommers, P. V. (1989). A system for drawing and drawing-related neuropsychology. *Cogn. Neuropsychol.* 6, 117–164. doi: 10.1080/02643298908253416

Strauss, H. (1924). Über konstructive Apraxie [On constructional apraxia]. *Mschr. Psychiatr.* 56, 65–124.

Subramanian, J., and Colby, C. L. (2014). Shape selectivity and remapping in dorsal stream visual area LIP. *J. Neurophysiol.* 111, 613–627. doi: 10.1152/jn.00841.2011

Takahashi, M., Sato, A., Nakajima, K., Inoue, A., Oishi, S., Ishii, T., et al. (2008). Poor performance in Clock-Drawing Test associated with visual memory deficit and reduced bilateral hippocampal and left temporoparietal regional blood flows in Alzheimer's disease patients. *Psychiatry Clin. Neurosci.* 62, 167–173. doi: 10.1111/j.1440-1819.2008.01750.x

Talwar, N. A., Churchill, N. W., Hird, M. A., Pshonyak, I., Tam, F., Fischer, C. E., et al. (2019). The neural correlates of the clock-drawing test in healthy aging. *Front. Hum. Neurosci.* 13:25. doi: 10.3389/fnhum.2019.00025

Tan, L. P. L., Herrmann, N., Mainland, B. J., and Shulman, K. (2015). Can clock drawing differentiate Alzheimer's disease from other dementias? *Int. Psychogeriatr.* 27, 1649–1660. doi: 10.1017/S1041610215000939

Tchalenko, J., and Chris Miall, R. (2009). Eye-hand strategies in copying complex lines. *Cortex* 45, 368–376. doi: 10.1016/j.cortex.2007.12.012

Toba, M. N., Migliaccio, R., Batrancourt, B., Bourlon, C., Duret, C., Pradat-Diehl, P., et al. (2018). Common brain networks for distinct deficits in visual neglect. A combined structural and tractography MRI approach. *Neuropsychologia* 115, 167–178. doi: 10.1016/j.neuropsychologia.2017.10.018

Torrance, E. P. (1972). Predictive validity of the torrance tests of creative thinking. *J. Creat. Behav.* 6, 236–252. doi: 10.1002/j.2162-6057.1972.tb00936.x

Tranel, D., Rudrauf, D., Vianna, E. P., and Damasio, H. (2008). Does the Clock Drawing Test have focal neuroanatomical correlates? *Neuropsychology* 22, 553–562. doi: 10.1037/0894-4105.22.5.553

Trojano, L., and Gainotti, G. (2016). Drawing disorders in Alzheimer's disease and other forms of dementia. *J. Alzheimers Dis.* 53, 31–52. doi: 10.3233/JAD-160009

Trojano, L., Grossi, D., and Flash, T. (2009). Cognitive neuroscience of drawing: contributions of neuropsychological, experimental and neurofunctional studies. *Cortex* 45, 269–277. doi: 10.1016/j.cortex.2008.11.015

van der Meer, A. L. H., and van der Weel, F. R. (2017). Only three fingers write, but the whole brain works†: a high-density EEG study showing advantages of drawing over typing for learning. *Front. Psychol.* 8:706. doi: 10.3389/fpsyg.2017.00706

Van der Stigchel, S., De Bresser, J., Heinen, R., Koek, H. L., Reijmer, Y. D., Biessels, G. J., et al. (2018). Parietal involvement in constructional apraxia as measured using the pentagon copying task. *Dement. Geriatr. Cogn. Disord.* 46, 50–59. doi: 10.1159/000491634

Vocat, R., Staub, F., Stroppini, T., and Vuilleumier, P. (2010). Anosognosia for hemiplegia: a clinical-anatomical prospective study. *Brain* 133, 3578–3597. doi: 10.1093/brain/awq297

Wang, C. T., Hung, G. U., Wei, C. Y., Tzeng, R. C., and Chiu, P. Y. (2020). An informant-based simple questionnaire for visuospatial dysfunction assessment in dementia. *Front. Neurosci.* 14:44. doi: 10.3389/fnins.2020.00044

Whitlock, J. R. (2017). Posterior parietal cortex. *Curr. Biol.* 27, R691–R695. doi: 10.1016/j.cub.2017.06.007

Wurtz, R. H. (2008). Neuronal mechanisms of visual stability. *Vis. Res.* 48, 2070–2089. doi: 10.1016/j.visres.2008.03.021

Xu, Y. (2018). The posterior parietal cortex in adaptive visual processing. *Trends Neurosci.* 41, 806–822. doi: 10.1016/j.tins.2018.07.012

Yoshii, F., Kawaguchi, C., Kohara, S., Shimizu, M., Onaka, H., Ryo, M., et al. (2018). Characteristic deterioration of ADAS-Jcog subscale scores and correlations with regional cerebral blood flow reductions in Alzheimer's disease. *Neurol. Sci.* 39, 909–918. doi: 10.1007/s10072-018-3277-6

Youn, Y. C., Pyun, J. M., Ryu, N., Baek, M. J., Jang, J. W., Park, Y. H., et al. (2021). Use of the Clock Drawing Test and the Rey-Osterrieth Complex Figure Test-copy with convolutional neural networks to predict cognitive impairment. *Alzheimers Res. Ther.* 13:85. doi: 10.1186/s13195-021-00821-8

Yuan, Y., and Brown, S. (2014). The neural basis of mark making: a functional MRI study of drawing. *PLoS One* 9:e108628. doi: 10.1371/journal.pone.0108628

Yuan, Y., and Brown, S. (2015). Drawing and writing: an ALE meta-analysis of sensorimotor activations. *Brain Cogn.* 98, 15–26. doi: 10.1016/j.bandc.2015.05.004

Zhu, L., Wang, Z., Du, Z., Qi, X., Shu, H., Liu, D., et al. (2020). Impaired parahippocampal gyrus-orbitofrontal cortex circuit associated with visuospatial memory deficit as a potential biomarker and interventional approach for Alzheimer disease. *Neurosci. Bull.* 36, 831–844. doi: 10.1007/s12264-020-00498-3

Zink, D. N., Miller, J. B., Caldwell, J. Z. K., Bird, C., and Banks, S. J. (2018). The relationship between neuropsychological tests of visuospatial function and lobar cortical thickness. *J. Clin. Exp. Neuropsychol.* 40, 518–527. doi: 10.1080/13803395.2017.1384799

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Aging Effect on Visuomotor Adaptation: Mediated by Cognitive Decline

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The question of whether and how aging affects humans' visuomotor adaptation remains controversial. This study investigates how the effect of aging on visuomotor adaptation is related to age-related cognitive declines. We compared the performance of 100 older people (age: 55–82 years) and 20 young adults (age: 18–27 years) on a visuomotor adaptation task and three cognition tasks. A decline in visuomotor adaptation of older people was well observed. However, this decline was not strongly correlated with chronological age increase but was associated to the age-related declines of cognitive functions and speed of motor planning. We then constructed a structural mediation model in which the declined cognitive resources mediated the effect of age increase on the decline in visuomotor adaptation. The data from the present study was well-explained by the mediation model. These findings indicate that the aging effect on visuomotor adaptation mainly reflects the age-related decline of cognitive functions, which results in insufficient explicit processing on visual perturbation during visuomotor control.

Keywords: aging, visuomotor adaptation, age-related cognitive decline, motor planning, online motor control

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INTRODUCTION

One fundamental function of humans' sensorimotor system is to adapt to extrinsic and/or intrinsic environmental changes. This function of visuomotor adaptation has been extensively studied by examining rapid adaptation in simple reaching tasks with deviated visual feedback. With this approach, many studies have found evidence that healthy young people can rapidly adapt to visual feedback deviation (i.e., extrinsic environmental changes) in simple reaching tasks (e.g., Krakauer et al., 1999; Ghilardi et al., 2000; Taylor and Ivry, 2013; Galea et al., 2015; Haar et al., 2015).

While rapid sensorimotor adaptation has been observed for healthy young people, it is not yet clear how aging affects sensorimotor adaptation. Given that the functioning of cognitive systems (Raz et al., 2000) and sensorimotor performance (Cerella, 1990) substantially decline across the human lifespan, it is intuitive and reasonable to expect that visuomotor adaptation would decline with age increase as well. However, previous empirical studies have reported mixed findings. Multiple studies have reported that the reaching adaptation of older people could be subject to minor decline or even be well-preserved compared to that of young adults (e.g., Buch et al., 2003; Heuer and Hegele, 2008b; Cressman et al., 2010). On the other hand, multiple studies found that older adults had significantly weaker adaptation (i.e., smaller angular deviation against the direction of perturbation) or slower adaptation (i.e., more trials before angular deviation reaches the maximum) than young adults (e.g., Buch et al., 2003; Bock, 2005; Bock and Girgenrath, 2006; Seidler, 2006; Heuer and Hegele, 2008a).

Roller et al. (2002) tested 73 subjects (age: 20–80 years) by asking them to throw balls while wearing a set of prisms that displaced the visual scene by 20° to the right. The researchers did not observe systematic change in measures of visuomotor plasticity with advancing age. However, a number of studies using a reaching task with visual perturbation have found that older people performed significantly worse than young adults under a condition in which online feedback of angular deviation could be explicitly noticed or participants did open-loop control (Buch et al., 2003; Bock, 2005; Bock and Girgenrath, 2006; Seidler, 2006; Heuer and Hegele, 2008a, 2009, 2011, 2014; Hegele and Heuer, 2010a,b, 2013). However, Heuer and Hegele (2008b) reported no age-related decline of adaptation with a simplified version of the reaching task. Likewise, both Cressman et al. (2010) and Buch et al. (2003) found that older people could perform the visuomotor adaptation task as well as young adults. They both suggested that adults over 60 years old recalibrated their sensory and motor systems to preserve visuomotor adaptation.

Despite a number of studies that have investigated the correlation between age and the decline of visuomotor adaptation in reaching, only two recent studies used large samples of older people. Wolpe et al. (2020) recruited 183 older participants (age: 50–89 years) and Vandevoorde and de Xivry (2019) recruited 71 (age: 59–76 years). One possible reason for the mixed results from previous studies could be that aging effects on visuomotor adaptation vary among different age ranges and tasks. The present study further investigates the issue using a relatively large sample of older people whose ages were evenly distributed in a wide range (55–82 years), providing better conditions for data analyses.

Another possible reason for the mixed results could be individual differences in functions other than visuomotor control. Aging affects cognitive functions, and this effect varies largely across individuals (Rapp and Amaral, 1992; McClearn et al., 1997). Previous research has suggested that interindividual variabilities of cognitive function, including decision-making, inhibition, and flexibility as measured by a battery of reaction-time tests, and of adaptive visuomotor control were larger within older subjects than within young subjects (Bock and Girgenrath, 2006). Despite recent studies that conducted cognitive-test batteries prior to the visuomotor adaptation task to check whether older subjects had declined cognitive functions compared to young adults (Heuer and Hegele, 2008a,b, 2009, 2011, 2014; Hegele and Heuer, 2010a,b; Vandevoorde and de Xivry, 2019), how cognitive functions and visuomotor adaptation covary across the life span is yet to be further investigated.

In addition, it is still controversial whether visuomotor adaptation is linked to cognitive functions. Simon and Bock (2017) observed that the aging effects on adaptation were associated with the ability for inhibition, whereas an earlier study (Bock and Girgenrath, 2006) did not find an association between declined inhibition function and aging effects on the visuomotor adaptation of older people. More importantly, according to our knowledge, only one study (Vandevoorde and de Xivry, 2019) has investigated the associations between declined cognitive functions and aging effects on adaptive visuomotor control using a relatively large sample of older people. To address this issue, the present study used a large sample of 100 older participants whose cognitive functions were evaluated to investigate their relationships with visuomotor adaptation.

The present study also investigated how decline in visuomotor adaptation was related to visuomotor planning and online visuomotor control. Prior to a movement's initiation, cognitive factors coupled with a visual "planning" representation together determine the following motor program (Glover, 2004). Initiation time (IT) refers to the duration of the planning phase, which included several sub-processes of target identification, response selection, and movement planning or reprogramming (Liu et al., 2008). For instance, when participants need to avoid collision with obstacles and reach a target, it would incur a larger reaction-time cost for movement preparation (Wong et al., 2016). Recent evidence has also shown that anticipatory motor planning proficiency rapidly declined around 70 years of age in an end-state comfort task (Scharoun et al., 2016; Stöckel et al., 2017; Wunsch et al., 2017). However, planning ability has not been sufficiently investigated for its role in the visuomotor adaptation across the life span. Therefore, this study tested the relationship between IT and visuomotor adaptation to investigate whether variation of visuomotor planning is related to visuomotor adaptation decline of older people.

Different from IT, movement time (MT) refers to an online control process that uses limited but quickly updated visual information to adjust movements during movement execution (Glover, 2004; Liu et al., 2008). Empirical evidence has suggested that online motor corrections are at least partially automatic. Correction of arm movement could be completed between 125 and 350 ms without awareness (Pisella et al., 2000; Johnson et al., 2002; Chen and Saunders, 2016). In this study, we used MT as a measure of the speed of online motor adjustment, so as to investigate the relationship between age-related changes in online motor control and the aging effect of visuomotor adaptation.

This study aimed to systematically investigate how aging effects on visuomotor adaptation vary across different age groups and the association between aging effects of visuomotor adaptation and the decline of cognitive functions, using a relatively large sample of older people (100 people) whose ages were evenly distributed in a wide range (56–82 years old). We conducted a typical rapid aiming task with 30°counterclockwise rotation (cursor relative to hand) perturbation, which was supposed to induce explicit visuomotor adaptation. 100 elderly people with a control group of 20 young people (age: 19–27 years) voluntarily participated in the study (see **Table 1**). We hypothesized that performance in visuomotor adaptation declined with aging and this decline was associated to worse performance on the cognitive tasks that measured inhibition control function, visual-spatial ability, and processing speed. We also analyzed whether the decline of visuomotor adaptation was associated to the age-related change of visuomotor planning and online visuomotor control, measured by the IT and MT of hand movement during the adaptation phase, respectively.

TABLE 1 | Summary of participant demographics across age groups.

Age			N	Sex (male/female)	Education (years)
Range	M	SD			
18.8–27.1	21.4	2.4	20	10/10	15.5
55.9–59.8	58.0	1.4	20	10/10	10.2
60.7–64.8	62.7	1.4	20	10/10	10.9
65.3–69.9	67.4	1.7	20	10/10	10.5
70.1–74.8	72.3	1.5	20	10/10	11.2
75.2–82.3	78.3	2.2	20	10/10	11.4

MATERIALS AND METHODS

Participants

One hundred and twenty participants in total volunteered for the present study. 100 healthy right-handed older participants were recruited and stratified by age and gender, resulting in 10 men and 10 women in each of five age brackets (55–59, 60–64, 65–69, 70–74, and 75+ years). Twenty additional healthy right-handed young participants (range: 18–28 years, mean: 21.4 years, and SD: 2.4 years, 10 women) were recruited as a control group. The handedness of the participants was checked using the Edinburgh Handedness Inventory (Oldfield, 1971). Visual acuity was measured binocularly for all participants to confirm normal or corrected-to-normal vision. No participant had a history of neurological diseases, psychiatric disorders, or musculoskeletal dysfunctions. All were paid 50 RMB for their participation. The study was approved by and conformed to the standards of the Human Research Ethics Committee for Non-Clinical Faculties at East China Normal University.

According to the existing literature, studies that investigated the differences of visuomotor adaptation between older and young people often used sample sizes around 20 people for each age group (e.g., Buch et al., 2003; Bock, 2005; Bock and Girgenrath, 2006; Seidler, 2006; Heuer and Hegele, 2008a,b, 2009, 2011, 2014; Cressman et al., 2010; Hegele and Heuer, 2010a,b). To match the designs and compare the results with the previous studies, we chose to recruit 20 people for each age group.

Apparatus

Figure 1 shows the experiment setup. The participant was seated comfortably in a dim room, facing an LCD monitor (NEC 192WG, 1440 × 768 pixels, 19-in., 60 Hz) which was positioned in the frontal plane 50 cm from the participants' eyes. To block the participant from the visual feedback of hand movement, a board was positioned under the participant's chin to make the right hand invisible. Hand movement trajectories were sampled at a rate of 40 Hz by a digitizer (216 × 135 mm, Wacom, Intuos). The experiment was programmed in MATLAB using the Psychtoolbox package (Brainard, 1997; Pelli, 1997; Kleiner et al., 2007).

Tasks and Procedure

Each participant first passed a line drawing task, through which participants who had visuomotor deficits would be screened out. Then the participant performed a computer-based visuomotor adaptation task with a visual perturbation of 30° rotation and three paper-based tests for cognitive functions. Each participant spent about 30–50 min to finish the whole experiment.

Line Drawing

The line drawing task was adapted from the task by Alty et al. (2017). The target was placed on an invisible ring whose center was located on the center of the square white paper and whose radius was 100 mm. Target directions were displayed 0°, ±22.5°, ±45°, and 180° relative to the vertical midline of the ring. Participants held the pen to draw straight lines from the center to the targets in a clockwise sequence. Those who showed obvious hand tremors during the straight line drawings would be screened out and not continue to participate in the visuomotor adaptation tasks.

Visuomotor Adaptation Task

As shown in **Figure 2A**, stimuli were presented against a gray background. In each trial, a hollow square with white edges (1.2° × 1.2° of visual angle) was presented at the center of the screen as the start position. A red point (1° of visual angle) was presented to index the position of the cursor online and always in the center of the start square at the beginning of each trial. A white circular target (diameter: 1.4° of visual angle) was placed on an invisible ring whose center was located in the center of the screen and whose radius was 20.3° of visual angle. Target positions were 0°, ±22.5°, and ±45° relative to the vertical midline line of the ring, randomly chosen for each trial. **Figure 2B** illustrates the procedure of a certain trial in the task. At the beginning of each trial, the participant moved the digitizer to the center of the tablet and a red point appeared on the center of the screen. The target was presented at the same time. The participant controlled the red point using the digitizer by the right hand and was asked to move the red point to reach the visual target as quickly and accurately as possible. The red point was kept visible for online feedback during the movement (i.e., closed-loop control). Both the red point and the target disappeared immediately when the red point moved beyond the invisible ring boundary. After that, the participant moved the digitizer back to the start position. The next trial would not start until the participant located the digitizer onto the start position. The whole movement trajectory was tracked and recorded online by the digitizer during the movement.

As **Figure 2C** shows, each participant first finished 15 trials without perturbation for practice and then started the formal experiment, in which the participant sequentially received 40 baseline trials and 80 adaptation trials. For each trial, the target position was randomly chosen from 5 alternative positions (i.e., 0°, ±22.5°, ±45°), and trials with different target positions were collapsed for data analysis.

Tests of Cognitive Capabilities

We measured three cognitive capabilities (i.e., inhibition control function, visual-spatial ability, and processing speed) for each participant. We first administered a Chinese version of the Stroop Color and Word Test, which was translated from the original version of Stroop Color and Word Test one (Stroop, 1935), as

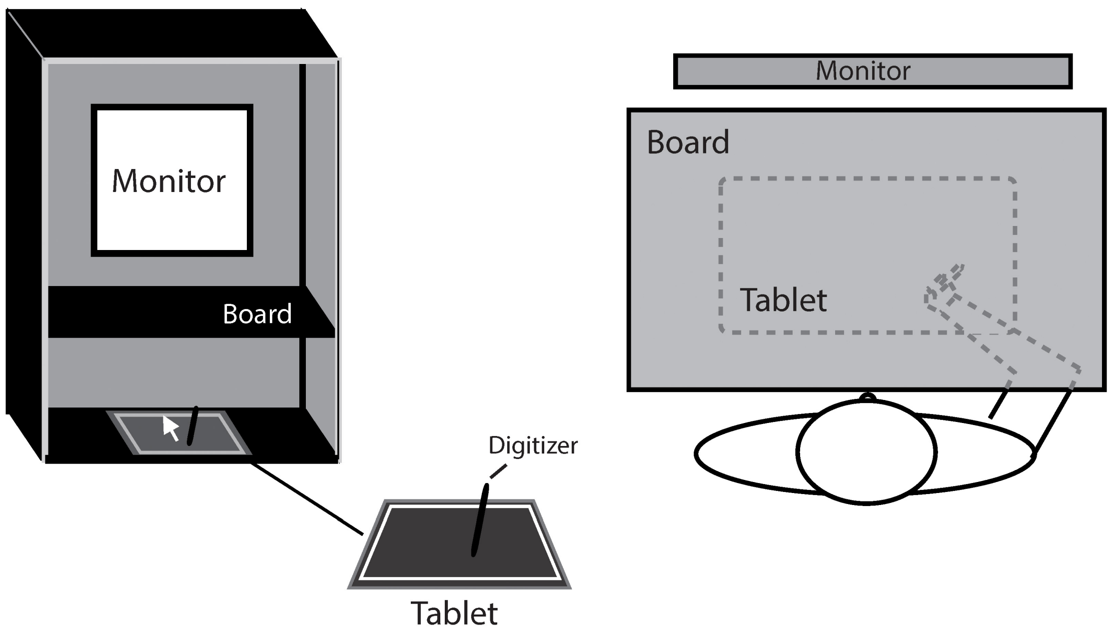

FIGURE 1 | The illustration of experiment setting.

a measure of the inhibition control function. In this test, the participant needed to name aloud the colors of colored rectangles (baseline conditions) or of color words that were printed in incongruent colors (inhibition conditions) in the different blocks. The participants were asked to respond as quickly and correctly as possible, and their reaction times were recorded manually. The inhibition control was measured by the mean RT difference between the correct trials in inhibition conditions and in baseline conditions for each participant.

The Block Design Test was from the Chinese version of Wechsler Adult Intelligence Scale (*abbr.* WAIS – RC; Gong, 1982). For the Block Design Test, the participant was presented with a set of blocks in different colors that were arranged into a specific pattern every time. The participant was asked to replicate the pattern in a limited time. The participant was tested with four blocks in the first 6 trials and then with nine blocks. The test would be terminated after three consecutive failures. This test was used to measure the individual's visual-spatial ability.

The Digit Symbol Test was also from WAIS-RC. In the Digit Symbol Test, each of the digits (i.e., 1–9) was mapped onto a unique, easy-to-draw symbol (e.g., "o," "=," and "×"). According to the mapping rule (shown at the top of the answer sheet), the participant was asked to fill the corresponding symbols under each of a set of randomly selected digits. The participant needed to fill as many symbols as possible in 90 s. This test was used to measure the individuals' processing speed. The experimenter would score the test by giving one point for each correct response.

For evaluation of cognitive functions, some of previous studies used more complete batteries of cognitive tests (e.g., Heuer and Hegele, 2008b, 2009; Hegele and Heuer, 2010a,b; Anguera et al., 2011). However, considering that a too long session might not be suitable for older participants, the present study only included three cognitive tests to maintain the duration of the whole experiment within 1 h for each participant. The three tests may not provide a most comprehensive evaluation of cognitive functions, but they together should be sufficient to give a reliable evaluation of a general cognitive function. The existing literature has shown that, despite multiple aspects of cognitive functions and various tests on those, individual differences of performances on most cognitive tests had moderate-to-high correlations with each other, indicating a common component that underlies performances on most cognitive tasks (e.g., McCabe et al., 2010; Huang et al., 2012; Kovacs and Conway, 2016; Shipstead et al., 2016). We also used structural equation modeling to construct a latent variable to represent a general cognitive resource so that the relationships among age, visuomotor adaptation and general cognitive functions could be further investigated (for details, see section *"Correlation Analyses of Visuomotor Adaptation, Kinematics, and Cognitive Functions"*).

Data Analysis

The hand movement onset for each trial was marked when the velocity first exceeded 5% of the peak velocity of the hand movement in this trial. The movement orientation of each trial was defined by direction from the movement onset point to the point on which peak velocity was reached, so as to minimize the influence from movement corrections based on feedback. To calculate the angular deviation of hand movement in each trial, a standard vector was defined from the position of the start point to the target point, and the angular deviation in this trial was defined as the orientation difference between the movement orientation and the orientation of the standard vector.

We measured the adaptation effect of hand movement by the mean angular deviations of hand movement from the last 15 adaptation trials minus the mean deviation from the baseline trials. This manipulation helped to remove the variation of individual biases in hand movement from the adaptation effects (Leow et al., 2012; McDougle et al., 2015; Song and Smiley-Oyen, 2017).

In addition, we analyzed the kinematics of the hand movements, including the IT of hand movement, which was defined by the time from stimulus presentation to the onset of movement for each trial, and the MT of hand movement, which was defined by the time from the onset of movement to when the cursor reached the invisible boundary for each trial.

RESULTS

Aging Effects on Visuomotor Adaptation

We first analyzed the mean angular deviations in the baseline phase of the reaching task to investigate whether the older and young participants had differences in constant biases in the reaching task. An ANOVA showed that they had no biases difference in the baseline trials [F (1,118) = 0.793, p = 0.375, and partial η^2 = 0.007], and both showed a small clockwise bias, namely, young adults (−1.54° ± 1.44°) and older adults (−1.13° ± 1.96°). This effect might be because all the participants were right-handed. Then, we compared the mean standard deviations of individuals' angular deviations in the baseline phase between two groups to test whether two groups differed in reaching precision, and found that the older participants had a significantly higher mean standard deviation [F (1,118) = 33.06, p < 0.001, and partial η^2 = 0.219], indicating that the visuomotor control of the older participants were less accurate than of the young participants.

Over the adaptation period, the cursor moving direction was rotated by 30°CCW. A best solution to counter cursor rotation was to adjust the hand movement direction by 30°clockwise with reference to the direction from the start point to the target point. **Figure 3A** illustrates how angular deviation varied across trials for three sample participants and **Figure 3B** shows the mean angular deviations of the young participants and the older participants across the experiment. One can see that, although both the young and older sample participants showed adaptation to compromise visual perturbation, the adaptation of the older participants were not as sufficient as of the young participants. The young adults group had a mean deviation of −24.04° (±0.88° s.e.) and older adults group −21.21° (±0.51° s.e.) in the last 15 trials (also see **Figure 3C**). An ANOVA showed a significant main effect of age groups, F (1,118) = 5.47, p = 0.021, and partial η^2 = 0.044, confirming more visuomotor adaptation of the young participants.

We then analyzed the adaptation effect among the five age groups (i.e., 55–60 years, 60–65 years, 65–70 years, 70–75 years, and over 75 years) of the older participants (see **Table 1** for more information of the groups). However, an ANOVA showed that the effect of age groups was not significant, F (4,95) = 0.881, p = 0.478, and partial η^2 = 0.036. We also calculated the correlation between age and adaptation and found a weak but significant correlation, r (98) = 0.20, p = 0.044 (see also **Figure 4A**). These results indicated that, despite the aging effect on visuomotor adaptation, the relationship between the increase of age and the decline of visuomotor adaptation was not strong within older participants.

Aging Effects on Kinematics: Initiation Time and Movement Time

To analyze the IT and MT differences between the young and older participants during the baseline phase and the adaptation phase (last 15 trials), we first performed two 2 (phase) × 2 (young vs. older) mixed-design ANOVAs for mean IT and MT, respectively. The main effects of phase were significant for both IT and MT [IT: F (1,118) = 8.95, p = 0.003, and partial η^2 = 0.071; MT: F (1,118) = 11.90, p = 0.001, and partial η^2 = 0.092], indicating longer IT and MT in the adaptation phase than in the baseline phase. For IT, we also found a significant main effect of young vs. older [F (1,118) = 29.76, p < 0.001, and partial η^2 = 0.201], indicating longer IT of the older participants. However, the main effect of young vs. older was not significant for MT, F (1,118) = 0.187, p = 0.666, and partial η^2 = 0.002. The interaction between two factors was not significant for IT [F (1,118) = 1.897, p = 0.173, and partial η^2 = 0.016] and significant for MT [F (1,118) = 4.63, p = 0.034, and partial η^2 = 0.038]. The significant interaction for MT indicated that the MT difference between the phases was larger for the older participants.

We then analyzed how IT and MT in the adaptation phases varied among the age groups of the older participants (see also **Figure 5**). The effect of age groups was significant for IT [F (4,95) = 3.45, p = 0.011, and partial η^2 = 0.127] but not for MT [F (4,95) = 0.937, p = 0.446, and partial η^2 = 0.038]. As shown in **Figure 4B**, IT increased with advancing age across the groups. The correlation analyses provided consistent results. The correlation was significant between age and IT [r (98) = 0.34, p = 0.001] but not significant between age and MT [r (98) = −0.02, also see **Figure 4C**].

Aging Effects on Cognitive Capabilities

The comparisons of cognitive capabilities showed that the older participants had significantly poorer performance on all three tasks (i.e., Digit Symbol Test, Block Design Test, and Stroop Color and Word Test), F (1,118) > 15.64, p < 0.001, and partial η^2 = 0.130. As depicted in **Figure 6**, we also analyzed trends in cognitive functions with age for the older participants. Considering that there were large differences in age between the older participants and the control group, the control group was not included in the correlation analyses that were directly related to age. Performance on the Digit Symbol Test and Stroop Color and Word Test both had significant correlations with age [Digit Symbol Test: r (98) = −0.35, p < 0.001; Stroop Color and Word Test: r (98) = 0.38, p < 0.001], whereas the correlation between performance on the Block Design Test and age was not significant [r (98) = −0.10, p = 0.333].

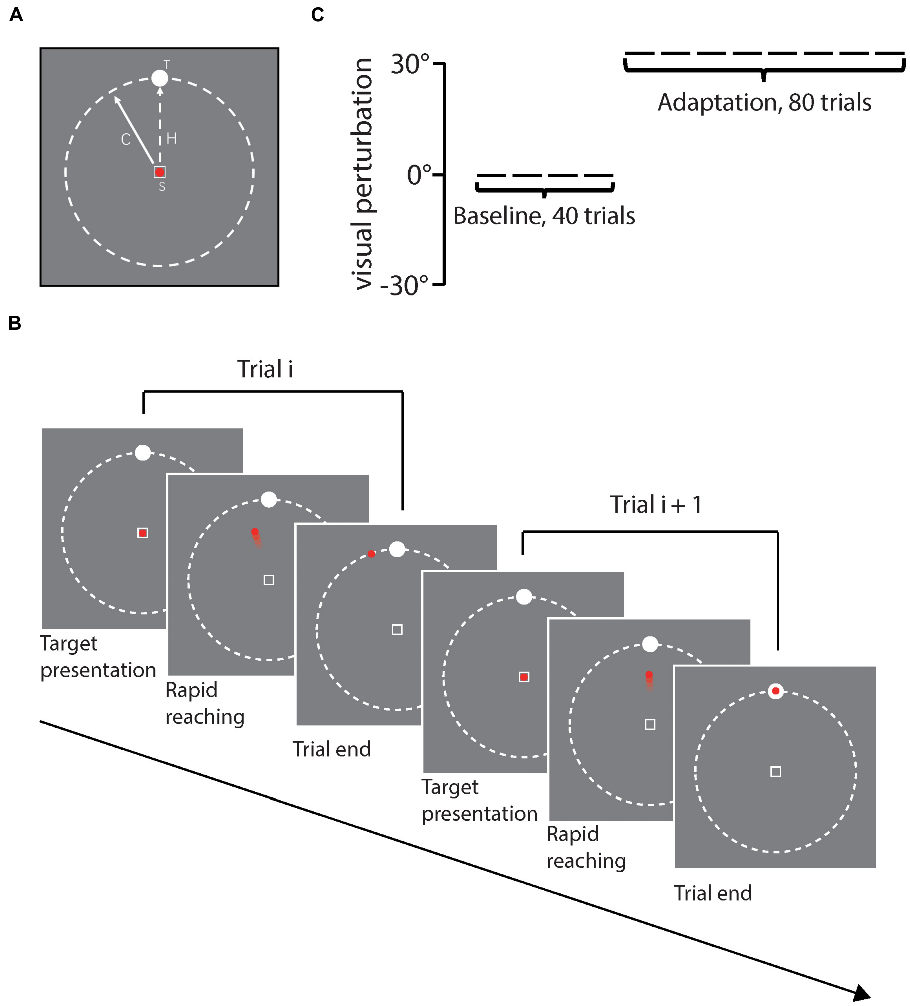

FIGURE 2 | (A) Illustrates stimuli presented on each trial, including the start position (S) with the red point cursor inside, and white circular target (T). The solid line with arrow represents the cursor moving direction and the dash line represents the actual hand movement direction (H). **(B)** Illustrates the task procedure of two sample trials, **(C)** illustrates the experiment design for each participant, including first 40 baseline trials and then 80 adaptation trials. Rotation direction perturbation was fixed to 30°counterclockwise in reference to the actual hand movement direction in the adaptation phase.

Correlation Analyses of Visuomotor Adaptation, Kinematics, and Cognitive Functions

As shown in **Figures 3**, **4**, the adaptive angular deviation and IT had a similar tendency for participants over 55 years old. Therefore, we conducted an analysis of correlation between them for all participants, which revealed that the correlation between angular deviation and IT was significant [r (118) = 0.33, $p < 0.001$]. We also tested whether the adaptive angular deviation and IT were correlated with performance on three cognitive tests (see **Figure 7**), respectively. For angular deviation, it was significantly related to scores of the Digit Symbol Test [r (118) = −0.32, $p < 0.001$] and the Block Design Test [r (118) = −0.37, $p < 0.001$] but not to scores of the Stroop Color and Word Test [r (118) = 0.13, $p = 0.167$]. The insignificant correlation between angular deviation and scores of the Stroop Color and Word Test might be due to that individual performances in this task were measured by differences between reaction times in different conditions. The process of finding differences might have resulted in the increase of measurement noise. For IT, all the correlations were significant [r (118) > 0.31, $p < 0.001$]. For the results of other correlation analyses, please see **Table 2**. Note that the correlation between MT and angular deviation was negative and statistically significant, indicating that the participants whose hand movements were faster showed more visuomotor adaptation. However, MT did not differ systematically with the participants' age. Thus, the MT-adaptation correlation was apparently not related with the aging effect on visuomotor and was not further analyzed.

The correlation analyses showed clear associations among performance on the cognitive tests and motor planning speed (i.e., IT) and similar aging effects on them. These findings together indicated that a common cognitive resource affected

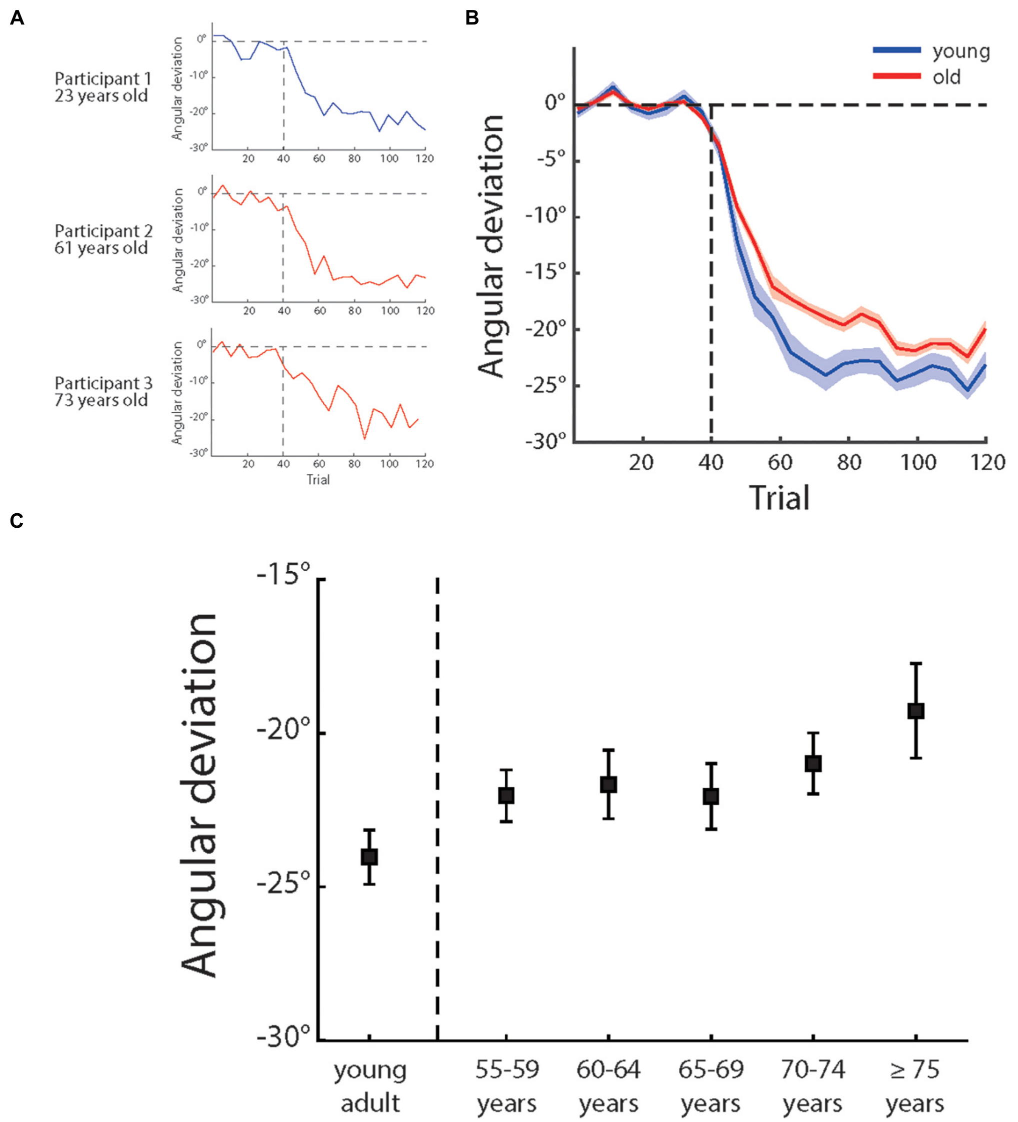

FIGURE 3 | (A) Illustrates the angular deviation as a function of trial number of three sample participants of different age groups and **(B)** illustrates the mean angular deviation as a function of trial number of young adults (blue) and older people (red). The shadow areas depict ± 1 standard errors, **(C)** illustrates the mean angular deviation of last 15 adaptation trials of different age groups (for each group, $n = 20$). The error bars depict ± 1 standard errors.

performance on both cognitive tests and motor planning and declined with increase of age. Moreover, the observed associations among performance on the cognitive tests, IT, and adaptive angular deviation indicated the possibility that there was an association between adaptive angular deviation and this hypothetical cognitive resource. Considering the relatively weak correlation between age and adaptation effect, we think that chronological age increase might not directly result in a decline of visuomotor adaptation, but this cognitive resource possibility mediated the relationship between age and adaptive angular deviation.

According to the cross-sectional design of the present study, we could not directly test causal relationship among chronological age increase, changes in visuomotor adaptation and cognitive function. However, to further test this possible mediation effect using a statistical approach, we did path analysis by constructing and fitting two structural equation models and using the data of all 120 participants. The structure of the models is illustrated in **Figures 8A,B**. We hypothesized a latent variable, labeled as "cognitive resource," and included it in both models as a mediator between aging and adaptation effect. Using the methods of path analysis and structural equation modeling, we could test (1) whether there was a general cognitive resource that affected both performance on the cognitive tests and motor planning/initiation (i.e., IT) and (2) whether this cognitive resource mediated the effect from age to adaptive angular deviation from a perspective of statistics. In addition, we could test whether there was a full or partial mediation effect by

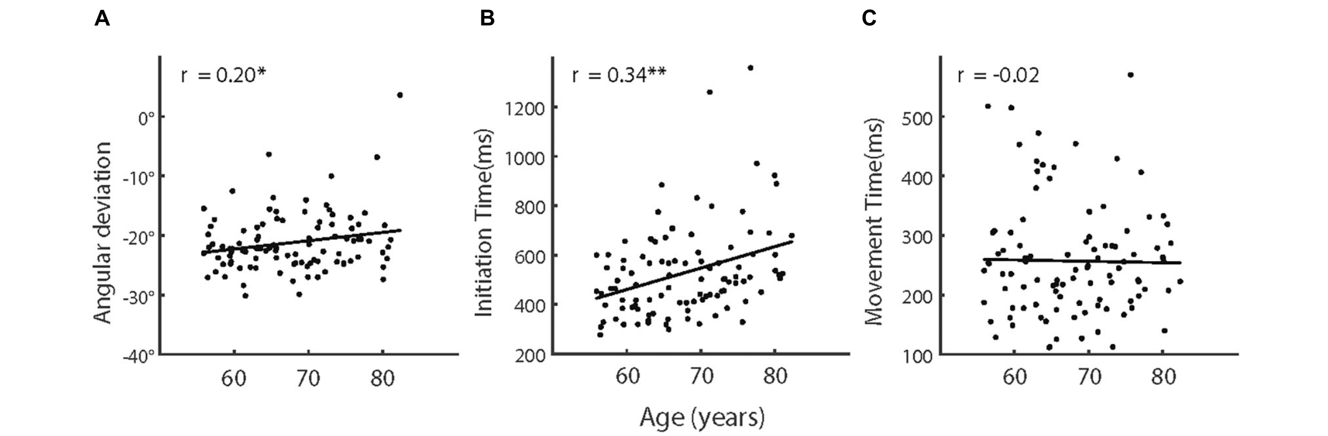

FIGURE 4 | (A) Adaptive angular deviation, **(B)** initiation time, and **(C)** movement time as a function of age of older participants. The solid lines indicate linear regression model fits and rs represent the Pearson correlations between variables. Note, *$p < 0.05$; **$p < 0.005$.

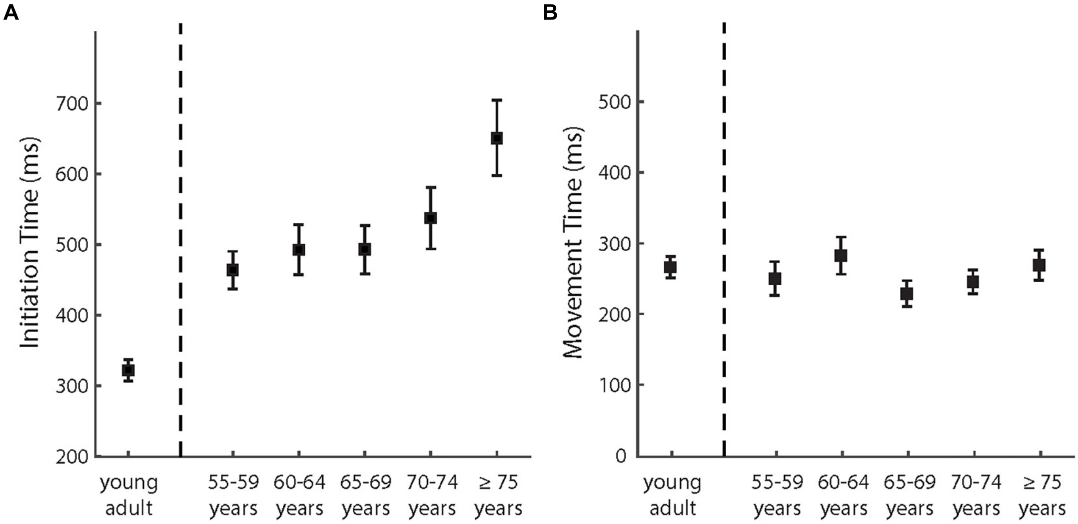

FIGURE 5 | (A) The mean initiation times and **(B)** the mean movement times of different age groups in the adaptation phase. The error bars depict ± 1 standard errors.

comparing models with/without a direct path between age and adaptive angular deviation (**Figures 8A,B**).

The model construction and fitting were implemented by Mplus 7 (Muthén and Muthén, 1998-2017). The results of model fitting and the indices of goodness-of-fit are presented in **Figure 8** and **Table 3**. The numbers on the diagrams refer to standardized coefficients of the paths. The indices of goodness of it were chosen according to a common practice (Schermelleh-Engel et al., 2003; Marsh et al., 2005). We also list the criteria for acceptable fit in **Table 3**. The full mediation model (**Figure 8A**) appeared to be acceptable based on the indices of goodness-of-fit, and both the paths related to mediation effect were significant, indicating that there was a significant mediation effect. On the other hand, the indices of goodness-of-fit indicated that the partial mediation model (**Figure 8B**) was acceptable as well. However, the direct path from age to adaptive angular deviation was not significant, indicating that the full mediation model was preferred. The full mediation effect suggested that aging did not directly result in decline of visuomotor adaptation, but the aging effect on visuomotor adaptation was more likely to be due to the age-related cognitive resource decline.

DISCUSSION

The present study is focused on how aging affects visuomotor adaptation. In brief, we found that the older participants (>55 years) had less adaptation to visual feedback perturbation in a reaching task, compared to the young adults. However, this aging effect on visuomotor adaptation was not strongly associated to the chronological age of the older participants; instead, we observed that the effect was more correlated with the

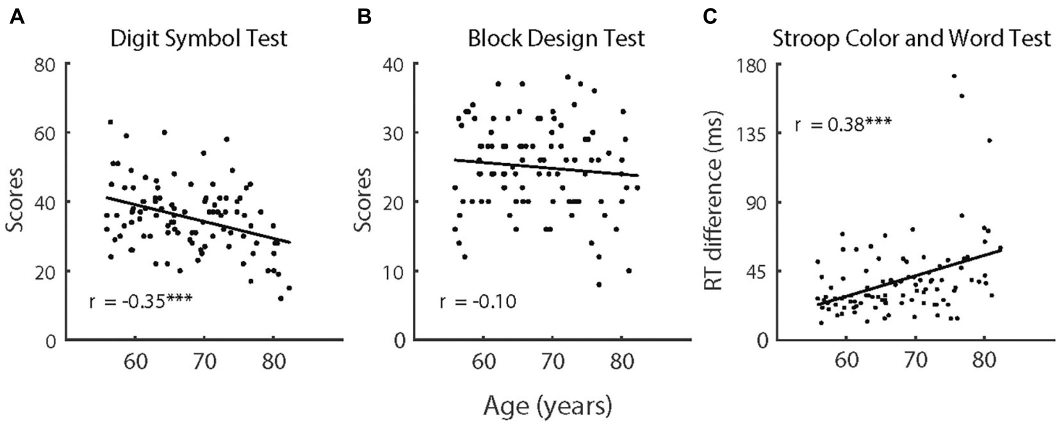

FIGURE 6 | (A) The scores in Digit Symbol Test, **(B)** the scores in Block Design Test, and **(C)** the reaction time difference in Stroop Color and Word Test as a function of age of older participants (n = 100). The solid lines indicate linear regression model fits and rs represent the Pearson correlations between variables. Note, ***$p < 0.001$.

decline of performance on the cognitive tests and speed of motor planning. We then tested a structural mediation model, in which we hypothesized a latent variable, entitled "cognitive resource," both accounted for performance on the cognitive tests and speed of motor planning and mediated the effect from chronological age to adaptive angular deviation. The fitting results confirmed this model and indicated that there was a full mediation effect of cognitive resource.

Aging and Visuomotor Adaptation

Multiple studies have reported that visuomotor adaptation, as an important function of the visuomotor feedback system, declines in older people compared to young adults (Buch et al., 2003; Bock, 2005; Bock and Girgenrath, 2006; Seidler, 2006; Heuer and Hegele, 2008a, 2009, 2011, 2014; Hegele and Heuer, 2010a,b, 2013). From this study, the data consistently showed that the older group had less adaptive angular deviation by visual feedback perturbation. With a relatively large sample, we further tested whether this aging effect was correlated with chronological age. Not much literature has addressed this issue. In a very recent study, Wolpe et al. (2020) found a considerable correlation of 0.35 between age and adaptive angular deviation, which appears to be higher than observed in the present study (0.20). This difference could be caused by the different age ranges of the participants in the two studies. Wolpe et al. tested the correlation across the span of adulthood (age: 18–89 years) while we focus on older people (age: 55–82 years). As shown in **Figure 2B** of Wolpe et al., older people apparently had a larger variation in adaptive angular deviation than young adults had, which could possibly have caused a lower correlation within the older group. We also tested the correlation between age and adaptive angular deviation using all the participants in this study (though this analysis apparently violated the assumption of normal distribution of sample), and found a slightly higher correlation [r (118) = 0.26, p = 0.004]. But considering the sample distribution, we don't think that any conclusion could be given with such a small difference. Another recent study also showed an insignificant correlation between age and visuomotor adaptation within older people (Vandevoorde and de Xivry, 2020).

Despite the observed weak correlation between chronological age and adaptive angular deviation, we found that adaptive angular deviation was also correlated with performance in cognitive tests, which was associated to adaptive angular deviation. These observed associations point toward the mediation effect of age-related cognitive function decline on the aging effect of visuomotor adaptation. The mediation model (**Figure 8A**) confirms this effect. Multiple previous studies have shown age-related cognitive function decline (Salthouse, 1996; Raz et al., 2000; Park et al., 2003). Recently, some studies have further noted that this age-related decline possibly contributed to the aging effect on visuomotor adaptation. For example, Vandevoorde and de Xivry (2019, 2020) found that age-related visuomotor adaptation decline was likely to link to the decline of working memory capacity by aging. Wolpe et al. (2020) also reported that aging effect on visuomotor adaptation was related to short-term memory decline. In an early study, Heuer and Hegele (2008a) did not find the correlations among age, visuomotor adaptation, and cognitive functions but still pointed out that both performance on the Digit Symbol Test and visuomotor adaptation declined with the increase of age. In addition, this study found that speed of visuomotor planning (i.e., IT) was related to the aging effect on visuomotor adaptation. The present finding was consistent with previous studies (Scharoun et al., 2016; Stöckel et al., 2017; Wunsch et al., 2017), which reported age-related decline in anticipatory motor planning.

The findings of this study can potentially explain why the aging effect on visuomotor adaptation was not observed in some studies. For instance, in Heuer and Hegele's (2008b) study, older people did not show a decline of visuomotor adaptation in a simplified visuomotor adaptation task. This could be because the simplification of the task decreased the involvement of explicit visuomotor planning, making the decline of cognitive resources less influential in the task performance. Similarly, in Buch et al. (2003) and Cressman et al. (2010), the researchers

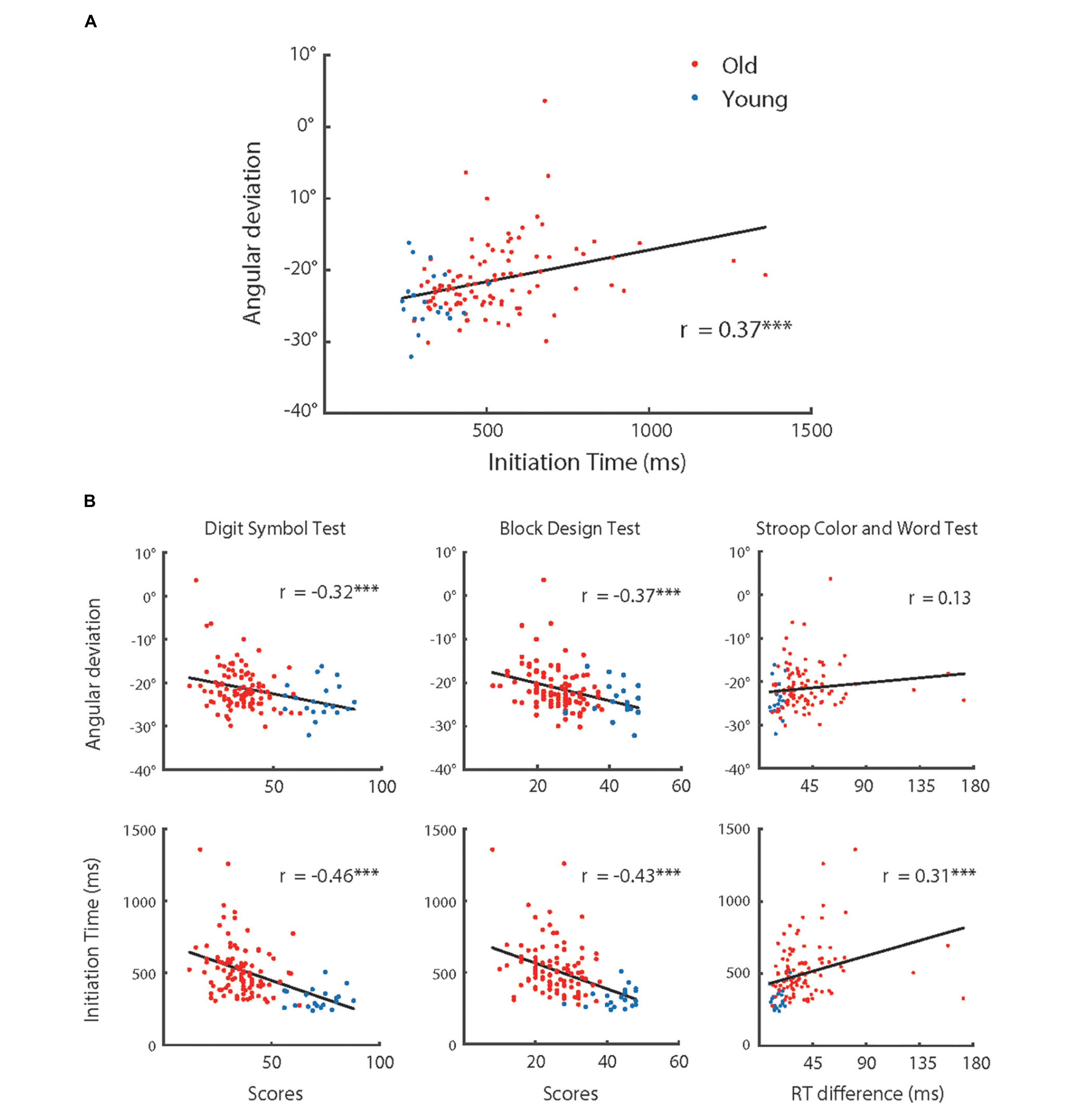

FIGURE 7 | (A) Adaptive angular deviation as a function of initiation time of hand movement, **(B)** adaptive angular deviation (upper row) and initiation time of hand movement (lower row) as functions of performance in cognitive tests (left: Digital Symbol Test; middle: Block Design Test; and right: Stroop Color and Word Test), respectively. The red dots represent the group of older participants (n = 100) and the blue dots represent the group of younger participants (n = 20). The solid lines indicate linear regression model fits and rs represent the Pearson correlations between variables. Note, ***p < 0.001.

gradually changed the visuomotor feedback and further provided proprioceptive feedback, both of which were likely to reduce the involvement of explicit visuomotor planning and potentially helped older people to perform as well as young adults. These previous findings are consistent with our conclusion that the decline of cognitive resources is the main cause of the aging effect on visuomotor adaptation.

Based on the findings that performance on the cognitive tests and speed of motor planning were correlated with both chronological age and adaptive angular deviation, we

TABLE 2 | Correlations between visuomotor adaptation, kinematics, and cognitive functions.

	Age	Angular deviation	IT	MT	Digit symbol test	Block design test
Age	–					
Angular deviation	0.26**	–				
IT	0.49***	0.33***	–			
MT	−0.04	−0.19*	−0.22*	–		
Digit symbol test	−0.83***	−0.32***	−0.46***	−0.02	–	
Block design test	−0.71***	−0.37***	−0.43***	0.02	0.77***	–
Stroop color and word test	0.45***	0.13	0.31***	0.13	−0.50***	−0.48***

*Note: *p < 0.05; **p < 0.01; and ***p < 0.001.*

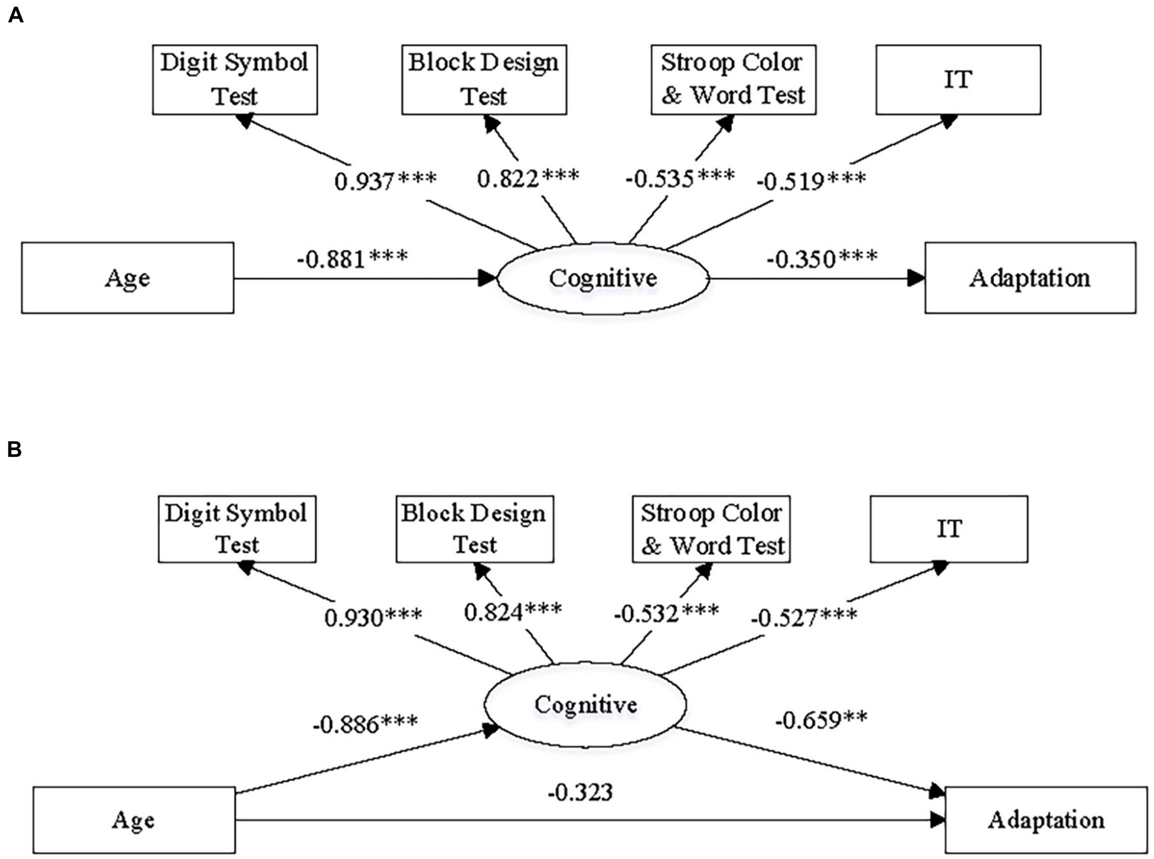

FIGURE 8 | The diagrams illustrate the structures and summary results of **(A)** the full mediation structural equation model and **(B)** the partial mediation structural equation model, respectively. The numbers on the paths of the diagrams refers to standardized coefficients. Note, (1) "Cognitive" refers to cognitive resources; "Adaptation" refers to adaptive angular deviation; "IT" refers to initiation time of hand movement; (2) ** $p < 0.005$ and *** $p < 0.001$.

TABLE 3 | Model fit indices for latent variable mediation model.

Model	χ^2	*df*	CFI (≥0.95)	TLI (≥0.95)	SRMR (≤0.10)	RMSEA (≤0.08)
Full mediation	14.558	9	0.984	0.973	0.040	0.072
Partial mediation	12.495	8	0.987	0.975	0.037	0.068

Note: the ranges in the brackets refer to criteria of acceptable fit on indices of goodness-of-fit.

propose a mediation model (**Figure 8A**), in which age-related decline of cognitive resources underlies the aging effect on visuomotor adaptation. The indices of goodness of fit show that the mediation model statistically explains the observed data well (see **Table 3**). In the next subsection, we further discuss the relationships among visuomotor adaptation, motor planning, and cognitive functions from a more general perspective.

Visuomotor Adaptation, Motor Planning, and Cognitive Functions

The results of the present study have demonstrated that the aging effect on visuomotor adaptation was mediated by age-related cognitive function decline. An explanation of these findings is that cognitive resources are shared for cognitive functions (e.g., working memory, spatial representation, and numerical representation), motor planning, and visuomotor adaptation (especially explicit visuomotor adaptation). This explanation is supported not only by evidence from research on older people but also by evidence from young adults and children. For example, studies on young adults have shown that both working memory capacity (Christou et al., 2016; Wolpe et al., 2020) and performance intelligence quotient (Anwar et al., 2015) could predict explicit visuomotor adaptation. Cognitive cost by dual task (Vandevoorde and de Xivry, 2020) and attentional disorders (Kurdziel et al., 2015) both affected visuomotor adaptation as well. These findings convergently indicated shared resources for visuomotor adaptation and cognitive functions. Moreover, Logan and Fischman (2011) reported that motor planning interfered with performance in memory recall, and Pennequin et al.'s (2010) research on child development found covariation between motor planning and executive functions, suggesting that motor planning and cognitive functions have shared resources.

Heuninckx et al. (2005, 2008) pointed out that aging results in more cognitive demand and increased neural recruitment during motor tasks. Vandevoorde and de Xivry (2020) further proposed a shared cognitive resource hypothesis to explain the aging effect on explicit visuomotor adaptation. This hypothesis is consistent with the findings of the present study that performance in cognitive functions and speed of motor planning predicted adaptive angular deviation better than chronological age. The mediation model tested in the present study also supports Vandevoorde and de Xivry's (2020) hypothesis by identifying shared cognitive resources change as a full mediator from chronological age increase to visuomotor adaptation decline. In other words, the findings of the present study, with the previous findings, indicate that the aging effect on visuomotor is not an independent effect but reflects the age-related decline of cognitive functions. Visuomotor adaptation at least partially relies on the same cognitive mechanisms that underlie a set of cognitive functions (e.g., working memory, spatial representations) and motor planning.

Recent evidence from neuroimaging studies also supports this explanation. Anguera et al. (2010) found that individual differences in visuomotor adaptation performance could be partially attributed to differences in spatial working memory and these two tasks activated overlapping brain regions, including the right dorsolateral prefrontal cortex and bilateral inferior parietal lobules. In a follow-up study (Anguera et al., 2011), they further found that reduced activation of these regions contributed to worse performances in both spatial working memory and visuomotor adaptation tasks. Wolpe et al. (2020) reported that the observed decline of visuomotor adaptation by aging was associated to the structural retention of the medial temporal lobe, which is related to cognitive functions such working memory and attention. In contrast, they did not observe an association between decline of visuomotor adaptation and retention of cerebellum, which involves in the internal model recalibration of motor control. All these results are consistent with the findings of the present study that aging effect on visuomotor adaptation was directly due to the age-related decline of cognitive functions, and support Vandevoorde and de Xivry (2019)'s argument that impaired internal model recalibration of motor control is not the main inducement of the age-related decline of visuomotor adaptation.

Despite that the shared cognitive resource hypothesis well explained the relationship between explicit visuomotor adaptation and cognitive functions, it apparently could not predict how aging affects implicit visuomotor adaptation. Previous studies have reported that explicit visuomotor adaptation was affected by aging, whereas implicit visuomotor adaptation was not (Bock and Girgenrath, 2006; Heuer and Hegele, 2009, 2011; Hegele and Heuer, 2010a,b, 2013; Huang et al., 2017). In the present study, we used a sudden rotation perturbation of 30°CCW, which could be easily noticed by participants. So, although we did not separately measure the explicit and implicit components, the participants apparently introduced explicit strategies for visuomotor adaptation. As mentioned above, explicit visuomotor adaptation is associated to cognitive functions, and from this perspective, our findings are generally consistent with the existing literature. However, we could not distinguish the contributions of the explicit and implicit components on the aging effect on visuomotor adaptation with the design. Note that a rotation perturbation of $\geq$30° is not a necessary condition for either explicit adaptation or detecting an age-related effect on adaptation. In both Buch et al. (2003) and Cressman et al. (2010), the final perturbation magnitude was equal to or larger than 30°. However, the perturbations were both gradually increased from zero to maximum, and neither study found a significant effect of aging on adaptation. So we consider that aging effect on adaptation is dependent on not only magnitude of perturbation but how perturbation is presented as well, which shall be further investigated in future research.

Compared to speed of motor planning (i.e., IT of hand movement), MT did not differ between young adults and older people in the present study. This was possibly because MT is more associated with online visuomotor control, which is generally considered as an automatic process (Pisella et al., 2000; Johnson et al., 2002; Chen and Saunders, 2016) and does not apparently involve explicit strategies. This also explains why MT was not significantly correlated with performance in cognitive functions. Although MT was negatively correlated with adaptive angular deviation, it was more likely to be due to individual differences in online visuomotor control than to age-related variation (see **Table 2**).

CONCLUSION

This study found an age-related decline of visuomotor adaptation that was mediated by performance in cognitive tests and speed of motor planning of individual participants. We proposed a structural model with a latent variable, entitled "cognitive resource," which was due to both performance in cognitive tests and speed of motor planning and mediated the association from aging to visuomotor adaptation decline. These findings are consistent and extend the existing literature on visuomotor adaptation and aging.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://osf.io/x2jnf/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Committee on Human Research Protection, East China Normal University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NL and ZC developed the conceptual framework, conceived and designed the experiments. NL and YX programmed and performed the experiments. NL, YX, and ZC analyzed the data. NL, GC, and ZC wrote the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

Alty, J., Cosgrove, J., Thorpe, D., and Kempster, P. (2017). How to use pen and paper tasks to aid tremor diagnosis in the clinic. *Pract. Neurol.* 17, 456–463. doi: 10.1136/practneurol-2017-001719

Anguera, J. A., Reuter-Lorenz, P. A., Willingham, D. T., and Seidler, R. D. (2010). Contributions of spatial working memory to visuomotor learning. *J. Cogn. Neurosci.* 22, 1917–1930. doi: 10.1162/jocn.2009.21351

Anguera, J. A., Reuter-Lorenz, P. A., Willingham, D. T., and Seidler, R. D. (2011). Failure to engage spatial working memory contributes to age-related declines in visuomotor learning. *J. Cogn. Neurosci.* 23, 11–25. doi: 10.1162/jocn.2010.21451

Anwar, M. N., Navid, M. S., Khan, M., and Kitajo, K. (2015). A possible correlation between performance IQ, visuomotor adaptation ability and mu suppression. *Brain Res.* 1603, 84–93. doi: 10.1016/j.brainres.2015.01.045

Bock, O. (2005). Components of sensorimotor adaptation in young and elderly subjects. *Exp. Brain Res.* 160, 259–263. doi: 10.1007/s00221-004-2133-5

Bock, O., and Girgenrath, M. (2006). Relationship between sensorimotor adaptation and cognitive functions in younger and older subjects. *Exp. Brain Res.* 169, 400–406. doi: 10.1007/s00221-005-0153-4

Brainard, D. H. (1997). The psychophysics toolbox. *Spat. Vis.* 10, 433–436. doi: 10.1163/156856897X00357

Buch, E. R., Young, S., and Contreras-Vidal, J. L. (2003). Visuomotor adaptation in normal aging. *Learn. Mem.* 10, 55–63. doi: 10.1101/lm.50303

Cerella, J. (1990). "Aging and information-processing rate," in *Handbook of the Psychology of Aging*, eds J. E. Birren and K. W. Schaie (San Diego, CA: Hartcourt), 210–221. doi: 10.1016/B978-0-12-101280-9.50018-8

Chen, Z., and Saunders, J. A. (2016). Automatic adjustments toward unseen visual targets during grasping movements. *Exp. Brain Res.* 234, 2091–2103. doi: 10.1007/s00221-016-4613-9

Christou, A. I., Miall, R. C., Mcnab, F., and Galea, J. M. (2016). Individual differences in explicit and implicit visuomotor learning and working memory capacity. *Sci. Rep.* 6:36633. doi: 10.1038/srep36633

Cressman, E. K., Salomonczyk, D., and Henriques, D. Y. (2010). Visuomotor adaptation and proprioceptive recalibration in older adults. *Exp. Brain Res.* 205, 533–544. doi: 10.1007/s00221-010-2392-2

Galea, J. M., Mallia, E., Rothwell, J., and Diedrichsen, J. (2015). The dissociable effects of punishment and reward on motor learning. *Nat. Neurosci.* 18, 597–602. doi: 10.1038/nn.3956

Ghilardi, M. F., Ghez, C., Dhawan, V., Moeller, J., and Eidelberg, D. (2000). Patterns of regional brain activation associated with different forms of motor learning. *Brain Res.* 871, 127–145. doi: 10.1016/S0006-8993(00)02365-9

Glover, S. (2004). Separate visual representations in the planning and control of action. *Behav. Brain Sci.* 27, 3–24;discussion24–78. doi: 10.1017/S0140525X04000020

Gong, Y. X. (1982). *Manual for the Wechsler Adult Intelligence Scale: Chinese Revision*. Changsha: Hunan Medical College.

Haar, S., Donchin, O., and Dinstein, I. (2015). Dissociating visual and motor directional selectivity using visuomotor adaptation. *J. Neurosci.* 35, 6813–6821. doi: 10.1523/JNEUROSCI.0182-15.2015

Hegele, M., and Heuer, H. (2010a). Adaptation to a direction-dependent visuomotor gain in the young and elderly. *Psychol. Res.* 74, 21–34. doi: 10.1007/s00426-008-0221-z

Hegele, M., and Heuer, H. (2010b). The impact of augmented information on visuo-motor adaptation in younger and older adults. *PLoS One* 5:e12071. doi: 10.1371/journal.pone.0012071

Hegele, M., and Heuer, H. (2013). Age-related variations of visuomotor adaptation result from both the acquisition and the application of explicit knowledge. *Psychol. Aging* 28, 333–339. doi: 10.1037/a0031914

Heuer, H., and Hegele, M. (2008b). Adaptation to visuomotor rotations in younger and older adults. *Psychol. Aging* 23, 190–202. doi: 10.1037/0882-7974.23.1.190

Heuer, H., and Hegele, M. (2008a). Adaptation to direction-dependent visuo-motor rotations and its decay in younger and older adults. *Acta Psychol.* 127, 369–381. doi: 10.1016/j.actpsy.2007.07.006

Heuer, H., and Hegele, M. (2009). Adjustment to a complex visuo-motor transformation at early and late working age. *Ergonomics* 52, 1039–1054. doi: 10.1080/00140130902912795

Heuer, H., and Hegele, M. (2011). Generalization of implicit and explicit adjustments to visuomotor rotations across the workspace in younger and older adults. *J. Neurophysiol.* 106, 2078–2085. doi: 10.1152/jn.00043.2011

Heuer, H., and Hegele, M. (2014). Age-related variations of visuo-motor adaptation beyond explicit knowledge. *Front. Aging Neurosci.* 6:152. doi: 10.3389/fnagi.2014.00152

Heuninckx, S., Wenderoth, N., and Swinnen, S. P. (2008). Systems neuroplasticity in the aging brain: recruiting additional neural resources for successful motor performance in elderly persons. *J. Neurosci.* 28, 91–99. doi: 10.1523/JNEUROSCI.3300-07.2008

Heuninckx, S., Wenderoth, N., Debaere, F., Peeters, R., and Swinnen, S. P. (2005). Neural basis of aging: the penetration of cognition into action control. *J. Neurosci.* 25, 6787–6796. doi: 10.1523/JNEUROSCI.1263-05.2005

Huang, J., Gegenfurtner, K. R., Schütz, A. C., and Billino, J. (2017). Age effects on saccadic adaptation: evidence from different paradigms reveals specific vulnerabilities. *J. Vis.* 17:9. doi: 10.1167/17.6.9

Huang, L., Mo, L., and Li, Y. (2012). Measuring the interrelations among multiple paradigms of visual attention: an individual differences approach. *J. Exp. Psychol. Hum. Percept. Perform.* 38:414. doi: 10.1037/a0026314

Johnson, H., van Beers, R. J., and Haggard, P. (2002). Action and awareness in pointing tasks. *Exp. Brain Res.* 146, 451–459. doi: 10.1007/s00221-002-1200-z

Kleiner, M. B., Brainard, D. H., Pelli, D. G., Ingling, A., and Broussard, C. (2007). What's new in psych toolbox-3? *Perception* 36, 301–307.

Kovacs, K., and Conway, A. R. (2016). Process overlap theory: a unified account of the general factor of intelligence. *Psychol. Inquiry* 27, 151–177. doi: 10.1080/1047840X.2016.1153946

Krakauer, J. W., Ghilardi, M. F., and Ghez, C. (1999). Independent learning of internal models for kinematic and dynamic control of reaching. *Nat. Neurosci.* 2, 1026–1031. doi: 10.1038/14826

Kurdziel, L. B., Dempsey, K., Zahara, M., Valera, E., and Spencer, R. M. (2015). Impaired visuomotor adaptation in adults with ADHD. *Exp. Brain Res.* 233, 1145–1153. doi: 10.1007/s00221-014-4190-8

Leow, L. A., Loftus, A. M., and Hammond, G. R. (2012). Impaired savings despite intact initial learning of motor adaptation in Parkinson's disease. *Exp. Brain Res.* 218, 295–304. doi: 10.1007/s00221-012-3060-5

Liu, G., Chua, R., and Enns, J. T. (2008). Attention for perception and action: task interference for action planning, but not for online control. *Exp. Brain Res.* 185, 709–717. doi: 10.1007/s00221-007-1196-5

Logan, S. W., and Fischman, M. G. (2011). The relationship between end-state comfort effects and memory performance in serial and free recall. *Acta Psychol.* 137, 292–299. doi: 10.1016/j.actpsy.2011.03.009

Marsh, H. W., Hau, K.-T., and Grayson, D. (2005). "Goodness of fit in structural equation models," in *Contemporary Psychometrics: A Festschrift for Roderick P. McDonald*, eds A. May-deu Olivares and J. J. McArdle (Mahwah, NJ: Lawrence Erlbaum).

McCabe, D. P., Roediger, H. L. III., McDaniel, M. A., Balota, D. A., and Hambrick, D. Z. (2010). The relationship between working memory capacity and executive functioning: evidence for a common executive attention construct. *Neuropsychology* 24:222. doi: 10.1037/a0017619

McClearn, G. E., Johansson, B., Berg, S., Pedersen, N. L., Ahern, F., Petrill, S. A., et al. (1997). Substantial genetic influence on cognitive abilities in twins 80 or more years old. *Science* 276, 1560–1563. doi: 10.1126/science.276.5318.1560

McDougle, S. D., Bond, K. M., and Taylor, J. A. (2015). Explicit and implicit processes constitute the fast and slow processes of sensorimotor learning. *J. Neurosci.* 35, 9568–9579. doi: 10.1523/JNEUROSCI.5061-14.2015

Muthén, L. K., and Muthén, B. O. (1998-2017). *Mplus User's Guide*, Sixth Edn. Los Angeles, CA: Muthén & Muthén.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113. doi: 10.1016/0028-3932(71)90067-4

Park, H. L., O'Connell, J. E., and Thomson, R. G. (2003). A systematic review of cognitive decline in the general elderly population. *Int. J. Geriatr. Psychiatry* 18, 1121–1134. doi: 10.1002/gps.1023

Pelli, D. G. (1997). The VideoToolbox software for visual psychophysics: transforming numbers into movies. *Spat. Vis.* 10, 437–442. doi: 10.1163/156856897X00366

Pennequin, V., Sorel, O., and Fontaine, R. (2010). Motor planning between 4 and 7 years of age: changes linked to executive functions. *Brain Cogn.* 74, 107–111. doi: 10.1016/j.bandc.2010.07.003

Pisella, L., Gréa, H., Tilikete, C., Vighetto, A., Desmurget, M., Rode, G., et al. (2000). An "automatic pilot" for the hand in human posterior parietal cortex: toward reinterpreting optic ataxia. *Nat. Neurosci.* 3, 729–736. doi: 10.1038/76694

Rapp, P. R., and Amaral, D. G. (1992). Individual differences in the cognitive and neurobiological consequences of normal aging. *Trends Neurosci.* 15:340. doi: 10.1016/0166-2236(92)90051-9

Raz, N., Williamson, A., Gunning-Dixon, F., Head, D., and Acker, J. D. (2000). Neuroanatomical and cognitive correlates of adult age differences in acquisition of a perceptual-motor skill. *Microsc. Res. Tech.* 51, 85–93. doi: 10.1002/1097-0029(20001001)51:1<85::AID-JEMT9>3.0.CO;2-0

Roller, C. A., Cohen, H. S., Kimball, K. T., and Bloomberg, J. J. (2002). Effects of normal aging on visuo-motor plasticity. *Neurobiol. Aging* 23, 117–123. doi: 10.1016/S0197-4580(01)00264-0

Salthouse, T. A. (1996). General and specific speed mediation of adult age differences in memory. *J. Gerontol. B Psychol. Sci. Soc. Sci*. 51, 30–42. doi: 10.1093/geronb/51B.1.P30

Scharoun, S. M., Gonzalez, D. A., Roy, E. A., and Bryden, P. J. (2016). How the mode of action affects evidence of planning and movement kinematics in aging: end-state comfort in older adults. *Dev. Psychobiol.* 58, 439–449. doi: 10.1002/dev.21386

Schermelleh-Engel, K., Moosbrugger, H., and Müller, H. (2003). Evaluating the fit of structural equation models: tests of significance and descriptive goodness-of-fit measures. *Methods Psychol. Res. Online* 8, 23–74.

Seidler, R. D. (2006). Differential effects of age on sequence learning and sensorimotor adaptation. *Brain Res. Bull.* 70, 337–346. doi: 10.1016/j.brainresbull.2006.06.008

Shipstead, Z., Harrison, T. L., and Engle, R. W. (2016). Working memory capacity and fluid intelligence: maintenance and disengagement. *Perspect. Psychol. Sci.* 11, 771–799. doi: 10.1177/1745691616650647

Simon, A., and Bock, O. (2017). The role of cognition for different stages of visuomotor adaptation in younger and older adults. *Hum. Mov. Sci.* 52, 215–222. doi: 10.1016/j.humov.2017.02.011

Song, Y., and Smiley-Oyen, A. L. (2017). Probability differently modulating the effects of reward and punishment on visuomotor adaptation. *Exp. Brain Res.* 235, 3605–3618. doi: 10.1007/s00221-017-5082-5

Stöckel, T., Wunsch, K., and Hughes, C. M. L. (2017). Age-related decline in anticipatory motor planning and its relation to cognitive and motor skill proficiency. *Front. Aging Neurosci.* 9:283. doi: 10.3389/fnagi.2017.00283

Stroop, J. R. (1935). Studies on interference in serial verbal reactions. *J. Exp. Psychol.* 18, 643–662. doi: 10.1037/h0054651

Taylor, J. A., and Ivry, R. B. (2013). Context-dependent generalization. *Front. Hum. Neurosci.* 7:171. doi: 10.3389/fnhum.2013.00171

Vandevoorde, K., and de Xivry, J. J. O. (2019). Internal model recalibration does not deteriorate with age while motor adaptation does. *Neurobiol. Aging* 80, 138–153. doi: 10.1016/j.neurobiolaging.2019.03.020

Vandevoorde, K., and de Xivry, J. J. O. (2020). Why is the explicit component of motor adaptation limited in elderly adults? *J. Neurophysiol.* 124, 152–167. doi: 10.1152/jn.00659.2019

Wolpe, N., Ingram, J. N., Tsvetanov, K. A., Henson, R. N., and Villis, L. (2020). Age-related reduction in motor adaptation: brain structural correlates and the role of explicit memory. *Neurobiol. Aging* 90, 13–23. doi: 10.1016/j.neurobiolaging.2020.02.016

Wong, A. L., Goldsmith, J., and Krakauer, J. W. (2016). A motor planning stage represents the shape of upcoming movement trajectories. *J. Neurophysiol.* 116:296–305. doi: 10.1152/jn.01064.2015

Wunsch, K., Weigelt, M., and Stöckel, T. (2017). Anticipatory motor planning in older adults. *J. Gerontol. Series B Psychol. Sci. Soc. Sci.* 72, 373–382.

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Dual-Task Performance in Hearing-Impaired Older Adults—Study Protocol for a Cross-Sectional Mobile Brain/Body Imaging Study

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Background: Hearing impairments are associated with reduced walking performance under Dual-task (DT) conditions. Little is known about the neural representation of DT performance while walking in this target group compared to healthy controls or younger adults. Therefore, utilizing the Mobile Brain/Body Imaging approach (MoBI), we aim at gaining deeper insights into the brain dynamics underlying the interaction of cognitive and motor processes during different DT conditions (visual and auditory) controlling for age and the potential performance decrements of older adults with hearing impairments.

Methods: The cross-sectional study integrates a multifactorial mixed-measure design. Between-subject factors grouping the sample will be age (younger vs. older adults) and hearing impairment (mild vs. not hearing impaired). The within-subject factors will be the task complexity (single- vs. DT) and cognitive task modality (visual vs. auditory). Stimuli of the cognitive task will vary according to the stimulus modality (visual vs. auditory), presentation side (left vs. right), and presentation-response compatibility (ipsilateral vs. contralateral). Analyses of DT costs and underlying neuronal correlates focus either on gait or cognitive performance. Based on an *a priori* sample size calculation 96 (48 healthy and 48 mildly hearing impaired) community-dwelling older adults (50–70 years) and 48 younger adults (20–30 years) will be recruited. Gait parameters of speed and rhythm will be captured. EEG activity will be recorded using 64 active electrodes.

Discussion: The study evaluates cognitive-motor interference (CMI) in groups of young and older adults as well as older adults with hearing impairment. The underlying processes of the interaction between motor and cognitive tasks will be identified at a behavioral and neurophysiological level comparing an auditory or a visual secondary task. We assume that performance differences are linked to different cognitive-motor processes, i.e., stimulus input, resource allocation, and movement execution. Moreover,

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for the different DT conditions (auditory vs. visual) we assume performance decrements within the auditory condition, especially for older, hearing-impaired adults. Findings will provide evidence of general mechanisms of CMI (ST vs. DT walking) as well as task-specific effects in dual-task performance while over ground walking.

Keywords: hearing impairment, MoBI, dual-task, overground walking, older adults

INTRODUCTION

Age-related decline in hearing is one of the most common chronic conditions in older adults, affecting nearly half of people over the age of 65 (Goman and Lin, 2016). In recent decades, a worldwide increase in the prevalence of hearing impairments has been observed. With 42 million people affected worldwide in 1985 (∼0.8%), the number increased more than eightfold to 360 million in 2011 (∼5.2%, Olusanya et al., 2014; Olusanya et al., 2019). According to current research, this number grew further to 466 million people (∼6.1%) in 2018 and is estimated to increase to 900 million in 2050 (World Health Organization, 2020). These numbers emphasize the increasing importance of hearing impairment as a public health burden.

Longitudinal studies have shown that hearing impairment is independently associated with poorer cognitive performance even when controlling for age and sex (Valentijn et al., 2005; Lin, 2011). Several researchers have tried to explain this association between age-related hearing impairment and cognitive decline (cf. Mudar and Husain, 2016). Some have proposed a common cause hypothesis, which explains hearing impairment and cognitive decline as a widespread neural degeneration that occurs during aging. Others have proposed an information degradation hypothesis, which suggests poorer cognitive performance as a result of hearing impairment. Presumably, additional cognitive resources are devoted to auditory processing, resulting in fewer resources available for other processes. The sensory deprivation hypothesis views poorer cognitive performance not as an instantaneous consequence of the hearing impairment as the information degradation hypothesis does, but as a long-term change in brain plasticity (Mudar and Husain, 2016).

Age-related changes in the auditory system can include both, higher pure-tone detection thresholds and supra-threshold auditory difficulties (Schneider et al., 2010), requiring a more deliberate allocation of resources to hearing. Consequently, hearing becomes more effortful and cognitively demanding (Pichora-Fuller et al., 2016). Beyond hearing difficulties, hearing impairment further affects physical activities (Chen et al., 2014; Gispen et al., 2014). As a result of cognitive and physical challenges, hearing impairment negatively affects several aspects of one's personal and social life, such as psychosocial well-being, quality of life, economic independence, and interpersonal communication (Mick et al., 2014). Frequently observed consequences encompass social isolation and stigmatization, substance abuse, psychiatric disturbance, depression, difficulties in relationships with partners and children as well as occupational stress (Olusanya et al., 2019). Moreover, activities of daily living (ADL) are further aggravated by hearing impairments in older adults (Chang et al., 2009; Gopinath et al., 2016). Effects of age-related hearing impairment on locomotion and cognition were examined in comparison to age-matched reference groups with hearing-impaired older adults exhibiting lower levels of physical activity and functional performance (Chen et al., 2014; Gispen et al., 2014). A decline in hearing has been found to correlate with balance impairments (Viljanen et al., 2009a,b), self-reported walking limitations (Chen et al., 2014), poor endurance (Gopinath et al., 2016), and increased frailty (Kamil et al., 2014). There are also findings on gait parameters that accompany hearing impairment. An increasing deficit of auditory perception has been found to negatively affect stride length as well as gait speed and cadence under dual-task conditions, independent of age and comorbidities (Wollesen et al., 2018). The effects of hearing impairment on gait even exceed the influence of age, disease, and previous falls (Lin and Ferrucci, 2012). Furthermore, both hearing impairment and decrements in gait quality are associated with the risk of falling in older adults (Lin and Ferrucci, 2012; Jiam et al., 2016).

Researchers have attempted to explain the association between hearing impairment and mobility decline in terms of competition for limited shared cognitive resources (Bruce et al., 2019). In everyday life, balancing or walking is rarely the only task performed at a time (single-task) and it is mostly performed together with another task (dual-task) or sometimes even as a multitasking activity (Faulkner et al., 2007). Cognitive-motor dual-task (CMDT) studies usually compare a single-task condition, such as a postural or walking task, with a dual-task condition, which combines the same motor task with a synchronous cognitive task. By comparing performance in both conditions, we can then calculate dual-task costs (DTCs: single-task minus dual-task performance divided by single-task performance) which indicate the degree of performance decline in one or both tasks due to limited cognitive capacity (Li and Lindenberger, 2002; Marusic et al., 2015; Janouch et al., 2018; Wollesen et al., 2018). CMDT studies have shown that as cognitive load increases during the manipulation of sensory information, older adults show greater postural performance decrements compared to their younger counterparts (Redfern et al., 2001; Doumas et al., 2008). Competition for cognitive capacity is also observed when auditory challenges are experimentally imposed on different motor tasks, such as balancing or walking (Nieborowska et al., 2019), or when older adults with hearing impairment undergo CMDT (Lau et al., 2016). The

Abbreviations: ADL, Activities of daily living; CMDT, Cognitive-motor dual-task; CMI, cognitive-motor interference; DT, Dual-task; DTC, Dual-task costs; EEG, electroencephalography; MoBI, Mobile Brain/Body Imaging; ST, Single-task.

so-called "posture-first" hypothesis or strategy (Shumway-Cook et al., 1997) describes the prioritization of physical safety by allocating more attention to motor performance than to cognitive performance. In older adults, such prioritization increases with task complexity, postural threat, or fear of falling (Li et al., 2001).

Since older adults often exhibit hearing impairments that severely affect their lives, investigating the interaction between age-related hearing impairment and decline in other domains (e.g., vision, cognition, and mobility) at the behavioral and neurophysiological levels could elucidate the underlying mechanisms. In addition, this research could lead to therapeutically promising insights by providing a better understanding of the risk of falls leading toward improved fall prevention programs.

Daily dual-task situations entail different levels of cognitive complexity and therefore will require different cognitive abilities. According to Colcombe and Kramer (2003), cognitive complexity can be classified as (1) simple stimulus-response reaction reflecting processing speed (e.g., reacting to stop at a red traffic light); (2) visuo-spatial tasks to orient in the environment (e.g., walking on uneven ground or avoiding puddles, detecting and deciding whether to evade an approaching object or person), and (3) executive tasks which represent action planning, and response-inhibition (e.g., crossing a street without traffic lights while constantly adapting movement to current traffic flow or remembering a shopping list). For all these daily activities visual information processing is ubiquitous and is relevant to walking itself (Rosano et al., 2012; Mahoney and Verghese, 2018; Owsley et al., 2018). Therefore, a visual dual-task condition while walking will be used as one experimental manipulation of this study. Furthermore, growing evidence indicates that hearing has an important influence on walking performance as well (Chang et al., 2009; Viljanen et al., 2009a; Gopinath et al., 2016; Wollesen et al., 2018). Moreover, daily situations requiring executive decision-making are often solved by a multi-sensory integration including hearing (e.g., the sound of approaching cars) and not only by vision (Wollesen et al., 2021). Therefore, this study will also look at neuronal correlates of dual-task walking with an auditory secondary task. As we assume that participants with hearing impairments compared to participants with normal hearing might have more difficulties during auditory dual-task walking situations, the study will allow for more insights about possible differences in cognitive processing (i) in the different dual-task situations and (ii) between the participants with and without hearing impairments.

Previous research on cognitive-motor interference (CMI) while dual-task walking showed that spatio-temporal gait parameters like walking speed, step length, and arm swing symmetry are affected by the secondary task (Mirelman et al., 2015; Killeen et al., 2017). Moreover, there is evidence that different pre-conditions of the individuals' cognitive-motor abilities, such as balance decline, concern about falling, and hearing impairments, negatively influence dual-task walking, that is reduced walking speed, step length, heel-strike, and foot-rolling movements (Wollesen et al., 2017a,b). These effects were maintained after controlling for age and comorbidities and showed that older adults with concerns about falling or hearing impairment have worse initial conditions on their gait quality and therefore have an increased risk of falling. More research is warranted to confirm these findings, as they relied purely on behavioral data with biomechanical walking measurements and cognitive performance through error counting or reaction times. Therefore, it is relevant to investigate the interaction between the motor and the cognitive system by analyzing the processes and conditions that influence older adults' gait performance in situations that require concurrent performance of sensorimotor and cognitive tasks.

The following experiment will use walking tasks with different complexities and priorities, and record behavioral (spatio-temporal gait parameters) as well as neurophysiological data.

Mobile Brain/Body Imaging to Evaluate Cognitive-Motor Interference

Mobile brain/body imaging (MoBI; Makeig et al., 2009; Gramann et al., 2011, 2014) combines mobile brain imaging (in most cases Electroencephalography; EEG) of freely moving participants with synchronized recordings of task performance and body movements. MoBI is the only brain imaging method that allows for investigating the neuronal correlates of dual-task costs during over ground walking. Motion capture provides the necessary biomechanical data as well as measures of gait quality including arm swing and hip rotation. Walking is associated with movement of the head and the eyes producing electrical activity that will, due to volume conduction, be recorded as a mixture with other active sources in the brain at the sensor level (Jung et al., 2000). Recording and analyzing EEG data from actively walking participants thus requires analysis approaches that differentiate between the brain and non-brain activity. It was demonstrated that brain dynamics can be recorded and successfully analyzed using independent component analysis (ICA) even when subjects walk or run on a treadmill (Gramann et al., 2010; Gwin et al., 2010, 2011; Seeber et al., 2013; Wagner et al., 2013, 2014). Importantly, event-related spectral perturbations (ERSPs) demonstrated a desynchronization of theta oscillation when transitioning from standing to walking while the P300 event-related potential (ERP) component revealed amplitude reductions while walking (Wagner et al., 2016). A similar reduction of an ERP component amplitude was found for the N2 in a Go/NoGo task for dual-task walking as compared to sitting with older adults revealing less pronounced component amplitudes and increased latencies compared to young adults reflecting increased dual-task costs during walking (Malcolm et al., 2015). These behavioral and brain dynamic results indicate that walking poses higher attentional demands compared to standing and thus leaves fewer resources during walking for solving a secondary task. This effect is even more detrimental for older adults with an increased difficulty to allocate attention selectively across several domains (Protzak and Gramann, 2021). Age-related sensory and cognitive decline leads to an increase in demand on attention allocation and working-memory. This was for example shown in a speech in noise perception task by Wong et al. (2009) using fMRI investigating healthy older adults.

Previous Neurophysiological Studies in Hearing Impaired

Evidence indicates several anatomical and functional brain alterations in hearing-impaired older adults. These changes occur not only in regions involved in auditory processing but also in regions involved in attention and emotional processing (cf. Mudar and Husain, 2016). For the present study, we will further describe the brain activity alterations in individuals with hearing impairment.

Two studies by Campbell and Sharma examined auditory (Campbell and Sharma, 2013) and visual evoked potentials (Campbell and Sharma, 2014) in adults with bilateral mild to moderate high-frequency (2–8 kHz) hearing loss and normal-hearing controls. In the auditory evoked potentials study (2013), performance on a speech-in-noise test was positively correlated with increased latencies of the frontal P2 component. Compared to the control group, the hearing-impaired participants showed increases in P2 latency and amplitude. Increased activation in the frontal cortex and decreased activation in the temporal cortex in hearing-impaired subjects compared to the control group were found using cortical source localization, indicating possible changes in the allocation of cortical resources. In the study published in 2014, Campbell and Sharma examined visual evoked potentials and correlated auditory performance in a speech perception task with the visual evoked N1 latency for persons with mild-moderate hearing loss. Adults with hearing loss showed decreased N1 latencies compared to controls and a negative correlation with auditory performance. Furthermore, the amplitudes of P1, N1, and P2 were significantly larger for hearing-impaired participants (Campbell and Sharma, 2014). Using source localization, the authors showed that the P1 component originated from similar brain areas (cerebellar and higher-order visual cortical regions) for both, hearing-impaired and healthy participants. However, for the N1 and P2 components, the hearing-impaired group showed increased activation in temporal areas, which are associated with auditory processing (e.g., superior temporal gyrus, medial temporal gyrus, and inferior temporal gyrus; Campbell and Sharma, 2014). This suggests visual cross-modal reorganization (i.e., intact visual systems can recruit and repurpose deprived audio cortices for processing of their input). Similarly, Cardon and Sharma (2018) investigated cross-modal reorganization between the auditory and somatosensory modalities in older adults with normal hearing and mild-moderate hearing in response to vibrotactile stimulation using high-density electroencephalography. Results showed activation of the somatosensory areas in both hearing-impaired and adults with normal hearing. However, adults with age-related hearing impairment also showed activation of auditory cortical regions in response to somatosensory stimulation.

Regarding the current literature, existing studies with hearing impaired older adults only addressed one of the described aspects but not the comparison of the two most relevant domains for daily activities (vision and hearing) for this target group. Moreover, the neural correlates of existing studies with hearing impaired participants were only examined in a sitting condition. It remains unclear if these findings can be transferred to daily situations that reflect dual-tasking aspects during real life activities. Therefore, the multicomponent MoBI-approach will help to overcome the research gap and gain deeper insights into the neural underpinnings of the interaction of motor and cognitive tasks in different dual-task conditions (visual and auditory). We will further systematically control for the impact of age and potential performance decrements of older adults with hearing impairments.

Aims and Research Questions for the Study

The present study is designed to investigate the following three foci using a MoBI approach:

Focus 1: General characteristics of dual-task walking of all participants.

- How does cognitive task performance differ when using visual or auditory stimuli in single- and dual-task conditions?
- How are dual-task costs represented in gait parameters?
- How are neuronal correlates of auditory and visual information processing impacted by dual-task interference during walking?

Focus 2: Age-related differences in dual-task walking.

- Can we replicate the age-related increase in dual-task costs?
- How are the age-related differences in performance reflected in the respective brain activity of younger and older adults?
- How do younger and older adults differ in their gait parameters and gait-phase related stimuli processing?

Focus 3: Differences of hearing-impaired and healthy older participants in dual-task walking.

- How do auditory vs. visual information processing and movement control vary with regards to the effect of hearing impairment represented in both cognitive task stimuli modalities and dual-task vs. single-task performance?
- How are dual-task costs reflected in biomechanical and neuropsychological measures of hearing-impaired participants?

The overall hypothesis is that there are differences in dual-task costs and their corresponding neuronal correlates between the three groups with the highest disadvantages for the group of older adults with impaired hearing. We hypothesize that the performance differences are linked to the different cognitive-motor processes; i.e., information or stimulus input, resource allocation, and movement execution. Further, we hypothesize that the increasing task complexity (from single-task to dual-task), as well as the stimulus modality (visual vs. auditory), will further diminish the walking performance and increase neuronal activity.

METHODS/STUDY DESIGN

This protocol paper was drafted according to the SPIRIT statement (Chan et al., 2013).

Trial Design

This protocol will reflect a multifactorial mixed-measure design with the two two-level between-subject factors, *age* (younger vs. older adults) and *hearing impairment* (mild hearing-impaired vs. not hearing impaired). The design will be incomplete as the sample contains older adults with hearing impairments and healthy controls matched by age and gender as well as a younger age group. No data of young hearing-impaired adults will be recorded.

The within-subject factors will be the *task condition* (single- vs. dual-task) and *cognitive task modality* (visual vs. auditory). Stimuli of the cognitive task will vary according to the *presentation side* (left vs. right), *modality-specific properties* (magenta vs. cyan or low vs. high pitch, respectively), and *presentation-response compatibility* (ipsilateral vs. contralateral). Analyses of dual-task costs and underlying neuronal correlates can focus either on gait parameters or cognitive task performance.

The chosen colors and tone pitch levels are the conclusion of extensive piloting. In case further testing reveals that other properties are more appropriate for the experimental paradigm, we keep the option open to change the modality-specific properties.

Participants, Interventions, and Outcomes

Ethical Approval

The study will be conducted in agreement with the principles of the Declaration of Helsinki and the guidelines of Good Clinical Practice. Written informed consent will be obtained from all participants before enrolment in the study. The local ethics committee of the TU Berlin, Germany, has approved the study protocol {BPN_WOL_1_210129}. The trial was registered at DRKS.de with registration number DRKS00024453 on April 14th, 2021.

Recruitment of Participants

To assure eligibility and recruitment of participants, community-dwelling older adults will be recruited from a database of the TU Berlin (e.g., "TUB-Versuchspersonenportal") as well as public advertisement and collaborating audiologists in the surrounding areas of Berlin and Hamburg.

Based on sample size calculation (for details see section "Sample Size Estimate/Power Calculations"), a group of 96 community-dwelling older adults (50–70 years) and 48 younger adults (20–30 years) will be recruited. The older experimental group will be divided into the following 2 equally sized subgroups: (1) hearing impaired, (2) not hearing impaired. The participants' allocation to the group will be done after prior assessment using a test battery in a first session. Data analyses will be done on anonymized data.

Confidentiality

All recorded data will be pseudonymized using a participants' number. Only the individual participant code recreated by the participant will allow identifying the participants number of the respective data set in case data deletion is requested within thirty days after end of the data recording. No questionnaire or digital data file will include names or other personal information that would allow identification of data-participant-relations. Video recordings will be stored only after pixelating the face (e.g., Sensarea). Raw data of video will be already deleted permanently on the day of the recording as soon as the pixelating is done.

Eligibility Criteria

The group assignment will be based on the severity of hearing impairment using 4-frequency (0.5, 1, 2, and 4 kHz) pure-tone average (PTA 0.5–4 kHz) and defining PTA 0.5–4 kHz $\leq$ 25 dB HL as normal and PTA 2–4 kHz = 26–40 dB HL as mild in the better hearing ear. Participants will be asked to do the hearing acuity testing with and without their hearing aid to record if their hearing ability was corrected to normal which has effects on the sensory stimulation of the brain.

Inclusion criteria for the healthy young participants will be (1) no diagnosis of hearing impairment (PTA 0.5–4 kHz $\leq$ 25 dB HL), (2) age range between 20 and 30 years, (3) no color blindness.

Inclusion criteria for the non-hearing-impaired older participants will be: (1) no diagnosis of hearing impairment (PTA 0.5–4 kHz $\leq$ 25 dB HL), (2) score > 7 for the Short Physical Performance Battery (SPPB), (3) living independently in the community, (4) maximally moderate risk of falls (< = 13% in the QuickScreen Clinical Falls Assessment Tool), (5) age range between 50 and 70 years, (6) no color blindness.

Inclusion criteria for the hearing-impaired older participants will be: (1) diagnosis of mild hearing impairment (PTA 2–4 kHz = 26–41 dB HL), (2) score > 7 for the SPPB, (3) living independently in the community, (4) maximally moderate risk of falls ($\leq$ 13% in the QuickScreen Clinical Falls Assessment Tool), (5) age range between 50 and 70 years, (6) no color blindness. The severity of hearing impairment will be based on the pure tone audiometry results (evaluated by qualified audiologists prior to the pre-screening session).

Exclusion criteria will be (1) severe hearing impairment (PTA 0.5–4 kHz $\geq$ 41 dB), (2) any acute or chronic diseases, especially of the peripheral and central nervous system, (3) recurrent falls, (4) impaired vision that is not corrected with e.g., glasses, (5) SPPB score $\leq$ 7, (6) indication for impaired cognition (MoCA), (7) risk of falls > 13% (QuickScreen Clinical Falls Assessment Tool).

Outcome Measures

The assessment will focus on behavioral, gait-related as well as neurophysiological markers to gain a deeper understanding of the CMI during dual-task walking. Standardized questionnaires and assessments, as described in the section "Secondary Outcomes," will be used to collect general health information and used to control for covarying factors.

Primary Outcomes

The primary outcome of the present study will be the dual-task cost occurring in over-ground walking with a cognitive secondary task. Gait parameters will be recorded for single and dual task walking, EEG measures will be conducted throughout the entire experiment (ST cognitive; ST walking; DT walking).

Cognitive Task Performance

Participants will receive an auditory or visual discrimination task which fits all criteria for the analyses of gait parameters and event-related as well as continuous brain activity. Task performance will be analyzed using response accuracy and response time.

Gait Performance

Gait parameters like walking speed, step length, double support time, etc., will be captured by the OptoGait system (Microgate, Italy). The OptoGait utilizes photoelectric bridges between LEDs and photodiodes to record ground contacts. Therefore, two parallel positioned rows of bars frame the area of measurement. The temporal resolution of the OptoGait is 1 kHz, with a spatial resolution of 1.041 cm. The OptoGait has already been cross-validated against a three-dimensional motion capture system (ICC 0.690–0.999; $p < 0.001$; Healy et al., 2019). The heel strike will be used as event to calculate gait parameters such as step length, swing phase, stance phase, double support phase and more. The heel strike has been proven to be the most suitable event for our purposes (Rudisch et al., 2021).

Arm swing and hip rotation will be recorded using the HTC Vive trackers and four lighthouse cameras (HTC Corporation, Taoyuan City, Taiwan). Both measures will be analyzed for regular and natural patterns using the amplitude and variability of the respective measure.

Brain Activity Changes

EEG activity will be recorded using 64 active electrodes on an elastic cap (actiCAP snap and LiveAmp 64, Brain Products GmBH, Gilching, Germany) with electrode positions of the 10% system (Oostenveld and Praamstra, 2001) and one electrooculography electrode placed on the cheek for capturing vertical eye movements. Brain activity data will be analyzed on the sensor- as well as source-level. Individual electrode positions will be recorded using a handheld scanner (CapTrak, Brain Products GmBH, Gilching, Germany).

Event-related measures of interest will be event-related potentials (ERPs, e.g., visual P1/N1, P3 over the occipital and parietal cortex, auditory P1/N2, P3 over the temporal and parietal cortex) as well as event-related spectral perturbations (ERSPs, visual and auditory evoked, and event-related desynchronization of mu (10–12 Hz) and beta (18–30 Hz) rhythms during walking). Further analyzed ERPs will be response-related slow cortical potentials (e.g., movement-related cortical potentials like the lateralized-readiness potential at left and right central electrode sites), and eye-movement as well as gait-phase related analysis. EEG data will be analyzed in the time and frequency domain. In addition, functional connectivity measures will be investigated.

Secondary Outcomes

Secondary outcome measures will be recorded in order to ensure the eligibility criteria and to control for the influence of various covarying factors.

Demographic and General Questionnaire Regarding Participants' Current State

Demographic data such as age, body height and body mass, sex, and socio-educational status will be collected, as well as data on the current state of health on the respective assessment day. As a possible contributing factor to the impact of the response side (e.g., on reaction time in cognitive tasks), participants will be asked for their handedness in ten everyday life situations.

Short Falls-Efficacy-Scale-International

The Short Falls-Efficacy-Scale-International (SFES-I) is a 7-item questionnaire addressing fear of falling during easy and complex physical activities as well as social activities (Yardley et al., 2005). A validated German version is available, the completion time is approximately 10 min.

QuickScreen Clinical Falls Assessment Tool—Translated to the German Language

The QuickScreen Clinical Falls Risk Assessment is a multifactorial assessment tool adapted to clinical settings. Measurement properties have already been confirmed in cohorts of community-dwelling older adults. The QuickScreen shows low measurement error, good reliability, and high sensitivity for physical status changes (Tiedemann et al., 2010). The instrument captures information on risk factors of falling in about 10 min. Assessed risk factors are (1) previous falls, (2) medication usage, (3) vision, (4) peripheral sensation, (5) lower limb strength, (6) balance, and (7) coordination. The number of affirmed risk factors is translated into the potential risk of falling for the respective participant, expressed as a percentage. The calculated percentage indicates the risk of falling within the next year. Therefore, a higher value represents a higher risk of falling.

Montreal Cognitive Assessment (MoCA)

The Montreal Cognitive Assessment is a one-page 30-items test developed for screening Mild Cognitive Impairment. It involves items to assess a range of cognitive domains, including executive functions, visuospatial abilities, language, attention, working memory, abstraction, and orientation to time and place. The internal consistency of the MoCA is good (Cronbach's alpha = 0.84; Wong et al., 2018) and a validated German version is available. The duration of the assessment is about 10 min.

Short Physical Performance Battery (SPPB)

The Short Physical Performance Battery (Guralnik et al., 1994) assesses the valid physical function of the lower extremity in older people. Participants are required to stand in an upright position under three conditions (Romberg stance, semi-tandem stance, tandem stance). After that, comfortable gait speed is assessed by measuring the time to walk a four-meter track, starting from a standing position and stopping when the first foot is at the four

TABLE 1 | Stimuli number of the cognitive tasks dissociated by task condition, presentation side, cognitive task modality, modality-specific properties, and presentation-response compatibility with shaded entries representing that the correct response is contralateral to presentation side.

		Visual		Auditory		
		Magenta	**Cyan**	**500 Hz**	**1,000 Hz**	**Σ**
Sitting	Left	50	50	50	50	200
	Right	50	50	50	50	200
Walking	Left	50	50	50	50	200
	Right	50	50	50	50	200
	Σ	200	200	200	200	800
Correct response is		Contra-lateral		Or ipsi-lateral to presentation side		

meters line. Finally, a five-time sit-to-stand transfer is completed as fast as possible. Each domain is scored between zero and four points; SPPB overall scores range from zero (low mobility) to twelve (full mobility). Participants with a score less than 8 will be excluded. The SPPB takes about 10 min.

Pure Tone Audiometry

Qualified audiologists with their medical-approved equipment will perform the audiometry on-site testing both ears of the participants. When hearing aids are used by the participant during everyday life, the measurement will be performed with and without a hearing aid. Special solutions for this situation will be conducted in cooperation with the hearing aid acoustician.

Dual-Task Strategy Assessment

Participants will be asked to answer a customized six yes/no-items questionnaire about the strategy used during dual-task walking with a modified version of the questionnaire used by Wollesen et al. (2017a):

> *Did you feel insecure while walking with the addition of the visual task?*
> *Did you feel insecure while walking with the addition of the auditory task?*
> *I was annoyed by the mistakes I made in the secondary tasks.*
> *Did you concentrate more on the secondary tasks compared to gait performance?*
> *Did you try to equally allocate attention to walking and the secondary tasks?*
> *Was your preferred walking speed slower while walking with a secondary task?*
> *(German Translation: Haben Sie sich unsicher gefühlt, als Sie während des Laufens die Farbe der Lichtblitze unterscheiden sollten? Haben sie sich unsicher gefühlt als Sie während des Laufens die Tonhöhe der Töne unterscheiden sollten? Ich habe mich über meine Fehler in den Entscheidungsaufgaben geärgert. Haben Sie sich mehr auf die Entscheidungsaufgabe konzentriert als auf das Gehen? Haben Sie versucht Ihre Aufmerksamkeit gleichermaßen auf Gehen und Entscheidungsaufgabe zu verteilen? Hat die Entscheidungsaufgabe dazu geführt, dass sich Ihre präferierte Ganggeschwindigkeit verlangsamt hat?)*

Procedure

Description of the Testing Procedure

The cross-sectional study will consist of 2 days of measurement for each participant. After recruitment and signing informed consent, participants' characteristics will be gathered via a standardized assessment (Prescreening) on day one lasting approximately 1.5 h. Questionnaires will be utilized to capture demographic characteristics, health assessment, fear of falls, fall risk, and cognitive capacity. The physical function will be rated by leg strength, gait- and balance testing. Pure tone audiometry and familiarization with the measurement setup of day two will complete the first day of measurement. The utilized instruments are listed in chronicle order of application below:

Measurement Day 1: Prescreening to Identify Confounders and Security Risks

a) Demographic and general questionnaire regarding participants' current state
b) Handedness Questionnaire
c) Short Falls Efficacy-Scale-International (SFES-I)
d) QuickScreen Clinical Falls Assessment Tool
e) Montreal Cognitive Assessment (MoCA)
f) Short Physical Performance Battery (SPPB)
g) Pure Tone Audiometry
h) Familiarization with the experimental setup

At the end of day one, participants fulfilling the requirements for inclusion in the study will be invited to return on another day for the second set of measurements. The measurements on day two will mainly comprise EEG measurements while sitting and walking under single- and dual-task conditions. The order of measurement conditions will be pseudo-randomized on day two, always starting with a walking condition and then constantly switching between walking and sitting conditions. Dependent on the task instructions, one of the combinations will represent motor-response ipsilateral (cyan-right, magenta-left, high pitch-right, low pitch-left) or contra-lateral (magenta-right, cyan-left, high pitch-left, low pitch-right) to the presentation side (**Table 1**). Following the questionnaire about the current state of the participant, familiarization trials for auditory and visual stimuli, and 3 min baseline recordings during sitting and walking will take place.

Measurement Day 2: Dual-Task Walking With EEG

a) General questionnaire regarding participants' current state
b) Baseline EEG and Gait Performance without response device
c) Single-Task-Walking with a response device

d) Cognitive tasks while sitting (Single-Task-Conditions)
e) Cognitive tasks while walking (Dual-Task-Conditions)

Measurement day 2 will take approximately 2.5–3.5 h per participant and will string together conditions of sitting and walking. Breaks will be at least 2 min between the conditions and may be extended as required. At the end of the measurement of day 2, the participants will be asked about their dual-task strategy.

Baseline Electroencephalography and Gait Performance Without Response Device

To collect EEG baseline data and to familiarize participants with the setting, participants will first sit quietly for 3 min and then walk at their preferred walking speed within a 10-m gangway of the OptoGait (Microgate, Bolzano, Italy) system without the response device (3 min). Following the baseline measurements, a 2 min break will take place.

Single-Task Walking With Response Device

Single-task walking will take place as one of five conditions in pseudo-randomized order. Participants will walk constantly 520 m (400 m within the OptoGait), but with the response devices in their hands. Participants will be able to choose their preferred walking speed and turn around by walking around a cone placed at least 1 m from the ends of the OptoGait gangway. From the single-task walking, we will also extract the distance walked within the first 6 min as a slightly modified measure of the 6-min walk test (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002).

Cognitive Tasks While Sitting—Single-Task-Conditions

Participants will be asked to perform cognitive tasks (stimulus-discrimination). During these tasks, participants will be wearing the EEG-system, a custom-made spectacle frame with two LEDs attached to present light stimuli in the peripheral visual field. In addition, participants will wear headphones for presenting auditory stimuli. While sitting in the middle of the OptoGait and performing the task, participants will be asked to look in a walking direction. 200 stimuli (in either the visual or the auditory condition) will be presented with a varying inter-stimulus interval (400–800 ms) and a duration of 100 ms. Participants will be asked to react within a time window of 900 ms to the stimuli by pressing a button on the Vive controller in the respective hand. Thus, the maximal trial duration will vary between 1.4–1.8 s. The participant's response will initiate the next trial and in case no response is given within the required time window, the next trial will start after 900 ms.

Visual task: Visual light stimuli, magenta (red and blue LED) and/or cyan (green and blue LED) flashes, will be presented counterbalanced and pseudo-randomized on the left or right side of the spectacle frame. Participants will have to which color (magenta or cyan) was presented (color discrimination task) with a right/left hand button press.

Auditory task: Auditory stimuli (high and low tone of 1000 and 500 Hz) will be presented for the duration of 100 ms either binaurally or to the left or right side with a volume of 50–60 dB (equals volume of an indoor conversation, Pearsons et al., 1977), regardless of presence and severity of the hearing impairment. Participants will have to indicate which pitch (low or high) was presented (pitch discrimination task) with a right/left hand button press.

Cognitive Tasks While Walking—Dual-Task-Conditions

For the dual-task conditions, a walking time of 6–7.5 min is estimated for each condition, including turnarounds at the end of the gangway. The same visual and auditory stimuli as described in the previous section will be used. Participants will be asked to simultaneously walk up and down the OptoGait gangway. Participants will be able to choose their preferred walking speed and turn around by walking around a cone, placed at least 1 m from the ends of the OptoGait gangway. Five stimuli will be presented each time participants walk the 10 m gangway of the OptoGait. Each task will end after the participants walked 520 m (400 m within the OptoGait) and 200 presented stimuli.

Data Collection, Management, and Analysis

Data Collection

Both, single-task (ST) and dual-task (DT) will be investigated in separate conditions in the experiment. For this purpose, over ground walking will serve as the primary task, while secondary tasks comprise visual or auditory stimulus discrimination. The within-subject comparison between conditions will enable the investigation of dual-task costs vs. task-specific demands. Furthermore, a between-subject comparison will allow for comparing the performance of hearing-impaired older persons with healthy young and older adults. All groups will be treated identically to allow for a comparison of results of dual-task performance across groups.

Data Management

All data gathered by questionnaires will be digitalized for further processing. Functional testing will be controlled via Unity3D (Unity Technologies, San Francisco, United States), which also assigns basic demographic data to the measurement data of each participant. All functional measurements will be streamed and synchronized using the LabStreamingLayer (Swartz Center for Computational Neuroscience, UCSD, US). Synchronized data streams will comprise gait analyses (OptoGait, Microgate, Bolzano, IT), EEG recording (LiveAMP, Brain Products, Gilching, DE), kinematics (VivePro, HTC, Taoyuan, TW), and secondary task performance (VivePro, HTC, Taoyuan, TW & Raspberry Pi, Raspberry Pi Foundation, Cambridge, GB).

Data processing and feature extraction will be done using customized MATLAB scripts (The MathWorks, Inc.), EEGLAB (Delorme and Makeig, 2004). After importing all synchronized Motion Capture and EEG data streams, we will preprocess the EEG data using the bemobil-pipeline.[1] This pipeline comprises filtering, data cleaning (channel and line noise), independent component analysis computation and equivalent dipole modeling for activity sources. Gait data will be analyzed

[1]https://github.com/BeMoBIL/bemobil-pipeline

separately as well as events will be extracted which in turn will be used in joint analyses like gait-phase-related brain activity changes. Following processing of the event-related potentials or spectral measures will be done with respective processing pipelines like the unfold-toolbox (Ehinger and Dimigen, 2019). Source-based analysis will apply repetitive k-means clustering to ensure a stable clustering solution for further analysis of clusters representing the brain regions of interest and connectivity measures.

Statistical Analysis

Descriptive data will be presented as mean (*M*) and standard deviation (*SD*). Normal distribution and homoscedasticity will be checked by the Shapiro-Wilk-Test and the Levene-Test, respectively. Dual-task costs will be analyzed using univariate analyses of variances (ANOVA) including the between-subject factors *age* (younger vs. older) and in case of older *hearing ability* (hearing impaired vs. non-hearing impaired) and the within-subject factors *task complexity* (single- vs. dual-task) and *stimulus modality* (visual vs. auditory).

Significance will be set at $\alpha = 0.05$. The effect size will be presented as partial eta squared. In all *post hoc* comparisons we will control for multiple comparisons (e.g., Bonferroni). Statistical analyses will be done by using SPSS (IBM, SPSS Inc., Chicago, IL, United States) or R (R Core Team, 2013).

Sample Size Estimate/Power Calculations

A g*power sample size calculation (*a priori*: *F*-tests; repeated measures, within-between interaction, effect size f = 0.25; alpha error prob = 0.05; power (1-beta error prob) = 0.8; number of groups = 3) revealed a total of $N = 36$ for each group. Due to an expected drop-out rate of about 20 percent, we will integrate at least 44 participants for each group. We aim to recruit 48 participants per group for the Prescreening.

DISCUSSION

This study aims to gain more insights into CMI while walking of older adults with hearing impairments by using a MoBI-approach. The analysis will be conducted to investigate whether older adults with and without hearing impairments as well as younger adults differ in their cognitive-motor performance while DT walking. Moreover, underlying processes of the interaction between motor and cognitive tasks will be identified at a behavioral and neurophysiological level comparing people with hearing impairments with healthy younger and older adults and while walking with an auditory or a visual secondary task. The overall hypothesis is that there are performance differences and corresponding neuronal correlates between the subgroups with the highest disadvantages for the group of hearing-impaired older adults. We hypothesize that the performance differences are linked to the different cognitive-motor processes; i.e., stimulus input, resource allocation, and movement execution. Moreover, for the different DT conditions (auditory vs. visual) we assume performance decrements within the auditory condition, especially for older, hearing-impaired adults.

As multitask performance mimics everyday life (Faulkner et al., 2007), an understanding of how we adapt to CMI is critical. For example, with increasing age, adults might need cognitive-motor strategies to reduce the risk of falling during daily walking situations (Lövdén et al., 2008; Godde and Voelcker-Rehage, 2010; Schaefer and Schumacher, 2011; Klotzbier et al., 2021). These strategies need to be tailored for adequate exercise interventions addressing different health-related problems, like hearing impairments, to overcome the CMI, for example in fall prevention. To gain more systematic and structured results of different aspects of cognitive-motor performance this study firstly addresses three blocks of behavioral and performance outcomes and their neurophysiological correlates.

Starting with the general characteristics of dual-task walking for all participants this study will compare the influence of visual or auditory secondary stimuli while walking. One might expect that with respect to age comparison the behavioral data might be different and that older adults show more changes in the observed gait parameters (e.g., speed, step length, double support time; refs). Because the walking performance between younger and older adults already differs at ST walking (Neider et al., 2011; Klotzbier et al., 2021), we expect especially the DT situation with additional visual input to lead to the highest performance decrements (for an overview cf. Beurskens and Bock, 2012). Additionally, there is first evidence that older and younger adults might show DT-related differences in walking patterns related to pace (like walking speed) or rhythm (like cadence or double support time; Beauchet et al., 2019; Klotzbier et al., 2021). The study by Klotzbier et al. (2021) showed that younger adults' gait performance during a verbal fluency DT (naming animals) only led to reduced walking speed, whereas for the older adults both elements of pace and rhythm were affected (Klotzbier et al., 2021). It is of interest if these results could be replicated for the integrated visual and auditory tasks within this study. Moreover, we expect first insights into the neuronal correlates of the interaction of the secondary task and the two dimensions of gait performance (parameters of rhythm vs. parameters of pace and effects on arm swing as well as hip rotation) as well as the different phases of a gait cycle (gait initiation, swing phases as well as double support phase; for example as shown for persons with Parkinson's disease; Fino et al., 2018).

Regarding the EEG, it is expected that during DT walking as compared to the single cognitive task, the early evoked P1 covaries in amplitude and latency with walking speed independent of age (Protzak et al., 2021). In addition, a reduction in the late positive complex in the dual-task setup as compared to the single task is expected only in young but not older participants (Protzak et al., 2021). However, older participants without hearing impairments might demonstrate less reduction in the late positive complex as compared to the hearing impaired group. Gait-related spectral modulations are expected in different frequency bands including alpha, beta, and gamma (Onton et al., 2005; Seeber et al., 2014; Wagner et al., 2016). Studies have shown that EEG spectral power in the μ and β band decreases over sensorimotor areas during walking on the treadmill (Severens et al., 2012) when compared to a static condition. The μ and β are suppressed during movement and their amplitudes are modulated locked to the gait-cycle phase during walking (Seeber et al., 2014). It remains unclear if this changes under DT conditions. Moreover, it needs to be investigated whether this also happens during over ground DT walking.

In addition, older participants with hearing impairments are expected to show reduced amplitudes in auditory evoked potentials compared to older participants with normal hearing and younger controls. Previous studies suggest that visual-evoked P1, N1, and P2 amplitudes might be significantly increased in hearing-impaired participants accompanied by increased activation of temporal areas underlying auditory processing. This suggests visual cross-modal reorganization (i.e., intact visual systems can recruit and repurpose deprived audio cortices for processing of their input (Campbell and Sharma, 2014). The described study within this protocol might have the potential to support this hypothesis while using two different sensory modalities and thus allowing for a direct comparison of the results within the same participants.

Findings will provide evidence of general mechanisms of CMI (ST vs. DT walking) as well as task-specific effects underlying changes in dual-task performance while over ground walking. We will use the newly acquired knowledge to tailor intervention programs on physical activity and falls prevention to the special needs of the target group of older adults with hearing impairments. Systematic assessment of individual dual-task performance compared to their healthy cohort, and gained insights into the neural-correlates of motor-control in different conditions will guide training interventions with the overall goal to reduce the number of falls within this target population.

ETHICS STATEMENT

The study was approved by the Ethics Committee of the Department of Psychology and Ergonomics of the Technical University Berlin (registration number BPN_WOL_1_210129). Written informed consent will be obtained from all participants or their legal guardians before enrolment in the study according to the Declaration of Helsinki. Participation in the study is voluntary and there will be no inappropriate financial incentives. The consent form explicitly points to the voluntary character of participation as well as the option to terminate the experiment at any given time without consequences and without giving reasons. All participant information and data will be stored securely and identified by a coded ID number only to maintain participants' confidentiality.

AUTHOR CONTRIBUTIONS

BW conceived of the study. AW with help of OV, MŠ, and BW drafted the manuscript. AW, OV, MŠ, MP, MF, KG, JP, UM, and BW initiated the study design and AW and OV helped with implementation. BW, UM, and KG were grant holders. All authors contributed to refinement of the study protocol and approved the final manuscript.

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REFERENCES

ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories (2002). ATS statement: guidelines for the six-minute walk test. *Am. J. Respir. Crit. Care Med.* 166, 111–117. doi: 10.1164/ajrccm.166.1.at1102

Beauchet, O., Launay, C. P., Sekhon, H., Montembeault, M., and Allali, G. (2019). Association of hippocampal volume with gait variability in pre-dementia and dementia stages of Alzheimer disease: Results from a cross-sectional study. *Exp. Gerontol.* 115, 55–61. doi: 10.1016/j.exger.2018.11.010

Beurskens, R., and Bock, O. (2012). Age-related deficits of dual-task walking: A review. *Neural Plastic.* 2012:131608. doi: 10.1155/2012/131608

Bruce, H., Aponte, D., St-Onge, N., Phillips, N., Gagné, J.-P., and Li, K. Z. H. (2019). The effects of age and hearing loss on dual-task balance and listening. *J. Gerontol.* 74, 275–283. doi: 10.1093/geronb/gbx047

Campbell, J., and Sharma, A. (2013). Compensatory changes in cortical resource allocation in adults with hearing loss. *Front. Syst. Neurosci.* 7:71. doi: 10.3389/fnsys.2013.00071

Campbell, J., and Sharma, A. (2014). Cross-modal re-organization in adults with early-stage hearing loss. *PLoS One* 9:e90594. doi: 10.1371/journal.pone.0090594

Cardon, G., and Sharma, A. (2018). Somatosensory cross-modal reorganization in adults with age-related, early-stage hearing loss. *Front. Hum. Neurosci.* 12:172. doi: 10.3389/fnhum.2018.00172

Chan, A. W., Tetzlaff, J. M., Gøtzsche, P. C., Altman, D. G., Mann, H., Berlin, J. A., et al. (2013). SPIRIT 2013 explanation and elaboration: Guidance for protocols of clinical trials. *BMJ* 346:e7586. doi: 10.1136/bmj.e7586

Chang, H. P., Ho, C. Y., and Chou, P. (2009). The factors associated with a self-perceived hearing handicap in elderly people with hearing impairment–results from a community-based study. *Ear Hearing* 30, 576–583. doi: 10.1097/AUD.0b013e3181ac127a

Chen, D. S., Genther, D. J., Betz, J., and Lin, F. R. (2014). Association between hearing impairment and self-reported difficulty in physical functioning. *J. Am. Geriatr. Soc.* 62, 850–856. doi: 10.1111/jgs.12800

Colcombe, S., and Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychol. Sci.* 14, 125–130. doi: 10.1111/1467-9280.t01-1-01430

Delorme, A., and Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods* 134, 9–21. doi: 10.1016/j.jneumeth.2003.10.009

Doumas, M., Smolders, C., and Krampe, R. T. (2008). Task prioritization in aging: Effects of sensory information on concurrent posture and memory performance. *Exp. Brain Res.* 187, 275–281. doi: 10.1007/s00221-008-1302-3

Ehinger, B. V., and Dimigen, O. (2019). Unfold: An integrated toolbox for overlap correction, non-linear modeling, and regression-based EEG analysis. *PeerJ* 7:e7838. doi: 10.7717/peerj.7838

Faulkner, K. A., Redfern, M. S., Cauley, J. A., Landsittel, D. P., Studenski, S. A., Rosano, C., et al. (2007). Multitasking: Association between poorer performance and a history of recurrent falls. *J. Am. Geriatr. Soc.* 55, 570–576. doi: 10.1111/j.1532-5415.2007.01147.x

Fino, P. C., Mancini, M., Curtze, C., Nutt, J. G., and Horak, F. B. (2018). Gait stability has phase-dependent dual-task costs in Parkinson's disease. *Front. Neurol.* 9:373. doi: 10.3389/fneur.2018.00373

Gispen, F. E., Chen, D. S., Genther, D. J., and Lin, F. R. (2014). Association between hearing impairment and lower levels of physical activity in older adults. *J. Am. Geriatr. Soc.* 62, 1427–1433. doi: 10.1111/jgs.12938

Godde, B., and Voelcker-Rehage, C. (2010). More automation and less cognitive control of imagined walking movements in high-versus low-fit older adults. *Front. Aging Neurosci.* 2:139. doi: 10.3389/fnagi.2010.00139

Goman, A. M., and Lin, F. R. (2016). Prevalence of hearing loss by severity in the United States. *Am. J. Public Health* 106, 1820–1822. doi: 10.2105/AJPH.2016.303299

Gopinath, B., McMahon, C. M., Burlutsky, G., and Mitchell, P. (2016). Hearing and vision impairment and the 5-year incidence of falls in older adults. *Age Ageing* 45, 409–414. doi: 10.1093/ageing/afw022

Gramann, K., Gwin, J. T., Bigdely-Shamlo, N., Ferris, D. P., and Makeig, S. (2010). Visual evoked responses during standing and walking. *Front. Hum. Neurosci.* 4:202. doi: 10.3389/fnhum.2010.00202

Gramann, K., Gwin, J. T., Ferris, D. P., Oie, K., Jung, T. P., Lin, C. T., et al. (2011). Cognition in action: Imaging brain/body dynamics in mobile humans. *Rev. Neurosci.* 22, 593–608. doi: 10.1515/RNS.2011.047

Gramann, K., Jung, T. P., Ferris, D. P., Lin, C. T., and Makeig, S. (2014). Toward a new cognitive neuroscience: Modeling natural brain dynamics. *Front. Hum. Neurosci.* 8:444. doi: 10.3389/fnhum.2014.00444

Guralnik, J. M., Simonsick, E. M., Ferrucci, L., Glynn, R. J., Berkman, L. F., Blazer, D. G., et al. (1994). A short physical performance battery assessing lower extremity function: Association with self-reported disability and prediction of mortality and nursing home admission. *J. Gerontol.* 49, M85–M94. doi: 10.1093/geronj/49.2.M85

Gwin, J. T., Gramann, K., Makeig, S., and Ferris, D. P. (2010). Removal of movement artifact from high-density EEG recorded during walking and running. *J. Neurophysiol.* 103, 3526–3534. doi: 10.1152/jn.00105.2010

Gwin, J. T., Gramann, K., Makeig, S., and Ferris, D. P. (2011). Electrocortical activity is coupled to gait cycle phase during treadmill walking. *NeuroImage* 54, 1289–1296. doi: 10.1016/j.neuroimage.2010.08.066

Healy, A., Linyard-Tough, K., and Chockalingam, N. (2019). Agreement between the spatiotemporal gait parameters of healthy adults from the OptoGait system and a traditional three-dimensional Motion Capture system. *J. Biomechan. Enginee.* 141:4041619. doi: 10.1115/1.4041619

Janouch, C., Drescher, U., Wechsler, K., Haeger, M., Bock, O., and Voelcker-Rehage, C. (2018). Cognitive—motor interference in an ecologically valid street crossing scenario. *Front. Psychol.* 9:602. doi: 10.3389/fpsyg.2018.00602

Jiam, N. T., Li, C., and Agrawal, Y. (2016). Hearing loss and falls: A systematic review and meta-analysis. *Laryngoscope* 126, 2587–2596. doi: 10.1002/lary.25927

Jung, T. P., Makeig, S., Humphries, C., Lee, T. W., McKeown, M. J., Iragui, V., et al. (2000). Removing electroencephalographic artifacts by blind source separation. *Psychophysiology* 37, 163–178. doi: 10.1111/1469-8986.3720163

Kamil, R. J., Li, L., and Lin, F. R. (2014). Association of hearing impairment and frailty in older adults. *J. Am. Geriatr. Soc.* 62, 1186–1188. doi: 10.1111/jgs.12860

Killeen, T., Easthope, C. S., Filli, L., Lőrincz, L., Schrafl-Altermatt, M., Brugger, P., et al. (2017). Increasing cognitive load attenuates right arm swing in healthy human walking. *R. Soc. Open Sci.* 4:160993. doi: 10.1098/rsos.160993

Klotzbier, T. J., Wollesen, B., Vogel, O., Rudisch, J., Cordes, T., Jöllenbeck, T., et al. (2021). An interrater reliability study of gait analysis systems with the dual task paradigm in healthy young and older adults. *Eur. Rev. Aging Physical Activ.* 18, 1–12. doi: 10.1186/s11556-021-00271-z

Lau, S. T., Pichora-Fuller, M. K., Li, K. Z. H., Singh, G., and Campos, J. L. (2016). Effects of hearing loss on dual-task performance in an audiovisual virtual reality simulation of listening while walking. *J. Am. Acad. Audiol.* 27, 567–587. doi: 10.3766/jaaa.15115

Li, K. Z. H., Lindenberger, U., Freund, A. M., and Baltes, P. B. (2001). Walking while memorizing: Age-related differences in compensatory behavior. *Psychol. Sci.* 12, 230–237. doi: 10.1111/1467-9280.00341

Li, K. Z., and Lindenberger, U. (2002). Relations between aging sensory/sensorimotor and cognitive functions. *Neurosci. Biobehav. Rev.* 26, 777–783. doi: 10.1016/S0149-7634(02)00073-8

Lin, F. R. (2011). Hearing loss and cognition among older adults in the United States. *J. Gerontol.* 66, 1131–1136. doi: 10.1093/gerona/glr115

Lin, F. R., and Ferrucci, L. (2012). Hearing loss and falls among older adults in the United States. *Arch. Internal Med.* 172, 369–371. doi: 10.1001/archinternmed.2011.728

Lövdén, M., Schäefer, S., Pohlmeyer, A. E., and Lindenberger, U. (2008). Walking variability and working-memory load in aging: a dual-process account relating cognitive control to motor control performance. *J. Gerontol. Ser. B Psychol. Sci. Soc. Sci.* 63, 121–128. doi: 10.1093/geronb/63.3.P121

Mahoney, J. R., and Verghese, J. (2018). Visual-somatosensory integration and quantitative gait performance in aging. *Front. Aging Neurosci.* 10:377. doi: 10.3389/fnagi.2018.00377

Makeig, S., Gramann, K., Jung, T. P., Sejnowski, T. J., and Poizner, H. (2009). Linking brain, mind and behavior. *Int. J. Psychophysiol.* 73, 95–100. doi: 10.1016/j.ijpsycho.2008.11.008

Malcolm, B. R., Foxe, J. J., Butler, J. S., and De Sanctis, P. (2015). The aging brain shows less flexible reallocation of cognitive resources during dual-task walking: a mobile brain/body imaging (MoBI) study. *Neuroimage* 117, 230–242. doi: 10.1016/j.neuroimage.2015.05.028

Marusic, U., Kavcic, V., Giordani, B., Gerževič, M., Meeusen, R., and Pišot, R. (2015). Computerized spatial navigation training during 14 days of bed rest in healthy older adult men: Effect on gait performance. *Psychol. Aging* 30:334. doi: 10.1037/pag0000021

Mick, P., Kawachi, I., and Lin, F. R. (2014). The association between hearing loss and social isolation in older adults. *Otolaryngol. Head Neck Surg.* 150, 378–384. doi: 10.1177/0194599813518021

Mirelman, A., Bernad-Elazari, H., Nobel, T., Thaler, A., Peruzzi, A., Plotnik, M., et al. (2015). Effects of aging on arm swing during gait: the role of gait speed and dual tasking. *PLoS One* 10:e0136043. doi: 10.1371/journal.pone.0136043

Mudar, R. A., and Husain, F. T. (2016). Neural alterations in acquired age-related hearing loss. *Front. Psychol.* 7:828. doi: 10.3389/fpsyg.2016.00828

Neider, M. B., Gaspar, J. G., McCarley, J. S., Crowell, J. A., Kaczmarski, H., and Kramer, A. F. (2011). Walking and talking: Dual-task effects on street crossing behavior in older adults. *Psychol. Aging* 26:260. doi: 10.1037/a0021566

Nieborowska, V., Lau, S.-T., Campos, J., Pichora-Fuller, M. K., Novak, A., and Li, K. Z. H. (2019). Effects of age on dual-task walking while listening. *J. Motor Behav.* 51, 416–427. doi: 10.1080/00222895.2018.1498318

Olusanya, B. O., Davis, A. C., and Hoffman, H. J. (2019). Hearing loss: Rising prevalence and impact. *Bull. World Health Organiz.* 97, 646A–646A. doi: 10.2471/BLT.19.224683

Olusanya, B. O., Neumann, K. J., and Saunders, J. E. (2014). The global burden of disabling hearing impairment: A call to action. *Bull. World Health Organiz.* 92, 367–373. doi: 10.2471/BLT.13.128728

Onton, J., Delorme, A., and Makeig, S. (2005). Frontal midline EEG dynamics during working memory. *NeuroImage* 27, 341–356. doi: 10.1016/j.neuroimage.2005.04.014

Oostenveld, R., and Praamstra, P. (2001). The five percent electrode system for high-resolution EEG and ERP measurements. *Clin. Neurophysiol.* 112, 713–719. doi: 10.1016/S1388-2457(00)00527-7

Owsley, C., Ghate, D., and Kedar, S. (2018). "Vision and aging," in *The Wiley Handbook on the Aging Mind and Brain*, eds M. Rizzo, S. Anderson, and B. Fritzsch (Hoboken, NJ: Wiley-Blackwell), 296–314. doi: 10.1002/9781118772034.ch15

Pearsons, K. S., Bennett, R. L., and Fidell, S. A. (1977). *Speech levels in various noise environments*. Washington, D.C: United States Environmental Protection Agency.

Pichora-Fuller, M. K., Kramer, S. E., Eckert, M. A., Edwards, B., Hornsby, B. W., Humes, L. E., et al. (2016). Hearing impairment and cognitive energy: The framework for understanding effortful listening (FUEL). *Ear Hearing* 37, 5S–27S. doi: 10.1097/AUD.0000000000000312

Protzak, J., and Gramann, K. (2021). EEG beta-modulations reflect age-specific motor resource allocation during dual-task walking. *Sci. Rep.* 11, 1–11. doi: 10.1038/s41598-021-94874-2

Protzak, J., Wiczorek, R., and Gramann, K. (2021). Peripheral visual perception during natural overground dual-task walking in older and younger adults. *Neurobiol. Aging* 98, 146–159. doi: 10.1016/j.neurobiolaging.2020.10.009

R Core Team (2013). *R: A language and environment for statistical computing.* Vienna: R Foundation for Statistical Computing.

Redfern, M. S., Jennings, J. R., Martin, C., and Furman, J. M. (2001). Attention influences sensory integration for postural control in older adults. *Gait Posture* 14, 211–216. doi: 10.1016/S0966-6362(01)00144-8

Rosano, C., Studenski, S. A., Aizenstein, H. J., Boudreau, R. M., Longstreth, W. T. Jr., and Newman, A. B. (2012). Slower gait, slower information processing and smaller prefrontal area in older adults. *Age Ageing* 41, 58–64. doi: 10.1093/ageing/afr113

Rudisch, J., Jöllenbeck, T., Vogt, L., Cordes, T., Klotzbier, T. J., Vogel, O., et al. (2021). Agreement and consistency of five different clinical gait analysis systems in the assessment of spatiotemporal gait parameters. *Gait Posture* 85, 55–64. doi: 10.1016/j.gaitpost.2021.01.013

Schaefer, S., and Schumacher, V. (2011). The interplay between cognitive and motor functioning in healthy older adults: findings from dual-task studies and suggestions for intervention. *Gerontology* 57, 239–246. doi: 10.1159/000322197

Schneider, B. A., Pichora-Fuller, M. K., and Daneman, M. (2010). "Effects of senescent changes in audition and cognition on spoken language comprehension," in *The Aging Auditory System*, ed. S. Gordon-Salant (New York, NY: Springer), 167–210. doi: 10.1007/978-1-4419-0993-0_7

Seeber, M., Scherer, R., Wagner, J., and Müller-Putz, G. R. (2013). Spatial-Spectral Identification Of M And B Eeg Rhythm Sourcrs During Robot-Assisted Walking. *Biomed. Engine.* 58:000010151520134433. doi: 10.1515/bmt-2013-4433

Seeber, M., Scherer, R., Wagner, J., Solis-Escalante, T., and Müller-Putz, G. R. (2014). EEG beta suppression and low gamma modulation are different elements of human upright walking. *Front. Hum. Neurosci.* 8:485. doi: 10.3389/fnhum.2014.00485

Severens, M., Nienhuis, B., Desain, P., and Duysens, J. (2012). Feasibility of measuring event related desynchronization with electroencephalography during walking. *Annu. Int. Confer. IEEE Engine. Med. Biol. Soc.* 2012, 2764–2767. doi: 10.1109/EMBC.2012.6346537

Shumway-Cook, A., Woollacott, M., Kerns, K. A., and Baldwin, M. (1997). The effects of two types of cognitive tasks on postural stability in older adults with and without a history of falls. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* 52, M232–M240. doi: 10.1093/gerona/52A.4.M232

Tiedemann, A., Lord, S. R., and Sherrington, C. (2010). The development and validation of a brief performance-based fall risk assessment tool for use in primary care. *J. Gerontol. Ser. A Biomed. Sci. Med. Sci.* 65, 896–903. doi: 10.1093/gerona/glq067

Valentijn, S. A., van Boxtel, M. P., van Hooren, S. A., Bosma, H., Beckers, H. J., Ponds, R. W., et al. (2005). Change in sensory functioning predicts change in cognitive functioning: Results from a 6-year follow-up in the Maastricht aging study. *J. Am. Geriatr. Soc.* 53, 374–380. doi: 10.1111/j.1532-5415.2005.53152.x

Viljanen, A., Kaprio, J., Pyykkö, I., Sorri, M., Koskenvuo, M., and Rantanen, T. (2009a). Hearing acuity as a predictor of walking difficulties in older women. *J. Am. Geriatr. Soc.* 57, 2282–2286. doi: 10.1111/j.1532-5415.2009.02553.x

Viljanen, A., Kaprio, J., Pyykkö, I., Sorri, M., Pajala, S., Kauppinen, M., et al. (2009b). Hearing as a predictor of falls and postural balance in older female twins. *J. Gerontol.* 64, 312–317. doi: 10.1093/gerona/gln015

Wagner, J., Makeig, S., Gola, M., Neuper, C., and Müller-Putz, G. (2016). Distinct β band oscillatory networks subserving motor and cognitive control during gait adaptation. *J. Neurosci.* 36, 2212–2226. doi: 10.1523/JNEUROSCI.3543-15.2016

Wagner, J., Solis-Escalante, T., Neuper, C., Scherer, R., and Müller-Putz, G. (2013). Robot assisted walking affects the synchrony between premotor and somatosensory areas. *Biomed. Engine.* 58:000010151520134434. doi: 10.1515/bmt-2013-4434

Wagner, J., Solis-Escalante, T., Scherer, R., Neuper, C., and Müller-Putz, G. (2014). It's how you get there: walking down a virtual alley activates premotor and parietal areas. *Front. Hum. Neurosci.* 8:93. doi: 10.3389/fnhum.2014.00093

Wollesen, B., Mattes, K., Schulz, S., Bischoff, L. L., Seydell, L., Bell, J. W., et al. (2017a). Effects of dual-task management and resistance training on gait performance in older individuals: A randomized controlled trial. *Front. Aging Neurosci.* 9:415. doi: 10.3389/fnagi.2017.00415

Wollesen, B., Schulz, S., Seydell, L., and Delbaere, K. (2017b). Does dual task training improve walking performance of older adults with concern of falling? *BMC Geriatr.* 17:213. doi: 10.1186/s12877-017-0610-5

Wollesen, B., Pocovi, N. C., Salvestro, K., Hurley, S., Seydell, L., Scrivener, K., et al. (2021). Multitask training to improve walking performance in older adults with hearing impairment: A feasibility study. *Aging Health Res.* 1:100028. doi: 10.1016/j.ahr.2021.100028

Wollesen, B., Scrivener, K., Soles, K., Billy, Y., Leung, A., Martin, F., et al. (2018). Dual-task walking performance in older persons with hearing impairment: Implications for interventions from a preliminary observational study. *Ear Hearing* 39, 337–343. doi: 10.1097/AUD.0000000000000489

Wong, A., Yiu, S., Nasreddine, Z., Leung, K. T., Lau, A., Soo, Y., et al. (2018). Validity and reliability of two alternate versions of the Montreal Cognitive Assessment (Hong Kong version) for screening of Mild Neurocognitive Disorder. *PLoS One* 13:e0196344. doi: 10.1371/journal.pone.0196344

Wong, P. C., Jin, J. X., Gunasekera, G. M., Abel, R., Lee, E. R., and Dhar, S. (2009). Aging and cortical mechanisms of speech perception in noise. *Neuropsychologia* 47, 693–703. doi: 10.1016/j.neuropsychologia.2008.11.032

World Health Organization (2020). *Deafness and hearing loss*. Geneva: WHO.

Yardley, L., Beyer, N., Hauer, K., Kempen, G., Piot-Ziegler, C., and Todd, C. (2005). Development and initial validation of the Falls Efficacy Scale-International (FES-I). *Age Ageing* 34, 614–619. doi: 10.1093/ageing/afi196

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Cerebral Microbleeds Were Related With Poor Cognitive Performances on the Dual Task Condition in Older Adults

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Background: The dual task (DT) was commonly used to assess the risk of falls in older adults and patients with neurological disorders. However, the performance on DT conditions has not been well investigated in patients with cerebral microbleed (CMB). This study is aimed to compare the performance in DT tests between older adults with and without CMB, and to explore the association between CMB and cognitive performances of DT.

Methods: This is a cross-sectional study. A total of 211 old adults participated, involving 68 CMB patients. The task protocol involved two global cognition tests, two single cognitive tests (serial 7 subtraction and semantic fluency), two single motor tasks [8-m walking and timed up and go test (TUG)], and three DT tests [walking and serial subtraction (WSS), walking and semantic fluency (WSF), and TUG and serial subtraction (TUGSS)]. The time taken to complete each task and the number of correct responses were recorded. For each DT condition, the correct response rate (CRR) and the dual-task effect (DTE) for the correct number were calculated.

Results: Compared with subjects without CMB, CMB patients had worse cognitive performances on DT condition in CRR of WSS ($p = 0.003$), WSF ($p = 0.030$) and TUGSS ($p = 0.006$), and DTE of WSS ($p = 0.017$). Binary logistic regression analysis showed that the presence of CMB was an independent risk factor for the impairment group for CRR of TUGSS (*OR*, 2.54; 95% CI, 1.11–5.82; $p = 0.027$) with the adjustment for confounders, rather than CRR of WSS and WSF, or DTE of WSS. Multiple linear regression analysis showed that CRR of TUGSS decreased with the increase of CMB number grades (β, -0.144; 95% CI, -0.027, -0.002; $p = 0.028$).

Conclusion: The present study indicated that CMBs were closely associated with poor cognitive performances on DT in the elderly. Strongest effect size was seen for CRR of TUGSS, where performance deficits increased in proportion to the degree of CMB burden.

Keywords: cerebral microbleed, dual task, cognitive-motor interference, cognition, motor

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INTRODUCTION

Dual task (DT) refers to a paradigm that an individual performs two attention-demanding tasks with different goals simultaneously. Taking two tasks concurrently has negative effects on the performance of both tasks (Nonnekes et al., 2020). The difference between the performance on each single task and DT provides an index of DT ability. In people's daily life, performing various activities requires the coordination of complex cognitive and motor functions. And the one-dimensional cognitive or motor test may not be accurate enough to assess people's ability of daily living. Thus, the DT may be an important method for the complemental assessment of physical function.

Previous studies have reported that the performance in DT tests of the elderly is significantly worse than that of the young (Lindenberger et al., 2000; Pothier et al., 2015; Papegaaij et al., 2017). White matter hyperintensity (WMH), a kind of aging-related small vessel lesions that is common in older adults, has been found a close relationship with poor gait performances on the DT condition (Ghanavati et al., 2018; Hairu et al., 2021). It's suggested that cerebral small vessel disease (CSVD) may be an underlying cause of poor DT performances in the elderly. Cerebral microbleed (CMB) is one of the crucial markers of CSVD, and its pathological mechanism is closely related to hypertension and cerebral amyloid angiopathy (Shuaib et al., 2019). Many studies have indicated that CMB is associated with the cognitive impairment or gait dysfunction (Akoudad et al., 2016; Chiu et al., 2018; Nyúl-Tóth et al., 2020; Li et al., 2021a; Sullivan et al., 2021). However, there are no studies specifically focusing on the effect of CMB lesions on DT performances.

The purpose of the current study is to investigate how performances of a cognitive-motor DT protocol differ between older adults with and without CMB, and to prove the association between CMB and cognitive performances under the DT condition. We hypothesize that the DT performance of old adults with CMB is worse than that of those without CMB, and that the presence and the severity of CMB are closely related to the cognitive performance decline in DT.

METHODS

Subjects

This study was designed as a cross-sectional study. Participants for physical examinations were recruited in the Neurology Department of Beijing Chao-yang Hospital, Capital Medical University from January 2021 to September 2021. Written informed consent was obtained from eligible participants. The study was performed in compliance with the Declaration of Helsinki and approved by the Ethics Committee of Beijing Chao-yang Hospital, Capital Medical University (2021-Sci-56).

Inclusion criteria were age ≥60 years, available clinical data and brain magnetic resonance imaging (MRI), and agreement to participate in this study. The exclusion criteria included: (1) acute cerebrovascular diseases such as acute cerebral infarction, cerebral hemorrhage, venous sinus thrombosis and so on; (2) history of the massive relevant cerebral infarction (recent infarct > 2.0 cm in diameter and the correspondent lacuna > 1.5 cm in diameter) and cerebral hemorrhage with neurological sequelae; (3) the neurodegenerative disease (Parkinson's disease, Alzheimer's disease, multiple system atrophy, etc.), history of nervous system infection, inflammatory demyelinating disease, brain trauma, poisoning, radioactive encephalopathy and metabolic encephalopathy; (4) severe neuropsychological diseases and mental illnesses affecting the results of cognitive function assessments; (5) patients with cardiac insufficiency, hepatic failure, kidney failure or other medical conditions that were too weak prevented the patients from performing a proper assessment; (6) orthopedic conditions or pain affecting natural motor function; (7) taking cognitive-affecting drugs within 24 h; (8) severe visual or hearing impairment; (9) incomplete data of clinical records, motor function assessments and neuropsychological tests, or brain MRI with poor quality.

Baseline information including age, gender, years of education, height, weight, smoking and drinking status, medication use and medical history of hypertension, diabetes, hyperlipidemia, stroke, transient ischemic attack, or coronary artery disease was collected from all participants according to medical records and questionnaires.

Neuroimaging Assessments

MRI was performed on a 3.0-T MRI scanner (Prisma; Siemens AG, Erlangen, Germany). The parameters of the MRI examination were as follows: T1-weighted imaging (repetition time = 2000.0 ms, echo time = 9.2 ms, slice thickness = 5 mm, and field of view = 220 × 220 mm^2), T2-weighted imaging (repetition time = 4,500.0 ms, echo time = 84.0 ms, slice thickness = 5.0 mm, and field of view = 220 × 220 mm^2), T2-weighted fluid-attenuated inversion recovery sequence (repetition time = 8,000.0 ms, echo time = 86.0 ms, slice thickness = 5.0 mm, and field of view = 199 × 220 mm^2), diffusion-weighted imaging (repetition time = 3,300.0 ms, echo time = 91.0 ms, slice thickness = 5.0 mm, field of view = 230 × 230 mm^2, and b = 0 and 1,000 s/mm^2), and susceptibility-weighted imaging (repetition time = 27.0 ms, echo time = 20.0 ms, slice thickness = 3.2 mm, and field of view = 172 × 230 mm^2).

Main neuroimaging markers of CSVD were defined according to the STandards for ReportIng Vascular changes on nEuroimaging published previously (Wardlaw et al., 2013). The location and number of CMB were collected based on the Microbleed Anatomical Rating Scale (Gregoire et al., 2009). And the severity of CMB was classified into four grades by the number of lesions (0 CMB, 1 CMB, 2 CMBs and ≥3 CMBs). The paraventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH) were graded according to the Fazekas scale ranging from 0 to 3, respectively (Fazekas et al., 1987). The burden of perivascular space (PVS) in centrum semiovale and basal ganglia (BG) was evaluated separately (grade 0 to 4) (Maclullich et al., 2004; Li et al., 2021b). The visual rating scale for posterior atrophy was used to assess the severity of brain atrophy ranging from 0 to 3 (Koedam et al., 2011). Moreover, we noted the total number and distribution of lacuna lesions.

Neuroimaging markers of CSVD were identified and labeled by consensus of two experienced neurologists blinded to clinical data. Disagreement was resolved by discussing with other coauthors.

Procedures

Cognitive Tests

Global cognition was assessed using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). Besides, the serial 7 subtraction task and semantic fluency task (animals) in MoCA were selected as two kinds of single cognitive tasks. For the serial 7 subtraction task, subjects were asked to calculate at least 60 s and at least five times. If the subject cannot perform the subtraction, the time for this item was limited to 60 s. For the semantic fluency task, subjects were asked to generate as many nouns as possible within 60 s. Besides, we recorded the subjects' responses and noted the number of correct answers. Cognitive assessments and DT tests were conducted within 5 days after the MRI scan.

Motor and Dual Tasks

Subjects performed all the following five tasks walking over a tiled floor. On the DT condition, subjects walked with the instruction to "perform both tasks as well as possible without giving priority to either motor or cognitive task". Subjects' responses were recorded, and we also noted the number of correct responses.

1. Eight-meter walking task: Participants were asked to walk on level ground along an 8-m pathway at their usual and comfortable pace.
2. Walking and serial subtraction task (WSS): Participants walked along the 8-m walkway while repeatedly subtracting 7 from a random number concurrently.
3. Walking and semantic fluency task (WSF): Participants were instructed to walked along the 8-m walkway while doing semantic fluency task (vegetables) concurrently.
4. Timed up and go test (TUG): Participants were asked to stand up from a chair, walk 3 m, turn 180°, then walk back, and sit down at their usual and comfortable speed.
5. TUG and serial subtraction task (TUGSS): Participants performed the TUG test and serial 7 subtraction task from a random number simultaneously.

To avoid the learning effects, the rater assigned different word categories (animals or vegetables) or random numbers (between 80 and 100) when assessing the single cognitive test and the DT test. And our pilot study found that different sets of numbers or word categories produced comparable difficulty among participants.

Subjects' motor data were captured using the Intelligent Device for Energy Expenditure and Activity (IDEEA®, MiniSun LLC) system. The main recorder of IDEEA system was secured on the left waistband. One sub-recorder was taped above each lateral malleolus. Five sensors were placed on the sternum and bilaterally on the plantar aspect of foot and midline of the anterior aspect of thigh. The IDEEA system automatically recognized the movement of body and the change of posture, and recorded various parameters of tests including the start and end time, duration, gait, etc. The data was downloaded from the recorder to the computer after performing tests on each subject. Two gait parameters on each DT condition, the walking speed (m/s) and stride length (m), were included in this analysis.

Dual Task Performance Assessments

The correct response rate (CRR) was calculated using the duration and the number of correct responses in each DT test for measuring the cognitive performance under the DT condition. The CRR was computed as (Yang et al., 2016):

$$CRR = \frac{number\ of\ correct\ reponses}{time}$$

We used the dual-task effect (DTE) to assess the influence of the added motor task on the cognitive performance. The DTE was computed as (Kelly et al., 2010):

$$DTE,\ \% = \frac{dual\ task\ -\ single\ task}{single\ task} \times 100\%$$

In this study, we calculated the DTE for the number of correct responses. The time limit given to count the answers in each single cognitive task was matched to the duration of the corresponding DT test. For example, if it took the subject 30 s to perform the DT of walking and subtraction, then we noted the number of correct responses in the first 30 s in the single task of subtraction in MoCA according to the recording. The negative value of the DTE indicates worse cognitive performance on the DT condition compared with the single task condition ("cognitive costs"), while the positive value indicates the improvement of performances ("cognitive benefits") (Al-Yahya et al., 2011; Pumpho et al., 2020).

The increased time of WSS, WSF and TUGSS was calculated as the duration of WSS minus the duration of 8-m walking, the duration of WSF minus the duration of 8-m walking, and the duration of TUGSS minus the duration of TUG task, respectively.

The increased numbers of WSS, WSF and TUGSS were calculated as the correct number of WSS minus the correct number of single subtraction task, the correct number of WSF (vegetables) minus the correct number of semantic fluency (animals), and the correct number of TUGSS minus the correct number of single subtraction task, respectively. The time to count responses in each single cognitive task was matched to the duration of the corresponding DT test.

Impaired cognitive performance on DT was defined as the lowest quartile of CRR or DTE. Those participants with impaired cognitive performance were considered as the impairment group, the others were assigned to the control group.

Statistical Analyses

Data were presented as n (%) for categorical variables, mean (standard deviation) for normally distributed variables, or median (quartiles) for continuous data with non-normal distribution. The severity grade of WMH, PVS and PA was represented by the median (range). Differences among groups were determined using χ^2, Mann-Whitney U or Kruskal-Wallis H test where appropriate.

The univariate analysis was used to identify the statistical differences of parameters in the cognitive performance between CMB patients and non-CMB subjects. Next, subjects were divided into the impairment group and the control group according to each parameter with statistical difference, separately. Then, age, sex, years of education and variables with significant differences between the impairment group and control group were adjusted in the following regression analysis as confounding factors.

Binary logistic regression analysis was performed to determine whether the presence of CMB was an independent risk factor of the DT performance. Multiple linear regression analysis was used to explore the trend of the DT performance with the increase of CMB number grades. All analyses were performed with Statistical Product and Service Solutions 22.0, and the statistical significance was considered at $p < 0.05$.

RESULTS

Sample characteristics are depicted in **Table 1**. A total of 211 elderly subjects were recruited in this study, including 116 males and 95 females with the median age of 70 years old. There were 68 patients with CMB and 143 subjects without CMB. As for the location of CMB, 24 patients had strictly lobar CMB, 16 patients had strictly deep CMB, two patients had strictly infratentorial CMB (cerebellum or brain stem, or both), 12 patients had mixed CMB (lobar, deep and infratentorial), 6 patients had mixed CMB (lobar and deep), 5 patents had mixed CMB (lobar and infratentorial), and 3 patients had mixed CMB (deep and infratentorial). There were 83 subjects with lacuna, including 32 patients with one lesion and 51 with multiple lesions. Six patients had lobar lacuna located in the cerebral lobe, 57 had lacuna in the basal ganglia, 39 had paraventricular lesion, and 20 had infratentorial lesion.

Compared with non-CMB subjects, CMB patients had lower scores of MMSE ($p = 0.012$) and MoCA ($p = 0.001$), and worse cognitive performances on DT in CRR of WSS ($p = 0.003$), WSF ($p = 0.030$) and TUGSS ($p = 0.006$), and DTE of WSS ($p = 0.017$). There were no significant differences in the increased correct number or time of WSS, WSF and TUGSS, or DTE of WSF and TUGSS between CMB patients and non-CMB subjects (all $p >$ 0.050) (**Table 2**). In CMB patients, numbers of correct answers of WSS and TUGSS were significantly lower than those of time-matched single subtraction tasks [1 (0, 2) vs. 2(1, 4), $p < 0.001$; 1 (0, 3) vs. 3 (1, 4), $p < 0.001$], while no significant difference was observed in the semantic fluency [7 (5, 8) vs. 7 (6, 8), $p = 0.713$]. After comparing gait parameters on each DT condition between two groups, CMB patients had slower stride speeds and shorter stride lengths, while the differences were statistically significant only in the stride length in TUGSS ($p = 0.045$) (**Table 2**).

Subjects were divided into the impairment group (the lowest quartile of CRR or DTE) and the control group (the other subjects) based on CRR of WSS, WSF and TUGSS, and DTE of WSS, respectively. Grouped by CRR of WSS, there were statistical differences in years of education ($p = 0.003$) and Fazekas scores of DWMH ($p = 0.046$) between the impairment group and the control group. Grouped by CRR of WSF, significant differences were found in diabetes ($p = 0.013$), hyperlipidemia ($p = 0.044$), antidiabetic drug ($p = 0.037$), presence or absence of lacuna ($p = 0.046$), Fazekas scores of DWMH ($p < 0.001$) and PVH ($p < 0.001$) and severity of BG-PVS ($p = 0.044$) between the impairment group and the control group. As for DTE of WSS, statistical differences were found in education ($p = 0.003$) and DWMH ($p = 0.046$) between two groups. In each grouping method, statistical differences were found in scores of MMSE ($p < 0.05$) and MoCA ($p < 0.05$) between the impairment group and the control group.

Grouped by CRR of TUGSS, there were significant differences in education ($p = 0.014$), smoking ($p = 0.022$), hyperlipidemia ($p = 0.011$), lipid-lowering drug ($p = 0.011$), MMSE ($p < 0.001$) and MoCA ($p < 0.001$) scores between the impairment group and the control group (**Table 3**). Binary logistic regression analysis showed that the presence of CMB was an independent risk factor for the impairment group of CRR of TUGSS (*OR*, 2.54;

TABLE 1 | Characteristics of the study population.

	All participants (n = 211)
Age[a], year	70.00 (64.00, 76.00)
Men, *n* (%)	116 (54.98)
Years of education[a], year	9 (9, 12)
Height[a], m	1.65 (1.59, 1.70)
Weight[a], kg	69.00 (60.00, 75.00)
MMSE[a]	28 (26, 29)
MoCA[a]	24 (22, 26)
Smoking, *n* (%)	65 (30.81)
Drinking, *n* (%)	36 (17.06)
Hypertension, *n* (%)	147 (69.67)
Diabetes mellitus, *n* (%)	63 (29.86)
CAD, *n* (%)	50 (23.70)
History of stroke/TIA, *n* (%)	46 (21.80)
Hyperlipemia, *n* (%)	76 (36.02)
Blood pressure-lowering medication, *n* (%)	129 (61.14)
Antiplatelet/anticoagulant drug, *n* (%)	66 (31.28)
Antidiabetic drug, *n* (%)	60 (28.44)
Lipid-lowering drug, *n* (%)	68 (32.23)
CSVD MRI markers	
Presence of lacune, *n* (%)	83 (39.34)
Presence of CMB, *n* (%)	68 (32.23)
PVH[b]	1 (1–3)
DWMH[b]	1 (0–3)
BG-PVS[b]	1 (1–4)
CSO-PVS[b]	2 (1–4)
PA [b]	1 (0–2)

MMSE, mini-mental state examination; MoCA, Montreal cognitive assessment; CAD, coronary artery disease; TIA, transient ischemic attack; CSVD, cerebral small vessel disease; MRI, magnetic resonance imaging; CMB, cerebral microbleed; PVH, periventricular hyperintensity; DWMH, deep white matter hyperintensity; BG, basal ganglia; CSO, centrum semiovale; PVS, perivascular space; PA, posterior atrophy.
[a]*Median (quartiles).*
[b]*Median (range).*

TABLE 2 | Comparison of cognitive performances and gait parameters between participants with and without CMB.

	CMB ($n = 68$)	No CMB ($n = 143$)	p
MMSE[a]	27 (25, 29)	28 (27, 29)	0.012*
MoCA[a]	23 (21, 25)	25 (23, 26)	0.001*
Increased number of WSS[a]	−1.00 (−2.00, 0.00)	−1.00 (−2.00, 0.00)	0.161
Increased number of WSF[a]	0.00 (−2.00, 1.00)	−1.00 (−2.00, 1.00)	0.530
Increased number of TUGSS[a]	−1.00 (−2.75, 0.00)	−1.00 (−2.00, 0.00)	0.274
Increased time of WSS[a], s	4.20 (2.50, 7.38)	3.47 (1.80, 7.10)	0.328
Increased time of WSF[a], s	2.43 (1.24, 4.96)	2.20 (1.03, 4.28)	0.317
Increased time of TUGSS[a], s	6.10 (2.68, 8.75)	4.27 (1.80, 7.50)	0.053
CRR of WSS[a]	0.06 (0.00, 0.16)	0.12 (0.04, 0.23)	0.003*
CRR of WSF[b]	0.49 (0.21)	0.56 (0.21)	0.030*
CRR of TUGSS[b]	0.08 (0.09)	0.12 (0.10)	0.006*
DTE of WSS[a], %	−58.33 (−100.00, 0.00)	−33.33 (−75.00, 0.00)	0.017*
DTE of WSF[a], %	0.00 (−29.64, 14.29)	−10.00 (−28.57, 20.00)	0.852
DTE of TUGSS[a], %	−53.57 (−100.00, 0.00)	−33.33 (−80.00, 0.00)	0.052
Speed in WSS[a], m/s	0.56 (0.38, 0.66)	0.58 (0.44, 0.77)	0.125
Stride length in WSS[a], m	0.78 (0.65, 0.90)	0.83 (0.67, 0.97)	0.054
Speed in WSF[a], m/s	0.60 (0.47, 0.76)	0.67 (0.49, 0.81)	0.189
Stride length in WSF [b], m	0.81 (0.20)	0.86 (0.18)	0.073
Speed in TUGSS[a], m/s	0.44 (0.33, 0.53)	0.48 (0.37, 0.56)	0.051
Stride length in TUGSS[a], m	0.63 (0.53, 0.79)	0.70 (0.57, 0.80)	0.045*

CMB, cerebral microbleed; MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assessment; WSS, walking and serial subtraction; WSF, walking and semantic fluency; TUGSS, timed up and go and serial subtraction; CRR, correct response rate; DTE, dual-task effect.
[a]*Median (quartiles).*
[b]*Mean (standard deviation).*
$^*P < 0.05$.

95% CI, 1.11–5.82; $p = 0.027$) with the adjustment of age, sex, education, smoking, hyperlipidemia, lipid-lowering drug, MMSE and MoCA (**Table 4**).

Participants were further classified into four grades according to the number of CMB lesions. There were 143 participants without CMB, 32 participants with 1 CMB, 12 participants with 2 CMB lesions and 24 participants with more than 2 CMB lesions. A significant difference was found in CRR of TUGSS among four CMB number grades ($p = 0.032$) (**Figure 1**). Multiple linear regression analysis showed that CRR of TUGSS decreased with the increase of CMB grades (β, −0.144; 95% CI, −0.027, −0.002; $p = 0.028$) after the correction of age, sex, education, smoking, hyperlipidemia, lipid-lowering drug, MMSE and MoCA.

Moreover, binary logistic regression analysis suggested that the presence of CMB was not an independent risk factor for the impairment group on CRR of WSS (*OR*, 1.79; 95% CI, 0.85–3.74; $p = 0.125$), CRR of WSF (*OR*, 1.15; 95% CI, 0.51–2.57; $p = 0.742$) or DTE of WSS (*OR*, 1.79; 95% CI, 0.85–3.74; $p = 0.125$) after adjusting confounding factors respectively (**Table 4**).

DISCUSSION

When people perform a cognitive task and a motor task at the same time, there will be competition or interference between different tasks leading to the deterioration in one or both task performances. This is known as cognitive-motor interference, a specific kind of DT interference (Leone et al., 2017). The underlying mechanisms are still unclear. Several theories exist to explain it in humans (Pashler, 1994; Leone et al., 2017): (1) the capacity-sharing theory, which means limited resources must be reallocated between two tasks when people are performing them at the same time; (2) the bottleneck theory, which means when two tasks need the same mechanism, a bottleneck occurs, and one or both tasks will be delayed or impaired; and (3) the cross-talk theory, which refers to the content-dependent degradation or outcome conflict of two tasks, and theorists have usually favored that it is more difficult to perform two tasks even if they involve similar information.

Based on these theories, DT tests have been widely used to study the cognitive-motor interference and the risk of falls in different populations, such as patients with stroke, Alzheimer's disease, Parkinson's disease, or multiple sclerosis (Mofateh et al., 2017; Feld et al., 2018; de Oliveira Silva et al., 2020; Penko et al., 2020). Some studies found that old people had greater DT costs compared to young adults, and this deficit was related to the high incidence of falls in the elderly (Lindenberger et al., 2000; Bock, 2008; Pothier et al., 2015; Papegaaij et al., 2017; Uematsu et al., 2018). An age-related decrease in gait and balance function was also found in studies, which was in greater need of "attentional resources" (Lindenberger et al., 2000; Pothier et al., 2015; Papegaaij et al., 2017). In recent years, more and more studies have focused on the role of CSVD in the decline of DT performance in old people. A recent cross-sectional study found that WMH volume was related to slower gait speed and reduced

TABLE 3 | Comparison of characteristics between the impairment group and the control group classified by CRR of TUGSS.

	Impairment group (n = 58)	Control group (n = 153)	p
Age[a], year	69.50 (63.00, 76.25)	70.00 (65.00, 75.50)	0.784
Men, n (%)	29 (50.00)	87 (56.86)	0.371
Years of education[a], year	9 (6, 12)	9 (9, 13)	0.014*
Height[a], m	1.65 (1.58, 1.70)	1.65 (1.60, 1.70)	0.630
Weight[a], kg	66.00 (60.00, 75.00)	69.00 (60.50, 76.50)	0.174
MMSE[a]	26 (24, 28)	28 (27, 29)	<0.001*
MoCA[a]	23 (20, 25)	25 (23, 26)	<0.001*
Smoking, n (%)	11 (18.97)	54 (35.29)	0.022*
Drinking, n (%)	7 (12.07)	29 (18.95)	0.235
Hypertension, n (%)	43 (74.14)	104 (67.97)	0.385
Diabetes mellitus, n (%)	15 (25.86)	48 (31.37)	0.435
CAD, n (%)	10 (17.24)	40 (26.14)	0.175
History of stroke/TIA, n (%)	11 (18.97)	35 (22.88)	0.539
Hyperlipemia, n (%)	13 (22.41)	63 (41.18)	0.011*
Blood pressure-lowering medication, n (%)	35 (60.34)	94 (61.44)	0.884
Antiplatelet/anticoagulant drug, n (%)	13 (22.41)	53 (34.64)	0.087
Antidiabetic drug, n (%)	13 (22.41)	47 (30.72)	0.232
Lipid-lowering drug, n (%)	11 (18.97)	57 (37.25)	0.011*
CSVD MRI markers			
Presence of lacune, n (%)	25 (43.10)	58 (37.91)	0.490
Presence of CMB, n (%)	26 (44.83)	42 (27.45)	0.016*
PVH[b]	1 (1–3)	1 (1–3)	0.812
DWMH[b]	1 (0–3)	1 (0–3)	0.198
BG-PVS[b]	1 (1–4)	1 (1–4)	0.332
CSO-PVS[b]	2 (1–4)	2 (1–4)	0.302
PA [b]	1 (0–2)	1 (0–2)	0.903

CRR, correct response rate; TUGSS, timed up and go and serial subtraction; MMSE, mini-mental state examination; MoCA, Montreal cognitive assessment; CAD, coronary artery disease; TIA, transient ischemic attack; CSVD, cerebral small vessel disease; MRI, magnetic resonance imaging; CMB, cerebral microbleed; PVH, periventricular hyperintensity; DWMH, deep white matter hyperintensity; BG, basal ganglia; CSO, centrum semiovale; PVS, perivascular space; PA, posterior atrophy.
[a]*Median (quartiles).*
[b]*Median (range).*
*$P < 0.05$.

stride length under DT conditions in dementia patients (Hairu et al., 2021). A study based on community-dwelling older people suggested the negative correlation between deep WMH volumes and the walking speed on DT conditions, which was mediated in part by global cognition and executive abilities specifically (Ghanavati et al., 2018). However, another study showed the opposite result that deep WMH was associated with impaired gait velocity of the single TUG test rather than DT walking (Hashimoto et al., 2014). Most studies have focused on gait disorders in the DT, and no studies have specifically targeted the DT performance of CMB patients. One study has collected the data of CMB, but the number of CMB patients was too small to find a difference between the gait disturbance group and the normal group (Hashimoto et al., 2014).

In this study, the combined protocol of various DT tests and single tasks was used to describe the feature of cognitive performances on DT of CMB patients. The results showed that the global cognitive function of CMB patients was worse than that of subjects without CMB, which was consistent with previous studies (Akoudad et al., 2016; Li et al., 2021a). Compared to subjects without CMB, CMB patients had worse cognitive performances on the DT condition in CRR of WSS, WSF and TUGSS, and DTE of WSS. In CMB patients, cognitive performances in two subtraction-DT tests were worse than those in single subtraction tasks, although the subjects were asked to perform two tasks without prioritization. Logistic regression analysis showed that the presence of CMB was a risk factor for the impairment group on CRR of TUGSS, independent of education, basic cognition and other confounders. These results also further confirmed the significant influence of CMB on cognitive function of the elderly.

As for the design of DT paradigm, the difficulty of DT can be changed by adjusting the level of complexity and novelty of each task (McIsaac et al., 2015). Verbal fluency and serial subtraction are widely used in CSVD patients to examine the sustained attention, information processing speed and executive function. One prior study has reported that the two tests are recommended for the assessment of TUG-cognitive task in stroke patients (Pumpho et al., 2020). Besides, two motor tasks of different levels of difficulty were used in this study, including 8-m walking and

TABLE 4 | Binary logistic regression analyses of the relationship between the presence of CMB and the cognitive performance on dual tasks based on different grouping methods.

Grouping method	CMB	Impairment group	Control group	*p*	*OR* (95% CI)	*p*
CRR of WSS	No CMB, *n*	31	112	0.020	1.79 (0.85, 3.74)	0.125[a]
	CMB, *n*	25	43			
CRR of WSF	No CMB, *n*	30	113	0.044	1.15 (0.51, 2.57)	0.742[b]
	CMB, *n*	23	45			
CRR of TUGSS	No CMB, *n*	32	111	0.016	2.54 (1.11, 5.82)	0.027*[c]
	CMB, *n*	26	42			
DTE of WSS	No CMB, *n*	31	112	0.020	1.79 (0.85, 3.74)	0.125[d]
	CMB, *n*	25	43			

CMB, cerebral microbleed; OR, odds ratio; WSS, walking and serial subtraction; WSF, walking and semantic fluency; TUGSS, timed up and go and serial subtraction; CRR, correct response rate; DTE, dual-task effect.

[a]Adjusting for age, sex, education, deep white matter hyperintensity, MMSE and MoCA; [b]adjusting for age, sex, education, diabetes, hyperlipidemia, antidiabetic drug, lacuna, deep white matter hyperintensity, paraventricular hyperintensity, basal ganglia perivascular space, MMSE and MoCA; [c]adjusting for age, sex, education, smoking, hyperlipidemia, lipid-lowering drug, MMSE and MoCA; [d]adjusting for age, sex, education, deep white matter hyperintensity, MMSE and MoCA.

**P<0.05.*

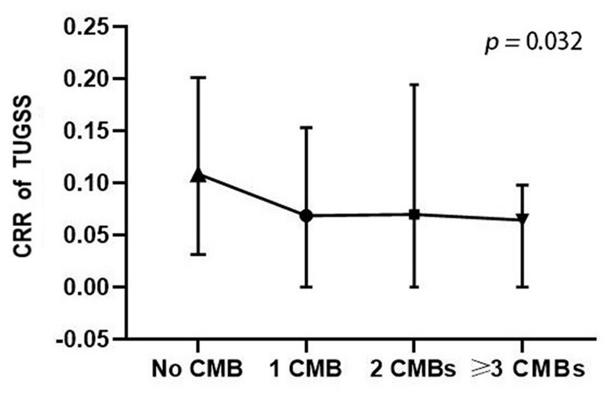

FIGURE 1 | Comparison of CRR of TUGSS among four CMB number grades (Kruskal-Wallis H test). CRR, correct response rate; TUGSS, timed up and go and serial subtraction; CMB, cerebral microbleed.

TUG tests. TUG is reliable and sensitive to detecting cognitive and mobility disorders, and can provide information about the gross motor function which is important for the maintenance of mobility in everyday tasks (Montero-Odasso et al., 2019). According to our results, CMB was an independent risk factor for the impairment group on CRR of TUGSS, where the performance worsened with the increasing degree of CMB burden. Thus, we propose that TUGSS may be a suitable DT test for evaluating the ability of CMB patients.

The underlying pathophysiological mechanisms of CMB-related cognitive and motor impairment have not been fully elucidated. The direct damage of CMB lesions on focal brain tissues may cause myelin loss, neuronal loss and variable extent of gliosis, and lead to the brain function disorder. The remote effects manifested by white matter microstructure changes and cortical thinning may also be an indirect damage to brain function caused by CSVD (Ter Telgte et al., 2018). Besides, CMBs are associated with the impairment of brain network, including longer path length and less global efficiency than people without CMB (Heringa et al., 2014; Reijmer et al., 2015). Another study in patients with cerebral amyloid angiopathy suggested that the brain network impairment worsened from posterior to frontal connections (in the fractional anisotropy) with the increasing disease severity (Reijmer et al., 2016). Moreover, a synergistic effect was found between CSVD and other neurodegenerative pathologies (such as Alzheimer's disease and Parkinson's disease) on patients' dysfunctions (Ter Telgte et al., 2018). Consequently, CMB lesions may lead to cognitive or motor disorders through the direct or indirect damage to the brain parenchyma and brain networks. Many prospective studies on the single cognitive task have demonstrated that the CMB is a crucial risk factor for cognitive deterioration and dementia (Akoudad et al., 2016; Ding et al., 2017). Our results expanded the above conclusion that CMB patients also had worse cognitive and gait performances on DT conditions than those without CMBs, especially in the decreased CRR and shortened stride length in TUGSS test. According to the therapy of reserve mechanisms (Ter Telgte et al., 2018), we speculated that for CMB patients with impaired reserve ability, the additional motor task on the basis of the single cognitive task would cause an aggravation of the cognitive dysfunction. On the other hand, the damaged brain tissue caused by CMB lesions made the cognitive-motor interference more significant. It might be related to the limited resources reallocated between two tasks and an inability to process the attentional demand of each task accurately (Leone et al., 2017; Ma et al., 2021). However, whether the influence of CMBs on motor function under DT conditions is directly caused by the lesions or mediated by cognitive dysfunction is an interesting question that needs further consideration and verification.

To our knowledge, this is the first study targeting the influence of CMB lesions on the cognitive performance under DT conditions in old adults. And the compound protocol of global cognition assessments, basic gait tests and different DT designs makes the functional assessment more diversified in this study. Moreover, the IDEEA, a microcomputer-based portable gait analysis system and physical activity monitor, has advantages in the detection and analysis of multiple gaits, postures, limb movements, and the energy expenditure with great accuracy (Huddleston et al., 2006).

However, there are still some limitations to this study. This is a single-center cross-sectional study, and the sample size is relatively small. So, we did not perform the subgroup analysis based on the CMB location or cognitive domains. Not all the gait parameters were included in the analysis, because this study paid more attention to the cognitive performance on DT that other studies had focused less on in CSVD patients. In the future, the sample size will be further expanded to conduct the interested subgroup analysis, and the motor function such as gait and balance will be complementally analyzed. In addition, those semi-quantitative scales were relatively subjective for the assessment of CSVD imaging markers. It may have some impact on the effectiveness of proving the tendency that cognitive performances on DT are changing with the severity of CMB burden. Further studies with advanced imaging techniques and post-processing methods may be of great value to provide more information and solve this problem.

CONCLUSION

The presence of CMB was an independent risk factor for the cognitive impairment group of TUGSS on the DT condition, where performance deficits increased in proportion to the degree of CMB burden. Failing to consider the effect of DT may lead to an underestimation of the difficulties in CMB patients' daily life, including those with mild impairments. In the future, more large-scale studies with longitudinal designs are needed to clarify the causality between CMB and DT performances and to explore the mechanisms using multimodal imaging techniques and experimental sciences.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Beijing Chao-yang Hospital, Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XL and WH contributed to conception and design of the study. XL, SY, WQ, YH, and QH collected the data. XL, YL, and SY performed the statistical analysis. XL wrote the first draft of the manuscript. WH, WQ, and LY contributed to the critical revision. All the authors contributed to manuscript revision, read, and approved the submitted version.

REFERENCES

Akoudad, S., Wolters, F. J., Viswanathan, A., de Bruijn, R. F., van der Lugt, A., Hofman, A., et al. (2016). Association of cerebral microbleeds with cognitive decline and dementia. *JAMA Neurol*. 73, 934–943. doi: 10.1001/jamaneurol.2016.1017

Al-Yahya, E., Dawes, H., Smith, L., Dennis, A., Howells, K., and Cockburn, J. (2011). Cognitive motor interference while walking: a systematic review and meta-analysis. *Neurosci. Biobehav. Rev*. 35, 715–728. doi: 10.1016/j.neubiorev.2010.08.008

Bock, O. (2008). Dual-task costs while walking increase in old age for some, but not for other tasks: an experimental study of healthy young and elderly persons. *J. Neuroeng. Rehabil*. 5:27. doi: 10.1186/1743-0003-5-27

Chiu, W. T., Chan, L., Wu, D., Ko, T. H., Chen, D. Y., and Hong, C. T. (2018). Cerebral microbleeds are associated with postural instability and gait disturbance subtype in people with Parkinson's disease. *Eur. Neurol*. 80, 335–340. doi: 10.1159/000499378

de Oliveira Silva, F., Ferreira, J. V., Plácido, J., Chagas, D., Praxedes, J., Guimarães, C., et al. (2020). Gait analysis with videogrammetry can differentiate healthy elderly, mild cognitive impairment, and Alzheimer's disease: a cross-sectional study. *Exp. Gerontol*. 131:110816. doi: 10.1016/j.exger.2019.110816

Ding, J., Sigurð*sson, S., Jónsson, P. V., Eiriksdottir, G., Meirelles, O., Kjartansson, O., et al. (2017). Space and location of cerebral microbleeds, cognitive decline, and dementia in the community. *Neurology*. 88, 2089–2097. doi: 10.1212/wnl.0000000000003983

Fazekas, F., Chawluk, J. B., Alavi, A., Hurtig, H. I., and Zimmerman, R. A. (1987). MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am. J. Roentgenol*. 149, 351–356. doi: 10.2214/ajr.149.2.351

Feld, J. A., Zukowski, L. A., Howard, A. G., Giuliani, C. A., Altmann, L. J. P., Najafi, B., et al. (2018). Relationship between dual-task gait speed and walking activity poststroke. *Stroke*. 49, 1296–1298. doi: 10.1161/strokeaha.117.019694

Ghanavati, T., Smitt, M. S., Lord, S. R., Sachdev, P., Wen, W., Kochan, N. A., et al. (2018). Deep white matter hyperintensities, microstructural integrity and dual task walking in older people. *Brain Imaging Behav*. 12, 1488–1496. doi: 10.1007/s11682-017-9787-7

Gregoire, S. M., Chaudhary, U. J., Brown, M. M., Yousry, T. A., Kallis, C., Jäger, H. R., et al. (2009). The Microbleed Anatomical Rating Scale (MARS): reliability of a tool to map brain microbleeds. *Neurology* 73, 1759–1766. doi: 10.1212/WNL.0b013e3181c34a7d

Hairu, R., Close, J. C. T., Lord, S. R., Delbaere, K., Wen, W., Jiang, J., et al. (2021). The association between white matter hyperintensity volume and gait performance under single and dual task conditions in older people with dementia: a cross-sectional study. *Arch. Gerontol. Geriatr*. 95:104427. doi: 10.1016/j.archger.2021.104427

Hashimoto, M., Takashima, Y., Uchino, A., Yuzuriha, T., and Yao, H. (2014). Dual task walking reveals cognitive dysfunction in community-dwelling elderly subjects: the Sefuri brain MRI study. *J. Stroke Cerebrovasc. Dis*. 23, 1770–1775. doi: 10.1016/j.jstrokecerebrovasdis.2014.05.008

Heringa, S. M., Reijmer, Y. D., Leemans, A., Koek, H. L., Kappelle, L. J., and Biessels, G. J. (2014). Multiple microbleeds are related to cerebral network disruptions in patients with early Alzheimer's disease. *J. Alzheimers. Dis*. 38, 211–221. doi: 10.3233/jad-130542

Huddleston, J., Alaiti, A., Goldvasser, D., Scarborough, D., Freiberg, A., Rubash, H., et al. (2006). Ambulatory measurement of knee motion and physical activity: preliminary evaluation of a smart activity monitor. *J. Neuroeng. Rehabil*. 3:21. doi: 10.1186/1743-0003-3-21

Kelly, V. E., Janke, A. A., and Shumway-Cook, A. (2010). Effects of instructed focus and task difficulty on concurrent walking and cognitive task performance in healthy young adults. *Exp. Brain Res*. 207, 65–73. doi: 10.1007/s00221-010-2429-6

Koedam, E. L., Lehmann, M., van der Flier, W. M., Scheltens, P., Pijnenburg, Y. A., Fox, N., et al. (2011). Visual assessment of posterior atrophy development of a MRI rating scale. *Eur. Radiol*. 21, 2618–2625. doi: 10.1007/s00330-011-2205-4

Leone, C., Feys, P., Moumdjian, L., D'Amico, E., Zappia, M., and Patti, F. (2017). Cognitive-motor dual-task interference: a systematic review of neural correlates. *Neurosci. Biobehav. Rev*. 75, 348–360. doi: 10.1016/j.neubiorev.2017.01.010

Li, X., Yuan, J., Qin, W., Yang, L., Yang, S., Li, Y., et al. (2021a). Cerebral microbleeds are associated with impairments in executive function and processing speed. *J. Alzheimers. Dis*. 81, 255–262. doi: 10.3233/jad-201202

Li, X., Yuan, J., Qin, W., Yang, L., Yang, S., Li, Y., et al. (2021b). Higher total cerebral small vessel disease burden was associated with mild cognitive impairment and overall cognitive dysfunction: a propensity score-matched case-control study. *Front. Aging Neurosci*. 13:695732. doi: 10.3389/fnagi.2021.695732

Lindenberger, U., Marsiske, M., and Baltes, P. B. (2000). Memorizing while walking: increase in dual-task costs from young adulthood to old age. *Psychol. Aging*. 15, 417–436. doi: 10.1037/0882-7974.15.3.417

Ma, R., Zhào, H., Wei, W., Liu, Y., and Huang, Y. (2021). Gait characteristics under single-/dual-task walking conditions in elderly patients with cerebral small vessel disease: analysis of gait variability, gait asymmetry and bilateral coordination of gait. *Gait Posture*. 92, 65–70. doi: 10.1016/j.gaitpost.2021.11.007

Maclullich, A. M., Wardlaw, J. M., Ferguson, K. J., Starr, J. M., Seckl, J. R., and Deary, I. J. (2004). Enlarged perivascular spaces are associated with cognitive function in healthy elderly men. *J. Neurol. Neurosurg. Psychiatr*. 75, 1519–1523. doi: 10.1136/jnnp.2003.030858

McIsaac, T. L., Lamberg, E. M., and Muratori, L. M. (2015). Building a framework for a dual task taxonomy. *Biomed. Res. Int*. 2015:591475. doi: 10.1155/2015/591475

Mofateh, R., Salehi, R., Negahban, H., Mehravar, M., and Tajali, S. (2017). Effects of cognitive versus motor dual-task on spatiotemporal gait parameters in healthy controls and multiple sclerosis patients with and without fall history. *Mult. Scler. Relat. Disord*. 18, 8–14. doi: 10.1016/j.msard.2017.09.002

Montero-Odasso, M., Almeida, Q. J., Bherer, L., Burhan, A. M., Camicioli, R., Doyon, J., et al. (2019). Consensus on shared measures of mobility and cognition: from the Canadian Consortium on neurodegeneration in aging (CCNA). *J. Gerontol. A Biol. Sci. Med. Sci*. 74, 897–909. doi: 10.1093/gerona/gly148

Nonnekes, J., Dibilio, V., Barthel, C., Solis-Escalante, T., Bloem, B. R., and Weerdesteyn, V. (2020). Understanding the dual-task costs of walking: a StartReact study. *Exp. Brain Res*. 238, 1359–1364. doi: 10.1007/s00221-020-05817-8

Nyúl-Tóth, Á., Tarantini, S., Kiss, T., Toth, P., Galvan, V., Tarantini, A., et al. (2020). Increases in hypertension-induced cerebral microhemorrhages exacerbate gait dysfunction in a mouse model of Alzheimer's disease. *Geroscience* 42, 1685–1698. doi: 10.1007/s11357-020-00256-3

Papegaaij, S., Hortobágyi, T., Godde, B., Kaan, W. A., Erhard, P., and Voelcker-Rehage, C. (2017). Neural correlates of motor-cognitive dual-tasking in young and old adults. *PLoS ONE* 12:e0189025. doi: 10.1371/journal.pone.0189025

Pashler, H. (1994) Dual-task interference in simple tasks: data and theory. (1994). *Psychol Bull*. 116, 220–244. doi: 10.1037/0033-2909.116.2.220

Penko, A. L., Streicher, M. C., Dey, T., Rosenfeldt, A. B., and Alberts, J. L. (2020). Parkinson's gait kinematics deteriorates across multiple cognitive domains under dual-task paradigms. *Clin. Neurol. Neurosurg*. 197:106083. doi: 10.1016/j.clineuro.2020.106083

Pothier, K., Benguigui, N., Kulpa, R., and Chavoix, C. (2015). Multiple object tracking while walking: similarities and differences between young, young-old, and old-old adults. *J. Gerontol. B Psychol. Sci. Soc. Sci*. 70, 840–849. doi: 10.1093/geronb/gbu047

Pumpho, A., Chaikeeree, N., Saengsirisuwan, V., and Boonsinsukh, R. (2020). Selection of the better dual-timed up and go cognitive task to be used in patients with stroke characterized by subtraction operation difficulties. *Front. Neurol*. 11:262. doi: 10.3389/fneur.2020.00262

Reijmer, Y. D., Fotiadis, P., Martinez-Ramirez, S., Salat, D. H., Schultz, A., Shoamanesh, A., et al. (2015). Structural network alterations and neurological dysfunction in cerebral amyloid angiopathy. *Brain*. 138(Pt 1), 179–188. doi: 10.1093/brain/awu316

Reijmer, Y. D., Fotiadis, P., Riley, G. A., Xiong, L., Charidimou, A., Boulouis, G., et al. (2016). Progression of brain network alterations in cerebral amyloid angiopathy. *Stroke*. 47, 2470–2475. doi: 10.1161/strokeaha.116.014337

Shuaib, A., Akhtar, N., Kamran, S., and Camicioli, R. (2019). Management of cerebral microbleeds in clinical practice. *Transl Stroke Res*. 10, 449–457. doi: 10.1007/s12975-018-0678-z

Sullivan, K. J., Ranadive, R., Su, D., Neyland, B. R., Hughes, T. M., Hugenschmidt, C. E., et al. (2021). Imaging-based indices of neuropathology and gait speed decline in older adults: the atherosclerosis risk in communities study. *Brain Imaging Behav*. 15, 2387–2396. doi: 10.1007/s11682-020-00435-y

Ter Telgte, A., van Leijsen, E. M. C., Wiegertjes, K., Klijn, C. J. M., Tuladhar, A. M., and de Leeuw, F. E. (2018). Cerebral small vessel disease: from a focal to a global perspective. *Nat. Rev. Neurol*. 14, 387–398. doi: 10.1038/s41582-018-0014-y

Uematsu, A., Tsuchiya, K., Suzuki, S., and Hortobágyi, T. (2018). Cognitive dual-tasking augments age-differences in dynamic balance quantified by beam walking distance: a pilot study. *Exp. Gerontol*. 114, 27–31. doi: 10.1016/j.exger.2018.10.016

Wardlaw, J. M., Smith, E. E., Biessels, G. J., Cordonnier, C., Fazekas, F., Frayne, R., et al. (2013). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 12, 822–838. doi: 10.1016/s1474-4422(13)70124-8

Yang, L., He, C., and Pang, M. Y. (2016). Reliability and validity of dual-task mobility assessments in people with chronic stroke. *PLoS ONE*. 11:e0147833. doi: 10.1371/journal.pone.0147833

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The Specificity of Cognitive-Motor Dual-Task Interference on Balance in Young and Older Adults

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Standing upright on stable and unstable surfaces requires postural control. Postural control declines as humans age, presenting greater risk of fall-related injury and other negative health outcomes. Secondary cognitive tasks can further impact balance, which highlights the importance of coordination between cognitive and motor processes. Past research indicates that this coordination relies on executive function (EF; the ability to control, maintain, and flexibly direct attention to achieve goals), which coincidentally declines as humans age. This suggests that secondary cognitive tasks requiring EF may exert a greater influence on balance compared to non-EF secondary tasks, and this interaction could be exaggerated among older adults. In the current study, we had younger and older adults complete two Surface Stability conditions (standing upright on stable vs. unstable surfaces) under varying Cognitive Load; participants completed EF (Shifting, Inhibiting, Updating) and non-EF (Processing Speed) secondary cognitive tasks on tablets, as well as a single task control scenario with no secondary cognitive task. Our primary balance measure of interest was sway area, which was measured with an array of wearable inertial measurement unit sensors. Replicating prior work, we found a main effect of Surface Stability with less sway on stable surfaces compared to unstable surfaces, and we found an interaction between Age and Surface Stability with older adults exhibiting significantly greater sway selectively on unstable surfaces compared to younger adults. New findings revealed a main effect of Cognitive Load on sway, with the single task condition having significantly less sway than two of the EF conditions (Updating and Shifting) and the non-EF condition (Processing Speed). We also found an interaction of Cognitive Load and Surface Stability on postural control, where Surface Stability impacted sway the most for the single task and two of the executive function conditions (Inhibition and Shifting). Interestingly, Age did not interact with Cognitive Load, suggesting that both age groups were equally impacted by secondary cognitive tasks, regardless the presence or type of secondary cognitive task. Taken together, these patterns suggest that cognitive demands vary in their impact on posture control across stable vs. unstable surfaces, and that EF involvement may not be the driving mechanism explaining cognitive-motor dual-task interference on balance.

Keywords: cognitive-motor multitasking, dual-tasking, executive function, aging, multitasking ability

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INTRODUCTION

Research over the past several decades has found that standing upright involves multiple levels of controlled and automatic processing to integrate multiple streams of information (Peterka, 2002; Boisgontier et al., 2013). Biologically speaking, postural control involves interactions between cerebellar and cortical regions (Jacobs and Horak, 2007), as well as interactions among fronto-striatal regions (Mihara et al., 2008).

To complicate matters even further, humans often face situations in which they must maintain balance on unstable, irregular surfaces (e.g., an uneven sidewalk or a muddy patch of grass), which may require additional neural resources to avoid falls and injuries (Peterka, 2002; Agrawal et al., 2009). In line with this, research has found reduced postural control with decreased surface stability (Dault et al., 2001b; Bayot et al., 2018), with the impact of these physical demands varying as a function of specific surface stability manipulations (Barbado Murillo et al., 2012; Remaud et al., 2012; Lanzarin et al., 2015).

Postural control is not just impacted by physical demands but also by concurrent cognitive demands (Pellecchia, 2003; Costa et al., 2020), which further emphasizes the importance of cortical areas for standing upright (Woollacott and Shumway-Cook, 2002). One finds evidence for this in studies that require participants to maintain balance while performing cognitive tasks, which leads to impaired postural control (Lajoie et al., 1993; Andersson et al., 2002; Huxhold et al., 2006). This cognitive-motor interaction may be due to limitations in how humans use higher-order cognitive processing to manage the coordination of multiple tasks. For instance, task performance costs may come from bottlenecks in our information-processing architecture (Pashler, 1994; Borst et al., 2010) or from competition for limited attentional resources (Wickens, 2002). If task performance costs come from information-processing bottlenecks, then we expect to see general interference regardless the specific tasks; however, if the costs come from limited attentional resources, then we expect to see greater interference for tasks that require similar attentional resources.

Postural control is especially important for older adults who are at a higher risk of injury from falls (Fuller, 2000). In general, aging has been associated with postural and balance problems (Hageman et al., 1995; Laughton et al., 2003; Laufer et al., 2006; Ambrose et al., 2013), including declines in postural stability (Gill et al., 2001; Choy et al., 2003). Even without additional cognitive demands, healthy older adults tend to exhibit more postural sway than their younger counterparts (Kim et al., 2010). Furthermore, in cognitive-motor dual-task settings, older adults have demonstrated poorer balance and cognitive performance compared to younger adults (Schaefer, 2014), which has implications for daily activities and risk of falls (Lajoie and Gallagher, 2004; Beauchet et al., 2009).

Interestingly, age-related differences in cognitive-motor dual-task interference differ depending on the nature of the secondary cognitive task, especially when both the postural task and cognitive task recruit common neural resources that may atrophy as humans age (Rypma et al., 2001; Johnson et al., 2004; Fraizer and Mitra, 2008). For example, one study had older and younger adults verbally list words or type words while standing on stable or unstable surfaces and found differences in how the verbal and texting tasks impacted postural control across their age groups (Hsiao et al., 2020).

The current study builds on this line of research by further exploring the specificity of cognitive-motor dual-task interference in younger and older adults within the same modality. In the cognitive domain, we focused on executive function, which consists of higher cognitive processes important for controlling goal-directed behaviors (Garavan et al., 2000; Jurado and Rosselli, 2007; Chan et al., 2008; Bayot et al., 2018). Contemporary models suggest that executive function is made up of distinct but related components that allow humans to control, maintain, and flexibly direct attention to achieve goals (Miyake et al., 2000; Li et al., 2017). Important for postural control, executive function purportedly relies on the same frontal neural systems supporting motor control (Stuss, 2011).

As humans age, motor control increasingly relies on executive function (Duncan and Owen, 2000; Seidler et al., 2010; Al-Yahya et al., 2011, 2019; Holtzer et al., 2014), yet executive function also declines with age (Elderkin-Thompson et al., 2008; Grady, 2012; King et al., 2013; Yuan and Raz, 2014). Thus, in cognitive-motor dual-task situations involving executive function tasks, older adults' restricted supply of executive function might result in greater performance costs compared to younger adults. In contrast, non-executive function tasks that do not rely as much on neural resources common to motor control may not result in comparable interference. This has not been directly tested in terms of balance performance; however, cognitive-motor dual-task interference from EF and non-EF tasks has been investigated in related motor domains such as gait (Beauchet et al., 2012). For example, one study measured gait for 20 younger adults and 17 older adults who completed single and dual-task walking scenarios. They found that EF-based secondary tasks slowed gait more non-EF tasks, and this EF-specific cognitive-motor dual-task interference was greater for older adults compared to younger adults (Walshe et al., 2015).

The current study builds on this prior research by investigating the specificity of cognitive-motor dual-task interference on balance using tablet-based executive function and non-executive function tasks, stable and unstable surfaces, and younger and older adults. Building on prior motor control research and leveraging a dominant model of EF (Miyake et al., 2000), we wanted to identify which combinations of cognitive load (i.e., non-EF demands, EF switching demands, EF updating demands, EF inhibition demands) and surface stability (i.e., stable, unstable) lead to the greatest impacts on sway, which could indicate situations where resources are most scarce (and thus, most shared). If secondary EF tasks lead to greater sway specifically on unstable surfaces compared to a non-EF task selectively, this would align more with models of limited attentional resources, such that performance declines as demand for a shared resource increases. This would also provide additional support for an overlap or taxation of concurrent processing between specific higher-level EFs and balance. On the other hand, if we see comparable impairment (i.e., greater sway) from the non-EF and EF tasks, then it's possible that cognitive-motor dual-task impairment is not specific and perhaps instead results from general information-processing bottlenecks (Maylor and Wing, 1996; Dault et al., 2001a). Furthermore, we were interested in whether or not levels of cognitive-motor dual-task interference on balance would be comparable for young and older adults since prior research found greater impairments on EF tasks for older adults in a related motor domain (Walshe et al., 2015).

MATERIALS AND METHODS

Participants

Based on prior research involving postural control, dual tasking, and young vs. older adults, our goal was to have at least 30 participants in each age group (Kerr et al., 1985; Yardley et al., 1999; Bergamin et al., 2014; Bohle et al., 2019; Hsiao et al., 2020). For the younger adults, we recruited 53 healthy adults (ages 18–35) and excluded 11 due to technical errors for a final sample of 42 younger adult participants (mean age = 23 years; 26F/16M). For the older adults, we recruited 37 healthy older adults (ages 60 or older (Walshe et al., 2015) and excluded 7 due to technical errors for a final sample of 30 older adult participants (mean age = 73 years; 27F/3M). For our convenience sample, we only recruited participants from the local community who could stand upright without assistance; had no balance impairments; were not taking any medication that could impact balance; were free from musculoskeletal and neurological disorders including dementia, depression, and other cognitive impairments; and had normal or corrected-to-normal vision. All participants provided written consent according to the Declaration of Helsinki, and our protocol was approved by the Tufts University IRB.

Protocol

Participants completed a single session lasting approximately 1.5 h. After participants provided informed consent, we placed wearable sensors that measured postural sway on them. Next, participants completed baseline standing conditions on firm and foam surfaces while holding a tablet, and then they completed four tablet-based cognitive tasks on the firm surface and on the foam surface (**Figure 1**). We counterbalanced surface type blocks (i.e., firm surface first and foam surface second vs. foam surface first and firm surface second), and we randomized cognitive tasks within each surface type block. Finally, participants completed a brief survey at the end of the study before being debriefed and compensated for their time. The post experiment survey included two measures of interest. First, participants completed the Activities-Specific Balance Confidence Scale (ABC), which was a 16-item scale that assessed balance confidence when performing activities, such as walking up/down stairs or getting into/out of a car (Powell and Myers, 1995). We summed the scores and then divided by 16 for an overall balance confidence rating. Second, participants completed the short version of the Mobile Device Proficiency Questionnaire (MDPQ-16). The MDPQ-16 measures mobile device proficiency across eight domains, such as mobile device basics and data/file storage, with two items per domain (Roque and Boot, 2018). We averaged each of the subscales and then summed across the eight domains for a total score.

Balance Procedure

We used six APDM Opal sensors to measure postural sway (Opal v2, APDM Inc., Portland, OR, United States). Participants wore these sensors on their feet, lumbar, sternum, and wrists (Deshmukh et al., 2012; Mancini et al., 2012; Martinez-Mendez et al., 2012; Doherty et al., 2017; Pissadaki et al., 2018; Morris et al., 2019). We measured center of pressure variability using the root mean square distance of sway acceleration (RMS Sway in m/s^2), which quantified the magnitude of center of pressure displacements (Maki et al., 1994; Prieto et al., 1996; Rocchi et al., 2004; Mancini et al., 2011a; King et al., 2017), and we used APDM Mobility Lab v2.0 to process postural sway data (Mancini et al., 2011b). To ensure consistent foot placement across all trials, we used a foot placement template so that participants had approximately 10 cm between the right and left heel with a 30-degree outward foot rotation (Chiari et al., 2002; Morris et al., 2019). Participants stood on the firm floor of the lab for the stable conditions, and they stood on an Airex Elite foam balance pad (approximately 6 cm in height) for the unstable conditions (Šarabon et al., 2010; Gera et al., 2018).

Computerized Cognitive Tasks

Participants completed tablet-based cognitive tasks administered through the mobile application BrainBaseline, which is a scientifically validated research tool (Lee et al., 2012; White et al., 2020; Ward et al., 2021). For our non-EF measure, participants completed a simple processing speed task in which they responded as quickly as possible whenever a circle appeared in the middle of the screen, and we used response time as our primary measure (Basner and Dinges, 2011). For our EF measures, participants completed a shifting task, an updating task, and an inhibition task (Miyake et al., 2000). For EF shifting, participants completed a task switching task in which they made parity (odd vs. even) or magnitude (less than 5 vs. greater than 5) judgments depending on the background color on each trial for a centrally presented number, and we calculated switch costs (i.e., the difference between correct switch trial RTs and correct repeat trial RTs) as our primary measure (Monsell, 2003). For EF updating, participants completed an N-back task which consisted of viewing a stream of sequentially presented numbers and determining whether the current number matched the number presented two trials previously, and we used 2-back accuracy as our primary measure (Owen et al., 2005). For EF inhibition, participants completed a Stroop task in which they responded to the font color of centrally presented words while ignoring the lexical content of the word, and we calculated the Stroop effect (i.e., the difference between correct incongruent RTs and correct congruent RTs) as our primary measure (Stroop, 1935; MacLeod, 1991). Full details on these four tasks have been described elsewhere (Lee et al., 2012).

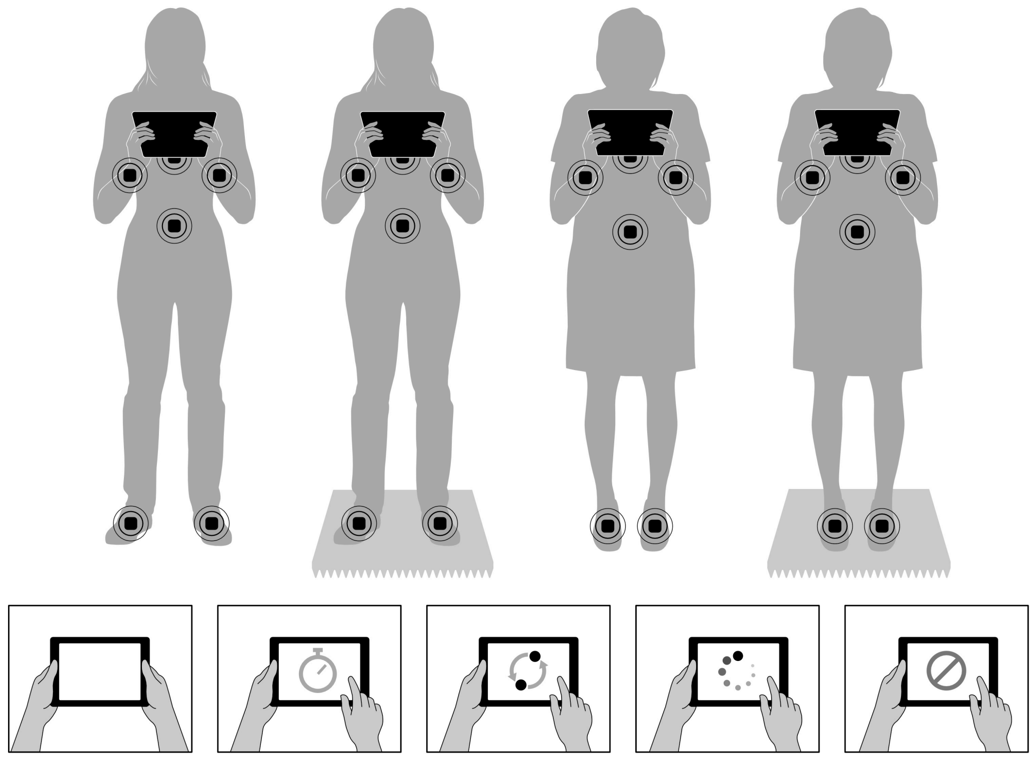

FIGURE 1 | Top figures represent sensor placement for both age groups as they performed the various conditions on stable and unstable surfaces. Bottom images depict the five experimental conditions, which were Baseline (no task), non-EF processing speed, EF shifting, EF updating, and EF inhibition.

TABLE 1 | Postural sway descriptive statistics.

		Age			
		Younger adults		Older adults	
Surface	**Cognitive load**	**Mean**	***SD***	**Mean**	***SD***
Firm	Baseline	0.026	0.013	0.022	0.010
	Processing speed	0.051	0.064	0.035	0.028
	EF Shifting	0.051	0.043	0.041	0.033
	EF Updating	0.051	0.091	0.037	0.033
	EF Inhibition	0.035	0.029	0.033	0.027
Foam	Baseline	0.042	0.015	0.065	0.041
	Processing speed	0.049	0.025	0.054	0.033
	EF Shifting	0.051	0.028	0.069	0.047
	EF Updating	0.051	0.023	0.057	0.042
	EF Inhibition	0.045	0.027	0.060	0.042

RESULTS

Balance Performance

For the postural sway data, we ran a 5 (Cognitive Load: Baseline vs. non-EF processing speed vs. EF shifting vs. EF updating vs. EF inhibition) × 2 (Surface Stability: firm vs. foam) × 2 (Age: younger vs. older) mixed model ANOVA (see **Table 1** for postural sway descriptive statistics).

We found a main effect of Cognitive Load [$F_{(4,\ 280)} = 3.89$, $p = 0.004$, $\eta^2_p = 0.05$]. As seen in **Figure 2**, planned comparisons revealed that sway was significantly lower in the baseline condition compared to the EF shifting ($p < 0.001$) and the EF updating ($p = 0.04$) conditions, as well as the non-EF processing speed condition ($p = 0.03$). Although numerically in the expected direction, the difference between baseline and EF inhibition was not significant ($p = 0.09$). Interestingly, the non-EF processing speed condition did not differ from the EF conditions (p's > 0.10), but the EF inhibition condition was significantly lower than the EF shifting condition ($p < 0.05$).

We also found a main effect of Surface Stability [$F_{(1,\ 70)} = 16.07$, $p < 0.001$, $\eta^2_p = 0.19$] with significantly less sway in the firm condition compared to the foam condition (**Figure 3**).

In addition, we found an interaction between Cognitive Load and Surface Stability [$F_{(4,\ 280)} = 2.84$, $p = 0.03$, $\eta^2_p = 0.04$]. As seen in **Figure 4**, postural sway on the firm surface was significantly lower than on the foam surface for the Baseline ($p < 0.001$), EF shifting ($p = 0.004$), and EF inhibition ($p = 0.001$) conditions.

Contrary to our expectations, we did not observe a main effect of Age [$F_{(1,\ 70)} = 0.17$, $p = 0.69$, $\eta^2_p = 0.002$] on sway, nor did we find an interaction between Age and Cognitive Load [$F_{(4,\ 280)} = 1.53$, $p = 0.19$, $\eta^2_p = 0.02$]. On the other hand, we observed an interaction between Age and Surface Stability [$F_{(1,\ 70)} = 8.09$, $p = 0.01$, $\eta^2_p = 0.10$]. As seen in **Figure 5**, the older adult group had significantly higher sway on the foam

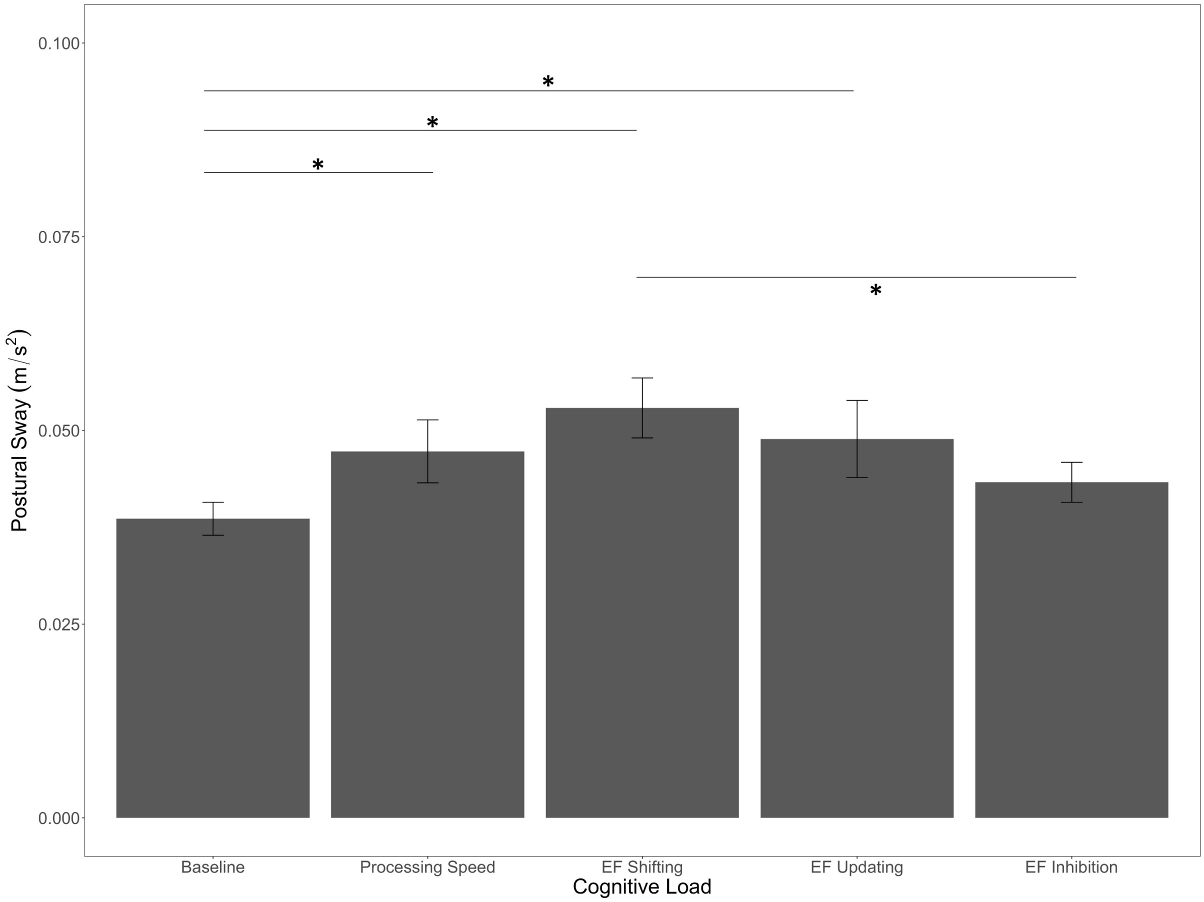

FIGURE 2 | Main effect of cognitive load on postural sway. Error bars are ± SE. Significant differences are indicated by asterisks: *$p < 0.05$.

surface compared to the firm surface ($p < 0.001$) whereas younger adults' postural control did not differ across the two surface types ($p = 0.37$). Importantly, the older adult group did not differ from the younger adult group on the stable, firm surface ($p = 0.22$), whereas they did significantly differ from them on the unstable, foam surface ($p = 0.03$). We did not observe any other significant interactions among our factors (see **Supplementary Materials** for all statistical tests).

To recap our balance performance findings, we found main effects on sway from Cognitive Load and Surface Stability, as well as from an interaction between these factors. We also found an interaction between Age and Surface Stability in terms of sway, but no other analyses were significant.

Cognitive Performance

For the cognitive data, we ran a series of mixed model ANOVAs for our different dependent measures with Surface Stability (firm vs. foam) as a within subjects factor and Age (younger vs. older) as a between subjects factor and used Bonferroni correction for an adjusted p-value of 0.0125 (see **Table 2** for cognitive task descriptive statistics).

For non-EF processing speed, we found a main effect of Age [$F_{(1,\ 70)} = 17.40$, $p < 0.001$, $\eta^2_p = 0.20$] with older adults producing significantly slower correct RTs compared to younger adults, which is seen in the top left of **Figure 6**. We did not find an effect of Surface Stability [$F_{(1,\ 70)} = 3.29$, $p = 0.07$, $\eta^2_p = 0.05$] nor an interaction between Age and Surface Stability in terms of non-EF processing speed [$F_{(1,\ 70)} = 1.32$, $p = 0.25$, $\eta^2_p = 0.02$].

For EF shifting, we found a main effect of Age [$F_{(1,\ 69)} = 6.60$, $p = 0.01$, $\eta^2_p = 0.09$] in which the older adults had higher switch costs compared to the younger adults, which is depicted in the top right of **Figure 6**. We did not find an effect of Surface Stability [$F_{(1,\ 69)} = 0.03$, $p = 0.85$, $\eta^2_p = 0.001$], nor did we find an interaction between Age and Surface Stability in terms of EF shifting [$F_{(1,\ 69)} < 0.001$, $p = 0.99$, $\eta^2_p < 0.001$].

For EF updating, we found a main effect of Age [$F_{(1,\ 70)} = 40.50$, $p < 0.001$, $\eta^2_p = 0.37$] with older adults exhibiting lower accuracy than younger adults, which is seen in the bottom left of **Figure 6**. We did not observe an effect of Surface Stability [$F_{(1,\ 70)} = 4.42$, $p = 0.04$, $\eta^2_p = 0.06$], nor did Age and Surface Stability interact in terms of EF updating [$F_{(1,\ 70)} = 0.01$, $p = 0.92$, $\eta^2_p < 0.001$].

Finally, for EF inhibition, we found an effect of Age [$F_{(1,\ 70)} = 61.20$, $p < 0.001$, $\eta^2_p = 0.47$] in which older adults had larger Stroop effects compared to younger adults, which is depicted in the bottom right of **Figure 6**. We did not find an effect of Surface

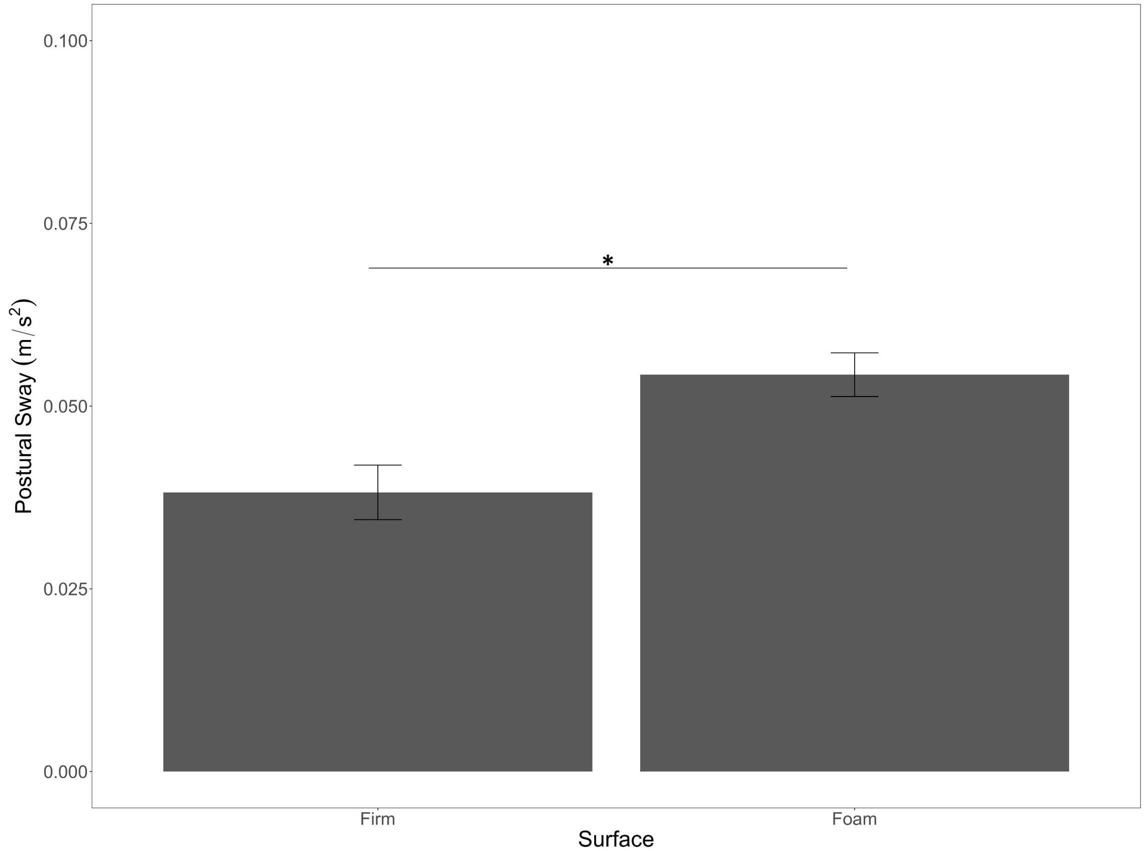

FIGURE 3 | Main effect of surface stability on postural sway. Error bars are ± SE. Significant differences are indicated by asterisks: $*p < 0.05$.

Stability [$F_{(1,\ 70)} = 0.01$, $p = 0.91$, $\eta^2{}_p < 0.001$], nor did we find an interaction between Age and Surface Stability in terms of EF inhibition [$F_{(1,\ 70)} = 0.13$, $p = 0.72$, $\eta^2{}_p = 0.002$].

To recap our cognitive performance findings, we found effects of Age on our EF and non-EF tasks, but there were no effects of Surface Stability and no interactions between Age and Surface Stability on any of the cognitive measures (see **Supplementary Materials** for all statistical tests).

Post-experiment Survey

Using the summary score on the ABC scale, we ran an independent samples t-test and found that younger adults reported significantly higher levels of confidence compared to the older adults [91% vs. 78%; *Welch's* $t(37) = 3.39$, $p = 0.002$, Cohen's $d = 0.88$]. Like with the ABC, we ran an independent samples t-test on the MDPQ total score and found that younger adults reported significantly higher levels of mobile device proficiency compared to the older adults [39 vs. 27; Welch's $t(27) = 5.62$, $p < 0.001$, Cohen's $d = 1.52$].

DISCUSSION

The current study is the first to examine the impact of cognitive demands of tablet-based EF and non-EF tasks among older and younger adults attempting to balance on surfaces of varying stability. We measured participants' postural control using center of pressure displacements obtained from an array of wearable IMU sensors (Mancini et al., 2011b, 2012; Deshmukh et al., 2012; Martinez-Mendez et al., 2012; Doherty et al., 2017), and we measured cognitive performance using response times and accuracy on the tablet tasks (Rossiter et al., 2017).

Balance Performance

In general, more sway was observed on unstable surfaces compared to stable surfaces as evidenced by a main effect of surface stability, which aligns with prior research (Barbado Murillo et al., 2012; Tse et al., 2013). Furthermore, older adults showed this effect in a more exaggerated fashion compared to younger adults, which also replicates prior work and suggests that older adults' motor control is more impacted by surface stability than younger adults (Abrahamová and Hlavacka, 2008; Boisgontier et al., 2013; Przysucha et al., 2020). One possible explanation for this comes from findings suggesting age-related declines in muscle mass needed for postural control, which can contribute to older adult risk of falling (Pijnappels et al., 2008). Another possible explanation for age-related sway differences in unstable conditions could stem from differences in balance confidence among older vs. younger adults. Indeed, the older

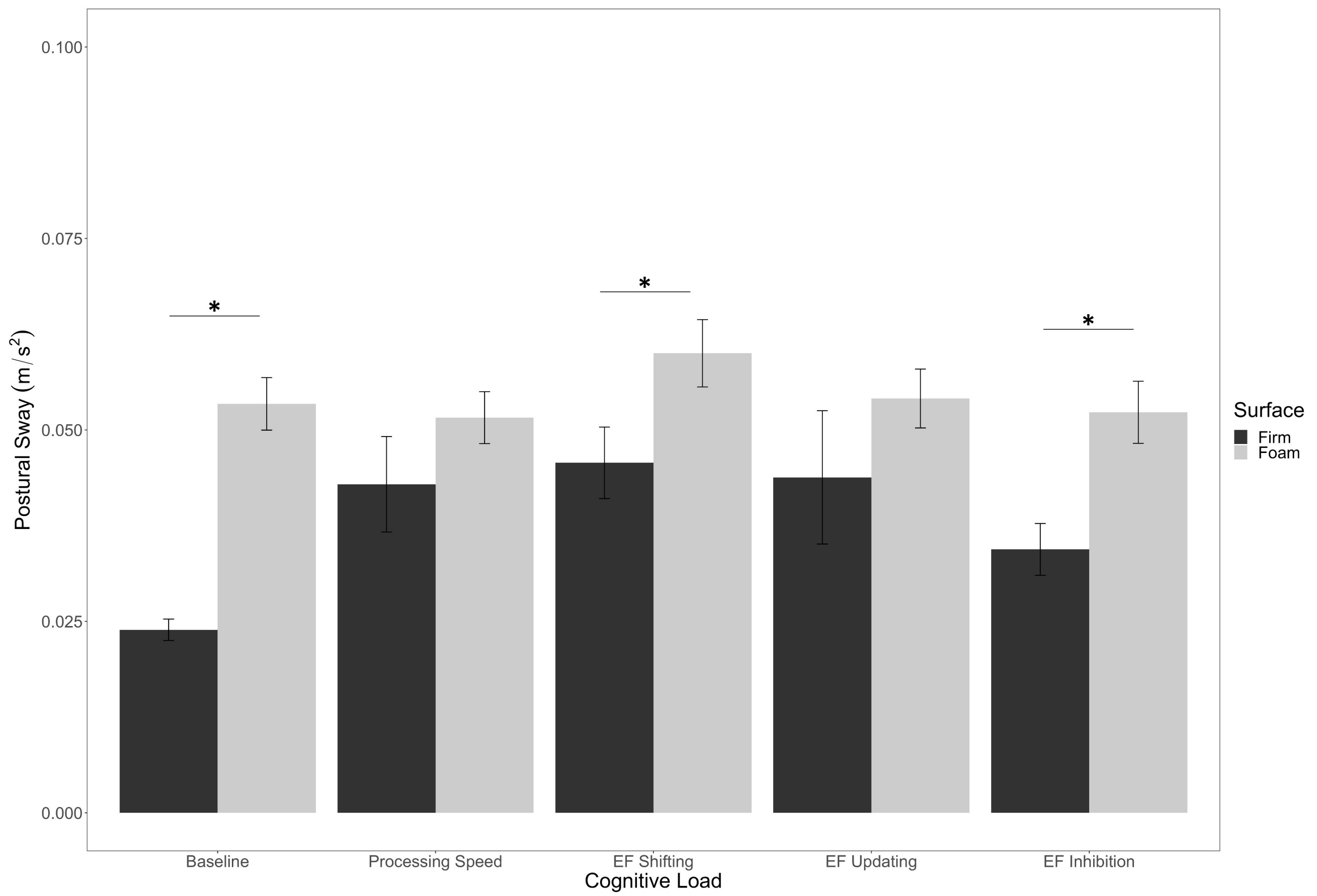

FIGURE 4 | Interaction of surface stability by cognitive load on postural sway. Error bars are ± SE. Significant differences are indicated by asterisks: $^*p < 0.05$.

adults in our study reported overall lower balance confidence than the younger adults. This suggests that they may have felt less equipped to perform the task, which may have introduced an additional cognitive demand for them, although this comes with some caveats. For instance, older adult balance performance was not actually correlated with balance confidence in our sample. That said, balance confidence scores were negatively correlated with postural sway in the EF updating and non-EF processing speed conditions for our younger adult group, although we refrain from making strong interpretations given that correlations tend not to reliably stabilize until much higher sample sizes (Schönbrodt and Perugini, 2013). Future studies should investigate possible role balance confidence may have on balance performance further with more comprehensive measures of balance confidence and with much larger samples.

In addition to being impacted by surface stability, postural control was impacted by cognitive load. Based on research in a motor ability related to postural control (i.e., gait; Walshe et al., 2015), we expected that EF and non-EF tasks would have differential effects on sway in part because of the purported overlap in neural resources for EF tasks and motor control, but this is not what we found. Instead, we observed that doing cognitive tasks in general on a tablet generated more sway compared to a baseline of holding an inactive tablet. Specifically, in our planned comparisons where we tested the difference in sway while performing each secondary task compared to sway during the baseline (single-task) condition, we observed significantly higher sway for all cognitive tasks relative to baseline except for EF inhibition, which instead trended in the same direction. This is surprising considering that our non-EF measure of processing speed supposedly imposes lower order cognitive demands than demands from EF measures (Maldonado et al., 2020); however, it's also important to note that some prior models have suggested that balance measures are independent from gait measures (Horak et al., 2016), which could also account for differences between our findings on balance with EF/non-EF tasks and prior work on gait with EF/non-EF tasks.

Furthermore, we expected that given age-related declines in EF resources required for coordinating cognitive and postural demands, older adults might specifically struggle in cognitive-motor dual-task conditions involving EF demands compared to non-EF demands; however, the type of cognitive task demand did not interact with age. Instead, we only had a main effect of cognitive load. This suggests that introducing a cognitive demand via tablet tasks *generally* impacts postural control for both age groups; that is, all participants demonstrated poorer

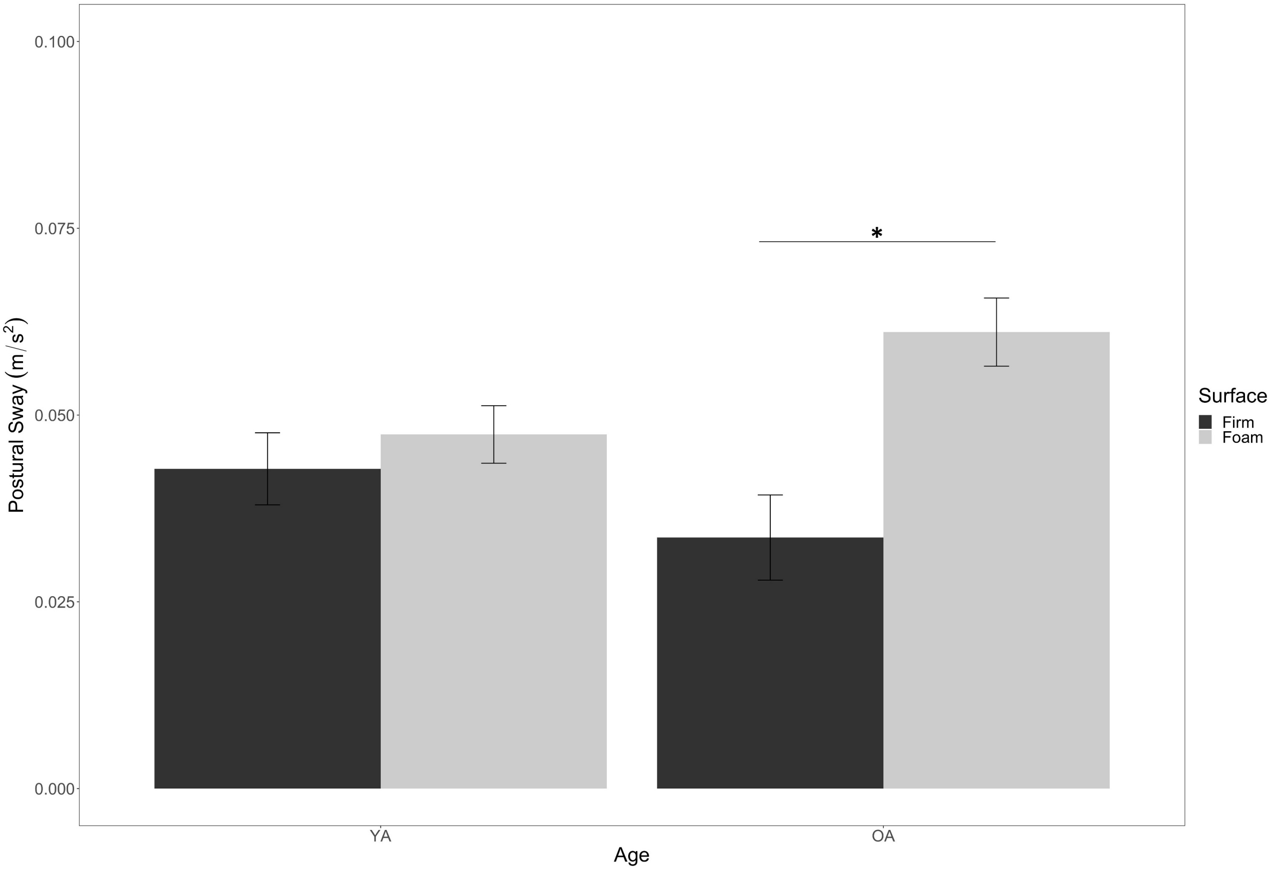

FIGURE 5 | Interaction of surface stability by age on postural sway. Error bars are ± SE. Significant differences are indicated by asterisks: $*p < 0.05$.

balance when actively engaged with a secondary task regardless of whether it was an EF task (Dault et al., 2001b; Bergamin et al., 2014). In addition, the overlap between neural resources needed for EF and motor control may not be the primary mechanism accounting for the present cognitive-motor dual-tasking effects, although more research with neuroimaging techniques (e.g., fNIRS) is needed to directly test such hypotheses related to limited cognitive resource overlap and multitasking bottlenecks (Rosso et al., 2017).

Despite the paucity of age effects, our results support the notion that postural control requires cognitive resources in general. In other words, engaging in a secondary cognitive task while standing upright generates cognitive-motor dual-task interference regardless of if the secondary cognitive task relies on EF or not and regardless of age group. This general interference account aligns more with one of two popular dual-tasking models. Bottleneck models posit that cognitive-motor dual-task interference results from serial processing restrictions when multiple tasks require similar information processing stages at the same time, which is not possible due to structural limitations (Pashler, 1994) or strategic control (Meyer and Kieras, 1997). Importantly, this model is somewhat agnostic in terms of the specific task combinations and would thus treat EF-related tasks similar to non-EF tasks. We found that both EF tasks and a non-EF task impacted balance compared to a single-task control condition, which is more compatible with the notion of general information processing bottlenecks.

Alternatively, according to capacity sharing models, cognitive-motor dual-task interference on balance results from limited-capacity parallel processing abilities to divide specific resources among the cognitive and motor tasks, which means that each task

TABLE 2 | Cognitive task descriptive statistics.

		Age			
		Younger adults		Older adults	
Surface	Cognitive load	Mean	*SD*	Mean	*SD*
Firm	Processing speed	357	47.3	427	103
	EF Shifting	186	185	302	338
	EF Updating	0.84	0.18	0.59	0.21
	EF Inhibition	146	82.4	348	203
Foam	Processing speed	360	53.6	441	108
	EF Shifting	179	234	296	260
	EF Updating	0.89	0.13	0.63	0.24
	EF Inhibition	135	93.3	353	197

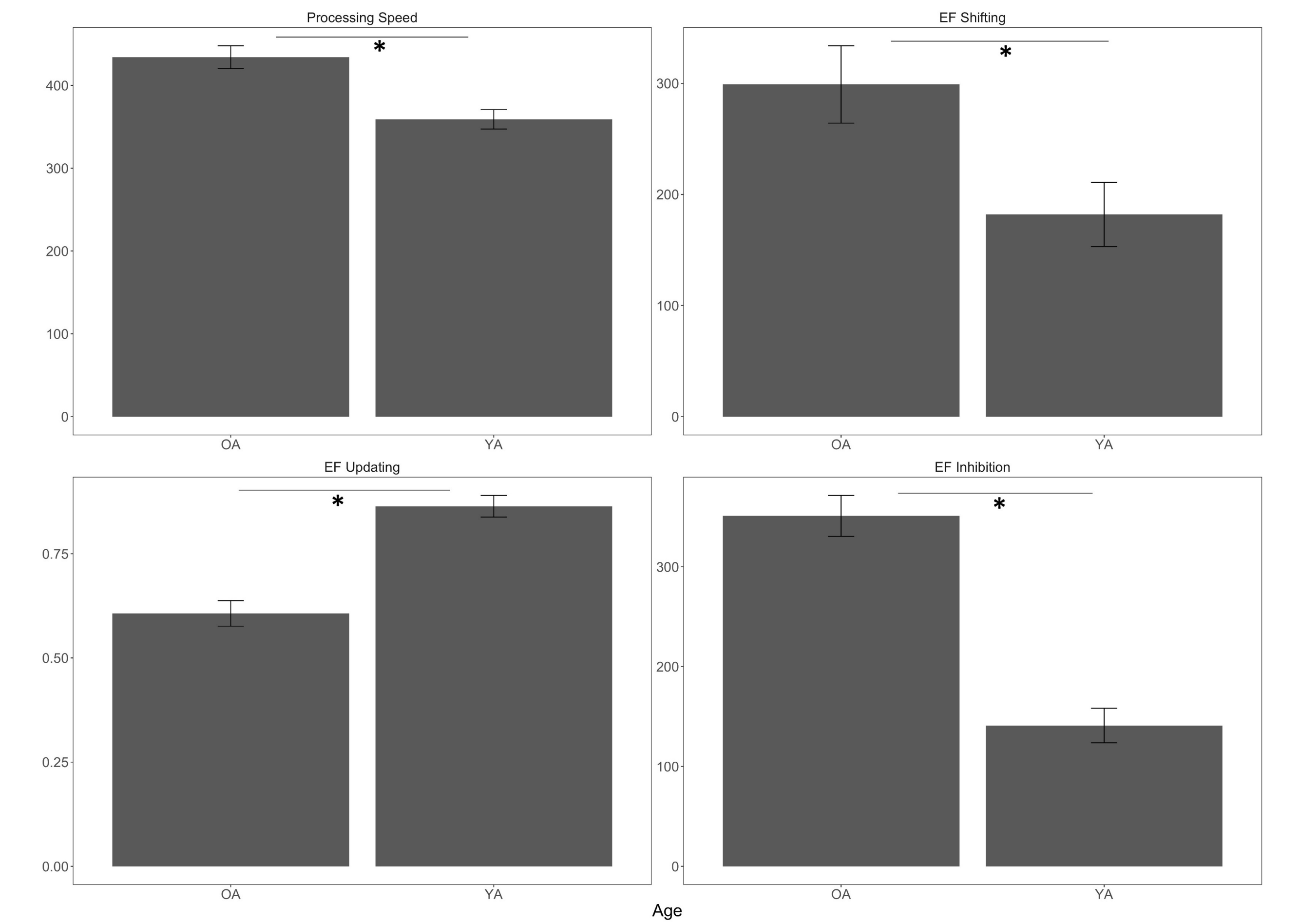

FIGURE 6 | Main effects of age on cognitive task performance. Top left is Processing Speed (RT in ms). Top right is EF Shifting (switch costs in ms). Bottom right is EF Inhibition (Stroop effect in ms). Bottom left is EF Updating (2-back accuracy). Error bars are ± SE. Significant differences are indicated by asterisks: *$p < 0.05$.

gets lower capacity leading to impairments (Navon and Gopher, 1979; Woollacott and Shumway-Cook, 2002). When similar resources are required for balance and EF-related cognitive task performance, interference should be greater than when less related attentional resources are required for balance and non-EF-related cognitive task performance. Once again, our results are less compatible with this theoretical account.

Regardless, more research is needed to further test assumptions of these models against a host of possible patterns observed in cognitive-motor dual-task research (Plummer et al., 2013; Bayot et al., 2018). For example, it is possible that when faced with competition for attentional resources, people must decide how to prioritize the two tasks, and in the current study, older and younger adults might have adopted similar task prioritization strategies, which is why we did not see more effects of age on balance (Yogev-Seligmann et al., 2012; Plummer and Eskes, 2015). Unfortunately, we did not think to ask participants if they prioritized balance performance over cognitive performance, nor do we know if these types of decisions are conscious and intentional. Future research manipulating participant instructions could help to more directly test the role that task prioritization might play in cognitive-motor dual-tasking settings.

Cognitive Performance

Although our main focus was on balance performance, we also measured performance on computerized cognitive tasks. In terms of cognitive performance, we noted age effects on all cognitive tasks, where older adults had worse performance (e.g., lower accuracy, slower responses) compared to younger adults. This replicates prior results that suggest age-related declines in cognitive function (Elderkin-Thompson et al., 2008; Grady, 2012; Fraser and Bherer, 2013; King et al., 2013; Yuan and Raz, 2014). In our case all tasks were performed on a tablet platform, thus it is also possible that the age-related effects on the cognitive tasks are due, in part, to differences in mobile device proficiency across older and younger adults (Roque and Boot, 2018). That said, others have found age-related effects on cognitive tasks in cognitive-motor dual-task studies that did not use tablets (Prado et al., 2007), so more research is needed to better understand the impact of technology proficiency on balance.

CONCLUSION

In today's society, standing upright is rarely done without additional cognitive tasks and on completely stable, regular surfaces. Furthermore, normal aging often entails cognitive and physical changes that impact balance and the risk of falling, which is why we wanted to investigate balance for younger and older adults engaged in different types of cognitive tasks on stable and unstable surfaces. We chose to use three EF tasks compared to a non-EF task to better understand the specificity of cognitive-motor dual-task interference on balance, and we instead found general interference from the cognitive tasks that patterned similarly for both age groups. We used tablet-based cognitive tasks in part because of the increasing role of devices in daily life. Indeed, other cognitive-motor dual-tasking studies have found that using mobile devices can impact postural control for both younger and older adults (Cho et al., 2014; Nurwulan et al., 2015; Laatar et al., 2017; Bruyneel and Duclos, 2020; Hsiao et al., 2020; Onofrei et al., 2020). Future work with larger samples is needed to extend investigations into the specificity of cognitive-motor dual-task interference on balance to more realistic tasks people complete on mobile devices.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Tufts University IRB. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NW and EH: conceptualization. AM, VU, and CR: data curation and investigation. NW and TW: formal analysis. NW, EH, VU, CR, and EM: methodology. NW and EM: resources and supervision. NW: writing—original draft. NW, EH, AM, VU, CR, TW, and EM: writing—review and editing. All authors have read and agree to the published version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.804936/full#supplementary-material

Supplementary Data Sheet 1 | De-identified data.

REFERENCES

Abrahamová, D., and Hlavacka, F. (2008). Age-related changes of human balance during quiet stance. *Physiol. Res.* 57, 957–964. doi: 10.33549/physiolres.931238

Agrawal, Y., Carey, J. P., Della Santina, C. C., Schubert, M. C., and Minor, L. B. (2009). Disorders of balance and vestibular function in US adults: data from the National Health and Nutrition Examination Survey, 2001-2004. *Arch. Intern. Med.* 169, 938–944. doi: 10.1001/archinternmed.2009.66

Al-Yahya, E., Dawes, H., Smith, L., Dennis, A., Howells, K., and Cockburn, J. (2011). Cognitive motor interference while walking: a systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* 35, 715–728. doi: 10.1016/j.neubiorev.2010.08.008

Al-Yahya, E., Mahmoud, W., Meester, D., Esser, P., and Dawes, H. (2019). Neural Substrates of Cognitive Motor Interference During Walking; Peripheral and Central Mechanisms. *Front. Hum. Neurosci.* 12:536. doi: 10.3389/fnhum.2018.00536

Ambrose, A. F., Paul, G., and Hausdorff, J. M. (2013). Risk factors for falls among older adults: a review of the literature. *Maturitas* 75, 51–61. doi: 10.1016/j.maturitas.2013.02.009

Andersson, G., Hagman, J., Talianzadeh, R., Svedberg, A., and Larsen, H. C. (2002). Effect of cognitive load on postural control. *Brain Res. Bull.* 58, 135–139. doi: 10.1016/S0361-9230(02)00770-0

Barbado Murillo, D., Sabido Solana, R., Vera-Garcia, F. J., Gusi Fuertes, N., and Moreno, F. J. (2012). Effect of increasing difficulty in standing balance tasks with visual feedback on postural sway and EMG: complexity and performance. *Hum. Mov. Sci.* 31, 1224–1237. doi: 10.1016/j.humov.2012.01.002

Basner, M., and Dinges, D. F. (2011). Maximizing sensitivity of the psychomotor vigilance test (PVT) to sleep loss. *Sleep* 34, 581–591. doi: 10.1093/sleep/34.5.581

Bayot, M., Dujardin, K., Tard, C., Defebvre, L., Bonnet, C. T., Allart, E., et al. (2018). The interaction between cognition and motor control: a theoretical framework for dual-task interference effects on posture, gait initiation, gait and turning. *Neurophysiol. Clin.* 48, 361–375. doi: 10.1016/j.neucli.2018.10.003

Beauchet, O., Annweiler, C., Dubost, V., Allali, G., Kressig, R. W., Bridenbaugh, S., et al. (2009). Stops walking when talking: a predictor of falls in older adults? *Eur. J. Neurol.* 16, 786–795. doi: 10.1111/j.1468-1331.2009.02612.x

Beauchet, O., Annweiler, C., Montero-Odasso, M., Fantino, B., Herrmann, F. R., and Allali, G. (2012). Gait control: a specific subdomain of executive function? *J. Neuroeng. Rehabil.* 9:12. doi: 10.1186/1743-0003-9-12

Bergamin, M., Gobbo, S., Zanotto, T., Sieverdes, J. C., Alberton, C. L., Zaccaria, M., et al. (2014). Influence of age on postural sway during different dual-task conditions. *Front. Aging Neurosci.* 6:271. doi: 10.3389/fnagi.2014.00271

Bohle, H., Rimpel, J., Schauenburg, G., Gebel, A., Stelzel, C., Heinzel, S., et al. (2019). Behavioral and Neural Correlates of Cognitive-Motor Interference during Multitasking in Young and Old Adults. *Neural Plast.* 2019:e9478656. doi: 10.1155/2019/9478656

Boisgontier, M. P., Beets, I. A. M., Duysens, J., Nieuwboer, A., Krampe, R. T., and Swinnen, S. P. (2013). Age-related differences in attentional cost associated with postural dual tasks: increased recruitment of generic cognitive resources in older adults. *Neurosci. Biobehav. Rev.* 37, 1824–1837. doi: 10.1016/j.neubiorev.2013.07.014

Borst, J. P., Taatgen, N. A., and van Rijn, H. (2010). The problem state: a cognitive bottleneck in multitasking. *J. Exp. Psychol. Learn. Mem. Cogn.* 36, 363–382. doi: 10.1037/a0018106

Bruyneel, A.-V., and Duclos, N. C. (2020). Effects of the use of mobile phone on postural and locomotor tasks: a scoping review. *Gait Posture* 82, 233–241. doi: 10.1016/j.gaitpost.2020.09.014

Chan, R. C. K., Shum, D., Toulopoulou, T., and Chen, E. Y. H. (2008). Assessment of executive functions: review of instruments and identification of critical issues. *Arch. Clin. Neuropsychol.* 23, 201–216. doi: 10.1016/j.acn.2007.08.010

Chiari, L., Rocchi, L., and Cappello, A. (2002). Stabilometric parameters are affected by anthropometry and foot placement. *Clin. Biomech.* 17, 666–677. doi: 10.1016/s0268-0033(02)00107-9

Cho, S.-H., Choi, M.-H., and Goo, B.-O. (2014). Effect of smart phone use on dynamic postural balance. *J. Phys. Ther. Sci.* 26, 1013–1015. doi: 10.1589/jpts.26.1013

Choy, N. L., Brauer, S., and Nitz, J. (2003). Changes in Postural Stability in Women Aged 20 to 80 Years. *J. Gerontol. Ser. A* 58, M525–M530. doi: 10.1093/gerona/58.6.M525

Costa, K. G., da Hussey, E. K., Fontes, E. B., Menta, A., Ramsay, J. W., Hancock, C. L., et al. (2020). Effects of Cognitive Over Postural Demands on Upright Standing Among Young Adults: perceptual and Motor Skills. *Percept. Mot. Skills* 128, 80-95. doi: 10.1177/0031512520972879

Dault, M. C., Frank, J. S., and Allard, F. (2001a). Influence of a visuo-spatial, verbal and central executive working memory task on postural control. *Gait Posture* 14, 110–116. doi: 10.1016/S0966-6362(01)00113-8

Dault, M. C., Geurts, A. C. H., Mulder, T. W., and Duysens, J. (2001b). Postural control and cognitive task performance in healthy participants while balancing on different support-surface configurations. *Gait Posture* 14, 248–255. doi: 10.1016/S0966-6362(01)00130-8

Deshmukh, P. M., Russell, C. M., Lucarino, L. E., and Robinovitch, S. N. (2012). Enhancing clinical measures of postural stability with wearable sensors. *Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.* 2012, 4521–4524. doi: 10.1109/EMBC.2012.6346972

Doherty, C., Zhao, L., Ryan, J., Komaba, Y., Inomata, A., and Caulfield, B. (2017). Quantification of postural control deficits in patients with recent concussion: an inertial-sensor based approach. *Clin. Biomech.* 42, 79–84. doi: 10.1016/j.clinbiomech.2017.01.007

Duncan, J., and Owen, A. M. (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci.* 23, 475–483. doi: 10.1016/S0166-2236(00)01633-7

Elderkin-Thompson, V., Ballmaier, M., Hellemann, G., Pham, D., and Kumar, A. (2008). Executive function and MRI prefrontal volumes among healthy older adults. *Neuropsychology* 22, 626–637. doi: 10.1037/0894-4105.22.5.626

Fraizer, E. V., and Mitra, S. (2008). Methodological and interpretive issues in posture-cognition dual-tasking in upright stance. *Gait Posture* 27, 271–279. doi: 10.1016/j.gaitpost.2007.04.002

Fraser, S., and Bherer, L. (2013). Age-related decline in divided-attention: from theoretical lab research to practical real-life situations. *Wiley Interdiscipl. Rev. Cogn. Sci.* 4, 623–640. doi: 10.1002/wcs.1252

Fuller, G. F. (2000). Falls in the elderly. *Am. Fam. Phys.* 61, 2173–2174.

Garavan, H., Ross, T. J., Li, S.-J., and Stein, E. A. (2000). A Parametric Manipulation of Central Executive Functioning. *Cereb. Cortex* 10, 585–592. doi: 10.1093/cercor/10.6.585

Gera, G., Chesnutt, J., Mancini, M., Horak, F. B., and King, L. A. (2018). Inertial Sensor-Based Assessment of Central Sensory Integration for Balance After Mild Traumatic Brain Injury. *Military Med.* 183, 327–332. doi: 10.1093/milmed/usx162

Gill, J., Allum, J. H. J., Carpenter, M. G., Held-Ziolkowska, M., Adkin, A. L., Honegger, F., et al. (2001). Trunk Sway Measures of Postural Stability During Clinical Balance Tests: effects of Age. *J. Gerontol. Ser. A* 56, M438–M447. doi: 10.1093/gerona/56.7.M438

Grady, C. (2012). The cognitive neuroscience of ageing. *Nat. Rev. Neurosci.* 13, 491–505. doi: 10.1038/nrn3256

Hageman, P. A., Leibowitz, J. M., and Blanke, D. (1995). Age and gender effects on postural control measures. *Arch. Phys. Med. Rehabil.* 76, 961–965. doi: 10.1016/S0003-9993(95)80075-1

Holtzer, R., Epstein, N., Mahoney, J. R., Izzetoglu, M., and Blumen, H. M. (2014). Neuroimaging of mobility in aging: a targeted review. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* 69, 1375–1388. doi: 10.1093/gerona/glu052

Horak, F. B., Mancini, M., Carlson-Kuhta, P., Nutt, J. G., and Salarian, A. (2016). Balance and Gait Represent Independent Domains of Mobility in Parkinson Disease. *Phys. Ther.* 96, 1364–1371. doi: 10.2522/ptj.20150580

Hsiao, D., Belur, P., Myers, P. S., Earhart, G. M., and Rawson, K. S. (2020). The impact of age, surface characteristics, and dual-tasking on postural sway. *Arch. Gerontol. Geriatrics* 87, 103973. doi: 10.1016/j.archger.2019.103973

Huxhold, O., Li, S.-C., Schmiedek, F., and Lindenberger, U. (2006). Dual-tasking postural control: aging and the effects of cognitive demand in conjunction with focus of attention. *Brain Res. Bull.* 69, 294–305. doi: 10.1016/j.brainresbull.2006.01.002

Jacobs, J. V., and Horak, F. B. (2007). Cortical control of postural responses. *J. Neural. Transm.* 114, 1339. doi: 10.1007/s00702-007-0657-0

Johnson, M. K., Mitchell, K. J., Raye, C. L., and Greene, E. J. (2004). An Age-Related Deficit in Prefrontal Cortical Function Associated With Refreshing Information. *Psychol. Sci.* 15, 127–132. doi: 10.1111/j.0963-7214.2004.01502009.x

Jurado, M. B., and Rosselli, M. (2007). The Elusive Nature of Executive Functions: a Review of our Current Understanding. *Neuropsychol. Rev.* 17, 213–233. doi: 10.1007/s11065-007-9040-z

Kerr, B., Condon, S. M., and McDonald, L. A. (1985). Cognitive spatial processing and the regulation of posture. *J. Exp. Psychol. Hum. Percept. Perform.* 11, 617–622. doi: 10.1037/0096-1523.11.5.617

Kim, J.-W., Eom, G.-M., Kim, C.-S., Kim, D.-H., Lee, J.-H., Park, B. K., et al. (2010). Sex differences in the postural sway characteristics of young and elderly subjects during quiet natural standing. *Geriatrics Gerontol. Int.* 10, 191–198. doi: 10.1111/j.1447-0594.2009.00582.x

King, B. R., Fogel, S. M., Albouy, G., and Doyon, J. (2013). Neural correlates of the age-related changes in motor sequence learning and motor adaptation in older adults. *Front. Hum. Neurosci.* 7:142. doi: 10.3389/fnhum.2013.00142

King, L. A., Mancini, M., Fino, P. C., Chesnutt, J., Swanson, C. W., Markwardt, S., et al. (2017). Sensor-Based Balance Measures Outperform Modified Balance Error Scoring System in Identifying Acute Concussion. *Ann. Biomed. Eng.* 45, 2135–2145. doi: 10.1007/s10439-017-1856-y

Laatar, R., Kachouri, H., Borji, R., Rebai, H., and Sahli, S. (2017). The effect of cell phone use on postural balance and mobility in older compared to young adults. *Physiol. Behav.* 173, 293–297. doi: 10.1016/j.physbeh.2017.02.031

Lajoie, Y., and Gallagher, S. P. (2004). Predicting falls within the elderly community: comparison of postural sway, reaction time, the Berg balance scale and the Activities-specific Balance Confidence (ABC) scale for comparing fallers and non-fallers. *Arch. Gerontol. Geriatrics* 38, 11–26. doi: 10.1016/S0167-4943(03)00082-7

Lajoie, Y., Teasdale, N., Bard, C., and Fleury, M. (1993). Attentional demands for static and dynamic equilibrium. *Exp. Brain Res.* 97, 139–144. doi: 10.1007/BF00228824

Lanzarin, M., Parizzoto, P., Libardoni, T., de, C., Sinhorim, L., Tavares, G. M. S., et al. (2015). The influence of dual-tasking on postural control in young adults. *Fisioter. Pesqui.* 22, 61–68.

Laufer, Y., Barak, Y., and Chemel, I. (2006). Age-Related Differences in the Effect of a Perceived Threat to Stability on Postural Control. *J. Gerontol. Ser. A* 61, 500–504. doi: 10.1093/gerona/61.5.500

Laughton, C. A., Slavin, M., Katdare, K., Nolan, L., Bean, J. F., Kerrigan, D. C., et al. (2003). Aging, muscle activity, and balance control: physiologic changes associated with balance impairment. *Gait Posture* 18, 101–108. doi: 10.1016/S0966-6362(02)00200-X

Lee, H., Baniqued, P. L., Cosman, J., Mullen, S., McAuley, E., Severson, J., et al. (2012). Examining cognitive function across the lifespan using a mobile application. *Comput. Hum. Behav.* 28, 1934–1946. doi: 10.1016/j.chb.2012.05.013

Li, K. Z. H., Vadaga, K. K., Bruce, H., and Lai, L. (2017). "Executive Function Development in Aging" in *Executive Function: development Across the Life Span*. Eds S. A. Wiebe, and J. Karbach. (New York: Routledge).

MacLeod, C. M. (1991). Half a Century of Research on the Stroop Effect: an Integrative Review. *Psychol. Bull.* 109, 163–203. doi: 10.1037/0033-2909.109.2.163

Maki, B. E., Holliday, P. J., and Topper, A. K. (1994). A prospective study of postural balance and risk of falling in an ambulatory and independent elderly population. *J. Gerontol.* 49, M72–M84. doi: 10.1093/geronj/49.2.m72

Maldonado, T., Orr, J. M., Goen, J. R. M., and Bernard, J. A. (2020). Age Differences in the Subcomponents of Executive Functioning. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 75, e31–e55. doi: 10.1093/geronb/gbaa005

Mancini, M., Horak, F. B., Zampieri, C., Carlson-Kuhta, P., Nutt, J. G., and Chiari, L. (2011a). Trunk accelerometry reveals postural instability in untreated Parkinson's disease. *Parkinson. Rel. Disord.* 17, 557–562. doi: 10.1016/j.parkreldis.2011.05.010

Mancini, M., King, L., Salarian, A., Holmstrom, L., McNames, J., and Horak, F. B. (2011b). Mobility Lab to Assess Balance and Gait with Synchronized Body-worn Sensors. *J. Bioeng. Biomed. Sci. Suppl.* 1:007. doi: 10.4172/2155-9538.S1-007

Mancini, M., Salarian, A., Carlson-Kuhta, P., Zampieri, C., King, L., Chiari, L., et al. (2012). ISway: a sensitive, valid and reliable measure of postural control. *J. Neuroeng. Rehabil.* 9:59. doi: 10.1186/1743-0003-9-59

Martinez-Mendez, R., Sekine, M., and Tamura, T. (2012). Postural sway parameters using a triaxial accelerometer: comparing elderly and young healthy adults. *Comput. Methods Biomech. Biomed. Eng.* 15, 899–910. doi: 10.1080/10255842.2011.565753

Maylor, E. A., and Wing, A. M. (1996). Age Differences in Postural Stability are Increased by Additional Cognitive Demands. *J. Gerontol. Ser. B* 51B, 143–154. doi: 10.1093/geronb/51B.3.P143

Meyer, D. E., and Kieras, D. E. (1997). A Computational Theory of Executive Cognitive Processes and Multiple-Task Performance: part 2. Accounts of Psychological Refractory-Period Phenomena. *Psychol. Rev.* 104, 749–791. doi: 10.1037/0033-295x.104.1.3

Mihara, M., Miyai, I., Hatakenaka, M., Kubota, K., and Sakoda, S. (2008). Role of the prefrontal cortex in human balance control. *NeuroImage* 43, 329–336. doi: 10.1016/j.neuroimage.2008.07.029

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., and Wager, T. D. (2000). The Unity and Diversity of Executive Functions and Their Contributions to Complex "Frontal Lobe" Tasks: a Latent Variable Analysis. *Cogn. Psychol.* 41, 49–100. doi: 10.1006/cogp.1999.0734

Monsell, S. (2003). Task switching. *Trends Cogn. Sci.* 7, 134–140. doi: 10.1016/S1364-6613(03)00028-7

Morris, R., Martini, D. N., Smulders, K., Kelly, V. E., Zabetian, C. P., Poston, K., et al. (2019). Cognitive associations with comprehensive gait and static balance measures in Parkinson's disease. *Parkinson. Rel. Disord.* 69, 104–110. doi: 10.1016/j.parkreldis.2019.06.014

Navon, D., and Gopher, D. (1979). On the economy of the human-processing system. *Psychol. Rev.* 86, 214–255. doi: 10.1037/0033-295X.86.3.214

Nurwulan, N. R., Jiang, B. C., and Iridiastadi, H. (2015). Posture and Texting: effect on Balance in Young Adults. *PLoS One* 10:e0134230. doi: 10.1371/journal.pone.0134230

Onofrei, R. R., Amaricai, E., Suciu, O., David, V. L., Rata, A. L., and Hogea, E. (2020). Smartphone Use and Postural Balance in Healthy Young Adults. *Int. J. Environ Res. Public Health* 17:E3307. doi: 10.3390/ijerph17093307

Owen, A. M., McMillan, K. M., Laird, A. R., and Bullmore, E. (2005). N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum. Brain Mapp.* 25, 46–59. doi: 10.1002/hbm.20131

Pashler, H. (1994). Dual-task interference in simple tasks: data and theory. *Psychol. Bull.* 116, 220–244. doi: 10.1037/0033-2909.116.2.220

Pellecchia, G. L. (2003). Postural sway increases with attentional demands of concurrent cognitive task. *Gait Posture* 18, 29–34. doi: 10.1016/s0966-6362(02)00138-8

Peterka, R. J. (2002). Sensorimotor Integration in Human Postural Control. *J. Neurophysiol.* 88, 1097–1118. doi: 10.1152/jn.2002.88.3.1097

Pijnappels, M., van, der Burg, Petra, J. C. E., Reeves, N. D., and van Dieën, J. H. (2008). Identification of elderly fallers by muscle strength measures. *Eur. J. Appl. Physiol.* 102, 585–592. doi: 10.1007/s00421-007-0613-6

Pissadaki, E. K., Abrami, A. G. S., Heisig, S. J., Bilal, E., Cavallo, M., Wacnik, P. W., et al. (2018). Decomposition of complex movements into primitives for Parkinson's disease assessment. *IBM J. Res. Dev.* 5:11. doi: 10.1147/JRD.2017.2768739

Plummer, P., and Eskes, G. (2015). Measuring treatment effects on dual-task performance: a framework for research and clinical practice. *Front. Hum. Neurosci.* 9:225. doi: 10.3389/fnhum.2015.00225

Plummer, P., Eskes, G., Wallace, S., Giuffrida, C., Fraas, M., Campbell, G., et al. (2013). Cognitive-Motor Interference during Functional Mobility after Stroke: state of the Science and Implications for Future Research. *Arch. Phys. Med. Rehabil.* 94, 2565–2574.e6. doi: 10.1016/j.apmr.2013.08.002

Powell, L. E., and Myers, A. M. (1995). The Activities-specific Balance Confidence (ABC) Scale. *J. Gerontol. A Biol. Sci. Med. Sci.* 50A, M28–M34.

Prado, J. M., Stoffregen, T. A., and Duarte, M. (2007). Postural sway during dual tasks in young and elderly adults. *Gerontology* 53, 274–281. doi: 10.1159/000102938

Prieto, T. E., Myklebust, J. B., Hoffmann, R. G., Lovett, E. G., and Myklebust, B. M. (1996). Measures of postural steadiness: differences between healthy young and elderly adults. *IEEE Trans. Biomed. Eng.* 43, 956–966. doi: 10.1109/10.532130

Przysucha, E., Vollebregt, B. A., and Zerpa, C. (2020). Impact of Attentional Loading and Task Constraints on Postural Control of Healthy Older Adults. *IJEACH* 2, 12–25. doi: 10.4018/IJEACH.2020070102

Remaud, A., Boyas, S., Caron, G. A. R., and Bilodeau, M. (2012). Attentional demands associated with postural control depend on task difficulty and visual condition. *J. Mot. Behav.* 44, 329–340. doi: 10.1080/00222895.2012.708680

Rocchi, L., Chiari, L., and Cappello, A. (2004). Feature selection of stabilometric parameters based on principal component analysis. *Med. Biol. Eng. Comput.* 42, 71–79. doi: 10.1007/BF02351013

Roque, N. A., and Boot, W. R. (2018). A New Tool for Assessing Mobile Device Proficiency in Older Adults: the Mobile Device Proficiency Questionnaire. *J. Appl. Gerontol.* 37, 131–156. doi: 10.1177/0733464816642582

Rossiter, A., Allsop, M. J., Raw, R. K., Howard, L., Holt, R. J., Wilkie, R. M., et al. (2017). Manual tracking impairs postural stability in older adults. *Br. J. Occup. Ther.* 80, 539–548. doi: 10.1177/0308022617712206

Rosso, A. L., Cenciarini, M., Sparto, P. J., Loughlin, P. J., Furman, J. M., and Huppert, T. J. (2017). Neuroimaging of an attention demanding dual-task during dynamic postural control. *Gait Posture* 57, 193–198. doi: 10.1016/j.gaitpost.2017.06.013

Rypma, B., Prabhakaran, V., Desmond, J. E., and Gabrieli, J. D. E. (2001). Age differences in prefrontal cortical activity in working memory. *Psychol. Aging* 16, 371–384. doi: 10.1037/0882-7974.16.3.371

Šarabon, N., Mlaker, B., and Markovic, G. (2010). A novel tool for the assessment of dynamic balance in healthy individuals. *Gait Posture* 31, 261–264. doi: 10.1016/j.gaitpost.2009.11.001

Schaefer, S. (2014). The ecological approach to cognitive–motor dual-tasking: findings on the effects of expertise and age. *Front. Psychol.* 5:1167. doi: 10.3389/fpsyg.2014.01167

Schönbrodt, F. D., and Perugini, M. (2013). At what sample size do correlations stabilize? *J. Res. Pers.* 47, 609–612. doi: 10.1016/j.jrp.2013.05.009

Seidler, R. D., Bernard, J. A., Burutolu, T. B., Fling, B. W., Gordon, M. T., Gwin, J. T., et al. (2010). Motor control and aging: links to age-related brain structural, functional, and biochemical effects. *Neurosci. Biobehav. Rev.* 34, 721–733. doi: 10.1016/j.neubiorev.2009.10.005

Stroop, J. (1935). Studies of interference in serial verbal reactions. *J. Exp. Psychol.* 18, 643–662. doi: 10.1037/h0054651

Stuss, D. T. (2011). Functions of the frontal lobes: relation to executive functions. *J. Int. Neuropsychol. Soc.* 17, 759–765. doi: 10.1017/S1355617711000695

Tse, Y. Y. F., Petrofsky, J. S., Berk, L., Daher, N., Lohman, E., Laymon, M. S., et al. (2013). Postural sway and Rhythmic Electroencephalography analysis of cortical activation during eight balance training tasks. *Med. Sci. Monit.* 19, 176–186. doi: 10.12659/MSM.883824

Walshe, E. A., Patterson, M. R., Commins, S., and Roche, R. A. P. (2015). Dual-task and electrophysiological markers of executive cognitive processing in older adult gait and fall-risk. *Front. Hum. Neurosci.* 9:200. doi: 10.3389/fnhum.2015.00200

Ward, N., Menta, A., Peach, S., White, S. A., Jaffe, S., Kowaleski, C., et al. (2021). Cognitive Motor Dual Task Costs in Older Adults with Motoric Cognitive Risk Syndrome. *J. Frailty Aging* 10, 337–342. doi: 10.14283/jfa.2021.27

White, S. A., Ward, N., Verghese, J., Kramer, A. F., Grandjean da Costa, K., Liu, C. K., et al. (2020). Nutritional risk status, dietary intake and cognitive performance in older adults with motoric cognitive risk syndrome. *J. Aging Res. Clin. Pract.* 9, 47–54. doi: 10.3390/nu13061786

Wickens, C. D. (2002). Multiple resources and performance prediction. *Theor. Issues Ergonom. Sci.* 3:159. doi: 10.1080/14639220210123806

Woollacott, M., and Shumway-Cook, A. (2002). Attention and the control of posture and gait: a review of an emerging area of research. *Gait Posture* 16, 1–14. doi: 10.1016/S0966-6362(01)00156-4

Yardley, L., Gardner, M., Leadbetter, A., and Lavie, N. (1999). Effect of articulatory and mental tasks on postural control. *Neuro Rep.* 10, 215–219. doi: 10.1097/00001756-199902050-00003

Yogev-Seligmann, G., Hausdorff, J. M., and Giladi, N. (2012). Do we always prioritize balance when walking? Towards an integrated model of task prioritization. *Mov. Disord.* 27, 765–770. doi: 10.1002/mds.24963

Yuan, P., and Raz, N. (2014). Prefrontal cortex and executive functions in healthy adults: a meta-analysis of structural neuroimaging studies. *Neurosci. Biobehav. Rev.* 42, 180–192. doi: 10.1016/j.neubiorev.2014.02.005

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Relationships Among Cognitive Function, Frailty, and Health Outcome in Community-Dwelling Older Adults

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Background: Frailty and cognitive impairment are significant problems faced by older adults, which have a significant impact on their activities of daily living, social activities, and quality of life.

Design: Cross-sectional study.

Methods: A total of 252 older adults in two communities in Yangzhou were randomly selected. The cognitive function of the elderly was assessed using the Memory and Executive Screening (MES). The frailty phenotype was used to evaluate the frail situation of older adults. The activity of daily living (ADL), functional activities questionnaire (FAQ), and European quality of 5-dimensions (EQ-5D) were used to evaluate health outcomes in the elderly. SEM was used to explore the direct and indirect relationship among cognitive function, frailty and health outcomes.

Results: There was a significant direct correlation between cognitive function and frailty; the direct effect was −0.521. The influence path of cognitive function on health outcomes included direct and indirect effects; the total effect was −0.759. The effect of frailty on health outcomes included direct and indirect effects; the total effect was 0.440.

Conclusion: According to SEM, cognitive function interacts with frailty and may reduce the quality of life, the ADL, and social activities among older adults directly and indirectly, so future assessments of older adults should consider both cognitive function and frailty, so as to further improve the health outcome of the elderly. When formulating relevant intervention measures in the future, we need to consider that it cannot only improve the cognitive function, but also improve the frail situation, so as to jointly improve the health outcomes of older adults.

Keywords: cognitive impairment, frailty, quality of life, activities of daily living, social activities

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INTRODUCTION

By the end of 2018 the population ≥ 60 years of age in China accounted for 17.90% of the total population, thus indicating that the degree of aging in China is on the rise (National Bureau of Statistics of China, 2019). Cognitive impairment and frailty are the most common geriatric syndromes in older adults, which pose a major threat to them, as specifically reflected in the aggravation of disability, a decline in the quality of life, and an increase in mortality (Fabrício et al., 2020). Cognitive impairment generally refers to various degrees of cognitive dysfunction caused by various reasons, including various stages from mild cognitive impairment (MCI) to Alzheimer's disease (AD). Cognitive impairment and frailty often occur in the same older adults and interact with each other. The coexistence of the two can accelerate the decline of physical and cognitive functions and form a vicious cycle (Brigola et al., 2015). Frailty refers to a weakening in strength and a disorder in physiological function, which will lead to an increase in dependency, vulnerability, and susceptibility to death (Dent et al., 2017). Older adults with frailty have a reduced ability to cope with acute diseases, and have a correspondingly increased risk of falls, disability and death (Fried et al., 2001). The study found that the risk of death, hospitalization, disability and fall in older adults with frailty was 1.7–4.4 times higher than those without frailty (Zheng et al., 2016).

Relationship Between Cognitive Function and Frailty

Aging is associated with physical frailty and cognitive decline. Frail older adults are at higher risk for cognitive decline (Calderón-Larrañaga et al., 2019; Grande et al., 2019). The studies showed that frailty was significantly correlated with the incidence of cognitive impairment (Armstrong et al., 2016; Tsutsumimoto et al., 2019), and the incidence of cognitive impairment in frail older adults was 8 times that of normal older adults (Kulmala et al., 2014). Meanwhile, frailty predicts a poorer cognitive development trajectory among MCI patients, and is associated with the high risk of developing MCI (Kiiti Borges et al., 2019). In addition, based on data from the Canadian Study of Health and Aging, Song et al. (2014) found that the incidence rate of cognitive impairment increased exponentially with the increase of frailty index, and frailty is an independent risk factor for cognitive impairment. Cognitive impairment is related to frailty, and both have common biological mechanisms, including genetic alternations, immune system dysfunction, and neuroinflammation (Sargent et al., 2020).

Effects of Cognitive Function and Frailty on Health Outcomes

Studies have shown that frailty interacts with cognitive impairment, which leads to adverse health outcomes, such as a poorer quality of life (Feng et al., 2017). Hussenoeder et al. (2020) showed that the quality of life in older adults with MCI is closely related to cognition and is lower than healthy older adults. Cognitive function can affect the ADL, social activities, and quality of life among older adults (Ginsberg et al., 2019). Frailty increases the risk of adverse health outcomes, such as falls, disability, decreased ADL, limited physical activity, falls, risk of admission to the hospital and death (Vermeiren et al., 2016; Panza et al., 2018; Zhang et al., 2019). Kojima (2018) showed that decreased ADL in frail older adults is significantly higher than that in healthy older adults. Meanwhile, Audai et al. (2020) found that frail older adults have a lower quality of life than non-frail older adults. Although MCI and frailty interact with each other, cognitive function and frailty affect ADL, social activities, and the quality of life, but a study of the interaction and influence has not been reported.

Structural equation modeling (SEM) is a method to establish, estimate and test causality models. It can study not only the explicit variables, but also the latent variables, and it can display the relationship and size of variables through path graph (Wu, 2010). Therefore, this study intends to use SEM to explore the direct and indirect relationship among cognitive function, frailty and health outcomes, so as to provide reference for the later development of intervention measures to improve the health level and quality of life of the older adults in the community.

MATERIALS AND METHODS

Participants

In general, the minimum sample size is required to be more than 200 to obtain a relatively stable model. Some scholars believe that the sample size should be 5–10 times of the free parameter to be estimated before it is considered acceptable (Kline, 2005; American Psychological Association, 2010). Therefore, a total of 252 older adults who lived in 2 Yangzhou City communities from September 2017 to June 2018 were selected using the random sampling and random number methods. The exclusion criteria were as follows:(1) older adults with mental disorders, such as depression and an unstable condition; (2) older adults with severe hearing and vision disorders who could not cooperate; (3) older adults with language communication disorders who could not complete the investigation; (4) older adults with central nervous system damage caused by severe diseases, such as tumors and infections; (5) older adults with cerebrovascular disease and an unstable condition; and (6) older adults who were unwilling to sign informed consent.

Cognitive Assessment

All subjects completed the MES. MES was developed by Guo et al. (2012) for the screening of AD and MCI, including memory factor and executive factor, with 50 points for each part. The higher the score, the better the cognitive function, and when the score is less than 72, amnestic MCI can be diagnosed. The memory test adopts immediate recall, short delayed recall and long delayed recall, and the executive function test mainly includes fluency, finger 1 test, visuospatial structure ability and finger 2 test, which can effectively reflect the major cognitive impairment areas (Guo et al., 2012). The correlation coefficients of MES-M and MES-E with MES were 0.89 and 0.88, and the intra-group correlation coefficients were 0.92 when tested again at an interval of 23–35 days, suggesting that MES has good reliability and validity (Guo et al., 2012). MES is simple to operate and execute, and is not affected by education level, and it is time-consuming and can quickly assess the degree of impairment of episodic memory and executive function in major cognitive areas without obvious ceiling and floor effects.

Frailty Assessment

Frailty phenotype assessment was proposed by Fried et al. (2001), including 5 items, which are (1) body mass decline: in the past year, body mass decline > 4.54 kg or > 5% of body mass; (2) Slow walking speed: measure the time required to walk 4 m, and judge whether the walking speed is slow according to height and gender, it involves measuring the 4-m distance on the open ground in advance, to instruct the older adults to walk normally as usual, and record the time with a stopwatch; (3) Grip strength weakening: use the grip dynamometer to measure the grip strength, and the patient was told to measure the hand strength twice with the dominant hand to get the maximum value, and whether the grip strength was weakened was judged according to gender and body mass index; (4) Low physical activity: use the international physical activity scale (Liou et al., 2008) to calculate the amount of exercise within 1 week. When the amount of exercise for men and women is less than 383 and 270 kcal, respectively, the amount of physical activity is low; (5) Fatigue: the items of self-rating depression scale were asked: "do you feel that you have to make efforts to do everything in the past week, which has occurred for several days" and "can't walk forward in the past week, which has occurred for several days" are used for inquiry. If one item lasts for more than 3 days, it is fatigue (Geriatrics Branch of the Chinese Medical Association, 2017). The value of each item is 1 point, 1 point will be counted if the item is satisfied, otherwise, no score will be scored. According to the frailty phenotype score as the gold standard, when the score is 0∼2, it is the non-frailty stage, when the score is ≥ 3, it is the frailty stage (Fried et al., 2001).

Health Outcome Assessment

The ADL was developed by Lawton and Brody (1969), which is composed of two parts, basic activities of daily living (BADL) and instrumental activities of daily living (IADL). There are 14 items in the scale, and the score of each item ranges from 1 to 4 points. If 2 or more items are ≥ 3, or the total score is ≥ 22 points, it indicates that the ability of daily living is significantly reduced. The FAQ was compiled by Pfeffer et al. (1982), with a total of 10 items, such as correct use of various tickets, timely payment of various bills, and self-shopping. The score was 0–3 points, with a total score of 0–30 points. The higher the score, the worse the social function. The EQ-5D was used to describe the QoL and health outcome (Gottschalk et al., 2020). It includes five dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each dimension has three levels, and respondents can make choices on five dimensions and three levels in the questionnaire, and calculate EQ-5D index scores through the utility value conversion table. The EQ-5D is the most widely used QoL assessment scale worldwide.

Quality Control

Before the survey, professional physicians conducted standardized training for team members, including subject-related professional knowledge, scale evaluation and survey terminology. After the training, the study can be carried out only after passing the assessment. The cognitive function of the subjects was assessed by the same neurologist. All surveys were conducted face-to-face in the community meeting room to ensure that there was no interference in the survey process. The final completed questionnaire was confirmed by two people to ensure the integrity of the questionnaire. Data was performed by two persons to ensure the correctness of data entry.

Statistical Analyses

All survey data were recorded by two persons using Excel software and SPSS 24.0 was used for statistical analysis. The measurement data are expressed in the mean ± standard deviation ($\bar{x} \pm s$). The exploratory factor analysis was carried out using SPSS 22.0 statistical software. The confirmatory factor analysis and SEM were established using AMOS21.0 statistical software. $P < 0.05$ was statistically significant.

RESULTS

Baseline Characteristics

There were 252 older adults in the communities, 82 of whom had MCI (prevalence rate = 32.54%). In terms of age distribution, the age of the subjects ranged from 60 to 89 years old, with an average age of (70.76 ± 7.88) years old. In terms of gender distribution, the proportion of men and women is balanced. The majority of older adults had hypertension, other variables such as education level, occupation, marital status and BMI are shown in **Table 1**.

Cognitive Function, Frailty, and Health Outcome Scores

Based on the assessment of cognitive function, frailty, and health outcomes of the elderly in the communities, it was shown that there is a huge range of scores in the assessment of them. The overall cognitive function score was 80.57 ± 8.91; the memory function score was 36.15 ± 6.70 and the executive function score was 44.41 ± 4.42. The total frailty score was 0.37 ± 0.65; the healthy outcome score was 14.50 ± 1.03 for ADL, 2.08 ± 2.55 for the FAQ, and 0.21 ± 0.06 for the EQ-5D; **Table 2**).

Relationships Between Cognitive Function, Frailty, and Health Outcome

Table 3 documents the results of correlation analyses of cognitive function, frailty, and health outcome. The results of the Pearson's correlation analyses showed that MES-M was significantly correlated with MES-E, ADL, FAQ, self-reported exhaustion and grip strength ($P < 0.05$). MES-E was significantly correlated with ADL, FAQ, self-reported exhaustion ($P < 0.05$). ADL was significantly correlated with FAQ and grip strength ($P < 0.05$). FAQ was significantly correlated with self-reported exhaustion and grip strength ($P < 0.05$). Also, self-reported exhaustion was significantly correlated with grip strength ($P < 0.05$).

Explorative Factor Analyses

Item Discriminant Validity Analyses

The size of the correlation between the test variables is the premise of explorative factor analysis. The judgment indicators

TABLE 1 | Characteristics of participants (*n* = 252).

Characteristics	Frequency	Proportion(%)
Gender		
Male	128	50.79
Female	124	49.21
Educational level		
Primary and below	54	21.43
Junior high	95	37.70
Senior high and above	103	40.87
Occupation		
Mental labor	115	45.63
Physical labor	137	54.37
Marital status		
Married	208	82.54
Divorced/Widowed	44	17.46
Hypertension		
No	120	47.62
Yes	132	52.38
Diabetes		
No	209	82.94
Yes	43	17.06
Coronary heart disease		
No	232	92.06
Yes	20	7.94
Cerebral infarction		
No	245	97.22
Yes	7	2.78
Hyperlipidemia		
No	217	86.11
Yes	35	13.89
Family history of dementia		
No	233	92.46
Yes	19	7.54
BMI		
18.5	10	3.97
18.5∼23.9	108	42.86
24∼27.9	98	38.89
28	36	14.29

TABLE 2 | Scores of cognitive function, frailty, and health outcome (*n* = 252).

Item	Minimum	Maximum	$\bar{x} \pm s$	95%CI
MES-T	57	97	80.57 ± 8.91	79.46, 81.67
MES-M	12	48	36.15 ± 6.70	35.29, 37.02
MES-E	32	50	44.41 ± 4.42	43.86, 44.96
ADL	14	18	14.50 ± 1.03	14.37, 14.63
FAQ	0	8	2.08 ± 2.55	1.76, 2.39
EQ-5D	0.15	0.42	0.21 ± 0.06	0.20, 0.22
Frailty phenotype	0	2	0.37 ± 0.65	0.29, 0.45
Grip strength (kg)	9.60	47.60	29.08 ± 7.97	28.09, 30.07
4 m Walking time (s)	2.60	8.50	4.36 ± 0.79	4.26, 4.46

MES-E, MES Executive; MES-M, MES Memory; ADL, Activity of Daily Living Scale; FAQ, Functional Activities Questionnaire; EQ-5D, European Quality of 5-Dimensions.

mainly included the Kaiser-Meyer-Olkin (KMO) value and Bartlett's test of sphericity. The KMO values were between 0 and 1. The larger the value, the better the result of factor analysis. A KMO value < 0.5 was not suitable for factor analysis (Wu and Pan, 2014). In the current study, the KMO value was 0.631 > 0.500 and the Bartlett test of sphericity χ^2 was 295.105 ($P < 0.001$); the difference was statistically significant, indicating that there was a strong correlation between the variables, and suitable for factor analysis.

Factor Analyses

Principal component analysis (PCA) was used to calculate the correlation matrix, eigenvalues, and eigenvectors among the variables. The eigenvalues were arranged from large-to-small to calculate the corresponding principal components.

The matrix of initial components was rotated by the maximum variance orthogonal rotation method, and the final factor loading matrix was obtained. There were three common factors with eigenvalues > 1. The first common factor was the total MES score, which is used to evaluate cognitive function, so this factor is referred to as cognitive function. The second common factor was ADLs, social activities, and QoL were similar, which was referred to as health outcomes. The frailty phenotype score was third common factor, which was referred to as frailty. The three common factors finally accounted for 65.431% of the total variation (**Supplementary Tables 1, 2**).

Construction of Structural Equation Modeling, Model Modification and Fit Change

The model was a non-recursive model, which had 10 observation variables and 33 parameters to be estimated. According to the *t* rule [$33 < 10 \times (10 + 1)/2$], the model was identified. The maximum likelihood (ML) method was selected as the model estimation method.

The fitting degree test of the initial model indicated that the fitting result was not ideal, so it was necessary to modify the initial model using a parameter test and correction index to achieve good fitting. Amos provided two model correction indices, including a modified index (MI) and critical ratio (CR) (Fang et al., 2018). In the process of model fitting, professional knowledge is also required. According to the CR (*t*-value) provided by Amos, model parameters with no significant difference were deleted. The results showed that body weight had no effect on frailty ($P = 0.132 > 0.05$), so this item was deleted, which was consistent with domestic and international studies (Moreira and Lourenço, 2013; Hou et al., 2018). The final structural equation model was determined and the modified model is shown in **Figure 1**.

Through the modified fitting, the overall fitness of the model reached a good state, and each fitting index also showed that the model fitted well (**Table 4**).

Factor Path Analyses

Table 5 shows the path and path coefficients of the cognitive function effects on health outcomes and frailty. It can be seen from **Table 5** that the interaction between cognitive function and frailty was a direct effect, and the path coefficient was −0.521, indicating that the better the cognitive function, the less likely

TABLE 3 | Pearson's correlation coefficient of study variables (n = 252).

	1	2	3	4	5	6	7	8	9
MES-M	1								
MES-E	0.173**	1							
ADL	−0.179**	−0.155*	1						
FAQ	−0.301**	−0.231**	0.452**	1					
EQ-5D	−0.019	−0.058	0.088	0.079	1				
Physical activity	0.039	−0.062	−0.009	0.067	0.005	1			
Self-reported exhaustion	−0.129*	−0.137*	0.066	0.181**	0.072	0.079	1		
4 m walking time	−0.006	−0.115	0.076	−0.042	−0.034	0.052	−0.057	1	
Grip strength	0.222**	0.063	−0.177**	−0.277**	−0.069	−0.074	−0.292**	−0.044	1

**P < 0.05, **P < 0.01.*

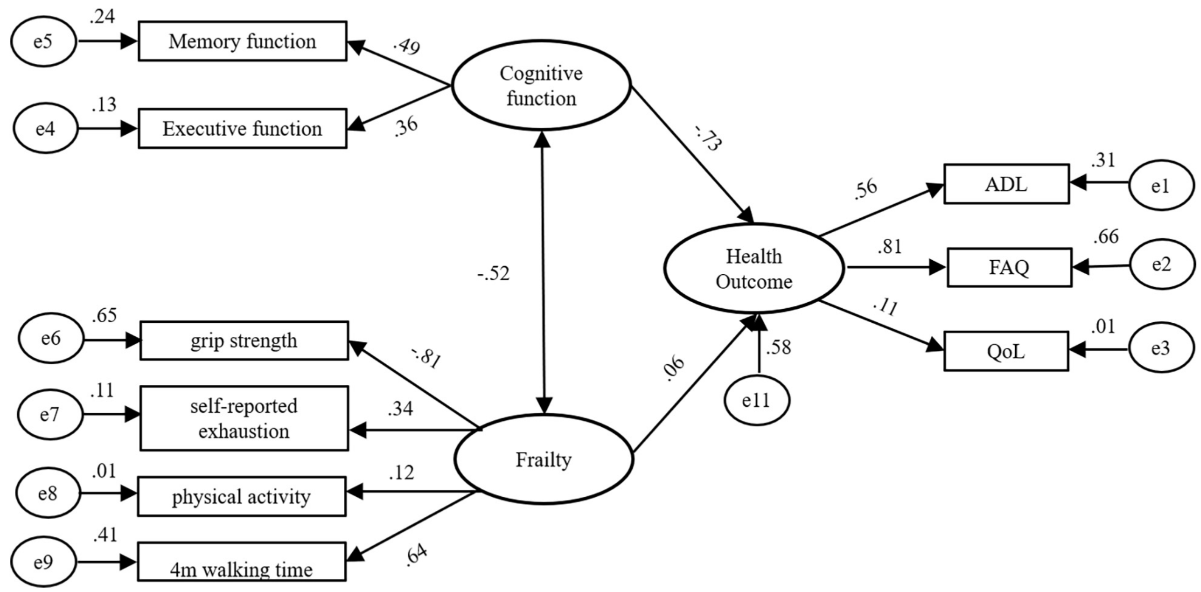

FIGURE 1 | A path diagram of direct and indirect influences of cognitive function, frailty and health outcome among community-dwelling elderly people.

frailty occurs. The influence of cognitive function on health outcomes included direct and indirect effects. There was one path of a direct effect with a path coefficient of −0.728, and there was one path coefficient with an indirect effect with a path coefficient of −0.031. The total effect of cognitive function on health outcomes was −0.759, indicating that the better cognitive function, the lower the health outcome score. The influence of frailty on health outcomes included direct and indirect effects. There was one path of a direct effect with a path coefficient of 0.060 and one path coefficient of an indirect effect with a path coefficient of 0.380. The total effect of decline on health outcome was 0.440, which indicated that the more severe the frailty, the worse the health outcomes (**Table 5**).

TABLE 4 | Model fit indices.

Index	Acceptable range	Value
χ^2-value		26.790
P-value	>0.050	0.314
RMSEA	<0.050	0.022
GFI	>0.900	0.978
AGFI	>0.900	0.958
CFI	>0.900	0.988
TLI	>0.900	.982

RMSEA, Root Mean Square Error of Approximation; GFI, Goodness of Fit Index; AGFI, Adjusted Goodness of Fit; CFI, Comparative Fit Index; TLI, Tucker-Lewis Index.

DISCUSSION

Studies have shown that the frail older adults have a higher risk of MCI (Borges et al., 2019), and the ADL and quality of life will decline (Audai et al., 2020). At the same time, the ADL, social activities, and QoL of the elderly with MCI will also be affected (Ginsberg et al., 2019), but the study on the interaction and connection between the three has not been demonstrated. Therefore, based on explorative analysis, SEM was applied to

TABLE 5 | Pattern effect results of cognitive function, frailty, and health outcome.

Influence path	Direct effect	Indirect effect	Total effect
Frailty↔ Cognitive function	−0.521		−0.521
Health outcome←Cognitive function	−0.728		−0.728
Health outcome←Frailty←Cognitive function		−0.031	−0.759
Health outcome←Frailty	0.060		0.060
Health outcome←Cognitive function←Frailty		0.380	0.440

construct a cognitive intervention model to provide support for later intervention. The results suggested that cognitive function, frailty and health outcomes are closely related. Specifically, cognitive function interacts with frailty and may reduce the quality of life, the ADL, and social activities among the elderly. Through modification, a well-fitted model was created, and the pathways and total effects of cognitive function on frailty and health outcomes are listed in the results.

Relationship Between Cognitive Function and Frailty

The results of path analysis showed that cognitive function and frailty interacted with each other, and the path coefficient was −0.521, which was consistent with international studies. De Cock et al. (2018) reported that frailty is associated with the decline in cognitive function, which is accompanied by accelerated aging. Grip strength and fatigue are the main causes of frailty in the elderly (Audai et al., 2020). Symeon et al. (2018) found that fatigue, as a sign of physical frailty, is related to cognitive function and can be used as a supplementary indicator of cognitive assessment. Grip strength is one of the manifestations of muscle loss, which can be used as a predictor of cognitive decline with age (Fritz et al., 2017).

Effects of Cognitive Function on Health Outcomes

In this study, the effect of cognitive function on health outcomes was −0.759, which was a significant effect. Altieri et al. (2021) found that compared with healthy older adults, the elderly with MCI had more difficulties with ADL, especially instruments of activities of daily living (IADL). Social activities require the participation of multiple cognitive domains, therefore, social activities of the elderly with MCI are also significantly reduced (Becker et al., 2021). Hussenoeder et al. (2020) found that QoL is closely related to cognitive function, and QoL of with MCI older adults is lower than healthy elderly. Cognitive impairment is the direct cause of the decline in the quality of life of the elderly (Marshall et al., 2011). Cognitive impairment, particularly those related to memory and executive function, can prevent patients from performing some activities of daily living. The main driving factors of the quality of life are: full of energy, pain free, ability to carry out activities of daily living and to move around (Salkeld et al., 2000; Molzahn et al., 2010). For MCI older adults, complex ADL is the most affected in the activities of daily living, while basic activities of daily living are often maintained to the AD stage. One of the main drivers of quality of life in older adults is the ability to carry out activities of daily living. Therefore, cognitive impairment can also affect the quality of life of the elderly.

In addition, the current study showed that cognitive function not only directly affected health outcomes, but also indirectly affected health outcomes through frailty. The quality of life (Dong, 2017) and ADL (Kojima, 2018) of the frail elderly will decline. With the increase of age, physical frailty (poor ability to perform daily living activities), psychological frailty (loneliness) and social frailty (social relationships) may occur to varying degrees due to the influence of personal factors and disease factors, which will eventually lead to the decline of quality of life (Gobbens et al., 2010). Fatigue is generally considered to be a key factor of frailty, and muscle fatigue (assessed by continuous grip strength) is associated with quality of life (Rizzoli et al., 2013). As a manifestation of muscle loss, grip strength is associated with cognitive function, which further affects quality of life.

Effects of Frailty on Health Outcomes

In the current study, the direct effect of frailty on health outcomes was 0.060, which was significantly less than the indirect effect, possibly because the decline in quality of life and ADL is not the main manifestation of frailty (Xi and Guo, 2014). Moreover, this study was conducted in the community. The quality of life and daily living ability of the elderly in the community are acceptable. Therefore, the direct effect of frailty on the health outcomes of the elderly in the community is not so significant. In the future, the impact of frailty on the health outcomes of the elderly in the communities and nursing institutions can be considered. In addition, there are many ways for health outcomes, including psychological status and sleep status. Frail older adults are more prone to depression (Soysal et al., 2017). Insomnia is far more common in frail older adults than in non-frail older adults (Lee et al., 2018), and sleep disorders are more likely to occur. In addition, the frail older adults are more likely to suffer from diseases, pain and taking a variety of drugs which will also reduce their sleep quality (Du, 2017). All of the above reasons may lead to the direct effect of frailty on health outcomes to be smaller than the indirect effect.

There are many other health outcomes for the elderly. In this study, health outcome as an endogenous potential variable has a measurement error of 0.58, indicating that the part of health outcomes that could not be explained by cognitive function and frailty was an error in the SEM. This suggests that we can expand the health outcomes of the elderly in the future, such as psychological status and sleep quality, so as to further improve the SEM. In this study, it was found that cognitive function can affect health outcomes in the elderly, and it can also affect health outcomes in the elderly by influencing frailty. Similarly, frailty can affect health outcomes in older adults, as well as by affecting cognitive function. Frailty and cognitive impairment are common geriatric syndromes, so future assessments of older adults should consider both cognitive function and frailty, so as to further improve the health outcome of the elderly. At the same time, we can explore the intervention methods suitable for cognitive impairment and weakness, so as to improve the quality of life of the elderly. At the same time, we can explore appropriate interventions for cognitive impairment and frailty to improve the health outcomes of the elderly.

CONCLUSION

In this study, SEM was used to explore the relationship among cognitive function, frailty and health outcomes among the elderly in the community. This model has a good fitting degree. When formulating relevant intervention measures in the future, we need to consider that it cannot only improve the cognitive function of the elderly, but also improve the frail situation, so as to jointly improve the health outcome of the elderly. In addition, there are other manifestations of health outcomes in the elderly, and we need to consider the impact of this aspect in future studies to improve the SEM. Moreover, although the model has a good degree of fitting, due to the limitation of sample size, the impact of the increase of data on the model needs to be verified in the later stage. And it would be great to test the model by a subset of data from new samples. Since this study was only carried out in Yangzhou community and did not include the elderly in hospital or in nursing institutions, the sample lacks certain representativeness, which can be further improved in the future.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Northern Jiangsu People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HX drafted the manuscript and performed statistical analyses. CH, YJ, XD, and DZ collected the data. QZ and SZ controlled the quality of data. DG and HX conceived and designed this research. All authors edited and approved the final manuscript.

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REFERENCES

Altieri, M., Garramone, F., and Santangelo, G. (2021). Functional autonomy in dementia of the Alzheimer's type, mild cognitive impairment, and healthy aging: a meta-analysis. *Neurol. Sci.* 42, 1773–1783. doi: 10.1007/s10072-021-05142-0

American Psychological Association (2010). *Publication Manual of the American Psychological Association*. Washington, DC: American Psychological Association.

Armstrong, J. J., Godin, J., Launer, L. J., White, L. R., Mitnitski, A., Rockwood, K., et al. (2016). Changes in frailty predict changes in cognition in older men: the honolulu-asia aging study. *J. Alzheimers Dis.* 53, 1003–1013. doi: 10.3233/JAD-151172

Audai, A., Hayajneh, H. H., Eman, S., Al-Satari, D. C. W., and Rababa, M. (2020). The relationship between frailty and depression, quality of life, disability, and hospitalization among community-dwelling older adults. *BMC Geriatr.* Available online at: https://orcid.org/0000-0002-8141-3530 (accessed November 20, 2020).

Becker, S., Boettinger, O., Sulzer, P., Hobert, M. A., Brockmann, K., Maetzler, W., et al. (2021). Everyday function in alzheimer's and Parkinson's patients with mild cognitive impairment. *J. Alzheimers Dis.* 79, 197–209. doi: 10.3233/JAD-200256

Borges, M. K., Canevelli, M., Cesari, M., and Aprahamian, I. (2019). Frailty as a predictor of cognitive disorders: a systematic review and meta-analysis. *Front. Med. (Lausanne)* 6:26. doi: 10.3389/fmed.2019.00026

Brigola, A. G., Rossetti, E. S., Dos Santos, B. R., Neri, A. L., Zazzetta, M. S., Inouye, K., et al. (2015). Relationship between cognition and frailty in elderly: a systematic review. *Dement Neuropsychol.* 9, 110–119. doi: 10.1590/1980-57642015DN92000005

Calderón-Larrañaga, A., Vetrano, D. L., Ferrucci, L., Mercer, S. W., Marengoni, A., Onder, G., et al. (2019). Multimorbidity and functional impairment-bidirectional interplay, synergistic effects and common pathways. *J. Intern. Med.* 285, 255–271. doi: 10.1111/joim.12843

De Cock, A. M., Perkisas, S., Verhoeven, V., Vandewoude, M., Fransen, E., and Remmen, R. (2018). The impact of cognitive impairment on the physical ageing process. *Aging Clin. Exp. Res.* 30, 1297–1306. doi: 10.1007/s40520-018-1016-8

Dent, E., Lien, C., Lim, W. S., Wong, W. C., Wong, C. H., Ng, T. P., et al. (2017). The asia-pacific clinical practice guidelines for the management of frailty. *J. Am. Med. Dir. Assoc.* 18, 564–575. doi: 10.1016/j.jamda.2017.04.018

Dong, L. J. (2017). *The Relationship Between Frailty and Health-Related Quality of Life Among Community-Dwelling Older People.Ph. D, Thesis*. Shandong (IL): Shandong University.

Du, H. F. Q. (2017). Analysis of sleep health management in old-age service centers and common sleep disorders of elderly population. *World J. Clin. Cases* 4, 84–89. doi: 10.3969/j.issn.2095-7130.2017.02.005

Fabrício, D. M., Chagas, M., and Diniz, B. S. (2020). Frailty and cognitive decline. *Transl. Res.* 221, 58–64. doi: 10.1016/j.trsl.2020.01.002

Fang, Q. W., Liu, Z. Q., Yuan, H. B., Cai, N., He, N., and Zhang, T. J. (2018). Construction of structural equation model and implementation of amos software. *Chin. J. Health Stat.* 35, 958–960.

Feng, L., Nyunt, M. S., Gao, Q., Feng, L., Lee, T. S., Tsoi, T., et al. (2017). Physical frailty, cognitive impairment, and the risk of neurocognitive disorder in the singapore longitudinal ageing studies. *J. Gerontol. A Biol. Sci. Med. Sci.* 72, 369–375. doi: 10.1093/gerona/glw050

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., et al. (2001). Frailty in older adults: evidence for a phenotype. *J. Gerontol. A Biol. Sci. Med. Sci.* 56, M146–M156. doi: 10.1093/gerona/56.3.m146

Fritz, N. E., McCarthy, C. J., and Adamo, D. E. (2017). Handgrip strength as a means of monitoring progression of cognitive decline -

a scoping review. *Ageing Res. Rev.* 35, 112–123. doi: 10.1016/j.arr.2017.01.004

Geriatrics Branch of the Chinese Medical Association (2017). Chinese experts consensus on evaluation and intervention for elderly patients with frailty. *Chin. J. Geriatr.* 36, 251–256. doi: 10.3760/cma.j.issn.0254-9026.2017.03.007

Ginsberg, T. B., Powell, L., Emrani, S., Wasserman, V., Higgins, S., Chopra, A., et al. (2019). Instrumental activities of daily living, neuropsychiatric symptoms, and neuropsychological impairment in mild cognitive impairment. *J. Am. Osteopath Assoc.* 119, 96–101. doi: 10.7556/jaoa.2019.015

Gobbens, R. J., Luijkx, K. G., Wijnen-Sponselee, M. T., and Schols, J. M. (2010). Toward a conceptual definition of frail community dwelling older people. *Nurs. Outlook* 58, 76–86. doi: 10.1016/j.outlook.2009.09.005

Gottschalk, S., König, H. H., Nejad, M., and Dams, J. (2020). Psychometric properties of the EQ-5D for the assessment of health-related quality of life in the population of middle-old and oldest-old persons: study protocol for a systematic review. *Front. Public Health* 8:578073. doi: 10.3389/fpubh.2020.578073

Grande, G., Haaksma, M. L., Rizzuto, D., Melis, R., Marengoni, A., Onder, G., et al. (2019). Co-occurrence of cognitive impairment and physical frailty, and incidence of dementia: systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* 107, 96–103. doi: 10.1016/j.neubiorev.2019.09.001

Guo, Q. H., Zhou, B., Zhao, Q. H., Wang, B., and Hong, Z. (2012). Memory and executive screening (MES): a brief cognitive test for detecting mild cognitive impairment. *BMC Neurol.* 12:119. doi: 10.1186/1471-2377-12-119

Hou, X. L., Wu, C. X., Bo, D. X., Xiang, Y. P., and Li, X. (2018). Prevalence and factors associated with frailty among institutional older adults. *Chin. J. Nurs.* 53, 88–93. doi: 10.3761/j.issn.0254-1769.2018.01.016

Hussenoeder, F. S., Conrad, I., Roehr, S., Fuchs, A., Pentzek, M., Bickel, H., et al. (2020). Mild cognitive impairment and quality of life in the oldest old: a closer look. *Qual. Life Res.* 29, 1675–1683. doi: 10.1007/s11136-020-02425-5

Kiiti Borges, M., Oiring de Castro Cezar, N., Silva Santos Siqueira, A., Yassuda, M., Cesari, M., and Aprahamian, I. (2019). The relationship between physical frailty and mild cognitive impairment in the elderly: a systematic review. *J. Frailty Aging* 8, 192–197. doi: 10.14283/jfa.2019.29

Kline, R. B. (2005). *Principles and Practice of structural equation modeling*, 2nd Edn. New York: Guilford Press.

Kojima, G. (2018). Quick and simple frail scale predicts incident activities of daily living (ADL) and instrumental ADL (IADL) disabilities: a systematic review and meta-analysis. *J. Am. Med. Dir. Assoc.* 19, 1063–1068. doi: 10.1016/j.jamda.2018.07.019

Kulmala, J., Nykänen, I., Mänty, M., and Hartikainen, S. (2014). Association between frailty and dementia: a population-based study. *Gerontology* 60, 16–21. doi: 10.1159/000353859

Lawton, M. P., and Brody, E. M. (1969). Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 9, 179–186.

Lee, D. R., Santo, E. C., Lo, J. C., Ritterman Weintraub, M. L., Patton, M., and Gordon, N. P. (2018). Understanding functional and social risk characteristics of frail older adults: a cross-sectional survey study. *BMC Fam. Pract.* 19:170. doi: 10.1186/s12875-018-0851-1

Liou, Y. M., Jwo, C. J., Yao, K. G., Chiang, L. C., and Huang, L. H. (2008). Selection of appropriate chinese terms to represent intensity and types of physical activity terms for use in the taiwan version of IPAQ. *J. Nurs. Res.* 16, 252–263. doi: 10.1097/01.jnr.0000387313.20386.0a

Marshall, G. A., Rentz, D. M., Frey, M. T., Locascio, J. J., Johnson, K. A., Sperling, R. A., et al. (2011). Executive function and instrumental activities of daily living in mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement* 7, 300–308. doi: 10.1016/j.jalz.2010.04.005

Molzahn, A., Skevington, S. M., Kalfoss, M., and Makaroff, K. S. (2010). The importance of facets of quality of life to older adults: an international investigation. *Qual. Life Res.* 19, 293–298. doi: 10.1007/s11136-009-9579-7

Moreira, V. G., and Lourenço, R. A. (2013). Prevalence and factors associated with frailty in an older population from the city of Rio de Janeiro, Brazil: the FIBRA-RJ study. *Clinics (Sao Paulo)* 68, 979–985. doi: 10.6061/clinics/2013(07)15

National Bureau of Statistics of China (2019). *The Main Target Set for Maintaining Economic Development Within An Appropriate Range in 2018 Was Well Met*. Available online at: http://www.stats.gov.cn/english/PressRelease/201901/t20190121_1645832.html (accessed January 21, 2019)

Panza, F., Lozupone, M., Solfrizzi, V., Sardone, R., Dibello, V., Di Lena, L., et al. (2018). Different cognitive frailty models and health- and cognitive-related outcomes in older age: from epidemiology to prevention. *J. Alzheimers Dis.* 62, 993–1012. doi: 10.3233/JAD-170963

Pfeffer, R. I., Kurosaki, T. T., Harrah, C. H. Jr., Chance, J. M., and Filos, S. (1982). Measurement of functional activities in older adults in the community. *J. Gerontol.* 37, 323–329. doi: 10.1093/geronj/37.3.323

Rizzoli, R., Reginster, J. Y., Arnal, J. F., Bautmans, I., Beaudart, C., Bischoff-Ferrari, H., et al. (2013). Quality of life in sarcopenia and frailty. *Calcif. Tissue Int.* 93, 101–120. doi: 10.1007/s00223-013-9758-y

Salkeld, G., Cameron, I. D., Cumming, R. G., Easter, S., Seymour, J., Kurrle, S. E., et al. (2000). Quality of life related to fear of falling and hip fracture in older women: a time trade off study. *BMJ* 320, 341–346. doi: 10.1136/bmj.320.7231.341

Sargent, L., Nalls, M., Amella, E. J., Slattum, P. W., Mueller, M., Bandinelli, S., et al. (2020). Shared mechanisms for cognitive impairment and physical frailty: a model for complex systems. *Alzheimers Dement* 6:e12027. doi: 10.1002/trc2.12027

Song, X., Mitnitski, A., and Rockwood, K. (2014). Age-related deficit accumulation and the risk of late-life dementia. *Alzheimer's Res. Ther.* 6:54. doi: 10.1186/s13195-014-0054-5

Soysal, P., Veronese, N., Thompson, T., Kahl, K. G., Fernandes, B. S., Prina, A. M., et al. (2017). Relationship between depression and frailty in older adults: a systematic review and meta-analysis. *Ageing Res. Rev.* 36, 78–87. doi: 10.1016/j.arr.2017.03.005

Symeon, H., Panagiotakis, P. S., Ioannis Zaganas, M. B., Garyfalia, S., Perysinaki, N. F., Maria Giaka, S. K., et al. (2018). Self-reported fatigue as a risk index for dementia diagnosis. *Eur. Geriatr. Med.* 9, 211–217. doi: 10.1007/s41999-017-0020-4

Tsutsumimoto, K., Doi, T., Nakakubo, S., Kim, M., Kurita, S., Ishii, H., et al. (2019). Impact of social frailty on Alzheimer's disease onset: a 53-month longitudinal cohort study. *J. Alzheimers Dis.* 70, 587–595. doi: 10.3233/JAD-181178

Vermeiren, S., Vella-Azzopardi, R., Beckwée, D., Habbig, A. K., Scafoglieri, A., Jansen, B., et al. (2016). Frailty and the prediction of negative health outcomes: a meta-analysis. *J. Am. Med. Dir. Assoc.* 17, 1163.e1–1163.e17. doi: 10.1016/j.jamda.2016.09.010

Wu, M. L. (2010). *Structural Equation Model-Operation and Application of AMOS*, 2nd Edn. Chongqing: Chongqing University Press.

Wu, S., and Pan, F. M. (2014). *SPSS Statistical Analysis*. Beijing: Tsinghua University Press.

Xi, X., and Guo, G. F. (2014). The current status and influencing factors of frailty among elders in community. *Chin. Nursing Manage.* 14, 1315–1319. doi: 10.3969/j.issn.1672-1756.2014.12.024

Zhang, X., Dou, Q., Zhang, W., Wang, C., Xie, X., Yang, Y., et al. (2019). Frailty as a predictor of all-cause mortality among older nursing home residents: a systematic review and meta-analysis. *J. Am. Med. Dir. Assoc.* 20, 657–663.e4. doi: 10.1016/j.jamda.2018.11.018

Zheng, Z., Guan, S., Ding, H., Wang, Z., Zhang, J., Zhao, J., et al. (2016). Prevalence and incidence of frailty in community-dwelling older people: beijing longitudinal study of aging II. *J. Am. Geriatr. Soc.* 64, 1281–1286. doi: 10.1111/jgs.14135

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SYSTEMATIC REVIEW
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A Scoping Review of Audiovisual Integration Methodology: Screening for Auditory and Visual Impairment in Younger and Older Adults

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With the rise of the aging population, many scientists studying multisensory integration have turned toward understanding how this process may change with age. This scoping review was conducted to understand and describe the scope and rigor with which researchers studying audiovisual sensory integration screen for hearing and vision impairment. A structured search in three licensed databases (Scopus, PubMed, and PsychInfo) using the key concepts of multisensory integration, audiovisual modality, and aging revealed 2,462 articles, which were screened for inclusion by two reviewers. Articles were included if they (1) tested healthy older adults (minimum mean or median age of 60) with younger adults as a comparison (mean or median age between 18 and 35), (2) measured auditory and visual integration, (3) were written in English, and (4) reported behavioral outcomes. Articles that included the following were excluded: (1) tested taste exclusively, (2) tested olfaction exclusively, (3) tested somatosensation exclusively, (4) tested emotion perception, (5) were not written in English, (6) were clinical commentaries, editorials, interviews, letters, newspaper articles, abstracts only, or non-peer reviewed literature (e.g., theses), and (7) focused on neuroimaging without a behavioral component. Data pertaining to the details of the study (e.g., country of publication, year of publication, etc.) were extracted, however, of higher importance to our research question, data pertaining to screening measures used for hearing and vision impairment (e.g., type of test used, whether hearing- and visual-aids were worn, thresholds used, etc.) were extracted, collated, and summarized. Our search revealed that only 64% of studies screened for age-abnormal hearing impairment, 51% screened for age-abnormal vision impairment, and that consistent definitions of normal or abnormal vision and hearing were not used among the studies that screened for sensory abilities. A total of 1,624 younger adults and 4,778 older participants were included in the scoping review with males composing approximately 44% and females composing 56% of the total sample and most of the data was obtained from only four countries. We recommend that studies investigating the effects of aging on multisensory integration should screen for normal vision and hearing by using the World Health Organization's (WHO) hearing loss and visual impairment cut-off scores in order to maintain consistency among other aging researchers. As mild cognitive impairment (MCI) has been defined as a "transitional" or a "transitory" stage between normal aging and dementia and because approximately 3–5% of the aging

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population will develop MCI each year, it is therefore important that when researchers aim to study a healthy aging population, that they appropriately screen for MCI. One of our secondary aims was to determine how often researchers were screening for cognitive impairment and the types of tests that were used to do so. Our results revealed that only 55 out of 72 studies tested for neurological and cognitive function, and only a subset used standardized tests. Additionally, among the studies that used standardized tests, the cut-off scores used were not always adequate for screening out mild cognitive impairment. An additional secondary aim of this scoping review was to determine the feasibility of whether a meta-analysis could be conducted in the future to further quantitatively evaluate the results (i.e., are the findings obtained from studies using self-reported vision and hearing impairment screening methods significantly different from those measuring vision and hearing impairment in the lab) and to assess the scope of this problem. We found that it may not be feasible to conduct a meta-analysis with the entire dataset of this scoping review. However, a meta-analysis can be conducted if stricter parameters are used (e.g., focusing on accuracy or response time data only).

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Keywords: aging, multisensory, integration, sensory perception, auditory acuity, visual acuity, audition, vision

INTRODUCTION

The proportion of the world's population over 60 years of age is estimated to increase to approximately 2 billion individuals by 2050, nearly doubling from 12% of the world population to 22% (World Health Organization, 2018a). With such a drastic shift in global demographics, the incidence of age-related chronic health conditions is also expected to increase. Indeed, the prevalence of audition and vision degradation increases with age and can have global impacts on cognition (Salthouse et al., 1996; Baltes and Lindenberger, 1997; Porto et al., 2016) and temporal perception (Gordon-Salant and Fitzgibbons, 1999; Grose and Mamo, 2010; de Boer-Schellekens and Vroomen, 2014; Brooks et al., 2018). Combining information across the senses can improve localization, discrimination, and speed of responses to objects, however, the central nervous system (CNS) must bind together the appropriate signals (Calvert et al., 2004). One cue that the CNS can use to determine whether or not stimuli should be bound together into a single percept (multisensory integration) is the temporal relation, how close in time two or more signals are to one another; research has revealed, using not only non-human animal models but also through studies conducted with humans, that signals that appear closer in time are more likely to be integrated [Vroomen and Keetels, 2010; see also King (2005) for a review of strategies used by the CNS to bind appropriate cues]. As temporal perception is affected by changes in unisensory processing, changes in auditory and visual acuities can act as indicators that may provide insight into changes associated with the multisensory integration processes within the aging population. Within the auditory domain, an estimated 466 million people worldwide have disabling hearing loss (World Health Organization, 2021a) and it is estimated that between 25 and 40% of older adults aged 65 and over, can be classified as having hearing impairment (Yueh et al., 2003). It has been found that the prevalence of hearing loss rises with age, ranging from 40 to 66% in adults over the age of 75 years and more than 80% in those older than 85 years of age (Cooper and Gates, 1991; Yueh et al., 2003; Walling and Dickson, 2012). Further it has been found that after the age of 60, hearing typically declines by about 1 dB annually and that men usually experience greater hearing loss and earlier onset compared to women (Lee et al., 2005). More than 90% of older individuals with hearing loss have age-related sensorineural hearing loss, which is a gradual symmetric loss of hearing—predominately of higher frequencies—that is worse in noisy environments (Yueh et al., 2003). Note however, that in an epidemiology study conducted by Lin et al. (2011) where data related to hearing abilities of older adults aged 70 and over was used from the 2005–2006 cycle of the National Health and Nutritional Examination Survey, it was found that the prevalence of hearing loss varied depending on the tonal frequencies, the audiometric thresholds used to define hearing loss, and whether hearing loss was considered in the better or worse hearing ear. They reported hearing loss prevalence rates from 16.5% when hearing loss was defined as using 0.5, 1, and 2 kHz (standard pure tone averages; PTA) with a 40 dB threshold in the better ear to 99.7% when hearing loss was defined as using 3, 4, 6, and 8 kHz (high-frequency PTAs) with a 15 dB threshold in the worse ear. Although they found that most reports of hearing loss prevalence used a 25 dB threshold, standard PTA (0.5, 1, and 2 kHz) or speech frequency PTA (0.5, 1, 2, and 4 kHz), and obtained measures in either the worse or better ear, there was still a high degree of variability of hearing loss reported. The range was narrower but spanned 44.8% when using the standard PTA in the better ear to 75.1% when using speech frequency PTA in the worse ear. Thus, the definition used when measuring hearing loss is crucial especially when some researchers may be utilizing a more rigid inclusion criteria as compared to others.

Shifting our focus toward the visual domain, worldwide, approximately 185 million people over the age of 50 years are visually impaired (World Health Organization, 2017), with cataracts, age-related macular disease, and refractive errors being the most common causes of visual impairment in older adults (Buch et al., 2001; World Health Organization, 2017). Although cost effective interventions such as cataract surgery and corrective glasses have shown to be effective, only 22 and 37% of individuals living in upper-middle and high-income countries respectively have reported having an eye exam during the preceding year (World Health Organization, 2017). The World Health Organization (WHO) defines visual impairment based on the International Classification of Diseases 11 (2018b) classification in the following categories for acuities measured at a distance of 2–4 m: mild visual impairment is defined as acuity worse than 6/12–6/18, moderate visual impairment is defined as acuity worse than 6/18–6/60, and severe visual impairment is defined as visual acuity that is worse than 6/60–3/60 in both eyes. In other words, the WHO defines visual impairment as best corrected visual acuity of $<$20/40 but $\geq$20/400, while many researchers (especially in the US) commonly define visual impairment as best corrected visual acuity that is worse than 20/40 but better than 20/200 in the better eye (Buch et al., 2001; World Health Organization, 2018; also see **Supplementary Table 1** for details regarding the WHO's definition of visual impairment. This table contains Snellen and LogMAR values). In a study conducted by Buch et al. (2001) comparing the prevalence of visual impairment in 944 individuals as defined by the WHO and the criteria most commonly used in the US, it was found that 2.6% of those aged 70–74 years and 4.8% of those aged 75–80 years had visual impairments according to the WHO's definition (worse than 20/60–20/400 in the better eye; World Health Organization, 2004). However, these values differed based on the criteria used in most US studies where 3.1% of those aged 70–74 years and 8.0% of those between 75 and 80 years of age had visual impairment. Here, once again, we are reminded that the definition of impairment used by researchers is crucial and that some researchers may be excluding more participants than others.

Given the changes in sensory acuities associated with aging, accounting for such changes in hearing and vision is crucial as it may increase the quality and validity of the data obtained. The integration of auditory and visual cues into a unified percept is a fundamental process with an evolutionary benefit as it allows the observer to respond to external events more quickly and accurately relative to unisensory information alone (Stein and Stanford, 2008). Such an ability to integrate auditory and visual cues into a coherent percept has been thought to be beneficial for everyday function, for example in improving perception of speech in noise (Sumby and Pollack, 1954) and in improving driving performance (Ramkhalawansingh et al., 2016), both of which are especially relevant for the aging population. Research has time and again revealed that there are three principles that underlie multisensory processing, the first two principles suggest that the more temporally and spatially coincident (Meredith et al., 1987; Stein et al., 2014; Baum and Stevenson, 2017) two sensory cues are, the more likely they are to be bound together and result in a unified percept. The third principle states that unisensory signals that are weakly effective on their own are more likely to benefit from integration (Stein et al., 2009, 2014; Baum and Stevenson, 2017). This third principle of inverse effectiveness however does not hold true when the unisensory component that would be bound into a multisensory percept becomes unreliable and can result in a reduction in multisensory benefits as observed through models of optimal integration (Ross et al., 2007; Ma et al., 2009; Baum and Stevenson, 2017). Indeed, effective multisensory integration is dependent on both peripheral sensory organs as well as higher cognitive processes. As significant changes in sensory systems (e.g., decrease in visual acuity and an increase in auditory acuity thresholds) and cognitive function (e.g., decline in executive function and memory) are associated with healthy aging, it is not surprising that multisensory integration also changes with age (Rapp and Heindel, 1994; Kalina, 1997; Liu and Yan, 2007; Mozolic et al., 2012; Baum and Stevenson, 2017; Fjell et al., 2017). Indeed, older adults have been found to have longer response times in audiovisual detection tasks (†Laurienti et al., 2006; †Mahoney et al., 2011; †Couth et al., 2018; †Basharat et al., 2019), exhibit wider temporal binding windows (TBWs; the window of time within which information from different modalities is integrated and perceived as simultaneous; †Setti et al., 2011b; †Bedard and Barnett-Cowan, 2016; †Basharat et al., 2019), are more likely to be distracted by irrelevant stimuli within and across modalities [Poliakoff et al., 2006; see de Dieuleveult et al. (2017) for a detailed review regarding the effects of aging on multisensory integration], but they are also more likely to exhibit greater multisensory enhancement [see Mozolic et al. (2012) and de Dieuleveult et al. (2017) for detailed reviews] compared to younger adults. Further, it has been found that such changes in multisensory integration are exacerbated in those living with mild cognitive impairment and dementia. Research has revealed that those living with MCI and dementia tend to have longer response times, exhibit wider temporal binding windows, are more likely to experience attention impairment, and are less likely to benefit from multisensory enhancement compared to healthy controls (Wu et al., 2012; Chan et al., 2015; Murray et al., 2018). These results suggest that both cognitive function and sensory abilities must be accounted for when conducting multisensory integration related research with the aging population.

A decline in sensory abilities can affect the reliability, or the precision of a sensory estimate, with which the central nervous system integrates cues from auditory and visual modalities and can thus reduce the benefits typically gained through the multisensory process (Ernst and Bülthoff, 2004; Odegaard and Shams, 2016). Note however, that reduced acuity may also help to explain the increased benefits of multisensory integration in the aging population through the lens of the principle of inverse effectiveness (Mozolic et al., 2012). With a decline in auditory and visual acuity, the unisensory cues from these modalities would be presented just above threshold levels, thus the principal of inverse effectiveness would predict that integration of these weakly effective cues would produce gains much larger than the sum of their parts, suggesting that individuals with reduced sensitivity or acuity (i.e., older adults) may experience enhanced sensory integration. Thus, accounting for age-related sensory loss is essential in multisensory literature as it impacts the reliability of the incoming information and thus the likelihood of integration. It should however be noted that in a recent review conducted by de Dieuleveult et al. (2017) where the performance of older adults was compared to younger adults on unisensory and multisensory stimuli, it was found that although older adults did not always exhibit slower response times on the unisensory stimuli, they continued to show multisensory facilitation, indicating that inverse effectiveness may be one of many processes involved in the enhancement observed for multisensory cues in older populations (†Peiffer et al., 2007; Guerreiro et al., 2014, 2015).

Regardless of the underlying mechanisms, some research shows that changes in audition and vision impact temporal perception, not just within each modality, but also between these sensory modalities. Within the auditory domain, older age impairs temporal order judgments (Gordon-Salant and Fitzgibbons, 1999), duration discrimination (Fitzgibbons and Gordon-Salant, 1994, 1995; Gordon-Salant and Fitzgibbons, 1999), and reduces sensitivity to temporal fine structure (Grose and Mamo, 2010). Within the visual modality, age also impairs visual temporal judgments (de Boer-Schellekens and Vroomen, 2014), reduces flicker sensitivity (Mayer et al., 1988; Kim and Mayer, 1994), and reduces critical flicker frequency (Lachenmayr et al., 1994). When assessing age-related changes to audiovisual temporal perception, researchers find that older adults are more susceptible to the sound-induced flash illusion (†Setti et al., 2011a; McGovern et al., 2014), are more susceptible to the temporal ventriloquist effect (de Boer-Schellekens and Vroomen, 2014), and have wider temporal binding windows (†Bedard and Barnett-Cowan, 2016; †Basharat et al., 2018, 2019). Further, as aging increases the prevalence of ocular disease and hearing loss, this can lead to impairment in temporal perception (Phipps et al., 2004; Gin et al., 2011; Gallun et al., 2014). Although many, but not all, audiovisual multisensory paradigms include auditory- and visual-only conditions to gain insight into the workings of auditory and visual systems, we believe that accounting and screening for age-abnormal changes in the auditory and visual modalities will allow researchers to draw more reliable conclusions related to how audiovisual integration (the binding of auditory and visual cues into a unified percept) changes with age without being confounded by uncorrected vison and hearing. Our preliminary search revealed that researchers are not employing as much scientific rigor as would be necessary to account for auditory and visual acuity changes within the multisensory integration literature. While some researchers rely on self-reported measures obtained from participants, and others measure acuities in the lab or research centers to determine eligibility, some researchers however do not collect or account for visual and/or auditory acuities whatsoever. Further, a standardized criterion for what constitutes "normal" vision and hearing does not seem to be used and does not exist within the multisensory integration literature (Brooks et al., 2018).

Here, we aimed to determine the scope of the problem and collected information regarding what practices researchers are following in the literature to screen for vision and hearing impairment. We collected descriptive statistics regarding the number of researchers who screened for auditory and visual acuities (and how they reported it), those who used self-reported measures, and finally those who did not utilize any form of acuity measurements. We also aimed to determine what cut-off scores are being used when researchers do measure the acuities within a research or laboratory setting and what types of questions are asked to obtain self-reported perceptions of auditory and visual acuities. In addition to visual and auditory acuity measures, we also assessed how researchers define healthy aging (e.g., if cognitive impairment is accounted for and if so, how it is being measured). This scoping study will help provide a map of the methods researchers are utilizing and will help determine whether or not a meta-analysis can be conducted to further understand the scope of the issue with the current dataset.

METHODS

The methods of the current study have been registered with the Open Science Framework (Basharat and Barnett-Cowan, 2020). The scoping review was conducted according to the framework proposed by Arksey and O'Malley (2005) and the suggestions that have been developed by Levac et al. (2010).

Identifying the Research Question

We posed our research questions as follows: what is known from existing literature about the types of auditory and visual impairment screening methods that are employed in the literature on multisensory integration perception in healthy aging to screen for inclusion. Based on the results obtained in this scoping study, a recommendation of whether or not a meta-analysis can be conducted to determine if significant differences exist in the findings and or conclusions drawn in studies that used self-reported vision and hearing impairment screening methods compared to studies that measured vision and hearing impairment in the laboratory will be made. We further aimed to determine the methods used to assess and classify cognitive impairment in this literature.

Identifying Relevant Studies

Following the Arskey and O'Malley framework (2010), this stage aimed to identify the criteria that was used to select studies for inclusion in the scoping study. Although scoping studies are designed to be broad, we chose specific criteria that would help guide the search. Relevant articles were identified in MEDLINE Pubmed (earliest records available—June 30th, 2020), MEDLINE Scopus (earliest records available—June 30th, 2020), and PsychInfo (earliest records available—June 30th, 2020). We chose these databases to ensure a comprehensive coverage of health, engineering, social sciences, and psychology journals. We believe that Pubmed comprehensively covers health related articles, Scopus acts as a complimentary multidisciplinary database that covers articles from engineering, social sciences, and health, and finally PsychInfo provides coverage of articles specifically from the psychology domain.

The key concepts used in the searches were as follows: multisensory integration, audiovisual modality, and aging (with younger adults as a comparator). The key concepts were combined using the Boolean operator AND, and the search words within each concept were combined with OR (Basharat and Barnett-Cowan, 2020). As suggested by Levac et al. (2010), the team used an iterative process to identify key search terms. Initially, AB identified key articles and created keywords for each category for this review. A research librarian was then consulted who advised on, and helped modify the search strategy for the various databases used. Once the search strategies had been finalized, articles were retrieved from each database and imported into the Mendeley reference management software. Note that if an article did not contain a combination of all the search terms (i.e., multisensory, audiovisual, and aging) in the abstract, title, or in the "keywords," it most likely did not appear in our search results.

Search Strategy Used for Scopus, PubMed, and PsychInfo

Scopus

(TITLE-ABS-KEY (multisensory OR sensory OR crossmodal OR cross-modal OR cross-sensory OR intersensory OR multimodal OR multi-modal OR asynchrony OR temporal OR temporal-order OR "temporal window" OR integration OR "window of integration" OR "temporal binding window" OR "sound-induced flash illusion" OR "reaction time" OR "response time" OR "race model" OR simultaneity OR "redundant target")) AND TITLE-ABS-KEY (audiovisual OR "audio-visual" OR "visual-audio" OR "auditory-visual" OR "visual-auditory") AND TITLE-ABS-KEY (aging OR aging OR "older adult*" OR older OR aged OR geriatr* OR gerontol* OR elderly OR "older persons"); 1,368 results obtained.

PubMed

(multisensory[tw] OR Sensory[tw] OR crossmodal[tw] OR cross-modal[tw] OR cross-sensory[tw] OR intersensory[tw] OR multimodal[tw] OR multi-modal[tw] OR asynchrony[tw] OR temporal[tw] OR "temporal window" OR temporal-order[tw] OR integration[tw] OR "temporal binding window"[tw] OR "sound-induced flash illusion"[tw] OR "reaction time"[tw] OR "response time"[tw] OR "redundant target"[tw] OR "race model"[tw] OR simultaneity[tw] OR Reaction Time [MESH] OR Discrimination, Psychological [MESH]) AND (Audiovisual[tw] OR Audio-visual[tw] or visual-audio[tw] OR auditory-visual[tw] OR visual-auditory[tw]) AND (aging[tw] OR aging[tw] OR older[tw] OR aged[tw] OR geriatr*[tw] OR gerontol*[tw] OR elderly[tw] OR Aged [MESH] OR Aged, 80 and over [MESH] OR Geriatrics [MESH]); 790 results obtained.

PsychInfo

((title: (multisensory) OR title: (sensory) OR title: (crossmodal) OR title: (cross-modal) OR title: (cross-sensory) OR title: (intersensory) OR title: (multimodal) OR title: (multi-modal) OR title: (asynchrony) OR title: (temporal) OR title: (temporal-order) OR title: ("temporal window") OR title: (integration) OR title: ("window of integration") OR title: ("temporal binding window") OR title: ("sound-induced flash illusion") OR title: ("reaction time") OR title: ("response time") OR title: ("race model") OR title: (simultaneity) OR title: ("redundant target")) OR (abstract: (multisensory) OR abstract: (sensory) OR abstract: (crossmodal) OR abstract: (cross-modal) OR abstract: (cross-sensory) OR abstract: (intersensory) OR abstract: (multimodal) OR abstract: (multi-modal) OR abstract: (asynchrony) OR abstract: (temporal) OR abstract: (temporal-order) OR abstract: ("temporal window") OR abstract: (integration) OR abstract: ("window of integration") OR abstract: ("temporal binding window") OR abstract: ("sound-induced flash illusion") OR abstract: ("reaction time") OR abstract: ("response time") OR abstract: ("race model") OR abstract: (simultaneity) OR abstract: ("redundant target")) OR (Index Terms: ("Sensory Integration") OR Index Terms: ("Intersensory Processing") OR Index Terms: ("Reaction Time") OR Index Terms: ("Causality") OR Index Terms: ("Perceptual Discrimination") OR Index Terms: ("Time Perception") OR Index Terms: ("Temporal Order (Judgment)"))) AND Any Field: ((title: (audiovisual) OR title: ("audio-visual") OR title: ("visual-audio") OR title: ("auditory-visual") OR title: ("visual-auditory")) OR (abstract: (audiovisual) OR abstract: ("audio-visual") OR abstract: ("visual-audio") OR abstract: ("auditory-visual") OR abstract: ("visual-auditory")) OR (Index Terms: ("Audiovisual Communication") OR Index Terms: ("Visual Perception") OR Index Terms: ("Auditory Perception"))) AND Any Field: ((title: (aging) OR title: (aging) OR title: ("older adult*") OR title: (older) OR title: (aged) OR title: (geriatr*) OR title: (gerontol*) OR title: (elderly) OR title: ("older persons")) OR (abstract: (aging) OR abstract: (aging) OR abstract: ("older adult*") OR abstract: (older) OR abstract: (aged) OR abstract: (geriatr*) OR abstract: (gerontol*) OR abstract: (elderly) OR abstract: ("older persons")) OR (Index Terms: (Aging) OR Index Terms: ("Age Differences") OR Index Terms: (Geriatrics) OR Index Terms: ("Individual Differences"))); 304 results obtained.

Study Selection

Following the Arksey and O'Malley framework, studies were identified to be included in the scoping study. All articles generated from the search for each journal were imported into Mendeley where duplicates were removed. Two team members (AB and AT) read the abstracts and titles of all the articles to screen the studies for inclusion based on the following criteria: (1) healthy older adults (minimum mean or median age of 60) were tested; where "healthy" was defined as not having a neurological disease (e.g., Parkinson's disease, Alzheimer's disease, cognitive impairment, depression), (2) healthy younger adults were tested (mean or median age between 18 and 35); where healthy was defined as no current, acute, or chronic disease, (3) auditory and visual integration was measured, (4) the article was written in English, (5) the article had behavioral results. Articles that included the following were excluded: (1) tested taste exclusively, (2) tested olfaction exclusively, (3) tested somatosensation exclusively, (4) tested emotion perception, (5) were not written in English, (6) were clinical commentaries, editorials, interviews, letters, newspaper articles, abstracts only, or non-peer reviewed literature (e.g., theses), and (7) focused on neuroimaging without a behavioral component. AB and AT met every week to compare their results and to discuss any issues. Any disagreements were discussed between the two reviewers until a consensus was reached or by arbitration of a third reviewer (MBC). Once this step was complete, full articles were retrieved for further evaluation. Note here, that five studies were included that tested only older adults (3,133 participants). Since they provided meaningful information, and because the primary question relates to auditory and visual thresholds, which are more affected in the older population, we decided to make an exception for these studies and included them in this scoping review.

Collating, Summarizing, and Reporting the Results

The results are presented below as described in the registered protocol for the current scoping review (Basharat and Barnett-Cowan, 2020). Descriptive data are presented in table format for variables of interest including but not limited to: title, author(s), year of publication, location(s); if the primary research question is addressed (i.e., if acuity was measured and if so, what the inclusion cut-off was, whether acuity was self-reported and if so, what questions were asked, or if acuity was unaccounted for); type of research article (original experimental research); description of participants (age, sex, inclusion/exclusion criteria); aim(s) of each study; methodology used [e.g., type of task used (e,g, detection response time (RT) task, simultaneity judgment (SJ), temporal order judgment (TOJ), etc.)]; outcome measures.

RESULTS

Description of Studies and Participant Characteristics

For this scoping review, 2,462 articles were retrieved, 903 duplicates were automatically removed by Mendeley ($n = 1{,}559$), Mendeley was then manually checked for duplicates and 13 pairs of duplicates were found which were subsequently removed, leaving 1,546 original articles. The titles and abstracts of all 1,546 articles were reviewed. Through this process, 105 articles were selected for full article review and for further evaluation; 35 articles did not meet the inclusion criteria due to reasons spanning from age (either older adults were not included, or age was not listed), lack of relation to audiovisual integration, lack of undergoing the peer review process (thesis), or because they were reviews that did not provide sufficient information or provided information that was not relevant to this scoping study (refer to **Figure 1** for further information). Note that two additional studies were included during the review process, as such, a total of 72 studies were used to assess the research questions.

We found that the United States produced the largest number of articles (see **Supplementary Tables 2, 3** for further details regarding the country of origin of the articles; note that the country of origin was determined by the affiliation of the all the authors listed on each manuscript). Various behavioral outcomes of interest were identified from the 72 studies; note that most studies extracted multiple outcomes of interest, thus the inclusion in one category does not preclude it from another category. The outcome variables of interest that were used by more than 5% of the studies are as follows: accuracy or proportion correct or percent correct ($n = 42$), mean or median response time ($n = 32$), race model as a measurement of enhancement ($n = 13$), enhancement in speech perception ($n = 11$), hit rate ($n = 10$), and the temporal binding window or temporal window of integration or the just noticeable difference ($n = 10$); see **Supplementary Tables 3, 4** for further information regarding the tasks used, the aim of each study, and the outcomes of interest. See also **Figure 2** for a visualization of the behavioral outcomes of interest.

As mentioned above, older adults were tested in all the articles, however, five studies did not include younger adults as a comparison. In total 6,402 participants were included where 1,624 participants consisted of younger adults while the majority of the participants (4,778) were older adults (see **Tables 1**, **2** for further breakdown of age and sex). Although age ranges were not included for all the studies, the majority of the studies did provide an age range for both younger and older adults (67.4% and 72.9% respectively). The following age ranges were reported for the younger group: 16–50 and 50–90 years were reported for older adults; we calculated the average range of 20.5–29.8 for younger adults and 62.0–78.7 for older adults based on the ranges provided by these studies. For studies that did not provide an age range, they provided mean ages; the following mean ages were found for younger and older adults: 22.3 and 67.8 years respectively. Many studies used normal vision (91.7%) and hearing (95.8%) as part of their inclusion criteria (measured or self-reported; see **Supplementary Table 5** for further details). Further, 76.4% of studies screened for neurological or cognitive disorders (measured in lab or self-reported) and of the studies that used a cognitive assessment to account for cognitive impairment, 47.2% used the Mini-Mental State Examination (MMSE) as part of their screening protocol, while only 18.1% used the Montreal Cognitive Assessment (MoCA; see **Table 3** as well as **Supplementary Table 5** for a comparison of cut off scores used for inclusion in studies using the MMSE and MoCA). Further, 13.9% of studies screened for traumatic brain injury (TBI). In total 35 inclusion criteria were used (see **Supplementary Table 5** for details).

Research Question 1: Description of Auditory and Visual Acuity Reporting

Of the 72 studies included 69 accounted for auditory acuity (i.e., measured or self-reported or both) while only 66 studies accounted for visual acuity. Of the studies investigated in this scoping review, substantially more studies both measured (46 vs. 37) and used self-reported acuity perception (41 vs. 39) to screen for auditory impairment as compared to visual impairment (see **Tables 4**, **5** for further information regarding how the studies included in this scoping review accounted for auditory and visual acuity). The exclusion criteria used to

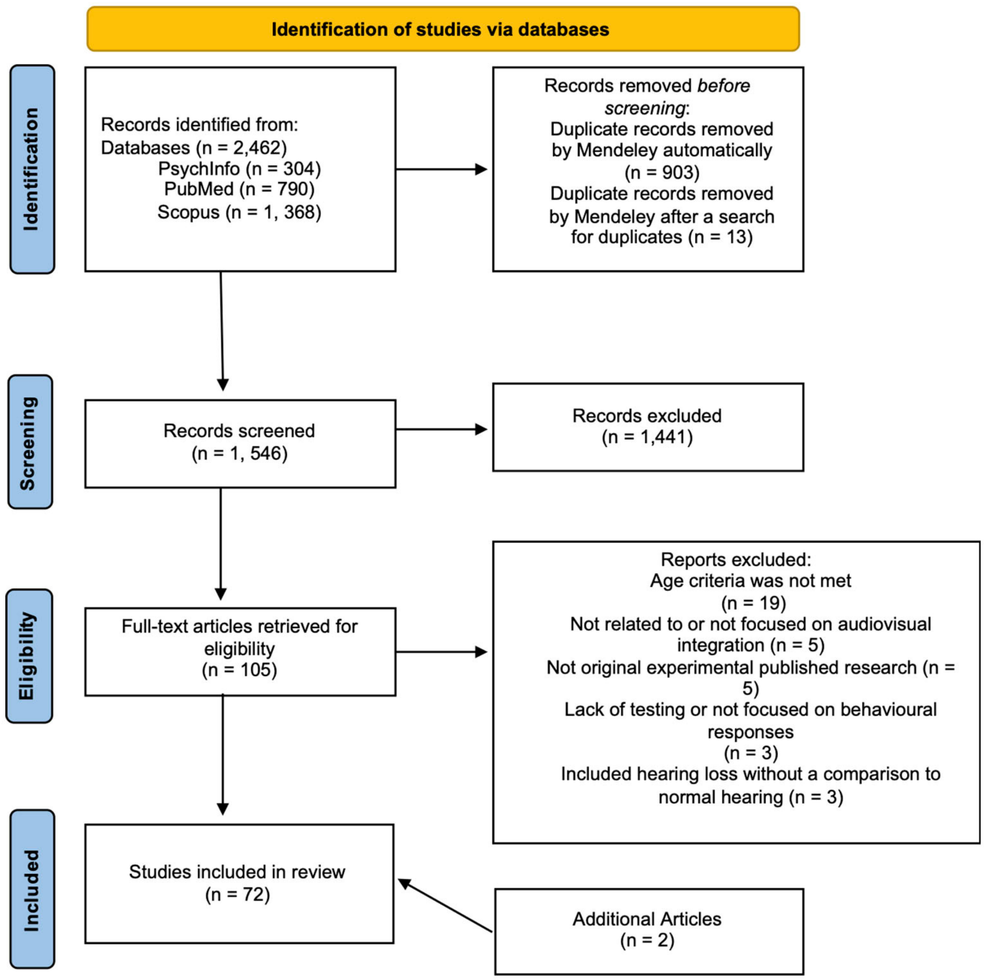

FIGURE 1 | PRISMA flow diagram. This flow diagram is adopted for this scoping study from the PRISMA flow diagram for systematic review (Page et al., 2021) and includes searches of databases only.

screen for auditory impairment were quite heterogeneous even when pure tone audiometry tests were used, with thresholds ranging from frequencies of 0.25 kHz on the lower end to 8 kHz on the higher end and intensities of 25–55 dB (see **Supplementary Table 6** as well as **Tables 6–8** below for details). Most studies used an auditory device (e.g., audiometer) to screen for hearing impairment, however a large majority of studies failed to report the type of test (e.g., device or custom) they used for screening eligibility. Further, only seven studies reported whether or not participants wore hearing aids, while 22 studies did not report which ear was used to screen for hearing impairment, indicating a need for improvement in reporting methods (see **Table 9** below for further details). The visual modality on the other hand was slightly more homogenous, where 36.7% of the studies that measured visual acuity used the same criteria [e.g., $\geq$ 20/40 (6/12 or 0.3 LogMAR)] (see **Supplementary Table 6** and **Tables 10**, **11** below for further details). Interestingly, only nine studies reported questions that were used for self-reported inclusion assessments for the auditory modality while only six studies reported the questions they used to screen for self-reported visual impairments. For the Auditory modality, these questions ranged from requiring simple "yes" or "no" responses to having more options for the participants to choose from such as "excellent," "very good," "good," "fair," and "poor." For vision, similar questions were reported (e.g., "do you have normal or corrected to normal vision?" "yes" or "no" and "is your vision: excellent, very good, good, fair, and poor") with an additional option of "or are you registered as legally blind" (see **Supplementary Table 6** and **Table 4** below for further details).

Research Question 2: Can a Meta-Analysis Be Conducted?

It is quite difficult to determine whether a meta-analysis can be conducted with the articles included in this scoping review. The data reveals heterogeneity not only in tasks that were used to measure multisensory integration (e.g., target discrimination, sound localization tasks, simultaneity

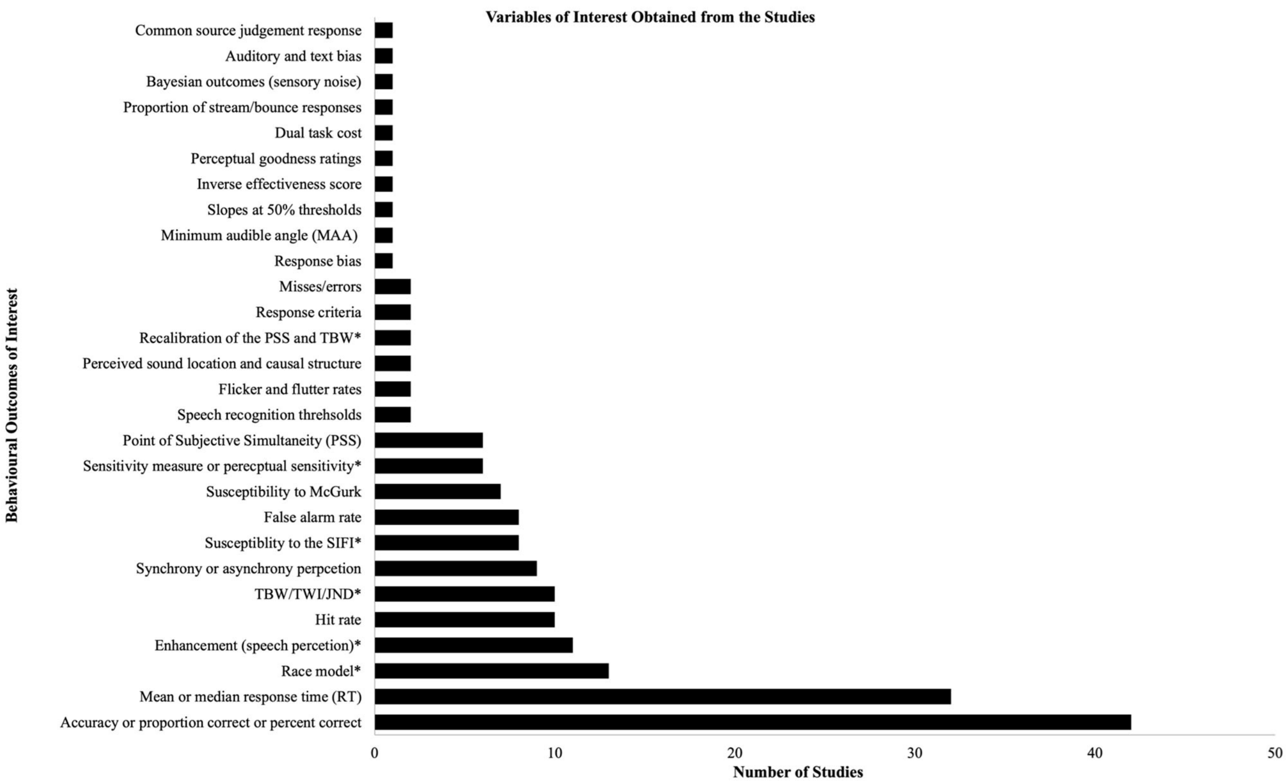

FIGURE 2 | Behavioral outcomes of interest. This figure provides a visual breakdown of the behavioral outcomes of interest for the studies included in this scoping review in the form of a bar graph. Please refer to **Supplementary Table 3** for further information regarding the behavioral outcomes of interest for each study as well as the type of tasks used to extract this information. Asterisks (*) in the figure indicate that further information is provided regarding their definition. Recalibration of the PSS and TBW = Recalibration of the point of subjective simultaneity and temporal binding window; sensitivity measure or perceptual sensitivity = an example is *d'*; susceptibility to the SIFI, susceptibility to the sound-induced flash illusion; TBW/TWI/JND, temporal binding window/temporal window of integration/just noticeable difference; enhancement (speech perception), auditory and/or visual enhancement for speech perception; race model, race model as a measure of enhancement (may include any or all of: cumulative distribution, difference probability, and area under the curve).

TABLE 1 | A breakdown of the participants included.

Description of the studies included	Young males	Young females	Older males	Older females
Number of participants	406	686	1,944	2,297
Percentage of sample (%)	37.18	62.82	45.84	54.16

Note here that the percent of sample was calculated separately for young and older adults (e.g., males made approximately 37% of the sample in the younger group and approximately 46% in the older group). Further, note here that five studies were included that tested only older adults (3,133 participants) which may help to explain the large difference in numbers found between young and older adults (see ***Table 2*** *for further information). Also note that some studies did not specify the gender of their participants.*

TABLE 2 | A further breakdown of the sample.

Age group	Young adults (age range)	Older adults (age range)	Total males	Total females
Sample size	1,624 (16–50)	4,778 (50–90)	2,350	2,983
Percentage of sample (%)	25.73	74.63	44.06	55.93

Note, again that there are more older adults and more females compared to younger adults and males included in this scoping review. Also note that some studies did not specify the gender of their participants.

judgment, temporal order judgment, etc.) and the behavioral outcome of interest (e.g., accuracy/proportion correct, mean or median response time, temporal binding window, etc.) but also in how hearing and visual impairment were screened. If meta-analyses are to be used to address specific research questions, we recommend that they use specific behavioral outcomes that were most used in the literature included in this scoping review (see **Supplementary Tables 3, 4** as well as **Figure 2** for further information regarding the behavioral outcomes of interest. See also **Supplementary Table 7** for main results). Additionally, many of the studies used unique stimuli and some did not to use control conditions, which may also impact the behavioral outcomes observed and thus should also be taken into account when thinking about conducting a meta-analysis (see **Tables 9**, **11** below as well as **Supplementary Tables 8, 9**).

DISCUSSION

Our review demonstrates that only 63.8 and 51.4% of studies examining audiovisual integration in aging, measure auditory thresholds and visual acuities respectively and that less than half of the studies (45.8%) that measure acuities screen both sensory modalities for age-abnormal changes. Further, a key finding is that a consistent definition of what constitutes normal hearing and vision is not employed within studies that screen for audiometric thresholds and visual acuities. Additionally, we found that although 41 and 39 studies use

TABLE 3 | Details regarding the number of studies that used and reported the Mini Mental State Examination (MMSE) and/or Montreal Cognitive Assessment (MoCA) scores to assess cognitive function and the various scores used as part of the inclusion criteria.

MMSE score	Number of studies	MoCA score	Number of studies
> or ≥ 24	6	≥ 22	1
≥ 25	2	> or ≥ 23	3
> 26	1	≥ 24	1
> or ≥ 27	2	≥ 26	2
≥ 28	1	-	-
<2.5 SD from mean	6	-	-

Note that some of the studies that used the MMSE and the MoCA (14 and 4 studies respectively) presented average values the participants achieved instead of a cut off score and are not reported in the table (see ***Supplementary Table 10*** *for further information). The average values for those additional studies ranged from 27.09 to 29.6 for the MMSE and 27.28 to 29 for the MoCA. Note that two studies utilizing the MMSE and two studies utilizing the MoCA did not present any results. SD, standard deviation.*

TABLE 4 | Details regarding the number of studies that reported auditory and visual acuity information.

Methods of accounting for auditory and visual acuity	Hearing (percentage)	Vision (percentage)	Hearing and vision (percentage)
Acuity criteria mentioned	69 (95.83)	66 (91.66)	64 (88.88)
Acuity self-reported	41(56.94)	39 (54.16)	37 (51.39)
Studies that reported self-reported questions in the manuscript	9 (12.50)	6 (8.33)	6 (8.33)
Acuity measured objectively	46 (63.89)	37 (51.39)	33 (45.83)

Note here, that inclusion in one category (e.g., auditory acuity measured objectively) does not exclude inclusion from a different category (e.g., auditory acuity self-reported measures).

TABLE 6 | Details regarding the frequencies used to assess auditory acuity for inclusion.

Frequency (kHz) used	Number of studies
0.125	2
0.2/0.25	15
0.5	22
1	25
1.25	1
1.5	2
1.6	1
2	27
2.5	3
3	6
3.15	1
4	20
5	1
6	3
6.3	1
8	6

Note that inclusion in one category does not preclude it from inclusion in another category. kHz, kilohertz.

TABLE 7 | Details regarding the thresholds used to assess auditory acuity for inclusion found in the studies included in this scoping review.

Thresholds reported	Number of studies
Hearing threshold lower than or equal to 15 dB	2
Hearing threshold lower than or equal to 20 dB	10
Hearing threshold lower than or equal to 25 dB	15
Hearing threshold lower than or equal to 30 dB	1
Hearing threshold lower than or equal to 35 dB	7
Hearing threshold lower than or equal to 40 dB	3
Hearing threshold lower than or equal to 50 dB	1
Hearing threshold lower than or equal to 55 dB	1

Note that inclusion in one category does not preclude it from inclusion in another category. dB, decibel.

TABLE 5 | Details regarding the number of studies that measured auditory and visual acuities in the lab, used self-reported measures, or used a combination of both to screen for inclusion.

Modality of interest	self-reported only (percentage)	Objectively measured only	Self-reported and objectively measured (percentage)	Measured and self-reported (percentage)	None (percentage)
Hearing	23 (31.94)	26 (36.11)	20 (27.78)	46 (63.89)	3 (4.17)
Vision	29 (40.28)	25 (34.72)	12 (16.67)	37 (51.39)	6 (8.33)

TABLE 8 | Details regarding the most commonly utilized auditory acuity inclusion criteria found in the studies included in this scoping review.

Most common auditory acuity criteria used for inclusion	Number of studies
≤25 dB hearing level (HL) at 0.25 – 3 kHz (both ears)	3
≤20 dB HL from 0.25 to 4 kHz (in both ears or not specified)	3
< or ≤ 35 dB HL at 4 kHz and < or ≤ 25 dB HL at 0.25, 0.5, 1, and 2 kHz	3
≤25 dB HL for 0.5, 1, 2, 4 kHz	2
0.2 – 4 kHz: no hearing loss up to 2 kHz (at ≤20 dB HL) and no more than mild hearing loss at 4 kHz (at ≤35 dB HL)	2
≤25 dB HL for 0.5, 1, 2 kHz in the better ear or in both ears	2

dB, decibels; kHz, kilohertz.

TABLE 9 | Details regarding the type of test used (using a device or a custom test), whether or not participants wore hearing aids, and the ear(s) that was used to assess inclusion.

Type of test and administration conditions	Number of studies
Audiometer used to test acuity	22
Custom test used to test acuity	8
Studies that did not report the type of test they used	16
Studies where participants wore hearing aids during testing	1
Studies where participants did not wear hearing aids during testing	8
Measured in both ears	22
Measured in better ear	4
Did not report which ear was used to measure acuity	26
Studies that included a control for auditory performance	55

TABLE 10 | Details regarding the criteria used to assess visual acuity for inclusion found in the studies included in this scoping review as obtained through various tests.

Visual acuity criteria used for inclusion	Number of studies
Approximately 20/20 (6/6 or 0 LogMAR)	4
≥ 20/25 (6/7.5 or 0.1 LogMAR)	8
≥ 20/30 (6/9.5 or 0.2 LogMAR)	5
≥ 20/40 (6/12 or 0.3 LogMAR)	11
≥ 20/50 (6/15 or 0.4 LogMAR)	1
≥ 20/125 (or 6/38 or 0.8 LogMAR)	1

Note that the most commonly used criteria for exclusion was if vision was worse than: 20/40, followed by 20/25, and thirdly 20/30.

self-reported measures to screen for normal hearing and vision respectively, only nine studies reported the questions that were presented to participants for auditory screening, while only six studies reported the questions used to screen for self-reported visual impairment (see **Tables 4**, **5** below and **Supplementary Table 6** for further information). In addition, as one may expect, a variety of tasks and behavioral outcomes of interest (e.g., discrimination or detection, mean response time, susceptibility to the sound induced flash illusion, etc.; see **Supplementary Tables 3, 4** and **Figure 2** above for details) were used in the studies selected for this scoping review; thus, the variability present in the data, from the screening measures to the multiple different tasks used makes it difficult to recommend a meta-analysis at the moment. It should however be noted that of the 2,462 articles, the 72 that were selected based on the inclusion and exclusion criteria specified above in the methods section and in the protocol for this review (https://osf.io/v3snz/; Basharat and Barnett-Cowan, 2021) were more focused on the aging process rather than on specific behavioral outcomes related to any specific task. Thus, future researchers whose research questions can be addressed using a meta-analysis can use either a rigid criterion (e.g., include studies that tested discrimination or detection response time only) to look for studies that use the same tasks or a more lenient criteria (e.g., compare the impact of aging on additional sensory modalities including somatosensation in a given task such as for detection or discrimination tasks) to capture a larger set of studies.

Our results indicate that more studies measured auditory thresholds compared to visual acuity (46 vs. 37 respectively; see **Table 4** for further information). This is not surprising given that the prevalence of hearing loss rises with age ranging from 46 to 60% to more than 80% in adults aged 75 and 85 years

TABLE 11 | Details regarding the type of test (computerized, chart, and custom) used to test vision, the required conditions to administer this test (e.g., whether a participant used optical correction, whether binocular vision was tested, the viewing distance, etc.), if vision impairment was accounted for, and if a control condition was included for measuring only visual performance as compared to audiovisual (experimental) condition.

Type of test and administration conditions	Number of studies
Computerized test or a specialized machine used to test acuity	2
Chart used to test acuity	21
Custom test used to test acuity	4
Didn't specify the type of test used to test acuity	12
Binocular testing	10
Did not report which eye the test was conducted in	28
Near viewing distance (defined by authors as ≤ 1 m or if defined as "near" in the study)	8
Far viewing distance (defined by authors as > 1 m or if defined as "far" in the study)	11
Viewing distance not reported	25
Vision health conditions (history of cataracts, glaucoma, age-related macular degeneration, visual impairment, etc.)	17
Studies that required eye exams	2
Optical correction used (if explicitly stated)	14
Contrast sensitivity reported measured	19
Studies that included a control for visual performance	49

respectively (Cooper and Gates, 1991; Yueh et al., 2003; Walling and Dickson, 2012) and is much higher than the prevalence for visual disorders that range from 2.6 to 8.0% in adults aged 70–74 and 75–80, respectively (Buch et al., 2001). However, we recommend testing both sensory modalities to ensure that stimuli presented to all participants are perceived at the appropriate thresholds (e.g., suprathreshold) required for accurate results. Note however that depending on the study design and the types of stimuli used, additional control conditions may be required. Further, and as alluded to above, the studies of audiovisual integration included in this review have adopted inconsistent screening definitions, especially for the auditory acuity, making it difficult to compare results between studies. A potential solution for this lack of standardization, is using the definitions of hearing loss and visual impairment that are recommended by the WHO; hearing loss is defined as "a speech-frequency pure-tone average at 0.5, 1, 2, and 4 kHz frequencies of >20 dB HL in both ears" and visual impairment is defined as "<20/40 (no visual impairment) but greater than or equal to 20/400 (severe visual impairment) in both eyes" (Mathers et al., 2000; World Health Organization, 2018b, 2021b). We also found that more females than males were tested, both in the younger (62.8%) and older (54.2%) adult populations. Surprisingly, 29.2 and 34.7% of the studies failed to report gender for older and younger adults respectively, which may impact the ratio of men to women currently seen in this review. Note here that five studies were included that only tested older adults and if those studies were removed, we would be left with a comparable sample to the younger population of 461 older males and 657 older females (compared to 406 younger males and 688 younger females). However, we decided to keep these articles in the scoping review as they provide useful information regarding the screening procedures for inclusion of older adults, used in the literature.

Although a large number of studies (76.39%) used cognitive reporting to ensure that the participants included were cognitively intact (MMSE, MoCA, and DemTect, a dementia screening test, self-reported lack of cognitive impairment), many different scores were used to include or exclude individuals (see **Table 3** and **Supplementary Table 5** for further information regarding the inclusion criteria used for cognitive impairment and for various other inclusion criteria used by the studies included in this review). Although the variability in scores was somewhat expected as various cut off scores have been used for the detection of mild cognitive impairment (MCI) for both the MoCA (26, 25, 24, and 23; Nasreddine et al., 2005; Luis et al., 2009; Davis et al., 2015; Ciesielska et al., 2016; Milani et al., 2018) and the MMSE (28, 27, 26, 24; Anderson et al., 2007; Markwick et al., 2012; Creavin et al., 2016; Kvitting et al., 2019; Erdodi et al., 2020), we were surprised by the preferred use of the MMSE over the MoCA. As the MMSE was designed to screen for dementia at a time where the concept of MCI did not exist, the MoCA has been found to be a more sensitive test for detection and screening for early cognitive impairment compared to the MMSE (Markwick et al., 2012; Ciesielska et al., 2016). Further, research reveals that performance on the MMSE is affected by race, education, language, and gender (Tombaugh and McIntyre, 1992; Grigoletto et al., 1999; Wood et al., 2006), while the MoCA was designed as an alternative method of cognitive screening and is thought to account for the limitations that affect the MMSE [Nasreddine et al., 2005; Ciesielska et al., 2016; however please see a review by Siqueira et al. (2019) which indicates that both the MoCA and the MMSE are impacted by educational level]. Moving forward, we recommend that researchers use the MoCA to detect MCI as it was specifically designed to screen for mild cognitive impairment and it accounts for educational level differences through the addition of a point to the final score for those with <12 years of formal schooling (Nasreddine et al., 2005; Siqueira et al., 2019).

Further, we found that the 72 studies included in this scoping review used different tasks with various methodology, aims, and varying behavioral outcomes of interest (refer to **Supplementary Tables 3, 4, 6, 8, 9** as well as **Figure 2** above for details). Overall, the most common behavioral outcomes were thus "accuracy or proportion correct or percent correct" and "mean and median response time" measures. Given that the articles included used 28 different outcomes of interest to assess multisensory integration, it is difficult to suggest conducting a meta-analysis with the specific articles that we have used in this scoping review. However, we strongly believe that there is a sufficient amount of data available in the 1,500+ articles that were screened for this scoping review and thus suggest utilizing either a more rigid inclusion criteria (e.g., utilizing only speech recognition or response time tasks) or a broader inclusion criteria (e.g., including studies that do not mention the aging process) for those interested in conducting a meta-analysis.

This scoping review is not without its limitations. An inherent limitation of any given scoping review is that it provides breadth rather than depth on a topic (Arksey and O'Malley, 2005; Levac et al., 2010). While this scoping review provides a broad view of how studies are screening for age-abnormal sensory changes through the use of auditory and visual acuities, we are unable to determine the effectiveness of accounting for unisensory changes in multisensory integration research within this scoping review. As such, future research using meta-analyses is necessary to determine whether the results obtained from studies that screen for auditory and visual acuities differ from those that only use self-reported measures. We do however believe that providing a breath of knowledge will prove to be useful for researchers in understanding and further investigating multisensory integration within the aging population. Another limitation is that the majority of the literature in this review stems from developed countries (Economic Analysis Policy Division, 2020) and therefore it is not clear whether these findings extend to developing countries. However, it is also not clear whether the recommendations to correct the limitations associated with accounting for sensory acuities would not be applicable to the research conducted in developing nations, thus, we would extend our recommendations to developing nations unless future research indicates otherwise.

Additional research with the inclusion of studies from developing nations is necessary to elucidate this matter. An additional limitation of the current study is that only studies published in English were included, limiting the review to articles that were either published in English-speaking countries, which may explain the predominance of the literature stemming from developed countries, or to those that had the funds for translation services. Finally, we conducted this scoping review using behavioral studies as we were concerned that behavioral studies may be conducted with less rigor as compared to neuroimaging studies, however, further research investigating the use of auditory and visual acuity screening methods with neuroimaging studies will not only provide insight, but is necessary to ensure standardized methods are used throughout the literature.

CONCLUSION

In conclusion, we found that only approximately 64 and 51% of studies measure for age-abnormal hearing and vision respectively and that within these studies a consistent definition of what constitutes normal hearing and vision is not found. Further, we found that many studies screen for one sensory modality (audition) more than the other modality. Here, we recommend screening for both age-abnormal hearing and vision and using the World Health Organization's definitions of hearing loss and visual impairment. Further, we find that many researchers use the MMSE for MCI screening instead of the MoCA and we recommend the utilization of the latter cognitive assessment as it has been found to be more sensitive toward the detection of MCI. We found that many different tasks were used to assess audiovisual integration in younger and older adults ranging from speech recognition to the stream bounce task, thus various behavioral outcomes were obtained ranging from accuracy to stream bounce susceptibility, making it difficult to suggest conducting a meta-analysis with this particular dataset. We do however believe that a meta-analysis can be conducted with the abundant data that exists within audiovisual literature; if you wish to conduct a meta-analysis, we recommend using either a more strict or a less strict inclusion criteria depending on your research question of interest.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

AB drafted the manuscript with input from AT and MB-C. AB and AT read the abstracts and titles of all 1,546 articles and 105 full-text articles to screen the studies for inclusion. Any disagreements were discussed between the two reviewers until a consensus was reached or by arbitration of a third reviewer MB-C. All authors contributed to study conception, development, manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.772112/full#supplementary-material

REFERENCES

Anderson, T. M., Sachdev, P. S., Brodaty, H., Trollor, J. N., and Andrews, G. (2007). Effects of sociodemographic and health variables on Mini-Mental State Exam scores in older Australians. *Am. J. Geriatr. Psychiatr*. 15, 467–476. doi: 10.1097/JGP.0b013e3180547053

†Andrés, P., Parmentier, F. B., and Escera, C. (2006). The effect of age on involuntary capture of attention by irrelevant sounds: a test of the frontal hypothesis of aging. *Neuropsychologia* 44, 2564–2568. doi: 10.1016/j.neuropsychologia.2006.05.005

Arksey, H., and O'Malley, L. (2005). Scoping studies: towards a methodological framework. *Int. J. Soc. Res. Methodol.* 8, 19–32. doi: 10.1080/1364557032000119616

†Avivi-Reich, M., Puka, K., and Schneider, B. A. (2018). Do age and linguistic background alter the audiovisual advantage when listening to speech in the presence of energetic and informational masking? *Attent. Percept. Psychophys.* 80, 242–261. doi: 10.3758/s13414-017-1423-5

Baltes, P. B., and Lindenberger, U. (1997). Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging? *Psychol. Aging* 12:12. doi: 10.1037/0882-7974.12.1.12

†Barrett, M. M., and Newell, F. N. (2015). Task-specific, age related effects in the cross-modal identification and localisation of objects. *Multisens. Res.* 28, 111–151. doi: 10.1163/22134808-00002479

†Basharat, A., Adams, M. S., Staines, W. R., and Barnett-Cowan, M. (2018). Simultaneity and temporal order judgments are coded differently and change with age: an event-related potential study. *Front. Integr. Neurosci.* 12:15. doi: 10.3389/fnint.2018.00015

Basharat, A., and Barnett-Cowan, M. (2020). *Scoping Review Protocol.* doi: 10.17605/OSF.IO/GTUHD

Basharat, A., and Barnett-Cowan, M. (2021). *Scoping Review Protocol.* Retrieved from: osf.io/v3snz

†Basharat, A., Mahoney, J. R., and Barnett-Cowan, M. (2019). Temporal metrics of multisensory processing change in the elderly. *Multisens. Res*. 32, 715–744. doi: 10.1163/22134808-20191458

Baum, S. H., and Stevenson, R. A. (2017). Shifts in audiovisual processing in healthy aging. *Curr. Behav. Neurosci. Rep*. 4, 198–208. doi: 10.1007/s40473-017-0124-7

†Bedard, G., and Barnett-Cowan, M. (2016). Impaired timing of audiovisual events in the elderly. *Exp. Brain Res*. 234, 331–340. doi: 10.1007/s00221-015-4466-7

†Brooks, C. J., Anderson, A. J., Roach, N. W., McGraw, P. V., and McKendrick, A. M. (2015). Age-related changes in auditory and visual interactions in temporal rate perception. *J. Vis*. 15, 2–2. doi: 10.1167/15.16.2

Brooks, C. J., Chan, Y. M., Anderson, A. J., and McKendrick, A. M. (2018). Audiovisual temporal perception in aging: The role of multisensory integration and age-related sensory loss. *Front. Hum. Neurosci*. 12:192. doi: 10.3389/fnhum.2018.00192

Buch, H., Vinding, T., and Nielsen, N. V. (2001). Prevalence and causes of visual impairment according to World Health Organization and United States criteria in an aged, urban Scandinavian population: the Copenhagen City Eye Study. *Ophthalmology* 108, 2347–2357. doi: 10.1016/S0161-6420(01)00823-5

Calvert, G., Spence, C., and Stein, B. E. (2004). *The Handbook of Multisensory Processes*. Cambridge, MA: MIT Press.

Chan, J. S., Kaiser, J., Brandl, M., Matura, S., Prvulovic, D., Hogan, M. J., et al. (2015). Expanded temporal binding windows in people with mild cognitive impairment. *Curr. Alzheimer Res*. 12, 61–68. doi: 10.2174/1567205012666141218124744

†Chan, Y. M., Pianta, M. J., Bode, S., and McKendrick, A. M. (2017). Spatio-temporal patterns of event-related potentials related to audiovisual synchrony judgments in older adults. *Neurobiol. Aging* 55, 38–48. doi: 10.1016/j.neurobiolaging.2017.03.011

†Chan, Y. M., Pianta, M. J., and McKendrick, A. M. (2014a). Older age results in difficulties separating auditory and visual signals in time. *J. Vis*. 14, 13–13. doi: 10.1167/14.11.13

†Chan, Y. M., Pianta, M. J., and McKendrick, A. M. (2014b). Reduced audiovisual recalibration in the elderly. *Front. Aging Neurosci*. 6:226. doi: 10.3389/fnagi.2014.00226

†Cid-Fernández, S., Lindín, M., and Díaz, F. (2014). Effects of aging and involuntary capture of attention on event-related potentials associated with the processing of and the response to a target stimulus. *Front. Hum Neurosci*. 8:745. doi: 10.3389/fnhum.2014.00745

†Cid-Fernández, S., Lindín, M., and Díaz, F. (2016). Information processing becomes slower and predominantly serial in aging: characterization of response-related brain potentials in an auditory–visual distraction–attention task. *Biol. Psychol*. 113, 12–23. doi: 10.1016/j.biopsycho.2015.11.002

†Cienkowski, K. M., and Carney, A. E. (2002). Auditory-visual speech perception and aging. *Ear Hear*. 23, 439–449. doi: 10.1097/00003446-200210000-00006

Ciesielska, N., Sokolowski, R., Mazur, E., Podhorecka, M., Polak-Szabela, A., and Kedziora-Kornatowska, K. (2016). Is the Montreal Cognitive Assessment (MoCA) test better suited than the Mini-Mental State Examination (MMSE) in mild cognitive impairment (MCI) detection among people aged over 60? Meta-analysis. *Psychiatr. Polska* 50, 1039–1052. doi: 10.12740/PP/45368

Cooper, Jr. J. C., and Gates, G. A. (1991). Hearing in the elderly—the Framingham cohort, 1983–1985: part II. Prevalence of central auditory processing disorders. *Ear Hear*. 12, 304–311. doi: 10.1097/00003446-199110000-00002

†Correa-Jaraba, K. S., Cid-Fernández, S., Lindín, M., and Díaz, F. (2016). Involuntary capture and voluntary reorienting of attention decline in middle-aged and old participants. *Front. Hum. Neurosci*. 10:129. doi: 10.3389/fnhum.2016.00129

†Couth, S., Gowen, E., and Poliakoff, E. (2018). Using race model violation to explore multisensory responses in older adults: enhanced multisensory integration or slower unisensory processing? *Multisens. Res*. 31, 151–174. doi: 10.1163/22134808-00002588

Creavin, S. T., Wisniewski, S., Noel-Storr, A. H., Trevelyan, C. M., Hampton, T., Rayment, D., et al. (2016). Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. *Cochr. Datab. Systemat. Rev*. 1:CD011145. doi: 10.1002/14651858.CD011145.pub2

Davis, D. H., Creavin, S. T., Yip, J. L., Noel-Storr, A. H., Brayne, C., and Cullum, S. (2015). Montreal Cognitive Assessment for the detection of dementia. *Cochr. Datab. Systemat. Rev*. 10:CD010775. doi: 10.1002/14651858.CD010775.pub3

†de Boer-Schellekens, L., and Vroomen, J. (2014). Multisensory integration compensates loss of sensitivity of visual temporal order in the elderly. *Exp. Brain Res*. 232, 253–262. doi: 10.1007/s00221-013-3736-5

de Dieuleveult, A. L., Siemonsma, P. C., van Erp, J. B., and Brouwer, A. M. (2017). Effects of aging in multisensory integration: a systematic review. *Front. Aging Neurosci*. 9:80. doi: 10.3389/fnagi.2017.00080

†DeLoss, D. J., Pierce, R. S., and Andersen, G. J. (2013). Multisensory integration, aging, and the sound-induced flash illusion. *Psychol. Aging* 28, 802–812. doi: 10.1037/a0033289

†Dey, A., and Sommers, M. S. (2015). Age-related differences in inhibitory control predict audiovisual speech perception. *Psychol. Aging* 30:634. doi: 10.1037/pag0000033

Economic Analysis and Policy Division (2020). *World Economic Situation Prospects*. New York, NY: United Nations. Available online at: https://www.un.org/development/desa/dpad/wp-content/uploads/sites/45/WESP2020_FullReport.pdf (accessed August 2021).

Erdodi, L. A., Shahein, A. G., Fareez, F., Rykulski, N., Sabelli, A. G., and Roth, R. M. (2020). Increasing the cutoff on the MMSE and DRS-2 improves clinical classification accuracy in highly educated older adults. *Psychol. Neurosci*. 13, 93–113. doi: 10.1037/pne0000185

Ernst, M. O., and Bülthoff, H. H. (2004). Merging the senses into a robust percept. *Trends Cogn. Sci*. 8, 162–169. doi: 10.1016/j.tics.2004.02.002

†Festa, E. K., Katz, A. P., Ott, B. R., Tremont, G., and Heindel, W. C. (2017). Dissociable effects of aging and mild cognitive impairment on bottom-up audiovisual integration. *J. Alzheimer's Dis*. 59, 155–167. doi: 10.3233/JAD-161062

†Fiacconi, C. M., Harvey, E. C., Sekuler, A. B., and Bennett, P. J. (2013). The influence of aging on audiovisual temporal order judgments. *Exp. Aging Res*. 39, 179–193. doi: 10.1080/0361073X.2013.761896

Fitzgibbons, P. J., and Gordon-Salant, S. (1994). Age effects on measures of auditory duration discrimination. *J. Speech Lang. Hear. Res*. 37, 662–670. doi: 10.1044/jshr.3703.662

Fitzgibbons, P. J., and Gordon-Salant, S. (1995). Age effects on duration discrimination with simple and complex stimuli. *J. Acoust. Soc. Am*. 98, 3140–3145. doi: 10.1121/1.413803

Fjell, A. M., Sneve, M. H., Grydeland, H., Storsve, A. B., and Walhovd, K. B. (2017). The disconnected brain and executive function decline in aging. *Cerebr. Cortex* 27, 2303–2317. doi: 10.1093/cercor/bhw082

Gallun, F. J., McMillan, G. P., Molis, M. R., Kampel, S. D., Dann, S. M., and Konrad-Martin, D. L. (2014). Relating age and hearing loss to monaural, bilateral, and binaural temporal sensitivity. *Front. Neurosci*. 8:172. doi: 10.3389/fnins.2014.00172

†Ganesh, A. C., Berthommier, F., and Schwartz, J. L. (2018). Audiovisual binding for speech perception in noise and in aging. *Lang. Learn*. 68, 193–220. doi: 10.1111/lang.12271

Gin, T. J., Luu, C. D., and Guymer, R. H. (2011). Central retinal function as measured by the multifocal electroretinogram and flicker perimetry in early age-related macular degeneration. *Investig. Ophthalmol. Vis. Sci*. 52, 9267–9274. doi: 10.1167/iovs.11-8517

†Gordon, M. S., and Allen, S. (2009). Audiovisual speech in older and younger adults: integrating a distorted visual signal with speech in noise. *Exp. Aging Res*. 35, 202–219. doi: 10.1080/03610730902720398

Gordon-Salant, S., and Fitzgibbons, P. J. (1999). Profile of auditory temporal processing in older listeners. *J. Speech Lang. Hear. Res*. 42, 300–311. doi: 10.1044/jslhr.4202.300

†Gordon-Salant, S., Yeni-Komshian, G. H., Fitzgibbons, P. J., Willison, H. M., and Freund, M. S. (2017). Recognition of asynchronous auditory-visual speech by younger and older listeners: a preliminary study. *J. Acoust. Soc. Am*. 142, 151–159. doi: 10.1121/1.4992026

†Gosselin, P. A., and Gagné, J. P. (2011). Older adults expend more listening effort than young adults recognizing audiovisual speech in noise. *Int. J. Audiol*. 50, 786–792. doi: 10.3109/14992027.2011.599870

Grigoletto, F., Zappalà, G., Anderson, D. W., and Lebowitz, B. D. (1999). Norms for the Mini-Mental State Examination in a healthy population. *Neurology* 53, 315–315. doi: 10.1212/WNL.53.2.315

Grose, J. H., and Mamo, S. K. (2010). Processing of temporal fine structure as a function of age. *Ear Hear*. 31:755. doi: 10.1097/AUD.0b013e3181e627e7

Guerreiro, M. J., Anguera, J. A., Mishra, J., Van Gerven, P. W., and Gazzaley, A. (2014). Age-equivalent top-down modulation during cross-modal selective attention. *J. Cogn. Neurosci*. 26, 2827–2839. doi: 10.1162/jocn_a_00685

Guerreiro, M. J., Eck, J., Moerel, M., Evers, E. A., and Van Gerven, P. W. (2015). Top-down modulation of visual and auditory cortical processing in aging. *Behav. Brain Res*. 278, 226–234. doi: 10.1016/j.bbr.2014.09.049

†Hernández, B., Setti, A., Kenny, R. A., and Newell, F. N. (2019). Individual differences in ageing, cognitive status, and sex on susceptibility to the sound-induced flash illusion: a large-scale study. *Psychol. Aging* 34:978. doi: 10.1037/pag0000396

†Hirst, R. J., Setti, A., Kenny, R. A., and Newell, F. N. (2019). Age-related sensory decline mediates the Sound-Induced Flash Illusion: evidence for reliability weighting models of multisensory perception. *Sci. Rep*. 9, 1–12. doi: 10.1038/s41598-019-55901-5

†Huyse, A., Leybaert, J., and Berthommier, F. (2014). Effects of aging on audio-visual speech integration. *J. Acoust. Soc. Am*. 136, 1918–1931. doi: 10.1121/1.4894685

†Jones, S. A., Beierholm, U., Meijer, D., and Noppeney, U. (2019). Older adults sacrifice response speed to preserve multisensory integration performance. *Neurobiol. Aging* 84, 148–157. doi: 10.1016/j.neurobiolaging.2019.08.017

Kalina, R. E. (1997). Seeing into the future. Vision and aging. *Western J. Med*. 167:253.

Kim, C. B., and Mayer, M. J. (1994). Foveal flicker sensitivity in healthy aging eyes. II. Cross-sectional aging trends from 18 through 77 years of age. *J. Opt. Soc. Am*. 11, 1958–1969. doi: 10.1364/JOSAA.11.001958

King, A. J. (2005). Multisensory integration: strategies for synchronization. *Curr. Biol.* 15, 339–341. doi: 10.1016/j.cub.2005.04.022

†Krull, V., and Humes, L. E. (2016). Text as a supplement to speech in young and older adults. *Ear Hear*. 37:164. doi: 10.1097/AUD.0000000000000234

Kvitting, A. S., Fällman, K., Wressle, E., and Marcusson, J. (2019). Age-normative MMSE data for older persons aged 85 to 93 in a Longitudinal Swedish Cohort. *J. Am. Geriatr. Soc*. 67, 534–538. doi: 10.1111/jgs.15694

Lachenmayr, B. J., Kojetinsky, S., Ostermaier, N., Angstwurm, K., Vivell, P. M., and Schaumberger, M. (1994). The different effects of aging on normal sensitivity in flicker and light-sense perimetry. *Investig. Ophthalmol. Vis. Sci*. 35, 2741–2748.

†Laurienti, P. J., Burdette, J. H., Maldjian, J. A., and Wallace, M. T. (2006). Enhanced multisensory integration in older adults. *Neurobiol. Aging* 27, 1155–1163. doi: 10.1016/j.neurobiolaging.2005.05.024

Lee, F. S., Matthews, L. J., Dubno, J. R., and Mills, J. H. (2005). Longitudinal study of pure-tone thresholds in older persons. *Ear Hear*. 26, 1–11. doi,: 10.1097/00003446-200502000-00001

†Legault, I., Gagné, J. P., Rhoualem, W., and Anderson-Gosselin, P. (2010). The effects of blurred vision on auditory-visual speech perception in younger and older adults. *Int. J. Audiol*. 49, 904–911. doi: 10.3109/14992027.2010.509112

†Leiva, A., Parmentier, F. B., and Andrés, P. (2015). Aging increases distraction by auditory oddballs in visual, but not auditory tasks. *Psychol. Res*. 79, 401–410. doi: 10.1007/s00426-014-0573-5

Levac, D., Colquhoun, H., and O'Brien, K. K. (2010). Scoping studies: advancing the methodology. *Implement. Sci*. 5, 1–9. doi: 10.1186/1748-5908-5-69

Lin, F. R., Thorpe, R., Gordon-Salant, S., and Ferrucci, L. (2011). Hearing loss prevalence and risk factors among older adults in the United States. *J. Gerontol. Ser. A Biomed. Sci. Med. Sci*. 66, 582–590. doi: 10.1093/gerona/glr002

Liu, X. Z., and Yan, D. (2007). Ageing and hearing loss. *J. Pathol*. 211, 188–197. doi: 10.1002/path.2102

Luis, C. A., Keegan, A. P., and Mullan, M. (2009). Cross validation of the Montreal Cognitive Assessment in community dwelling older adults residing in the Southeastern US. *Int. J. Geriatr. Psychiatr*. 24, 197–201. doi: 10.1002/gps.2101

Ma, W. J., Zhou, X., Ross, L. A., Foxe, J. J., and Parra, L. C. (2009). Lip-reading aids word recognition most in moderate noise: a Bayesian explanation using high-dimensional feature space. *PLoS ONE* 4:e4638. doi: 10.1371/journal.pone.0004638

†Maguinness, C., Setti, A., Burke, K., Kenny, R. A., and Newell, F. N. (2011). The effect of combined sensory and semantic components on audio-visual speech perception in older adults. *Front. Aging Neurosci*. 3:19. doi: 10.3389/fnagi.2011.00019

†Mahoney, J. R., Li, P. C. C., Oh-Park, M., Verghese, J., and Holtzer, R. (2011). Multisensory integration across the senses in young and old adults. *Brain Res*. 1426, 43–53. doi: 10.1016/j.brainres.2011.09.017

Markwick, A., Zamboni, G., and De Jager, C. A. (2012). Profiles of cognitive subtest impairment in the Montreal Cognitive Assessment (MoCA) in a research cohort with normal Mini-Mental State Examination (MMSE) scores. *J. Clin. Exp. Neuropsychol*. 34, 750–757. doi: 10.1080/13803395.2012.672966

Mathers, C., Smith, A., and Concha, M. (2000). Global burden of hearing loss in the year 2000. *Glob. Burden Dis*. 18, 1–30. Available online at: http://www.who.int/healthinfo/statistics/bod_hearingloss.pdf

Mayer, M. J., Glucs, A., Kim, C. B. Y., and Svingos, A. (1988). Foveal flicker sensitivity in healthy aging eyes. I. Compensating for pupil variation. *J. Opt. Soc. Am*. 5, 2201–2209. doi: 10.1364/JOSAA.5.002201

†McGovern, D. P., Roudaia, E., Stapleton, J., McGinnity, T. M., and Newell, F. N. (2014). The sound-induced flash illusion reveals dissociable age-related effects in multisensory integration. *Front. Aging Neurosci*. 6:250. doi: 10.3389/fnagi.2014.00250

Meredith, M. A., Nemitz, J. W., and Stein, B. E. (1987). Determinants of multisensory integration in superior colliculus neurons. I. Temporal factors. *J. Neurosci*. 7, 3215–3229. doi: 10.1523/JNEUROSCI.07-10-03215.1987

Milani, S. A., Marsiske, M., Cottler, L. B., Chen, X., and Striley, C. W. (2018). Optimal cutoffs for the Montreal Cognitive Assessment vary by race and ethnicity. *Alzheimer Dement*. 10, 773–781. doi: 10.1016/j.dadm.2018.09.003

†Mishra, J., and Gazzaley, A. (2013). Preserved discrimination performance and neural processing during crossmodal attention in aging. *PLoS ONE* 8:e81894. doi: 10.1371/journal.pone.0081894

Mozolic, J. L., Hugenschmidt, C. E., Peiffer, A. M., and Laurienti, P. J. (2012). "Integration in aging," in *The Neural Bases of Multisensory Processes,* eds M. M. Murray and M. T. Wallace (Boca Raton, FL: CRC Press), 381–394. Available online at: https://europepmc.org/article/nbk/nbk92841

Murray, M. M., Eardley, A. F., Edginton, T., Oyekan, R., Smyth, E., and Matusz, P. J. (2018). Sensory dominance and multisensory integration as screening tools in aging. *Sci. Rep*. 8, 1–11. doi: 10.1038/s41598-018-27288-2

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., et al. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc*. 53, 695–699. doi: 10.1111/j.1532-5415.2005.53221.x

†Noel, J. P., De Niear, M., Van der Burg, E., and Wallace, M. T. (2016). Audiovisual simultaneity judgment and rapid recalibration throughout the lifespan. *PLoS ONE* 11:e0161698. doi: 10.1371/journal.pone.0161698

†O'Brien, J., Ottoboni, G., Tessari, A., and Setti, A. (2017). One bout of open skill exercise improves cross-modal perception and immediate memory in healthy older adults who habitually exercise. *PLoS ONE* 12:e0178739. doi: 10.1371/journal.pone.0178739

Odegaard, B., and Shams, L. (2016). The brain's tendency to bind audiovisual signals is stable but not general. *Psychol. Sci*. 27, 583–591. doi: 10.1177/0956797616628860

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Bmj*. 372. doi: 10.1136/bmj.n71

†Peiffer, A. M., Mozolic, J. L., Hugenschmidt, C. E., and Laurienti, P. J. (2007). Age-related multisensory enhancement in a simple audiovisual detection task. *Neuroreport*. 18, 1077–1081. doi: 10.1097/WNR.0b013e3281e72ae7

Phipps, J. A., Dang, T. M., Vingrys, A. J., and Guymer, R. H. (2004). Flicker perimetry losses in age-related macular degeneration. *Investig. Ophthalmol. Vis. Sci*. 45, 3355–3360. doi: 10.1167/iovs,.04-0253

†Pitts, B. J., and Sarter, N. (2018). What you don't notice can harm you: age-related differences in detecting concurrent visual, auditory, and tactile cues. *Hum. Fact*. 60, 445–464. doi: 10.1177/0018720818759102

Poliakoff, E., Ashworth, S., Lowe, C., and Spence, C. (2006). Vision and touch in ageing: crossmodal selective attention and visuotactile spatial interactions. *Neuropsychologia* 44, 507–517. doi: 10.1016/j.neuropsychologia.2005.07.004

Porto, F. H., Tusch, E. S., Fox, A. M., Alperin, B. R., Holcomb, P. J., and Daffner, K. R. (2016). One of the most well-established age-related changes in neural activity disappears after controlling for visual acuity. *NeuroImage* 130, 115–122. doi: 10.1016/j.neuroimage.2016.01.035

†Puschmann, S., Sandmann, P., Bendixen, A., and Thiel, C. M. (2014). Age-related hearing loss increases cross-modal distractibility. *Hear. Res*. 316, 28–36. doi: 10.1016/j.heares.2014.07.005

Ramkhalawansingh, R., Keshavarz, B., Haycock, B., Shahab, S., and Campos, J. L. (2016). Age differences in visual-auditory self-motion perception during a simulated driving task. *Front. Psychol*. 7:595. doi: 10.3389/fpsyg.2016.00595

Rapp, P. R., and Heindel, W. C. (1994). Memory systems in normal and pathological aging. *Curr. Opin. Neurol.* 7, 294–298. doi: 10.1097/00019052-199408000-00003

†Ren, Y., Ren, Y., Yang, W., Tang, X., Wu, F., Wu, Q., et al. (2018). Comparison for younger and older adults: stimulus temporal asynchrony modulates audiovisual integration. *Int. J. Psychophysiol.* 124, 1–11. doi: 10.1016/j.ijpsycho.2017.12.004

†Ren, Y., Yang, W., Nakahashi, K., Takahashi, S., and Wu, J. (2017). Audiovisual integration delayed by stimulus onset asynchrony between auditory and visual stimuli in older adults. *Perception* 46, 205–218. doi: 10.1177/0301006616673850

†Ren, Y., Yang, W., Wu, Q., Wu, F., Takahashi, S., Yoshimichi, E., et al. (2016). "Study of audiovisual asynchrony signal processing: robot recognition system of different ages," in *2016 IEEE International Conference on Mechatronics and Automation*, 2320–2325. doi: 10.1109/ICMA.2016.7558927

†Ren, Y. N., Yang, W., Takahashi, S., Nakahashi, K., and Wu, J. (2015). "Temporal gap between visual and auditory stimuli lessen audiovisual integration in aging under cross-modal attention," in *2015 IEEE International Conference on Mechatronics and Automation (ICMA)* (Piscataway, NJ: IEEE), 511–516. doi: 10.1109/ICMA.2015.7237538

Ross, L. A., Saint-Amour, D., Leavitt, V. M., Javitt, D. C., and Foxe, J. J. (2007). Do you see what i am saying? Exploring visual enhancement of speech comprehension in noisy environments. *Cerebr. Cortex* 17, 1147–1153. doi: 10.1093/cercor/bhl024

†Roudaia, E., Calabro, F. J., Vaina, L. M., and Newell, F. N. (2018). Aging impairs audiovisual facilitation of object motion within self-motion. *Multisens. Res.* 31, 251–272. doi: 10.1163/22134808-00002600

†Roudaia, E., Sekuler, A. B., Bennett, P. J., and Sekuler, R. (2013). Aging and audio-visual and multi-cue integration in motion. *Front. Psychol.* 4:267. doi: 10.3389/fpsyg.2013.00267

Salthouse, T. A., Hancock, H. E., Meinz, E. J., and Hambrick, D. Z. (1996). Interrelations of age, visual acuity, and cognitive functioning. *J. Gerontol. B. Psychol. Sci. Soc. Sci.* 51, 317–330. doi: 10.1093/geronb/51B.6.P317

†Sekiyama, K., Soshi, T., and Sakamoto, S. (2014). Enhanced audiovisual integration with aging in speech perception: a heightened McGurk effect in older adults. *Front. Psychol.* 5:323. doi: 10.3389/fpsyg.2014.00323

†Setti, A., Burke, K. E., Kenny, R. A., and Newell, F. N. (2011a). Is inefficient multisensory processing associated with falls in older people? *Exp. Brain Res.* 209, 375–384. doi: 10.1007/s00221-011-2560-z

†Setti, A., Burke, K. E., Kenny, R. A., and Newell, F. N. (2013). Susceptibility to a multisensory speech illusion in older persons is driven by perceptual processes. *Front. Psychol.* 4:575. doi: 10.3389/fpsyg.2013.00575

†Setti, A., Finnigan, S., Sobolewski, R., McLaren, L., Robertson, I. H., Reilly, R. B., et al. (2011b). Audiovisual temporal discrimination is less efficient with aging: an event-related potential study. *Neuroreport* 22, 554–558. doi: 10.1097/WNR.0b013e328348c731

†Setti, A., Stapleton, J., Leahy, D., Walsh, C., Kenny, R. A., and Newell, F. N. (2014). Improving the efficiency of multisensory integration in older adults: audio-visual temporal discrimination training reduces susceptibility to the sound-induced flash illusion. *Neuropsychologia*. 61, 259–268. doi: 10.1016/j.neuropsychologia.2014.06.027

Siqueira, G. S., Hagemann, P. D. M., Coelho, D. D. S., Santos, F. H. D., and Bertolucci, P. H. (2019). Can MoCA and MMSE be interchangeable cognitive screening tools? A systematic review. *Gerontologist* 59, e743–e763. doi: 10.1093/geront/gny126

†Sommers, M. S., Tye-Murray, N., and Spehar, B. (2005). Auditory-visual speech perception and auditory-visual enhancement in normal-hearing younger and older adults. *Ear Hear*. 26, 263–275. doi: 10.1097/00003446-200506000-00003

†Sparrow, W. A., Bradshaw, E. J., Lamoureux, E., and Tirosh, O. (2002). Ageing effects on the attention demands of walking. *Hum. Mov. Sci.* 21, 961–972. doi: 10.1016/S0167-9457(02)00154-9

†Spehar, B. P., Tye-Murray, N., and Sommers, M. S. (2008). Intra- versus intermodal integration in young and older adults. *J. Acoust. Soc. Am*. 123, 2858–2866. doi: 10.1121/1.2890748

†Stawicki, M., Majdak, P., and Başkent, D. (2019). Ventriloquist illusion produced with virtual acoustic spatial cues and asynchronous audiovisual stimuli in both young and older individuals. *Multisens. Res.* 32, 745–770. doi: 10.1163/22134808-20191430

Stein, B. E., and Stanford, T. R. (2008). Multisensory integration: current issues from the perspective of the single neuron. *Nat. Rev. Neurosci*. 9, 255–266. doi: 10.1038/nrn2331

Stein, B. E., Stanford, T. R., Ramachandran, R., Perrault, T. J., and Rowland, B. A. (2009). Challenges in quantifying multisensory integration: alternative criteria, models, and inverse effectiveness. *Exp. Brain Res.* 198:113. doi: 10.1007/s00221-009-1880-8

Stein, B. E., Stanford, T. R., and Rowland, B. A. (2014). Development of multisensory integration from the perspective of the individual neuron. *Nat. Rev. Neurosci*. 15, 520–535. doi: 10.1038/nrn3742

†Stevenson, R. A., Baum, S. H., Krueger, J., Newhouse, P. A., and Wallace, M. T. (2018). Links between temporal acuity and multisensory integration across life span. *J. Exp. Psychol. Hum. Percept. Perform.* 44, 106–116. doi: 10.1037/xhp0000424

†Stothart, G., and Kazanina, N. (2016). Auditory perception in the aging brain: the role of inhibition and facilitation in early processing. *Neurobiol. Aging* 47, 23–34. doi: 10.1016/j.neurobiolaging.2016.06.022

Sumby, W. H., and Pollack, I. (1954). Visual contribution to speech intelligibility in noise. *J. Acoust. Soc. Am*. 26, 212–215. doi: 10.1121/1.1907309

†Sun, Y., Liu, X., Li, B., Sava-Segal, C., Wang, A., and Zhang, M. (2020). Effects of repetition suppression on sound induced flash illusion with aging. *Front. Psychol.* 11:216. doi: 10.3389/fpsyg.2020.00216

†Taitelbaum-Swead, R., and Fostick, L. (2016). Auditory and visual information in speech perception: a developmental perspective. *Clin. Linguist. Phonet*. 30, 531–545. doi: 10.3109/02699206.2016.1151938

†Talsma, D., Kok, A., and Ridderinkhof, K. R. (2006). Selective attention to spatial and non-spatial visual stimuli is affected differentially by age: effects on event-related brain potentials and performance data. *Int. J. Psychophysiol*. 62, 249–261. doi: 10.1016/j.ijpsycho.2006.04.006

Tombaugh, T. N., and McIntyre, N. J. (1992). The mini-mental state examination: a comprehensive review. *J. Am. Geriatr. Soc*. 40, 922–935. doi: 10.1111/j.1532-5415.1992.tb01992.x

†Tye-Murray, N., Sommers, M., and Spehar, B. (2007). Auditory and visual lexical neighborhoods in audiovisual speech perception. *Trends Amplificat*. 11, 233–241. doi: 10.1177/1084713807307409

†Tye-Murray, N., Sommers, M., Spehar, B., Myerson, J., and Hale, S. (2010). Aging, audiovisual integration, and the principle of inverse effectiveness. *Ear Hear*. 31, 636–644. doi: 10.1097/AUD.0b013e3181ddf7ff

†Tye-Murray, N., Spehar, B., Myerson, J., Hale, S., and Sommers, M. (2016). Lipreading and audiovisual speech recognition across the adult lifespan: implications for audiovisual integration. *Psychol. Aging* 31:380. doi: 10.1037/pag0000094

†Tye-Murray, N., Spehar, B., Myerson, J., Sommers, M. S., and Hale, S. (2011). Cross-modal enhancement of speech detection in young and older adults: does signal content matter? *Ear Hear*. 32, 650–655. doi: 10.1097/AUD.0b013e31821a4578

Vroomen, J., and Keetels, M. (2010). Perception of intersensory synchrony: A tutorial view. *Atten. Percept. Psychophys.* 72, 871–884. doi: 10.3758/APP.72.4.871

Walling, A., and Dickson, G. (2012). Hearing loss in older adults. *Am. Family Physician* 85, 1150–1156. Available online at: https://www.aafp.org/afp/2012/0615/p1150.html

†Wang, B., Li, P., Li, D., Niu, Y., Yan, T., Li, T., et al. (2018). Increased functional brain network efficiency during audiovisual temporal asynchrony integration task in aging. *Front. Aging Neurosci*. 10:316. doi: 10.3389/fnagi.2018.00316

†Wang, L., Wang, W., Yan, T., Song, J., Yang, W., Wang, B., et al. (2017). Beta-band functional connectivity influences audiovisual integration in older age: an EEG study. *Front. Aging Neurosci*. 9:239. doi: 10.3389/fnagi.2017.00239

†Winneke, A. H., and Phillips, N. A. (2011). Does audiovisual speech offer a fountain of youth for old ears? An event-related brain potential study of age differences in audiovisual speech perception. *Psychol. Aging* 26, 427–438. doi: 10.1037/a0021683

Wood, R. Y., Giuliano, K. K., Bignell, C. U., and Pritham, W. W. (2006). Assessing cognitive ability in research: use of MMSE with minority populations and elderly adults with low education levels. *J. Gerontol. Nurs*. 32, 45–54. doi: 10.3928/00989134-20060401-08

World Health Organization (2004). *ICD-10: International Statistical Classification of Diseases and Related Health Problems: Tenth Revision, 2nd ed*. World Health Organization. Available online at: https://apps.who.int/iris/handle/10665/42980

World Health Organization (2017). *Integrated Care for Older People: Guidelines on Community-Level Interventions to Manage Declines in Intrinsic Capacity*. Available online at: https://apps.who.int/iris/handle/10665/258981 (accessed August 11, 2021).

World Health Organization (2018a). *Aging and Health*. Available online at: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health (accessed August 11, 2021).

World Health Organization (2018b). *International Statistical Classification of Diseases and Related Health Problems, 11th Revision, Fifth Edn, Vol. 1*. World Health Organization. Available online at: https://icd.who.int/browse11/l-m/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f1103667651 (accessed December 13, 2021).

World Health Organization (2021a). *Deafness and Hearing Loss*. Available online at: https://www.who.int/health-topics/hearing-loss#tab=tab_1 (accessed August 11, 2021).

World Health Organization (2021b). *Blindness and Vision Impairment*. Available online at: https://www.who.int/news-room/fact-sheets/detail/blindness-and-visual-impairment (accessed August 11, 2021).

Wu, J., Yang, J., Yu, Y., Li, Q., Nakamura, N., Shen, Y., et al. (2012). Delayed audiovisual integration of patients with mild cognitive impairment and Alzheimer's disease compared with normal aged controls. *J. Alzheimer's Dis.* 32, 317–328. doi: 10.3233/JAD-2012-111070

†References indicated with a † symbol are those included in the scoping review.

†Yang, W., Guo, A., Li, Y., Qiu, J., Li, S., Yin, S., et al. (2018). Audio-visual spatiotemporal perceptual training enhances the P300 component in healthy older adults. *Front. Psychol*. 9:2537. doi: 10.3389/fpsyg.2018.02537

Yueh, B., Shapiro, N., MacLean, C. H., and Shekelle, P. G. (2003). Screening and management of adult hearing loss in primary care: scientific review. *J. Am. Med. Assoc*. 289, 1976–1985. doi: 10.1001/jama.289.15.1976

†Zou, Z., Chau, B. K., Ting, K. H., and Chan, C. C. (2017). Aging effect on audiovisual integrative processing in spatial discrimination task. *Front. Aging Neurosci*. 9:374. doi: 10.3389/fnagi.2017.00374

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"CityQuest," A Custom-Designed Serious Game, Enhances Spatial Memory Performance in Older Adults

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Spatial cognition is known to decline with aging. However, little is known about whether training can reduce or eliminate age-related deficits in spatial memory. We investigated whether a custom-designed video game involving spatial navigation, obstacle avoidance, and balance control would improve spatial memory in older adults. Specifically, 56 healthy adults aged 65 to 84 years received 10 sessions of multicomponent video game training, based on a virtual cityscape, over 5 weeks. Participants were allocated to one of three training conditions: the main intervention, the "CityQuest" group ($n = 19$), and two control groups, spatial navigation without obstacle avoidance ("Spatial Navigation-only" group, $n = 21$) and obstacle avoidance without spatial navigation ("Obstacles-only" group, $n = 15$). Performance on object recognition, egocentric and allocentric spatial memory (incorporating direction judgment tasks and landmark location tasks, respectively), navigation strategy preference, and executive functioning was assessed in pre- and post-intervention sessions. The results showed an overall benefit on performance in a number of spatial memory measures and executive function for participants who received spatial navigation training, particularly the CityQuest group, who also showed significant improvement on the landmark location task. However, there was no evidence of a shift from egocentric to allocentric strategy preference. We conclude that spatial memory in healthy older participants is amenable to improvement with training over a short term. Moreover, technology based on age-appropriate, multicomponent video games may play a key role in cognitive training in older adults.

Keywords: aging, spatial navigation, video game, training intervention, balance control

INTRODUCTION

Spatial navigation, the ability to find our way between locations in an environment, is a complex cognitive function. To navigate successfully, an individual must recognize and remember salient landmarks, their relative locations, and the directions of previously taken routes. Two separate spatial strategies are thought to support these processes. First, an egocentric strategy involves the encoding of information related to the spatiotemporal sequence of environmental features relative to oneself, such as landmarks, and the sequence of movements necessary to get from one landmark to the next (Hartley et al., 2003; Wolbers et al., 2004). Second, an allocentric spatial strategy involves a more global representation or "cognitive map" of the environment where landmark locations are identified by their spatial relationship to one another (Tolman, 1948; O'Keefe and Nadel, 1978; Maguire et al., 1998).

Spatial navigation abilities have been shown to deteriorate as we age, often resulting in older adults avoiding unfamiliar environments which can, in turn, impact negatively on quality of life (Burns, 1999). It is widely accepted that older adults show impairments in allocentric processing and, to some extent, egocentric processing during spatial navigation tasks (Moffat, 2009; Klencklen et al., 2012; Lithfous et al., 2013; Colombo et al., 2017; Lester et al., 2017). Corresponding with declines in spatial abilities, older adults show reduced volume in the hippocampus and caudate nucleus (Raz et al., 2003; Raz and Rodrigue, 2006) which are key brain areas involved in allocentric and egocentric strategies, respectively.

Spatial navigation is also supported by the vestibular system (Brandt et al., 2005), which plays a crucial role in maintaining one's balance and postural control (Allen et al., 2004; Angelaki and Cullen, 2008; St George and Fitzpatrick, 2011). Vestibular function also declines with age (Anson and Jeka, 2016), impacting self-motion perception and the coding of the body's orientation and position in space. A typical finding is that older adults perform worse than their younger counterparts in a triangular completion task, i.e., returning to the starting point of a triangular path after being led along two angles of the triangle with their eyes closed (Adamo et al., 2012; Barrett et al., 2013). Even though vestibular function declines with aging, older adults rely more on vestibular information during spatial navigation, even when the visual cues are more reliable (Bates and Wolbers, 2014).

With aging, the cognitive demands of navigating through an environment may lead to resource competition between maintaining balance control and completing the navigation task, resulting in either reduced balance control (Simieli et al., 2015) or reduced performance in navigation (Lester et al., 2017), depending on task demands. This trade-off was observed in a study by Lövdén et al. (2005), in which younger and older adults walked on a treadmill while exploring a virtual museum, either with a handrail for support or without. Older adults showed a more unstable gait when navigating through the museum compared to when simply walking on the treadmill. Furthermore, age differences in spatial learning performance were more pronounced when no handrail support was supplied, whereas the performance of older adults improved in terms of both speed and accuracy with the provision of the handrail. Executive function has been shown to mediate navigational ability in aging (Taillade et al., 2013a). Navigating within a virtual environment using a joystick, balance board, or treadmill may be considered as a motor-cognitive dual-task condition, as cognitive processes are required both for motor and balance control, as well as for knowledge acquisition within the spatial environment.

Recent research in spatial navigation has benefited from the use of computer technology, with Virtual Reality (VR) in particular adopted as a means to assess spatial cognitive abilities in a wide range of groups, from healthy participants to patient studies. Relative to real-world environments, the use of virtual environments (VE) offer a number of benefits for studies of spatial cognition: VEs facilitate the study of large-scale spatial navigation within ecologically valid contexts while allowing for standardized protocols to be adopted across studies and also offer a high degree of experimental control (Diersch and Wolbers, 2019). For example, Merriman et al. (2016) embedded objects into a virtual rendering of both highly familiar and unfamiliar areas of a real university campus and reported a benefit of environment familiarity on spatial memory in older adults. Moreover, VR allows for the stimulation of multiple sensory systems (e.g., vision, audition, proprioception, vestibular system) whilst tracking and assessing the behavioral responses to the integration of different sensory cues (Dehn et al., 2018; Carr et al., 2019; Appel et al., 2020). Importantly, experimental manipulations that would be impossible in real-world scenarios of navigation can be used to understand the influence of different sensory information during specific aspects of navigation (Diersch and Wolbers, 2019).

The availability of VR has also allowed for the development of human analogs of spatial navigation tasks more typically used in rodent studies, such as the Morris Water Maze Task (Morris, 1981). The virtual Morris Water Maze Task (vWMT) has been used widely to assess spatial navigation abilities in both younger and older adults, with performance suggesting a specific decline in allocentric processing with aging (e.g., Moffat and Resnick, 2002; Antonova et al., 2009; Rodgers et al., 2012; Gazova et al., 2013; Daugherty et al., 2016). For example, Head and Isom (2010) found that older adults performed worse than younger adults on allocentric tasks embedded in a virtual maze, such as judging the temporal order of landmarks and the direction and relative distances associated with these landmarks. Wiener et al. (2013) also reported that, compared to younger adults, older adults were unable to use an allocentric spatial strategy when approaching a learned route from a novel direction or when required to repeat and retrace a learned route (Wiener et al., 2012), demonstrating allocentric but not egocentric deficits in spatial memory performance of older adults. In a novel study using dynamic VEs, Merriman et al. (2018a) reported that the presence of virtual crowds further impaired spatial memory performance in older but not younger adults. The use of VR/VE thus permits the carefully controlled study of the impact of ecologically valid everyday occurrences (i.e., crowded streets, obstacles) on older adults' spatial memory.

Although spatial navigation abilities decline with aging, evidence is emerging that training can lead to improvements in this skill in older adults. For example, Lövdén et al. (2012) trained younger and older participants in a VE spatial navigation task combined with treadmill walking. Following 4 months of training, the authors reported reduced age-related deficits in spatial navigation in the experimental group, relative to a group that only walked on the treadmill, without spatial navigation training. Furthermore, neuroimaging suggested that the spatial memory training had a protective effect as the hippocampal volume of the intervention group of older adults remained constant between post-intervention and at 4 months follow up, while the hippocampal volume of the treadmill-only control group decreased consistent with longitudinal age-related decline

(Lövdén et al., 2012). Thus, spatial navigation training appears to enhance navigation performance and protect the hippocampal structure from age-related decline. In addition, West et al. (2017) found that playing a 3D-platform video game (namely Super Mario 64©), for approximately 70 h over 6 months resulted in an increase in hippocampal gray matter volume in older adults compared to two control groups, an active, computerized music lesson group and a passive control group (West et al., 2017). Similar results were reported by Kühn et al. (2014) for a cohort of younger adults who played Super Mario 64® for a period of 2 months compared to a passive control group. Importantly, the increase in hippocampal gray matter volume was associated with a shift from an egocentric strategy to an allocentric strategy, suggesting a link with hippocampal volume and performance on virtual navigation tasks. These and other studies (e.g., Hötting et al., 2013) suggest that spatial navigation training in virtual environments can confer similar benefits on spatial cognition that were previously reported for tasks involving real-world navigation (i.e., London taxi drivers, Woollett and Maguire, 2011; Brunec et al., 2019).

The current study builds on our previous findings that older adults are more adversely affected by the presence of crowds while navigating than younger adults (Merriman et al., 2018a), and other reports that attentional resources are shared between balance control and spatial navigation (Taillade et al., 2013b). Specifically, this study sought to investigate whether playing a video game that required active navigation in a 3D virtual environment of increasing complexity while avoiding obstacles would improve spatial memory performance and executive function in older adults. We developed a multicomponent intervention, named "CityQuest" that trained spatial navigation in unfamiliar, crowded environments that required the participant to use balance control to navigate through a city landscape whilst avoiding obstacles and pedestrians. To provide a better understanding of the contribution of spatial memory and the obstacle avoidance components of CityQuest, we used a component control manipulation (Boot et al., 2013) and created two control conditions, one without the spatial memory task but which involved obstacle avoidance and balance control (Obstacles-only), and the other without obstacle avoidance but which involved spatial memory and balance control (Spatial Navigation-only). While the Spatial Navigation-only condition involves dual-task training of postural stability and navigation, the CityQuest condition involves multi-task training, with an extra layer of complexity that requires additional executive functioning to avoid obstacles. We hypothesized that the "CityQuest" intervention training using a realistic, ecologically valid virtual environment would lead to improvements in spatial memory relative to spatial navigation training only or obstacle avoidance training only, due to the involvement of more cognitively demanding multi-tasking components (Van Impe et al., 2013; Moreau and Conway, 2014).

All participants were required to perform two 60-min sessions of training per week over 5 weeks, i.e., a total of 10 h of training. This time frame was based on a number of previous cognitive training studies which have suggested that 4 weeks or 10 training sessions are of sufficient duration for training gains to occur (Kelly et al., 2014; Schoene et al., 2014). Before and after the intervention, spatial memory was assessed with measures of object recognition, direction judgment (egocentric processing), and cognitive mapping abilities (allocentric processing). Furthermore, we were interested in whether spatial navigation training in general would lead to a change from a more egocentric-based navigation strategy to a more efficient allocentric spatial strategy as measured by the strategy maze assessment (see Wiener et al., 2013).

MATERIALS AND METHODS

Participants

Participants were recruited through advertisements placed in local aging organizations and local media seeking community-dwelling adults aged 65 years or older in the Dublin area, in good general health, with no cognitive, visual, or hearing impairments, and able to maintain balance independently. A total of 70 older participants met inclusion criteria and were enrolled in the study. Fourteen participants did not complete the study: 5 withdrew due to ill health and 9 due to other commitments. Thus, the final sample included a total of 56 participants (35 female; $M = 71.82$, SD = 4.64; age range 65–84). All participants reported normal or corrected-to-normal vision and hearing, no cognitive impairment, and none reported a history of psychiatric or neurological illness. Following baseline measures (see below), participants were pseudo-randomly assigned to one of the three training intervention conditions. There were 21 participants (7 male, 14 female) assigned to the "CityQuest" training, 20 (8 male, 12 female) assigned to the "Spatial Navigation-only" training and 15 (6 male, 9 female) assigned to the "Obstacles-only" training group.

Experimental Protocol and Design

The protocol consisted of three sets of assessments: baseline measures; pre- and post-training measures, and the training intervention itself. The overall experimental design was based on a mixed, factorial design with participant group (CityQuest, Spatial Navigation-only, or Obstacles-only) as the between group factor. Participants were enrolled on an ongoing basis and randomly allocated to the CityQuest or Spatial-navigation condition first. Participants were then recruited for the Obstacles-only condition. The experiment protocol and recruitment procedures were approved by the School of Psychology Research Ethics Committee prior to the start of the study. Accordingly, all participants provided informed, written consent prior to taking part in the experiment.

Stimuli and Apparatus

The study took place in a dedicated testing laboratory in Trinity College Institute of Neuroscience. Two different and unique virtual environments were created for the purpose of the pre- and post-assessments: a VE for the Spatial Navigation Assessment and a VE for the Spatial Strategy Assessment task. The VEs were designed using a proprietary engine based on Ogre 3D and converted into video format. All pre- and post- training

VE assessments were programmed and responses recorded using Presentation® software[1]. The VE assessments were presented on a Dell Latitude E4300 laptop and viewed by the participant on a HP L1710 17″ LCD color monitor (resolution 1,024 × 768 pixels). Participants were seated approximately 57 cm in front of this monitor.

The intervention training games were presented using either a Dell Alienware Aurora 875W computer connected to a 50″ Sony Bravia LED-backlit LCD flat panel display with a refresh rate of 120 Hz, or through a Dell Optiplex 7010 computer with a refresh rate of 60 Hz connected to a standard projector directed at a white screen. This dual set-up allowed us to test two participants at the same time and participants were trained on both apparatus (i.e., each participant performed five training sessions with the LCD display and 5 with the projector display). A Wii Balance Board (WBB; Nintendo, Kyoto, Japan) was connected to each PC *via* Bluetooth. Each WBB was positioned approximately 2 m away from the display, embedded into a compliant surface mat measuring approximately 2 m × 2 m that was flush with the platform floor (for an illustration of this set-up, see Merriman et al., 2018b). For added safety, a waist-high support frame was secured around the WBB which the participant could use for support when required. The sounds from the games were presented *via* Sennheiser HD 202 headphones (we used wired and wireless versions).

Baseline Measures

Prior to the intervention, participants' ability across a range of sensory and cognitive measures were measured during a "baseline" session. Measures of visual acuity and contrast sensitivity were taken using the ETDRS acuity chart and the Pelli-Robson Contrast Sensitivity Test, respectively. Hearing ability was assessed with the Hughson-Westlake Audiogram at 4 kHz. Global cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), with performance of below a score of 23 indicative of cognitive impairment (Luis et al., 2009). Participants' self-reported sense of direction was assessed with the Santa Barbara Sense of Direction Scale [SBSOD; $M = 4.74$, SD = 0.92; (Hegarty et al., 2002)]. This scale ranged from 1 to 7, with higher scores on this measure indicating a better sense of direction.

Assessment Measures (Pre- and Post-training Assessments)

We included two main tasks (described below) to assess the effectiveness and generalizability of the training intervention on aspects of spatial cognition: the Spatial Navigation Assessment task and the Spatial Strategy Assessment task. We also included a measure of executive function which was assessed using the standardized Trail Making Test (TMT) (Reitan, 1958). The performance in the TMT was evaluated by scoring the time needed for the completion of two parts, A and B. To eliminate the motor component involved in this test, both parts of the TMT were contrasted by a difference score (TMT Part B—TMT Part A) (Corrigan and Hinkeldey, 1987). The pre- and post-assessments also included measures of balance control, ratings of balance confidence and we also tested whether measures of perceptual functioning (i.e., useful field of view and motion coherence threshold assessments) were affected by the training intervention. The effect of training on measures of balance and perceptual function are reported elsewhere (O'Callaghan et al., 2018; Roudaia et al., in prep).

[1]http://www.neurobs.com

A

B

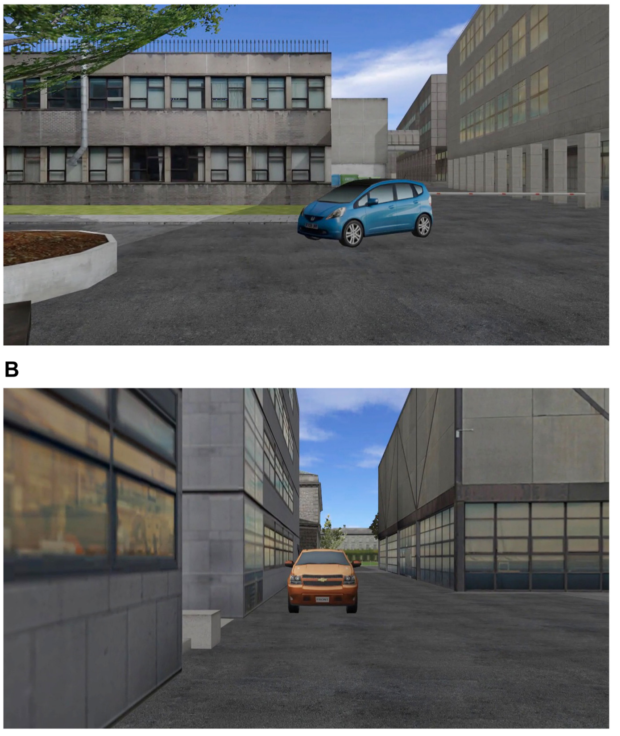

FIGURE 1 | Example imagesof target objects embedded at intersections along **(A)** Route A; and **(B)** Route B of the Spatial Navigation Assessment.

Spatial Navigation Assessment

The Spatial Navigation assessment was implemented in a VE that was a simulation of an area within the campus of Trinity College Dublin (Merriman et al., 2016). We created separate videos for two distinct virtual routes through this area of the VE campus and target objects were embedded at different intersections along these routes. Two separate video clips depicted a first person view of different routes taken through the VE which participants were required to learn. Each video clip was approximately 2 min in duration. Each route comprised eight intersections and at each intersection, a left turn (3 intersections), a right turn (3) or a straight ahead (2) direction was followed. Whenever the virtual camera approached an intersection within 20 m, a unique target object would appear, which participants were asked to learn (see **Figures 1A,B**). There were 16 target objects in all, divided into two sets and each set was allocated to one route across all participants. The presentation order of the two routes was counterbalanced across participants and across testing sessions (pre- or post-training).

Each assessment began with a learning phase, in which participants were shown a video clip of a route twice in a row and asked to remember the route and the objects encountered in the route. Directly following learning of the route, participants were tested using the following four tasks in the same sequential order, to minimize cross-over effects.

First, participants completed the Object Recognition Task, which assessed target object recall using an Old/New recognition memory design (Merriman et al., 2016). Previous research has found that the neural activity in the parahippocampal gyrus to target objects placed at decision points along a route reflects the navigational relevance of an object's location in the learning environment. This suggests that the automatic storage of navigationally-relevant object location in the parahippocampal gyrus is part of the neural mechanism underlying successful navigation (Janzen and van Turennout, 2004). Participants were presented with either a target object or distractor object image and asked to indicate as quickly and as accurately as possible whether or not they had seen the object along the learned route by pressing one of two assigned keys ("z" and "m") respectively, indicating a "yes" or "no" response on the keyboard. Distractors were different exemplar objects from the same category as each target object. This task consisted of 16 trials (8 targets and eight distractors) presented in random order.

Next, participants completed a Direction Judgment Task that measured egocentric spatial processing (see Head and Isom, 2010; Merriman et al., 2016). There were eight trials in this task. In each trial, participants were presented with an image of one of the eight target objects from the learned route and asked to indicate as accurately as possible whether the object was associated with a right turn, left turn or maintained a straight-ahead course by pressing one of three corresponding keys (i.e., left, up or right arrow) on a keyboard. Trial order was randomized across participants.

The third task was a "pen and paper" Target Landmark Location Task that measured allocentric processing or "cognitive mapping" (Moffat and Resnick, 2002). In this task, participants were presented with a 2D, scaled map of the learned VE campus without any target objects indicated. For each of the target objects, participants were asked to indicate its location by marking "X" on the map, without naming the target.

The fourth task was a "Target Landmark Naming" Task, in which participants were presented with another copy of the 2D, scaled map of the VE campus but this time the map was marked with "X"s which each indicated the location of a target object along the route. Participants were required to write the name of the target object at each location indicated on the map.

Spatial Strategy Assessment

This test was designed to measure the participant's ability to use allocentric processing for route navigation and if this strategy were more likely to be adopted following training. The test was based on a novel virtual environment which consisted of a route taken through a maze, and was adapted from Wiener et al. (2013). The maze consisted of two straight paths intersecting with two other perpendicular paths, resulting in four intersection points. The route traversed four intersections, identifiable by two unique landmarks, located on diagonally opposite corners (see **Figure 2**). These landmarks consisted of an image of an object presented on four sides of a cube (side length: 0.5 m), suspended 2 m above the floor. Each intersection was obscured by fog and whilst the camera approached the intersection, the object became visible from 12.5 m with a quadratic increase in light intensity.

Participants were first presented with a video clip of a first person view of a route taken through this custom-designed VE maze, populated by landmark objects, which they were required to learn. They were then tested on their spatial memory of the route.

A test trial consisted of a 6 s video clip sampled from the learned path that traversed one arm of the maze, stopping at the first intersection (see **Figure 2A**) and depicting the landmark objects in their original locations. These segments were presented either traveling in the same direction (same direction trials) or a different (but not reverse) direction (different direction trials) as in the learned route (see **Figures 2B,C**). Each clip was immediately followed by an image of white arrows pointing either left, upward, or right, prompting participants to report in which direction the learned route proceeded at this intersection by pressing the appropriate arrow key on the keyboard. There were six experimental blocks of 12 trials per block totaling 72 trials. These same and different direction trials tested different spatial processing abilities: "same direction" trials assessed egocentric strategies (associative cue or beacon strategies; Wiener et al., 2012, 2013), whereas "different direction" trials require more allocentric processing of the spatial relationships between landmarks. Spatial strategy preference was measured by calculating the percentage of responses in line with each of the three spatial strategies (associative cue, beacon and allocentric) of the "different direction" trials that distinguished between all strategies.

Description of the CityQuest Training Intervention

The main version of the training intervention, that is the "CityQuest" game, was custom-built and created by Testaluna© using Unity software. In the game, the participant navigates a virtual cityscape using their balance to guide the movements of their virtual avatar by shifting their weight on a Wii balance board. The participant's task was to learn the locations of four target landmarks (e.g., pharmacy, cinema, bank, jewelers) located throughout the city during a learning phase, and then navigate to these locations using the fastest route on three subsequent game levels. At the same time, participants had to ensure that their avatar avoided obstacles in their way. The obstacles included static (e.g., puddles or bollards) or dynamic (e.g., moving balls or pedestrians) objects which were presented with semantically congruent auditory sounds (e.g., sound of rolling wheels). During game training, participants navigated from a first person perspective, however, their position was also simultaneously displayed on a smaller map of the environment presented in an aerial view from a fixed orientation in the top left-hand corner of the screen. Target landmarks were not displayed in the smaller map.

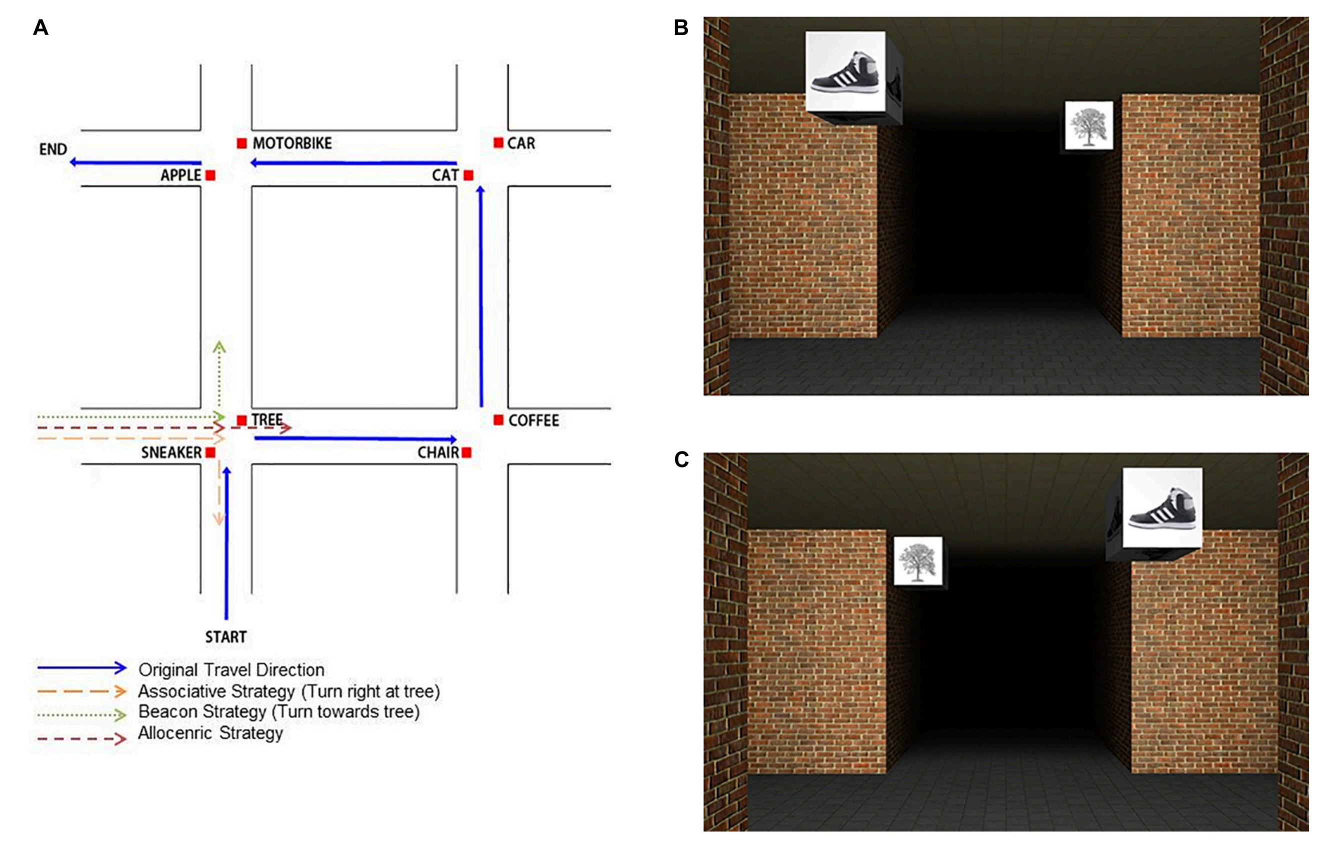

FIGURE 2 | Spatial Strategy Assessment: **(A)** Schematic overview of the learning route during the spatial strategy assessment; Example image of an intersection from the maze approached from **(B)** the original learned direction (correct response: right turn); and **(C)** from a different direction to that from learning (correct response: straight ahead).

Game difficulty was adapted to each participant's performance across sessions. The spatial navigation difficulty varied across sessions by changing the complexity of the cityscape, i.e., the number of intersections crossed in the city layout. There was a total of four complexity levels to the cityscapes corresponding to 8, 12, 16, and 22 intersections (labeled 1 to 4, respectively). Furthermore, obstacle complexity was manipulated by increasing the transparency of the obstacles, the number or density of obstacles on each street, and the speed of moving obstacles. There were eight complexity levels of obstacle avoidance in total. Performance on the game was constantly measured and points awarded (and displayed on the screen) for achievements including successful obstacle avoidance, and reaching a target landmark using the most efficient or fastest route. To ensure better learning and to sustain motivation, the difficulty and complexity in all three games was adapted to participants' performance across different sessions (Green and Bavelier, 2008). Specifically, task difficulty was increased to the next level if the participant reached a criterion level of performance in each component (obstacle avoidance, spatial navigation). Otherwise, the participant remained at the same game level for the subsequent session. For more details of the training intervention see Merriman et al. (2018b).

CityQuest Training Intervention and Control Conditions

The main aim of the "CityQuest" game intervention was to locate specific target landmarks by navigating the avatar to each landmark using the most efficient route possible. Participants first learned to navigate through the virtual city by shifting their weight on a WBB to control the movements of an avatar embedded in the city. During the learning phase, participants were familiarized with the location of target landmarks within the city through active exploration. They were presented with three levels of difficulty in the game, each associated with locating the same landmarks but from different starting points within the same virtual city. During the navigation of the virtual city the participant had to also ensure that the avatar avoided obstacles by shifting their weight on the balance board.

The CityQuest game was also used as the basis for the design of two control conditions of the game, which were created to examine the effect of specific characteristics of the CityQuest game on spatial cognition and obstacle avoidance. The "Spatial Navigation-only" version of the game was identical to the CityQuest game, except that the obstacles were not included. For the "Obstacles-only" version there was no requirement to navigate to a target location. Instead, this version of the game required avoiding the same static and dynamic obstacles whilst moving through the city to collect gems located along the middle of the path within a time limit. Thus, by comparing performance in the CityQuest with performance in these control conditions, we aimed to unpick the relative contribution of spatial navigation and obstacle avoidance on the effect of the intervention on our outcome measures.

Game training performance on each session was assessed using two different measures for all training conditions, that is, the time taken at decision points and the number of intersections traversed (which was an approximation for how efficiently the cityscape was explored). There were also two different measures for the CityQuest and Spatial Navigation-only games (since the Obstacle avoidance task was time-limited) including the time taken to complete each level and navigation efficiency. Navigation efficiency was calculated by dividing the distance of the most efficient route possible to locate the target (e.g., 100 distance units) by the actual distance traveled by the participant (e.g., 130 distance units, to yield a score of 0.77) in the virtual space. Other measures of performance included obstacle avoidance efficiency (CityQuest and Obstacles-only training groups only). Obstacle avoidance efficiency was calculated as the number of obstacles successfully avoided during training divided by the total number of obstacles encountered (e.g., if 37 of the 42 objects were successfully avoided, this yielded a score of 0.88).

Procedure

The entire study (including all baseline, assessments, and training sessions) took place over several weeks and required a site visit to a dedicated testing lab in Trinity College for the duration of the experiment. All participants first completed the baseline measures in a single session. Participants were then assigned to one of the three training groups. All participants performed the pre-assessment tests (spatial cognition, executive function, perceptual function, balance) over two different sessions. Participants were also invited to volunteer for neuroimaging (MRI) testing before and after the training sessions (for further details see Merriman, 2016; O'Callaghan et al., 2018). All participants were informed that training on the intervention required them to perform two by 60 min sessions of training per week over 5 weeks, totaling 10 training sessions. A member of the research team was present at all times during training to troubleshoot any issues raised by participants and to monitor training compliance. A minimum of a 1 day break was required between sessions to allow for sufficient levels of rest and recovery (see Montana et al., 2019). After the last training block, participants completed the post-training assessments (a repeat of the pre-training assessments).

Data Analysis

All statistical analyses were conducted using SPSS 26 (SPSS Inc., Chicago, Illinois). The general significance level was set to $p = 0.05$ (two-tailed) unless otherwise stated. Baseline measures were analyzed using independent *t*-tests. Group differences in baseline characteristics were analyzed using a series of one-way analyses of variance (ANOVAs).

Group differences in the progress of participants' performance through three levels of 10 training sessions on game measures were analyzed through a series of mixed ANOVAs or mixed ANCOVAs, depending on group differences in baseline characteristics, and are available under **Supplementary Material**. These performance measures included: (a) the amount of time taken at decision points during training; (b) the number of intersections traversed during training; (c) the time taken to complete each level during training (CityQuest and Spatial Navigation-only as time was held constant for those in Obstacles-only); (d) navigation efficiency during training (CityQuest and Spatial Navigation-only); and (e) obstacle avoidance efficiency during training (CityQuest and Obstacles-only).

The hypothesized advantage of the CityQuest game training was tested by the interaction of the factors "group" (CityQuest, Spatial Navigation-only, or Obstacles-only) and "time" (pre- and post-training) in mixed ANOVAs/ANCOVAs (depending on group differences in baseline characteristics) using performance differences across three different assessments as dependent outcome variables: accuracy to the spatial navigation assessment, accuracy to the spatial strategy assessment and time taken to complete the TMT (executive function).

For an exploration of any differences on measures of spatial navigation ability and executive function associated with improvement through training in the CityQuest and Spatial Navigation-only game conditions (i.e., progressing to at least the third difficulty level) compared either to those who did not train successfully in these conditions, or those training on the Obstacles-only condition, please see the **Supplementary Material**. Successful spatial navigation training was characterized by progressing to at least the 3rd difficulty level (out of a possible four difficulty levels) of the game during training.

Critical tests for distinguishing performance across groups were conducted, where appropriate, using six planned comparisons in which the effects of each training condition were compared one-on-one using paired *t*-tests at pre- and post-training, and using a Bonferroni-corrected alpha level of 0.008 (unless otherwise stated).

RESULTS

Training Group Baseline Characteristics

All participants had normal or corrected to normal visual function (Sandlin et al., 2014) and hearing for their age (Müller et al., 2009; Merriman et al., 2018b). None scored below the Montreal Cognitive Assessment (MoCA) cut-off score for mild cognitive impairment (MoCA; $M = 26.93$, SD = 2.03). All participants self-reported a good sense of direction (SBSOD; $M = 4.74$, SD = 0.92).

Table 1 summarizes the results of each of the baseline measures for participants grouped by training conditions. Separate, one-way ANOVAs were conducted on each of the baseline measures with training group (3: CityQuest, Spatial Navigation-only, Obstacles-only) as the between group factor. A main effect of training group on age revealed that participants assigned to the CityQuest group were younger than those assigned to either the Spatial Navigation-only ($p = 0.016$) or Obstacles-only ($p = 0.01$) groups. There was no effect of group

TABLE 1 | Mean age profile and baseline characteristics of those allocated to the CityQuest, Spatial Navigation-only and Obstacles-only training conditions (with standard deviations in parentheses).

	CityQuest (*N* = 21)	Spatial navigation-only (*N* = 20)	Obstacles-only (*N* = 15)	F ratio	*P* value
Age (years)	69.27 (2.68)	73.10 (4.59)	73.67 (5.46)	6.10	0.004*
MoCA score	27.52 (1.83)	26.85 (2.30)	26.20 (1.78)	1.94	0.154
SBSOD rating	4.63 (1.26)	4.68 (0.66)	5.00 (0.59)	0.81	0.452
Visual Acuity (LogMAR)	0.04 (0.07)	0.15 (0.12)	0.07 (0.07)	7.20	0.002*
Contrast Sensitivity (logCS)	1.95 (0.00)	1.91 (0.12)	1.95 (0.00)	2.51	0.091
Hearing Acuity (Db)	30.96 (15.36)	35.13 (16.37)	35.00 (17.32)	0.29	0.751

**significant at $p < 0.05$.*

on MoCA score, suggesting that participants were matched in global cognitive ability. Also, there was no evidence for a group effect on participants' rated sense of direction (SBSOD). Although visual acuity was within the normal range for all participants, a main effect of training group suggested participants in the CityQuest ($p = 0.001$) and Obstacles-only ($p = 0.041$) groups had significantly better visual acuity compared to those in the Spatial Navigation-only group. However, there was no evidence for a group difference in measures of contrast sensitivity. The groups were also matched on measures of hearing acuity.

Game Training Performance

Details of the results of training performance across the groups on all training measures (time taken to complete training; navigation efficiency; obstacle avoidance efficiency) can be found in **Supplementary Material**. In summary, although most participants improved their performance on the training game, of the 41 participants assigned to both the CityQuest and Spatial Navigation-only training conditions, 22 (10 male, 12 female; 9 CityQuest, 13 Spatial Navigation-only) successfully trained to the most difficult levels in the spatial navigation component (i.e. levels 3 and 4). Improvement in spatial navigation training was characterized by progressing to at least the third difficulty level (out of four difficulty levels) in terms of city complexity during training. In contrast, 19 (5 male, 14 female; 12 CityQuest, 7 Spatial Navigation-only) failed to improve or sufficiently progress to the required difficulty level across the 10 training sessions. Details of a series of exploratory analyses comparing performance on each of the assessment tasks between the participants whose performance improved with training and those whose performance did not improve with training can be found under **Supplementary Material**.

Pre- and Post-intervention Assessment Measures

Performance on each of the pre- and post-training assessments was used to measure the effect of training, and is summarized in **Table 2**. As the training groups differed in age and visual acuity, these factors were initially included as covariates in the analyses of the spatial navigation assessment, spatial strategy assessment, and Trail Making Test (TMT). However, these factors did not correlate with any of the studied dependent measures (all ps = n.s.). Furthermore, there was no effect of age (all F ratios < 1) or visual acuity [F ratios < 1; landmark location task $F(1, 51) = 1.83$, $p = 0.183$, $\eta_p{}^2 = 0.04$; landmark naming task $F(1, 51) = 1.72$, $p = 0.82$, $\eta_p{}^2 = 0.01$] in any of the spatial navigation tasks, the same and different direction trials of the spatial strategy assessment, or the TMT, nor did the covariates interact with any of the dependent variables (all ps = n.s.).

Spatial Navigation Assessment

See **Table 2** for mean performance accuracy across training groups on the spatial navigation assessments. We hypothesized that those in the CityQuest and Obstacles-only group would improve across pre- and post-training assessments on the object recognition task within the Spatial Navigation assessment, as training involved recognizing obstacles to avoid under increasing levels of difficulty which was common to both groups. For the remaining tasks in the spatial navigation assessment, we expected that those in the CityQuest and Spatial Navigation-only groups would perform better than those in the Obstacles-only group across pre- and post-training assessment of spatial navigation.

A series of mixed ANOVAs with group (3: CityQuest, Spatial Navigation-only, Obstacles-only) as the between group factor and time (2: pre-, post-training) as the within group factor were conducted on performance accuracy to the object recognition task, direction judgment task, landmark location task, and landmark naming task in the spatial navigation assessment. A series of one-way ANOVAs confirmed no differences at pre-training assessment among the training groups on the spatial navigation assessment, spatial strategy assessment, or TMT [all ps > 0.15].

An ANOVA of performance on the object recognition task showed no main effect training group [$F(2, 53) < 1$]. There was a main effect of time [$F(1, 53) = 7.49$, $p = 0.008$, $\eta_p{}^2 = 0.12$], with better performance post- ($M = 89.84$, SD = 10.5) than pre-training assessment ($M = 85.16$, SD = 10.83, $p = 0.014$). There was no evidence for an interaction between training group and time [$F(2, 53) = 1.57$, $p = 0.22$, $\eta_p{}^2 = 0.06$].

An analysis of performance accuracy on the direction judgment task, revealed no effect of training group [$F(2, 53) < 1$], no effect of time [$F(1, 53) = 3.07$, $p = 0.086$, $\eta_p{}^2 = 0.06$], and no interaction between training group and time [$F(2, 53) < 1$].

An ANOVA of performance on the landmark location task revealed no effect of training group [$F(2, 53) < 1$]. There was a main effect of time [$F(1, 53) = 9.87$, $p = 0.003$, $\eta_p{}^2 = 0.16$], with performance on this assessment improving from pre- ($M = 56.47$, SD = 22.42) to post- training ($M = 66.96$,

TABLE 2 | Mean performance accuracy across the spatial navigation and spatial strategy assessments, percentage strategy preference, and completion times for the trail making test at pre- and post-training across each of the training groups (with standard deviations in parentheses).

	Pre-training			Post-training		
	CityQuest $N = 21$	**Spatial navigation-only** $N = 19$	**Obstacles-only** $N = 15$	**CityQuest** $N = 21$	**Spatial navigation-only** $N = 19$	**Obstacles-only** $N = 15$
Spatial navigation assessment						
Object recognition	86.01 (9.86)	85.31 (11.70)	83.75 (11.52)	91.07 (7.01)	86.25 (13.99)	92.92 (8.14)
Direction judgment	70.24 (16.52)	66.25 (21.50)	60.83 (20.52)	72.62 (18.38)	71.88 (22.53)	69.17 (15.57)
Landmark location	50.89 (22.21)	61.25 (22.73)	57.92 (22.09)	71.73 (22.93)	67.50 (26.25)	59.59 (27.74)
Landmark naming	66.07 (27.71)	60.63 (26.99)	61.67 (24.31)	66.67 (30.19)	66.88 (27.29)	64.17 (24.94)
Spatial strategy assessment						
Same direction	84.33 (13.56)	74.17 (21.23)	76.39 (15.40)	87.50 (10.12)	81.04 (19.84)	81.11 (13.26)
Different direction	34.92 (12.75)	31.15 (11.74)	33.75 (12.10)	36.21 (14.81)	39.37 (8.89)	36.67 (21.89)
Strategy preference						
Associative	47.62 (17.31)	46.25 (15.17)	45.56 (15.06)	49.21 (17.66)	45.83 (17.42)	42.78 (13.31)
Beacon	40.87 (14.17)	43.75 (12.35)	43.33 (7.18)	33.73 (17.18)	42.50 (19.85)	37.22 (14.73)
Allocentric	10.71 (15.84)	9.58 (14.38)	8.89 (12.39)	15.87 (19.53)	10.42 (14.27)	18.89 (19.79)
Trail making test						
Completion time (B-A)	54.93 (20.72)	60.60 (43.95)	57.53 (26.09)	35.31 (12.07)	48.02 (37.49)	49.93 (23.92)

SD = 25.47, $p = 0.002$), and a significant interaction between training group and time [$F(1 = 2, 53) = 3.7$, $p = 0.031$, $\eta_p^2 = 0.12$]. The CityQuest group improved in performance on this task from pre- to post-training training ($p = 0.001$), whereas there was no such improvement found for the Spatial Navigation-only ($p = 0.16$) and Obstacles-only ($p = 0.8$) groups.

Finally, an analysis of performance on the landmark naming task revealed no effect of training group, no effect of time and no interaction between these factors [all F ratios < 1].

Spatial Strategy Assessment

We hypothesized that those who received spatial navigation training would perform better than those in the Obstacles-only group across pre- and post-training assessments on the same direction and different direction trials. In particular we expected that those in the Spatial Navigation-only group would show greater improvement than those assigned to the other two training groups on the different direction trials as their training took place in an empty city, similar to the empty corridors utilized in this maze assessment (see **Figures 2B,C**). We were also interested in whether strategy preference would change across groups as a result of training. For the spatial strategy assessment, a series of mixed ANOVAs were carried out on performance accuracy to the same and different direction trials and in the spatial strategy preference analysis. See **Table 2** for mean performance accuracy across training groups on this spatial strategy assessment measures.

The ANOVA on performance to the "same direction" trials showed no effect training group [$F(2, 53) = 2.18$, $p = 0.12$, $\eta_p^2 = 0.08$]. There was a main effect of time [$F(1, 53) = 4.56$, $p = 0.037$, $\eta_p^2 = 0.08$], with performance improving from pre- ($M = 78.57$, SD = 17.43) to post-training ($M = 83.48$, SD = 15.1, $p = 0.033$). There was no interaction between the training group and time [$F(2, 53) < 1$].

An analysis of performance to the "different direction" trials suggested that it was generally poor: performance across the three training conditions was not significantly better than chance (33%) at either pre-training or post-training [all t values < 1], with the exception of the performance of the Spatial Navigation-only group at post-training [$t(19) = 3.21$, $p = 0.005$]. An analysis of performance to the "different direction" trials revealed no effect training group [$F(2, 53) < 1$]. However, there was a main effect of time [$F(1, 53) = 4.26$, $p = 0.044$, $\eta_p^2 = 0.07$], with performance significantly improving from pre- ($M = 33.26$, SD = 12.11) to post-training ($M = 37.46$, SD = 15.2, $p = 0.04$) across all groups. There was no interaction between training group and time [$F(2, 53) = 1.19$, $p = 0.31$, $\eta_p^2 = 0.04$].

To assess participants' preferred strategy for navigation, for each participant we calculated the percentage of their responses which were consistent with each of the three navigation strategies (i.e., use of an associative cue, beacon, or allocentric strategy) in the "different direction" trials that distinguished between all strategies (see example in **Figures 2B,C**), at pre- and post-training. We conducted a mixed ANOVA with training group (3) as the between group factor, and time (2: pre-, post-training) and strategy type (3: associative cue, beacon, allocentric) as the within group factors. There was no effect of group or time [all F ratios < 1] but a main effect of strategy was found [$F(2, 52) = 62.06$, $p < 0.001$, $\eta_p^2 = 0.71$]. This main effect indicated a greater preference for the associative cue ($M = 46.43$, SD = 11.82) and beacon strategies ($M = 40.18$, SD = 11.5) compared to the allocentric strategy ($M = 12.28$, SD = 13.49, $p < 0.001$) for the participants. There were no interactions between group and time [$F(2, 52) < 1$] nor between strategy and time [$F(2, 52) = 3.06$, $p = 0.055$, $\eta_p^2 = 0.11$]. There were no other significant interactions found (all F ratios < 1).

Training Effect on Executive Function

We hypothesized that executive function performance of those allocated to the CityQuest condition would improve across pre- and post-training as this condition involved a higher level of multitasking than the Spatial Navigation-only or Obstacles-only conditions. Performance across groups on the TMT was analyzed pre- and post-training with a mixed ANOVA using the difference score (TMT B—TMT A) described above. The mixed ANOVA showed no effect of training group [$F(2, 51) < 1$]. There was a main effect of time [$F(1, 51) = 11.54$, $p = 0.001$, $\eta_p{}^2 = 0.18$], with performance improving from pre- ($M = 57.65$, SD $= 31.56$) to post-training ($M = 43.84$, SD $= 26.93$, $p = 0.001$). There was no interaction between training group and time [$F(2, 51) < 1$]. However, planned comparisons revealed that the CityQuest trained group performed the TMT more quickly following training (post-assessment stage) than before training ($p = 0.005$) compared to either the Spatial Navigation-only ($p = 0.042$) or Obstacles-only ($p = 0.39$) groups.

DISCUSSION

This study was designed to investigate whether a spatial navigation and obstacle avoidance intervention, coupled with a balance control component using the Wii balance board, improved spatial memory performance and executive function in older adults. To that end, participants embarked on a training intervention over several weeks and their performance was compared to participants enrolled in one of two control conditions involving training on spatial navigation only or obstacle avoidance only. Our findings indicated that all three training conditions resulted in improvements for older adults in general on different but not all outcome measures, namely the object recognition task, the landmark location task, different direction trials of the spatial strategy assessment, and executive function.

Assessment of Spatial Navigation Following Training

The CityQuest intervention condition contained multiple components (i.e., locating target landmarks while avoiding obstacles and maintaining balance), a training approach which has been shown to result in the most effective cognitive enhancement of older adults (Basak et al., 2008; Anguera et al., 2013). We expected older adults allocated to the CityQuest group and the Spatial Navigation-only group to improve on all measures of the spatial navigation task, but not those in the Obstacles-only group, as their training did not have a spatial learning component. However, we found no improvement on the direction judgment or landmark naming tasks in the performance of any of the groups following training. One reason that may account for this lack of improvement is that performance was already quite good on both of these tasks for all training groups at the pre-training stage (66 and 64%, respectively per assessment) and it is possible that older adults had reached ceiling effects in terms of their performance (Whitlock et al., 2012).

We hypothesized that following training, both the CityQuest and Obstacles-only group would improve on the object recognition task relative to the Spatial Navigation-only group since object avoidance was common to their interventions. While the performance of the Obstacles-only group improved significantly following training, only a modest but non-significant performance improvement was found in the CityQuest group. During training, participants in the Obstacles-only group had greater obstacle avoidance efficiency (see **Supplementary Material**) which may explain their relatively better performance on the post-training, object recognition assessment. Moreover, this group was trained to focus specifically on the objects they encountered whilst the layout of the VE was task irrelevant. In contrast, those trained in spatial navigation focused on remembering the routes to the various landmarks during training and the city layout, without a requirement to remember specific obstacles. There may, therefore, have been a difference in the allocation of cognitive resources across groups: the Obstacle-avoidance group may have focused more on objects, whereas the spatial navigation groups focused more on the route. Although the spatial navigation groups did not improve their object recognition performance, the results from the current study indicate that it is nevertheless possible to improve performance in older adults, such as object recognition, using training that is targeted at a specific cognitive domain.

Age-related change in spatial abilities may be due in part to declines in general cognitive function, such as attention and working memory, speed of processing, executive function etc. (Sanders et al., 2008; Lester et al., 2017). However, not all spatial abilities show the same pattern of age-related decline, suggesting that global cognitive factors do not fully characterize specific spatial memory deficits as we get older (Lester et al., 2017; Yamamoto et al., 2019). Relatively preserved egocentric processing in older adults has been widely reported (Wiener et al., 2012; Gazova et al., 2013; Montefinese et al., 2015; Colombo et al., 2017; Fricke and Bock, 2018), particularly when compared to allocentric processing (Merriman et al., 2016, 2018a; Ruggiero et al., 2016; Caffò et al., 2020). Reliance on egocentric spatial strategies may represent a less cognitively demanding approach to achieve successful navigation and may constitute a strategic way to compensate for an age-related decline in both allocentric processing and general cognition, particularly of attentional and executive functioning (Colombo et al., 2017).

The CityQuest condition was designed to target several cognitive abilities (i.e., spatial navigation, obstacle avoidance, balance control), therefore we predicted a broader transfer of training benefits from this condition than the more focused Spatial Navigation-only or Obstacles-only conditions (Lustig et al., 2009; Moreau and Conway, 2013). As predicted, those assigned to the CityQuest group showed significant improvement on the landmark location task compared to those in the Spatial Navigation-only or Obstacles-only groups, although this group difference did not generalize to the landmark naming task. However, those who showed improvement in spatial navigation training performed significantly better on both the landmark location task and landmark naming task compared to those who did not improve in spatial navigation training (see **Supplementary Material**). The ability to recall the location of target landmarks presented on a 2D survey view map is considered a measure of "cognitive mapping" ability (Moffat and Resnick, 2002). During game training, all training groups navigated from first person perspective, however, their position was also simultaneously displayed on a smaller map of the environment presented in an aerial view from a fixed orientation. This 2D map may have provided sufficient visual cues to complete the task by associating egocentric directional information with a location. For example, the 2D map contained an outline of the buildings in the area which may have provided an adequate context to elicit an association between a particular target object with a given location. Therefore, it is unclear whether participants may have referred to the aerial map to recall target locations from an egocentric perspective or relied on their own allocentric cognitive map for the landmark location and naming tasks. Indeed, impairments in spatial learning may be emphasized in tasks requiring the processing of multiple orientations of an environment (i.e., survey, first person) during spatial memory formation (Yamamoto et al., 2019). Performance in the spatial strategy assessment task may therefore be more insightful regarding the type of spatial strategy adopted that led to improvement on the landmark location and naming tasks.

Spatial Strategy Assessment

Wiener et al. (2013) previously reported that older adults rely more on an egocentric strategy when an allocentric strategy is required for successful navigation. The results of the current study support their finding, with egocentric strategies more likely to be adopted, such as associative cue or beacon following training, as opposed to an allocentric strategy. For the "same direction" trials of the strategy assessment, navigation can be most efficiently solved using an egocentric spatial strategy. Performance of older adults in general was quite good on the same direction trials (78%), indicating that they could successfully judge the direction to be taken based on their recall of the original route during the learning phase. As with the direction judgment task in the spatial navigation assessment (also a measure of egocentric processing), it is possible that older adults' performance was at ceiling prior to the training thus there was effectively little room for improvement on this task following training.

However, some evidence suggests that older adults tend to rely on an egocentric strategy during many spatial navigation tasks, even if an allocentric spatial strategy would be more efficient (Head and Isom, 2010; Rodgers et al., 2012; Wiener et al., 2013). Performance on the different direction trials in the current study was quite poor for older adults in general, remaining at chance level prior to training, with only those in the Spatial Navigation-only training group reaching levels above chance at the post-training assessment. This result suggests that even those older adults who performed well on route learning on the same direction trials were unable to form a cognitive map and utilize an allocentric strategy to solve the task when the route was approached from an unfamiliar direction. Although the performance in the different direction trials of some older adults (particularly those allocated to the Spatial Navigation-only condition and those who showed improvement in spatial navigation training, see **Supplementary Material**) improved across assessments, there was no obvious change in their strategy preference from an associative cue one to an allocentric strategy as a result of spatial navigation training. Therefore it is possible that those whose performance improved on different direction trials did so using an egocentric spatial strategy rather than a switch to an allocentric strategy.

Executive Function

Although executive function and working memory are different cognitive domains, both play an important role in successful spatial navigation, e.g., selecting the correct spatial strategy, switching to alternative strategies when appropriate, maintaining navigational goals, computing directions and distances to goals, translation of spatial representations (Wolbers and Hegarty, 2010). Similarly Weisberg and Newcombe (2016) provided evidence that integrators and non-integrators of spatial information have better verbal and spatial working memory performance than imprecise navigators. Therefore age-related spatial memory deficits for large-scale environments could partially be the consequence of reduced executive functioning and working memory function (Colombo et al., 2017). Executive function has also been shown to mediate navigational ability in aging (Taillade et al., 2013b). As the CityQuest condition is a complex, multitask training condition, we anticipated that training on this condition would significantly improve performance on executive function typically measured using the Trail Making Test (TMT). We found that while all participants slightly improved on the TMT following training, the performance of the CityQuest group significantly improved from pre- to post-assessment.

Vestibular Contributions

The CityQuest training intervention also included a balance control component, where participants had to shift their weight on the WBB to control the location of the virtual character to locate target landmarks and avoid obstacles within the virtual environment. The inclusion of a postural control element while training spatial navigation adds to the ecological validity of the intervention as real-life navigation is a complex motor-cognitive dual-task, where attentional resources need to be allocated to both motor control and spatial knowledge acquisition at the same time. To examine the effect of training on cortical areas involved in motor control and the vestibular system, a subset of participants were scanned with MRI following the baseline assessment and at completion of the study. These neuroimaging findings along with additional measures of balance control and balance confidence were reported by O'Callaghan et al. (2018). While no significant differences were found across the balance control and confidence measure, we found that successful completion of the intervention training was associated with an increase in gray matter volume in the precentral gyrus (an area associated with motor control) for all participants. The precentral gyrus is subject to age-related atrophy (Good et al., 2001, 2002; Lemaître et al., 2005), however, our findings demonstrated that spatial navigation training which incorporates body movements associated with balance control can attenuate the aging effect on this cortical region important for vestibular functioning.

Implications for Future Research

While this study demonstrated transfer of training effects of those allocated to the CityQuest and Spatial Navigation-only conditions to some measures of spatial memory and to a measure of executive function, we did not find that training benefited performance across all spatial tasks. One possible reason for this may include the duration of training. While a number of reviews of cognitive training studies have suggested that 4 weeks or 10 training sessions may be sufficient for training gains to occur (see Kelly et al., 2014; Schoene et al., 2014), other studies have found that longer interventions show greater training benefits. For example Basak et al. (2008) found that while 23.5 h of training was sufficient to observe beneficial effects of cognitive training in older adults, an assessment carried out mid-way through training (i.e., following 12 h of training) revealed 12 h of training was insufficient for any training benefit to be found. Similarly Stern et al. (2011) found that relative to the ten sessions used in training younger adults on an executive function game named "Space Fortress," it was necessary to increase the duration of the intervention to three times longer when training older adults. A review of the use of virtual environments to train spatial abilities in stroke patients found that 8–15 training sessions of between 40–45 min duration were sufficient to show training benefits (Montana et al., 2019). However, delivering a spatial navigation intervention over a shorter time period but more intensely (e.g., 10 sessions over a 2 week instead of 5 week period) may also lead to improvements in spatial abilities (McLaren-Gradinaru et al., 2020).

Future research should aim to determine whether increasing the hours of training and/or the intensity of training would induce transfer to other tasks or lead the unsuccessfully trained to improve their navigation efficiency. Furthermore the CityQuest condition, which trained spatial navigation, obstacle avoidance, and balance control simultaneously could be considered "full emphasis training," where all components of the training are given equal priority (Gopher et al., 1989). However, some studies have shown that the use of variable priority training, where participants are instructed to play the entire game at all times, but to shift their emphasis to different components of the game at different times during training led to greater transfer of a training benefit to untrained tasks (Gopher et al., 1989; Kramer et al., 1995; Silsupadol et al., 2009; Boot et al., 2010; Stern et al., 2011). Future iterations of the CityQuest game should apply this approach in order to investigate whether variable priority training might result in greater transfer to the outcome measures assessed.

CONCLUSION

In sum, our findings add to the literature on cognitive training interventions in that an intervention involving a video game incorporating spatial navigation and obstacle avoidance training with a balance control component in a virtual environment was successful in improving egocentric spatial processing and executive function in older adults. Training in spatial navigation does not facilitate a switch from egocentric to allocentric spatial strategies in older adults, but may lead to more efficient use of egocentric spatial strategies. Furthermore, spatial navigation training within an ecologically valid virtual environment complete with obstacles to avoid can result in more performance gains than training in an empty unpopulated virtual environment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by School of Psychology Research Ethics Committee, Trinity College Dublin, Ireland. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NM and ER designed the experiment and collected the data. JO, CO'S, MR, and IO developed the virtual environments used for assessment and training. NM wrote the manuscript, performed the data and statistical analysis with assistance on approach and interpretation from ER and FN. FN critically evaluated the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.806418/full#supplementary-material

REFERENCES

Adamo, D. E., Briceno, E. M., Sindone, J. A., Alexander, N. B., and Moffat, S. D. (2012). Age differences in virtual environment and real world path integration. *Front. Aging Neurosci.* 4:26. doi: 10.3389/fnagi.2012.00026

Allen, G. L., Kirasic, K. C., Rashotte, M. A., and Haun, D. B. M. (2004). Aging and path integration skill: kinesthetic and vestibular contributions to wayfinding. *Percept. Psychophys.* 66, 170–179. doi: 10.3758/BF03194870

Angelaki, D. E., and Cullen, K. E. (2008). Vestibular system: the many facets of a multimodal sense. *Annu. Rev. Neurosci.* 31, 125–150. doi: 10.1146/annurev.neuro.31.060407.125555

Anguera, J. A., Boccanfuso, J., Rintoul, J. L., Al-Hashimi, O., Faraji, F., Janowich, J., et al. (2013). Video game training enhances cognitive control in older adults. *Nature* 501, 97–101. doi: 10.1038/nature12486

Anson, E., and Jeka, J. (2016). Perspectives on aging vestibular function. *Front. Neurol.* 6:269. doi: 10.3389/fneur.2015.00269

Antonova, E., Parslow, D., Brammer, M., Dawson, G. R., Jackson, S. H., and Morris, R. G. (2009). Age-related neural activity during allocentric spatial memory. *Memory* 17, 125–143. doi: 10.1080/09658210802077348

Appel, L., Appel, E., Bogler, O., Wiseman, M., Cohen, L., Ein, N., et al. (2020). Older Adults With Cognitive and/or Physical Impairments Can Benefit From Immersive Virtual Reality Experiences: a Feasibility Study. *Front. Med.* 6:329. doi: 10.3389/fmed.2019.00329

Barrett, M. M., Doheny, E. P., Setti, A., Maguinness, C., Foran, T. G., Kenny, R. A., et al. (2013). Reduced vision selectively impairs spatial updating in fall-prone older adults. *Multisens. Res.* 26, 69–94. doi: 10.1163/22134808-00002412

Basak, C., Boot, W. R., Voss, M. W., and Kramer, A. F. (2008). Can training in a real-time strategy video game attenuate cognitive decline in older adults? *Psychol. Aging* 23, 765–777. doi: 10.1037/a0013494

Bates, S. L., and Wolbers, T. (2014). How cognitive aging affects multisensory integration of navigational cues. *Neurobiol. Aging* 35, 2761–2769. doi: 10.1016/j.neurobiolaging.2014.04.003

Boot, W. R., Basak, C., Erickson, K. I., Neider, M., Simons, D. J., Fabiani, M., et al. (2010). Transfer of skill engendered by complex task training under conditions of variable priority. *Acta Psychol.* 135, 349–357. doi: 10.1016/j.actpsy.2010.09.005

Boot, W. R., Simons, D. J., Stothart, C., and Stutts, C. (2013). The pervasive problem with placebos in psychology: why active control groups are not sufficient to rule out placebo effects. *Perspect. Psychol. Sci.* 8, 445–454. doi: 10.1177/1745691613491271

Brandt, T., Schautzer, F., Hamilton, D. A., Brüning, R., Markowitsch, H. J., Kalla, R., et al. (2005). Vestibular loss causes hippocampal atrophy and impaired spatial memory in humans. *Brain* 128, 2732–2741. doi: 10.1093/brain/awh617

Brunec, I. K., Robin, J., Patai, E. Z., Ozubko, J. D., Javadi, A. H., Barense, M. D., et al. (2019). Cognitive mapping style relates to posterior–anterior hippocampal volume ratio. *Hippocampus* 29, 748–754. doi: 10.1002/hipo.23072

Burns, P. C. (1999). Navigation and the mobility of older drivers. *J. Gerontol. Ser. B Psychol. Sci. Soc. Sci.* 54, S49–S55. doi: 10.1093/geronb/54B.1.S49

Caffò, A. O., Lopez, A., Spano, G., Cipresso, P., Riva, G., and Bosco, A. (2020). The differential effect of normal and pathological aging on egocentric and allocentric spatial memory in navigational and reaching space. *Neurol. Sci*. 41, 1741–1749. doi: 10.1007/s10072-020-04261-4

Carr, S., Pichora-Fuller, M. K., Li, K. Z. H., Phillips, N., and Campos, J. L. (2019). Multisensory, Multi-Tasking Performance of Older Adults With and Without Subjective Cognitive Decline. *Multisens. Res.* 32, 797–829. doi: 10.1163/22134808-20191426

Colombo, D., Serino, S., Tuena, C., Pedroli, E., Dakanalis, A., Cipresso, P., et al. (2017). Egocentric and allocentric spatial reference frames in aging: a systematic review. *Neurosci. Biobehav. Rev.* 80, 605–621. doi: 10.1016/j.neubiorev.2017.07.012

Corrigan, J. D., and Hinkeldey, N. S. (1987). Relationships between parts A and B of the Trail Making Test. *J. Clin. Psychol.* 43, 402–409. doi: 10.1002/1097-4679(198707)43:4<402::AID-JCLP2270430411>3.0.CO;2-E

Daugherty, A. M., Bender, A. R., Yuan, P., and Raz, N. (2016). Changes in search path complexity and length during learning of a Virtual Water Maze: age differences and differential associations with hippocampal subfield volumes. *Cereb. Cortex* 26, 2391–2401. doi: 10.1093/cercor/bhv061

Dehn, L. B., Kater, L., Piefke, M., Botsch, M., Driessen, M., and Beblo, T. (2018). Training in a comprehensive everyday-like virtual reality environment compared to computerized cognitive training for patients with depression. *Comput. Hum. Behav.* 79, 40–52. doi: 10.1016/j.chb.2017.10.019

Diersch, N., and Wolbers, T. (2019). The potential of virtual reality for spatial navigation research across the adult lifespan. *J. Exp. Biol.* 222(Suppl. 1), jeb187252. doi: 10.1242/jeb.187252

Fricke, M., and Bock, O. (2018). Egocentric navigation is age-resistant: first direct behavioral evidence. *Curr. Neurobiol.* 9, 69–75.

Gazova, I., Laczó, J., Rubinova, E., Mokrisova, I., Hyncicova, E., Andel, R., et al. (2013). Spatial navigation in young versus older adults. *Front. Aging Neurosci.* 5:94. doi: 10.3389/fnagi.2013.00094

Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N. A., Friston, K. J., and Frackowiak, R. S. J. (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. *NeuroImage* 14, 21–36. doi: 10.1006/nimg.2001.0786

Good, C. D., Scahill, R. I., Fox, N. C., Ashburner, J., Friston, K. J., Chan, D., et al. (2002). Automatic differentiation of anatomical patterns in the human brain: validation with studies of degenerative dementias. *NeuroImage* 17, 29–46. doi: 10.1006/nimg.2002.1202

Gopher, D., Weil, M., and Siegel, D. (1989). Practice under changing priorities: an approach to the training of complex skills. *Acta Psychol.* 71, 147–177. doi: 10.1016/0001-6918(89)90007-3

Green, C. S., and Bavelier, D. (2008). Exercising your brain: a review of human brain plasticity and training-induced learning. *Psychol. Aging* 23, 692–701. doi: 10.1037/a0014345.Exercising

Hartley, T., Maguire, E. A., Spiers, H. J., and Burgess, N. (2003). The well-worn route and the path less traveled: distinct neural bases of route following and wayfinding in humans. *Neuron* 37, 877–888. doi: 10.1016/S0896-6273(03)00095-3

Head, D., and Isom, M. (2010). Age effects on wayfinding and route learning skills. *Behav. Brain Res.* 209, 49–58. doi: 10.1016/j.bbr.2010.01.012

Hegarty, M., Richardson, A. E., Montello, D. R., Lovelace, K., and Subbiah, I. (2002). Development of a self-report measure of environmental spatial ability. *Intelligence* 30, 425–447. doi: 10.1016/S0160-2896(02)00116-2

Hötting, K., Holzschneider, K., Stenzel, A., Wolbers, T., Röder, B., Roder, B., et al. (2013). Effects of a cognitive training on spatial learning and associated functional brain activations. *BMC Neurosci.* 14:73. doi: 10.1186/1471-2202-14-73

Janzen, G., and van Turennout, M. (2004). Selective neural representation of objects relevant for navigation. *Nat. Neurosci.* 7, 673–677. doi: 10.1038/nn1257

Kelly, M. E., Loughrey, D., Lawlor, B. A., Robertson, I. H., Walsh, C., and Brennan, S. (2014). The impact of cognitive training and mental stimulation on cognitive and everyday functioning of healthy older adults: a systematic review and meta-analysis. *Aging Res. Rev.* 15, 28–43. doi: 10.1016/j.arr.2014.02.004

Klencklen, G., Després, O., and Dufour, A. (2012). What do we know about aging and spatial cognition? Reviews and perspectives. *Aging Res. Rev.* 11, 123–135. doi: 10.1016/j.arr.2011.10.001

Kramer, A. F., Larish, J. F., and Strayer, D. L. (1995). Training for attentional control in dual task settings: a comparison of young and old adults. *J. Exp. Psychol.* 1, 50–76. doi: 10.1037/1076-898X.1.1.50

Kühn, S., Gleich, T., Lorenz, R. C., Lindenberger, U., and Gallinat, J. (2014). Playing Super Mario induces structural brain plasticity: gray matter changes resulting from training with a commercial video game. *Mol. Psychiatry* 19, 265–271. doi: 10.1038/mp.2013.120

Lemaître, H., Crivello, F., Grassiot, B., Alpérovitch, A., Tzourio, C., and Mazoyer, B. (2005). Age- and sex-related effects on the neuroanatomy of healthy elderly. *NeuroImage* 26, 900–911. doi: 10.1016/j.neuroimage.2005.02.042

Lester, A. W., Moffat, S. D., Wiener, J. M., Barnes, C. A., and Wolbers, T. (2017). The Aging Navigational System. *Neuron* 95, 1019–1035. doi: 10.1016/j.neuron.2017.06.037

Lithfous, S., Dufour, A., and Després, O. (2013). Spatial navigation in normal aging and the prodromal stage of Alzheimer's disease: insights from imaging and behavioral studies. *Aging Res. Rev.* 12, 201–213. doi: 10.1016/j.arr.2012.04.007

Lövdén, M., Schaefer, S., Noack, H., Bodammer, N. C., Kühn, S., Heinze, H. J., et al. (2012). Spatial navigation training protects the hippocampus against age-related changes during early and late adulthood. *Neurobiol. Aging* 33, .e9–.e620. doi: 10.1016/j.neurobiolaging.2011.02.013

Lövdén, M., Schellenbach, M., Grossman-Hutter, B., Krüger, A., and Lindenberger, U. (2005). Environmental topography and postural control demands shape aging-associated decrements in spatial navigation performance. *Psychol. Aging* 20, 683–694. doi: 10.1037/0882-7974.20.4.683

Luis, C. A., Keegan, A. P., and Mullan, M. (2009). Cross validation of the Montreal Cognitive Assessment in community dwelling older adults residing in the Southeastern US. *Int. J. Geriatr. Psychiatry* 24, 197–201. doi: 10.1002/gps

Lustig, C., Shah, P., Seidler, R., and Reuter-Lorenz, P. A. (2009). Aging, training, and the brain: a review and future directions. *Neuropsychol. Rev.* 19, 504–522. doi: 10.1007/s11065-009-9119-9

Maguire, E. A., Burgess, N., Donnett, J. G., Frackowiak, R. S. J., Frith, C. D., and O'Keefe, J. (1998). Knowing where and getting there: a human navigation network. *Science* 280, 921–924. doi: 10.1126/science.280.5365.921

McLaren-Gradinaru, M., Burles, F., Dhillon, I., Retsinas, A., Umiltà, A., Hannah, J., et al. (2020). A Novel Training Program to Improve Human Spatial Orientation: preliminary Findings. *Front. Hum. Neurosci.* 14:5. doi: 10.3389/fnhum.2020.00005

Merriman, N. A. (2016). *Assessing Cognitive Factors and Individual Differences that Modulate Spatial Navigation Ability in Older Adults*. [PhD Thesis]. Dublin: Trinity College, the University of Dublin.

Merriman, N. A., Ondřej, J., Roudaia, E., O'Sullivan, C., and Newell, F. N. (2016). Familiar environments enhance object and spatial memory in both younger and older adults. *Exp. Brain Res.* 234, 1555–1574. doi: 10.1007/s00221-016-4557-0

Merriman, N. A., Ondřej, J., Rybicki, A., Roudaia, E., O'Sullivan, C., and Newell, F. N. (2018a). Crowded environments reduce spatial memory in older but not younger adults. *Psychol. Res.* 82, 407–428. doi: 10.1007/s00426-016-0819-5

Merriman, N. A., Roudaia, E., Romagnoli, M., Orvieto, I., and Newell, F. N. (2018b). Acceptability of a custom-designed game, CityQuest, aimed at improving balance confidence and spatial cognition in fall-prone and healthy older adults. *Behav. Inf. Technol.* 37, 538–557. doi: 10.1080/0144929X.2018.1462402

Moffat, S. D. (2009). Aging and spatial navigation: what do we know and where do we go? *Neuropsychol. Rev.* 19, 478–489. doi: 10.1007/s11065-009-9120-3

Moffat, S. D., and Resnick, S. M. (2002). Effects of age on virtual environment place navigation and allocentric cognitive mapping. *Behav. Neurosci.* 116, 851–859. doi: 10.1037//0735-7044.116.5.851

Montana, J. I., Tuena, C., Serino, S., Cipresso, P., and Riva, G. (2019). Neurorehabilitation of spatial memory using virtual environments: a systematic review. *J. Clin. Med.* 8:1516. doi: 10.3390/jcm8101516

Montefinese, M., Sulpizio, V., Galati, G., and Committeri, G. (2015). Age-related effects on spatial memory across viewpoint changes relative to different reference frames. *Psychol. Res.* 79, 687–697. doi: 10.1007/s00426-014-0598-9

Moreau, D., and Conway, A. R. A. (2013). Cognitive enhancement: a comparative review of computerized and athletic training programs. *Int. Rev. Sport Exerc. Psychol.* 6, 155–183. doi: 10.1080/1750984X.2012.758763

Moreau, D., and Conway, A. R. A. (2014). The case for an ecological approach to cognitive training. *Trends Cogn. Sci.* 18, 334–336. doi: 10.1016/j.tics.2014.03.009

Morris, R. G. M. (1981). Spatial localization does not require the presence of local cues. *Learn. Motiv.* 12, 239–260. doi: 10.1016/0023-9690(81)90020-5

Müller, V., Gruber, W., Klimesch, W., and Lindenberger, U. (2009). Lifespan differences in cortical dynamics of auditory perception. *Dev. Sci.* 12, 839–853. doi: 10.1111/j.1467-7687.2009.00834.x

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., et al. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* 53, 695–699. doi: 10.1111/j.1532-5415.2005.53221.x

O'Callaghan, G., O'Dowd, A., Stapleton, J., Merriman, N. A., Roudaia, E., and Newell, F. N. (2018). Changes in regional brain grey-matter volume following successful completion of a sensori-motor intervention targeted at healthy and fall-prone older adults. *Multisens. Res.* 31, 317–344. doi: 10.1163/22134808-00002604

O'Keefe, J., and Nadel, L. (1978). *The Hippocampus as a Cognitive Map*. Oxford: Oxford University Press.

Raz, N., and Rodrigue, K. M. (2006). Differential aging of the brain: patterns, cognitive correlates and modifiers. *Neurosci. Biobehav. Rev.* 30, 730–748. doi: 10.1016/j.neubiorev.2006.07.001

Raz, N., Rodrigue, K. M., Kennedy, K. M., Head, D., Gunning-Dixon, F., and Acker, J. D. (2003). Differential aging of the human striatum: longitudinal evidence. *Am. J. Neuroradiol.* 24, 1849–1856.

Reitan, R. M. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Percept. Mot. Skills* 8, 271–276.

Rodgers, M. K., Sindone, J. A. III, and Moffat, S. D. (2012). Effects of age on navigation strategy. *Neurobiol. Aging* 33, 202.e15–22. doi: 10.1016/j.neurobiolaging.2010.07.021

Ruggiero, G., D'Errico, O., and Iachini, T. (2016). Development of egocentric and allocentric spatial representations from childhood to elderly age. *Psychol. Res.* 80, 259–272. doi: 10.1007/s00426-015-0658-9

Sanders, A. E., Holtzer, R., Lipton, R. B., Hall, C., and Verghese, J. (2008). Egocentric and exocentric navigation skills in older adults. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* 63:1356. doi: 10.1093/gerona/63.12.1356

Sandlin, D., McGwin, G., and Owsley, C. (2014). Association between vision impairment and driving exposure in older adults aged 70 years and over: a population-based examination. *Acta Ophthalmol.* 92, 207–212. doi: 10.1111/aos.12050

Schoene, D., Valenzuela, T., Lord, S. R., and de Bruin, E. D. (2014). The effect of interactive cognitive-motor training in reducing fall risk in older people: a systematic review. *BMC Geriatr.* 14:107. doi: 10.1186/1471-2318-14-107

Silsupadol, P., Lugade, V., Shumway-Cook, A., van Donkelaar, P., Chou, L. S., Mayr, U., et al. (2009). Training-related changes in dual-task walking performance of elderly persons with balance impairment: a double-blind, randomized controlled trial. *Gait Posture* 29, 634–639. doi: 10.1016/j.gaitpost.2009.01.006

Simieli, L., Barbieri, F. A., Orcioli-Silva, D., Lirani-Silva, E., Stella, F., and Gobbi, L. T. B. (2015). Obstacle crossing with dual tasking is a danger for individuals with Alzheimer's disease and for healthy older people. *J. Alzheimers Dis.* 43, 435–441. doi: 10.3233/JAD-140807

St George, R. J., and Fitzpatrick, R. C. (2011). The sense of self-motion, orientation and balance explored by vestibular stimulation. *J. Physiol.* 589(Pt 4), 807–813. doi: 10.1113/jphysiol.2010.197665

Stern, Y., Blumen, H. M., Rich, L. W., Richards, A., Herzberg, G., and Gopher, D. (2011). Space Fortress game training and executive control in older adults: a pilot intervention. *Aging Neuropsychol. Cogn.* 18, 653–677. doi: 10.1080/13825585.2011.613450

Taillade, M., Sauzéon, H., Arvind Pala, P., Déjos, M., Larrue, F., Gross, C., et al. (2013a). Age-related wayfinding differences in real large-scale environments: detrimental motor control effects during spatial learning are mediated by executive decline? *PloS One* 8:e67193. doi: 10.1371/journal.pone.0067193

Taillade, M., Sauzéon, H., Déjos, M., Arvind Pala, P., Larrue, F., Wallet, G., et al. (2013b). Executive and memory correlates of age-related differences in wayfinding performances using a virtual reality application. *Aging Neuropsychol. Cogn.* 20, 298–319. doi: 10.1080/13825585.2012.706247

Tolman, E. C. (1948). Cognitive maps in rats and men. *Psychol. Rev.* 55, 189–208. doi: 10.1037/h0061626

Van Impe, A., Bruijn, S. M., Coxon, J. P., Wenderoth, N., Sunaert, S., Duysens, J., et al. (2013). Age-related neural correlates of cognitive task performance under increased postural load. *Age* 35, 2111–2124. doi: 10.1007/s11357-012-9499-2

Weisberg, S. M., and Newcombe, N. S. (2016). How do (some) people make a cognitive map? Routes, places, and working memory. *J. Exp. Psychol. Learn. Memory Cogn.* 42, 768–785. doi: 10.1037/xlm0000200

West, G. L., Zendel, B. R., Konishi, K., Benady-Chorney, J., Bohbot, V. D., Peretz, I., et al. (2017). Playing Super Mario 64 increases hippocampal grey matter in older adults. *PLoS One* 12:e0187779. doi: 10.1371/journal.pone.0187779

Whitlock, L. A., McLaughlin, A. C., and Allaire, J. C. (2012). Individual differences in response to cognitive training: using a multi-modal, attentionally demanding game-based intervention for older adults. *Comput. Hum. Behav.* 28, 1091–1096. doi: 10.1016/j.chb.2012.01.012

Wiener, J. M., de Condappa, O., Harris, M. A., and Wolbers, T. (2013). Maladaptive bias for extrahippocampal navigation strategies in aging humans. *J. Neurosci.* 33, 6012–6017. doi: 10.1523/jneurosci.0717-12.2013

Wiener, J. M., Kmecova, H., and de Condappa, O. (2012). Route repetition and route retracing: effects of cognitive aging. *Front. Aging Neurosci.* 4:7. doi: 10.3389/fnagi.2012.00007

Wolbers, T., and Hegarty, M. (2010). What determines our navigational abilities? *Trends Cogn. Sci.* 14, 138–146. doi: 10.1016/j.tics.2010.01.001

Wolbers, T., Weiller, C., and Büchel, C. (2004). Neural foundations of emerging route knowledge in complex spatial environments. *Cogn. Brain Res.* 21, 401–411. doi: 10.1016/j.cogbrainres.2004.06.013

Woollett, K., and Maguire, E. A. (2011). Acquiring "the Knowledge" of London's layout drives structural brain changes. *Curr. Biol.* 21, 2109–2114. doi: 10.1016/j.cub.2011.11.018

Yamamoto, N., Fox, M. J., Boys, E., and Ord, J. (2019). Effects of orientation change during environmental learning on age-related difference in spatial memory. *Behav. Brain Res.* 365, 125–132. doi: 10.1016/j.bbr.2019.03.012

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Neural Bases of Age-Related Sensorimotor Slowing in the Upper and Lower Limbs

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With advanced age, there is a loss of reaction speed that may contribute to an increased risk of tripping and falling. Avoiding falls and injuries requires awareness of the threat, followed by selection and execution of the appropriate motor response. Using event-related potentials (ERPs) and a simple visual reaction task (RT), the goal of our study was to distinguish sensory and motor processing in the upper- and lower-limbs while attempting to uncover the main cause of age-related behavioral slowing. Strength (amplitudes) as well as timing and speed (latencies) of various stages of stimulus- and motor-related processing were analyzed in 48 healthy individuals (young adults, n = 24, mean age = 34 years; older adults, n = 24, mean age = 67 years). The behavioral results showed a significant age-related slowing, where the younger compared to older adults exhibited shorter RTs for the upper- (222 vs. 255 ms; p = 0.006, respectively) and the lower limb (257 vs. 274 ms; p = 0.048, respectively) as well as lower variability in both modalities (p = 0.001). Using ERP indices, age-related slowing of visual stimulus processing was characterized by overall larger amplitudes with delayed latencies of endogenous potentials in older compared with younger adults. While no differences were found in the P1 component, the later components of recorded potentials for visual stimuli processing were most affected by age. This was characterized by increased N1 and P2 amplitudes and delayed P2 latencies in both upper and lower extremities. The analysis of motor-related cortical potentials (MRCPs) revealed stronger MRCP amplitude for upper- and a non-significant trend for lower limbs in older adults. The MRCP amplitude was smaller and peaked closer to the actual motor response for the upper- than for the lower limb in both age groups. There were longer MRCP onset latencies for lower- compared to upper-limb in younger adults, and a non-significant trend was seen in older adults. Multiple regression analyses showed that the onset of the MRCP peak consistently predicted reaction time across both age groups and limbs tested. However, MRCP rise time and P2 latency were also significant predictors of simple reaction time, but only in older adults and only for the upper limbs. Our study suggests that motor cortical processes contribute most strongly to the slowing of simple reaction time in advanced age. However, late-stage cortical processing related to sensory stimuli also appears to play a role in upper limb responses in the elderly. This process most likely reflects less efficient recruitment of neuronal resources required for the upper and lower extremity response task in older adults.

Keywords: aging, event-related potential (ERP), visual-evoked potential (VEP), motor-related potential, finger and foot responses

INTRODUCTION

To avoid falls and injuries in our environment, we must perceive the threat and then select and execute the appropriate response. Bypassing unprecedented external perturbations in one's immediate proximity, such as stepping over an uneven surface and maintaining balance, requires sensory sharpness and fast reactions to the perceived sensory stimulus (Stelmach and Worringham, 1985). Loss of sensory acuity (Cavazzana et al., 2018) and reaction speed (Deary and Der, 2005) associated with advancing age may contribute to factors like increased risks of falls and trips. For example, older fallers are more likely to suffer from impaired sensory acuity than older non-fallers (Lord et al., 1991; Brundle et al., 2015). Similarly, evidence obtained from reaction time (RT) tasks in older adults have demonstrated that increased RT of finger pressing is a significant and independent risk factor for falls (Lord et al., 1991, 1994; Lord and Clark, 1996). From the perspective of avoiding danger, such as rebalancing when confronted with an obstacle or slipping, rapid foot movements to maintain balance play an essential role (Pijnappels et al., 2010; Cai et al., 2020) which might be even more important than the upper-limb movement reactions. In a standardized clinical testing protocol, lower-limb RTs to visual stimuli discriminated between single and multiple fallers, providing a simple, cost- and time-effective way of identifying people at greatest risk of falling (Maver et al., 2011). However, the investigation of simple RT of the lower limbs remains a severely under investigated area. This study aimed to fill this gap and provide the first insights into the origin of sensorimotor delay in the upper- *and* lower limbs using electroencephalography (EEG).

Age-related behavioral slowing is typically reflected in longer RTs to simple auditory and visual stimuli (Woodruff and Kramer, 1979; Gottsdanker, 1982; Fozard et al., 1994; Inui, 1997; Deary and Der, 2005), and even more so in the tasks of higher-level cognition, such as sustained and selective attention, inhibitory control, working memory, and executive control (Finnigan et al., 2011; Gajewski and Falkenstein, 2014; Reuter et al., 2019). In a simple RT task, Woods et al. (2015) showed a 0.55-millisecond increase per year in mean simple RT in a visual paradigm, whereas Gottsdanker (1982) showed a 2-millisecond increase per decade in an auditory paradigm. In a more challenging GO/NOGO paradigm, Kropotov et al. (2016) demonstrated that early perceptual components (100–200 milliseconds) of event-related potentials (ERP) increased their peak latencies for 5–6 milliseconds per decade, while the later components (400–500 milliseconds) showed approximately 16 milliseconds increase pre decade. The structural damage to the myelin sheath and the reduction of the total number of nerve fibers in aged individuals (Salat, 2011), might undermine the functional efficacy of information flow by disrupting precisely timed communication patterns or rhythmic synchronization among cortical regions (Fries, 2015). Age-related behavioral slowing or motor impairments are not limited to associated changes in white matter structure (demyelization), but also manifest due to changes in gray matter (reduced volume, atrophy), biochemical effects (including reduced dopamine levels, receptors, transmission and transporters) and functional neural recruitment (for a review, see Seidler et al., 2010).

Simple RT, a basic measure of the minimal time required to respond to a stimulus, provides an estimate of the overall alertness and motor speed and is highly dependent on sensorimotor integration (Azim and Kazuhiko, 2019). Responses in a simple RT task can be therefore broken into a sensory processing stage in which a stimulus is perceived or detected, followed by a motor processing stage, during which the necessary movement is prepared and executed as a response (Woods et al., 2015). Despite being primarily used to assess processing speed, the RT task is nevertheless a cognitive-based test as attentional resources are needed not only for stimulus detection but also for movement initiation (Cai et al., 2020). Recorded reaction times comprise a summed duration of these events. Given that sensory and motor processing stages are functionally different, determining the basis of the behavioral slowing is an important step for an adequate understanding of aging-related changes and for intervention development. Attempts of estimating and dividing the stimulus detection time from movement initiation time were done on a behavioral level and suggest that the age-related sensorimotor slowing occurs primarily due to slowed motor output rather than the stimulus detection time (Woods et al., 2015). However, the characteristics of sensory- and motor-related processing stages of RTs investigated from the angle of their respective neurodynamic signatures remain spared for the upper extremities and have not yet been studied in the lower extremities.

Electroencephalography offers a way to investigate the origins of age-related sensorimotor delay by analyzing the time course of internal responses to sensorimotor information processing in conjunction with RT tasks. In the stimulus processing stage, the recognition of the stimulus occurs, which is captured by the early stimulus-locked ERP (s-ERP) components – P1 and N1 (Gazzaniga et al., 2019). The components' latencies indicate speed, while their amplitudes indicate the intensity of early perceptual mechanisms (Amenedo and Díaz, 1998). Visually evoked P1 peak is typically detected within the 40–140 millisecond range after the stimulus presentation, while the N1 is detected within the 120–200 millisecond range

(Yordanova et al., 2004; Zalar et al., 2015; Gazzaniga et al., 2019). P1 and N1 are proposed to reflect gain control of the sensory processing (Luck et al., 1990; Klimesch et al., 2004, 2007), and can be modulated by attention (Gazzaley et al., 2008; Gazzaniga et al., 2019). In the visual paradigm, the P1 and N1 components are observed and generated in the extrastriate cortex (Natale et al., 2006). Later component – P2, typically peaks at/after 200 milliseconds after stimulus presentation and is evidently generated in parieto-occipital regions, rostral to extrastriate cortex (Freunberger et al., 2007). P2 component has primarily been associated with higher-level cognitive functions, such as working memory (Wolach and Pratt, 2001; Lefebvre et al., 2005), encoding (Dunn et al., 1998) and semantic processing (Freunberger et al., 2007), and is therefore not surprising that its generating source corresponds to the parieto-occipital association cortex.

Motor processing can be examined by the motor-related cortical potentials (MRCPs), which are computed by averaging response-locked ERPs (r-ERPs) at the contralateral motor cortical sites (Taniguchi et al., 2001). This allows for the analysis of the latency and amplitude of the most negative MRCP peak and its comparison between older and younger adults. Yordanova et al. (2004) report no differences in the peak MRCP amplitude between the older and younger adults on the contralateral side to the responding hand, however, significantly larger ipsilateral activity detected in older adults might be indicative of deviant functional asymmetry and functional dysregulation of the motor cortex activation in older adults (Mattay et al., 2002; Ward and Frackowiak, 2003; Heuninckx et al., 2005, 2008). Despite the absence of evidence of behavioral RT slowing in older compared to younger adults in Yordanova et al. (2004), their findings are indicative of age-related neural deterioration. It remains unclear, however, whether the generally observed slowing of simple reaction times in older adults originates from the perceptual processing stage or motor-related processing stage. Evidence obtained in a task with higher complexity (choice RT) indicated amplitude increase and prolongation of the MRCP contralateral to the responding hand. This was not due to changes in the sensory stimulus processing phase, as observed in the latency and amplitude of the early ERP components, or in the response selection phase, which was investigated by the onset of the lateralized readiness potential (LRP) (Yordanova et al., 2004; Falkenstein et al., 2006).

Taken together, the evidence shows that the sensorimotor slowing observed in RT tasks in aged individuals may be primarily due to alterations of motor-related processing rather that stimulus detection processing. However, this statement is not strongly supported in the context of the simple RT task. In addition, the electrophysiological underpinnings of the lower-limb simple RT performance have never been investigated before. It remains unclear how the typically observed age-related sensorimotor slowing in the context of simple RT tasks relates to the associated neurodynamics at the level of stimulus detection and motor processing stages. In the present study, we investigate the simple RTs of the upper- and lower extremities in younger and older adults to assess the effects of aging on processing speed. Therefore, the aim is to investigate the origin of age-related behavioral sensorimotor slowing on a neural level for the upper limb and, for the first time, in the lower limb.

MATERIALS AND METHODS

Study Design and Participants

This cross-sectional study was conducted with a sample of 48 healthy adults, half of whom were younger (N = 24; mean age = 34 years; 11 men) and the other half were older adults (N = 24; mean age = 67 years; 9 men). All procedures were carried out in accordance with the ethical standards of the 1964 Declaration of Helsinki and were approved by the National Medical Ethics Committee (No. KME 57/06/17). Written informed consent was obtained from all participants prior to study enrollment.

Table 1 represents the basic characteristics of both groups. The younger adults were higher educated compared to older adults (16 years vs. 13 years, respectively, $p < 0.001$). Also, younger adults were taller compared to older adults (176 cm vs. 166 cm, respectively, $p = 0.010$). All participants stated that they were satisfied with their current health status, and no older adults reported an incidence of cardiovascular or neurological disease or took medication against it. Four young adults reported a left-hand preference, and all older adults reported a right-hand preference. All participants reported normal or corrected to normal vision and were able to clearly understand and follow the instructions of the simple RT task with upper- and lower limbs.

Neuropsychological Assessment

The *Montreal Cognitive Assessment* (MoCA) was used to obtain a general level of cognitive performance and to test for cognitive impairment only in the sample of older adults (Nasreddine et al., 2005). The MoCA test refers to several cognitive domains, namely visual-spatial abilities, short-term memory, executive functions, attention, concentration, working memory, language, and temporal and spatial orientation. The final score ranges from 0 to 30 points, with scores $\geq$ 26 indicating no cognitive impairment.

The *Trail-Making Test* (TMT; Reitan, 1958; Tombaugh, 2004) was used to assess the speed of processing and executive function. In TMT-A, 25 encircled numbers randomly distributed on an A4

TABLE 1 | Table of basic characteristics of young and older adults.

Variables	Young adults	Older adults	*p* value
N	24	24	
Sex (m/f)	11/13	9/15	
Age (years)	34.1 ± 2.3	66.8 ± 4.4	<0.001
BMI (kg/m^2)	24.0 ± 2.1	26.9 ± 6.2	0.206
Education (years)	16.4 ± 2.0	13.4 ± 1.8	<0.001
MoCA score (0–30)		27.5 ± 1.6	
TMT-A (sec)	24.7 ± 5.5	41.5 ± 18.2	<0.001
TMT-B (sec)	40.0 ± 26.9	76.5 ± 26.3	<0.001

BMI, body mass index; MoCA, Montreal Cognitive Assessment; TMT, trail-making test.

paper format must be connected with a single line in ascending order, starting at 1 and ending at 25. In TMT-B, a line must be drawn connecting numbers (1 – 12) and letters (A – L) in an alternating and increasing fashion (1-A-2-B-3-C. . .12-L). The scores for each part are given in time to completion (in seconds).

A Simple Visual Reaction Task

A simple visual reaction task (also called the psychomotor vigilance task) is a sustained attention reaction-timed performance task that measures the speed with which participants respond to a visual stimulus (Dinges and Powell, 1985). The experimental setup is presented in **Figure 1**. Participants were assessed while seated in a neutral position and instructed to perform a simple reaction time test in response to 70 visual stimuli presented with a random interstimulus interval between 2 and 5 s on a 17.0-inch flat panel LCD monitor (120-Hz refresh rate) situated approximately 50 centimeters in front of them. Their task was to press the response button as quickly as possible with (a) their index finger of their dominant hand and (b) the bottom of the right foot (second metatarsal head). The two conditions were applied in separate blocks (upper- and lower-limb). The order of these blocks was randomized. In both cases, the finger and foot rested on the response pad between responses. The response pad was connected to a trigger box (g.tec TRIGbox). The visual stimuli were presented in the center of the monitor (circular disc with a 5 cm radius was presented against a black background at the center of the display, duration 150 ms, intensity 50 cd/m2, visual angles 1° horizontal/1.5° vertical) placed directly in front of the participant's visual field. Additional visual stimuli (not visible to the participant) were simultaneously presented with experimental stimuli and were recorded using photodiodes connected directly to the trigger box – a methodology that afforded precise stimulus onset and offset trigger times that were subsequently embedded within each participants raw EEG data file. RTs were then extracted from an event/marker list for each subject using a script written for the MATLAB software (The MathWorks, Inc., Natick, MA, United States, version MATLAB R2021a). Trials with RTs latencies less than 110 ms and greater than 1,000 ms were excluded as outliers (Woods et al., 2015). Based on this criterion, up to four and seven trials were discarded in a group of young and older adults, respectively.

Electroencephalography Recording and Analysis

Scalp EEG activity was recorded using g.tec medical engineering equipment (Schiedlberg, Austria), with 32 Ag/AgCl active electrodes, arranged according to the International 10–20 System. Included electrodes correspond to Fp1, Fp2, AF3, AF4, F7, F3, Fz, F4, F8, FC5, FC1, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, PO3, PO4, O1, Oz, and O2 predefined positions. The reference electrode was placed on the left earlobe and the ground electrode was placed in the AFz position. During EEG measurements, low-pass and high-pass filters were set to 100 and 0.1 Hz, respectively, for real-time display only. The notch filter was set to 50 Hz. Impedances were maintained below 10 kΩ for each channel and balanced across all channels within a 5 kΩ range. The sampling rate was 512 Hz with a 32-bit resolution. Before performing the simple visual reaction task, a baseline measurement was routinely performed with eyes open and eyes closed (3 min each) to check the quality of the EEG signal.

All data were preprocessed and analyzed using custom scripts in the EEGLAB toolbox (Delorme and Makeig, 2004) of the MATLAB software (The MathWorks, Inc., Natick, MA, United States, version MATLAB R2021a). First, the upper- and lower-limb recordings of single participants were concatenated into a single data file, down sampled to 256 Hz, high-pass filtered at 1 Hz. Second, a copy of the original concatenated EEG data file (copyEEG) was created. The copyEEG was average re-referenced, automatic bad channel detection algorithm *clean_artifacts* was applied (*FlatLineCriterion* was set to 10 s, *ChannelCriterion* to 0.80, and *ChannelCriterionMaxBadTime* to 0.5) and the bad channels detected were interpolated using the spherical method. Next, the CopyEEG was epoched to stimulus-locked intervals [−200 800 ms], and an inspection of rejected and accepted epochs was made using the amplitude threshold of $>100\ \mu V$. This intermediate inspection determined if the automated bad channel detection and interpolation sufficiently cleaned the data or more channels had to be interpolated as a tradeoff to preserve the highest possible number of epochs and consequently grant the highest quality of the ERP signal. If a channel (i) was exceeding the 100 μV on a significant number of epochs and (ii) was not of primary interest to our analyses (other than occipital and central electrode sites) and (iii) was not detected by the automatic procedure, it was manually rejected and interpolated at this stage. The labels of the automatically and manually interpolated channels were saved into a variable and CopyEEG was discarded. The rationale for using CopyEEG was to first discover bad channels to then be able to interpolate them in the original concatenated EEG dataset *before* re-referencing it to the average reference. This approach offers a way to restrict the bad channel information from contributing to the average re-reference as it represents the non-meaningful information we are aiming to delineate from the signal of interest and reject.

In the original EEG dataset, bad channels were interpolated, and the data were re-referenced to the average reference. Time-domain cleaning eliminated data segments characterized by muscle artifacts, electrode pops, and other major perturbations. Next, the Adaptive Mixture Independent Component Analysis (AMICA) was performed using 2,000 iterations and subject-specific reduction of the data rank was considered (the number of interpolated channels plus one accounting for average re-referencing). The DIPFIT plugin for source localization was used to estimate single equivalent dipoles, co-registering the channel locations to *standard_BEM* head models. Lastly, the ICLabel plugin (Pion-Tonachini et al., 2019) was used to label the independent components. This procedure delivered a single independent component solution per subject and the concatenated data file was not used for further analyses.

In the final stage of the preprocessing, we returned to the separate condition data files (upper and lower limb files) which were treated in the same manner as described above (down sampling to 256 Hz, high pass filtering at

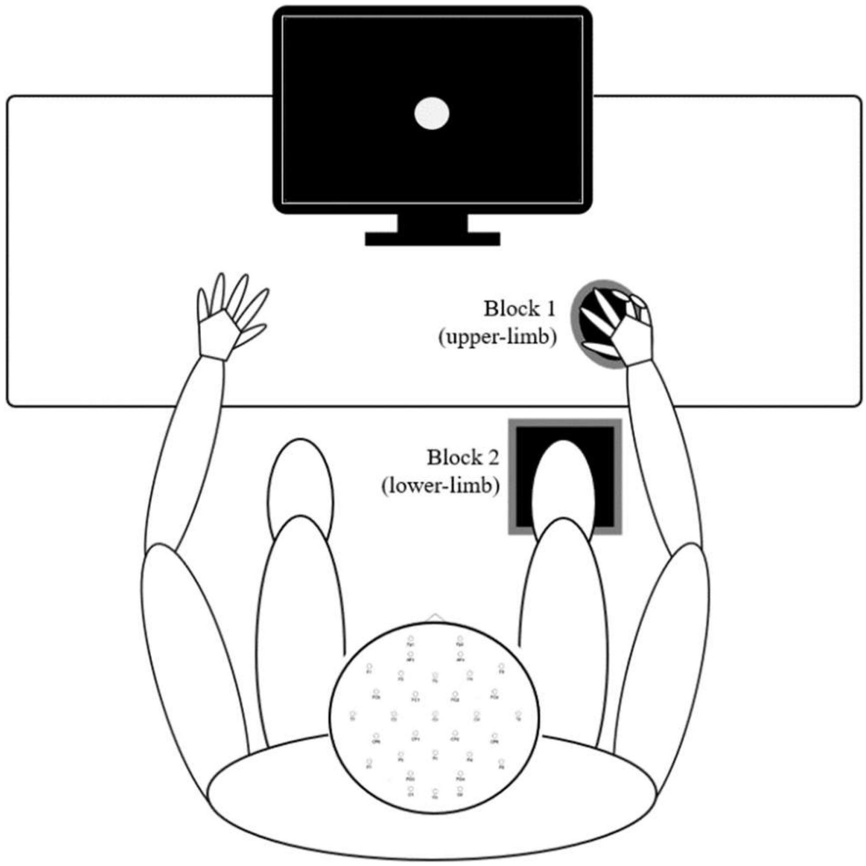

FIGURE 1 | Experimental procedures – Participants sat in a natural posture on a comfortable chair while maintaining visual fixation in the center of the screen in front of them. The two conditions (upper- and lower-limb) were applied in separate blocks, and the order of these blocks was randomized. In both conditions, the finger and foot rested on the response pad between responses.

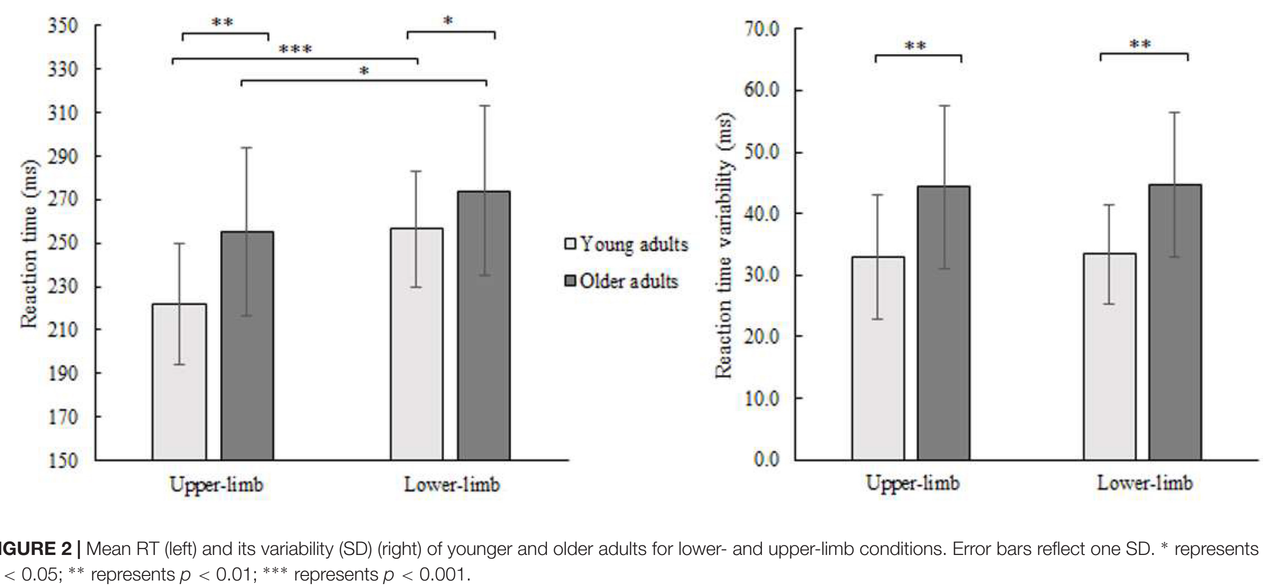

FIGURE 2 | Mean RT (left) and its variability (SD) (right) of younger and older adults for lower- and upper-limb conditions. Error bars reflect one SD. * represents $p < 0.05$; ** represents $p < 0.01$; *** represents $p < 0.001$.

1 Hz, automatic and manual bad channel interpolation, and average re-referencing). Next, subject-specific AMICA (*icaweights*, *icasphere, icaact, icawinv, icachansind*) and DIPFIT information were copied to the subject's separate condition data files and ICLabel was used. Independent components labeled as "eye" were automatically rejected if they met the threshold of $\geq$ 85%. Components expressing clear horizontal or vertical eye-movement profiles based on topography, spectral plot, and time-domain signature, but failed to reach 85% eye labeling threshold, were rejected manually.

For each experimental condition, the ERP analyses were performed on a single subject level. Stimulus-locked event-related potentials (s-ERPs) were segmented to −200 to + 800 ms epochs with a baseline correction set to −200 to 0 milliseconds. Epochs were rejected using the amplitude cutoff value of 100 μV (Yordanova et al., 2004). In all cases, a minimum of 50 stimuli epochs were averaged. ERPs to visual stimulation were assessed over the occipital locations where responses were most strongly represented (the occipital electrodes O1, Oz, and O2). The following peak-detection analyses were performed: (i) P1 was detected as the most positive peak (amplitude and latency) within the range 40–140 milliseconds after the stimuli occurred, (ii) N1 was the most negative peak (amplitude and latency) within the range of 80–140 milliseconds, and (iii) P2 was the first positive peak (amplitude and latency) after 200 milliseconds (Yordanova et al., 2004).

Additionally, the response-locked ERPs (r-ERP; for the upper- and lower-limb) were segmented to −500 to + 500 milliseconds epochs with the baseline set to −500 to −300 milliseconds before the response occurred. The exact methodological procedures implemented for the s-ERP epoch extraction (see above) were also utilized for the r-ERP extraction. r-ERPs, or motor-related cortical potentials (MRCPs) for simple reaction times, were analyzed over the C3 or C4 electrode, which was positioned on the contralateral side of the dominant hand above the motor cortex as well as above the Cz electrode, which overlays the sensorimotor cortices on the homunculus. The following parameters were extracted from each MRCP: the most negative displacement of MRCP (peak latency and amplitude), the onset latency of the MRCP with a threshold of 15% of MRCP maximum peak, and the duration of the motor-related activation, known as MRCP rise time (Yordanova et al., 2004). Because we focused on the pre-motor response potentials, we did not statistically evaluate the post-response potentials [the movement-monitoring potential known to be a component of performance control (Shakeel et al., 2015)], but we presented them in ERP and topographic figures for display purposes.

Statistical Analyses

The mean reaction time and its within-subject variability [standard deviation (SD) across trials] were computed and analyzed with a custom script written for MATLAB software (MathWorks, Natick, MA, United States). The behavioral and ERP results were statistically processed in the SPSS software version 26.0 (IBM, Chicago, IL, United States). Homogeneity of variances and normality of distribution of parameters was tested using Levene's test and Shapiro-Wilk test, respectively. A repeated-measures analysis of variance (RM ANOVA) with a within-subject factor of condition (upper- and lower-limb) and between-subject factor of age (young and older adults) was used to assess the main effects (age and condition) and the two-way interaction effect between age and condition. For significant effects, effect size as partial η^2 was reported and Bonferroni *post hoc* tests were applied. This included *post hoc* analysis for each significant main effect, primarily to present the mean differences and statistics related to the two levels in more detail. Multiple stepwise regression analysis was performed separately for age (young and older adults) and limb condition (upper- and lower-limb) to identify significant surviving predictors of RTs. Four models were run in which all ERP variables in each category (younger, older adults, upper- and lower-limb) were entered to predict RTs. Statistical conclusions were drawn at a *p*-value of 0.05.

RESULTS

Behavioral Data

Average finger and foot RTs for younger and older adults are presented in **Figure 2**. The RM ANOVA showed that each of the main effects were significant, with age- [$F(1,46) = 6.452$, $p = 0.008$, Partial $\eta^2 = 0.126$], and condition-related differences [$F(1,46) = 43.118$, $p < 0.001$, Partial $\eta^2 = 0.496$]. The interaction was not significant ($p = 0.110$). Both groups had longer RTs responding with lower- compared to the upper-limb (older $p = 0.038$; younger $p < 0.001$) as well as older adults had longer RTs responding with upper- ($p = 0.006$) and lower-limb ($p = 0.048$) compared to their younger counterparts.

The variability of RTs (SD) showed a significant age effect [$F(1,46) = 16.687$, $p < 0.001$, Partial $\eta^2 = 0.294$] and no condition ($p = 0.371$) or interaction effect ($p = 0.975$). There was greater variability in older compared to younger adults while responding with the upper- ($p = 0.001$) as well as with lower limbs ($p = 0.001$).

Electrophysiological Data

Supplementary Figure 1 shows the stimulus-locked event-related potentials (s-ERPs) on the scalp. An average s-ERP above the occipital cortex (electrode O1, Oz, and O2) is shown in **Figure 3** with topographic patterns of P1, N1, and P2 components. Processing of visual stimuli was further investigated over the occipital electrodes and shows overall larger amplitudes with delayed latencies of endogenous potentials in older compared to younger adults.

P1 Amplitude and Latency

The RM ANOVA for P1 amplitude did not show a significant effect of age ($p = 0.141$), condition ($p = 0.374$), or interaction ($p = 0.432$). Similarly, age ($p = 0.337$), condition ($p = 0.271$), and interaction ($p = 0.263$) effects were not significant for the P1 latency.

N1 Amplitude and Latency

The N1 amplitude showed a significant age [$F(1,46) = 12.160$, $p = 0.001$, Partial $\eta^2 = 0.311$], but no condition ($p = 0.404$) nor

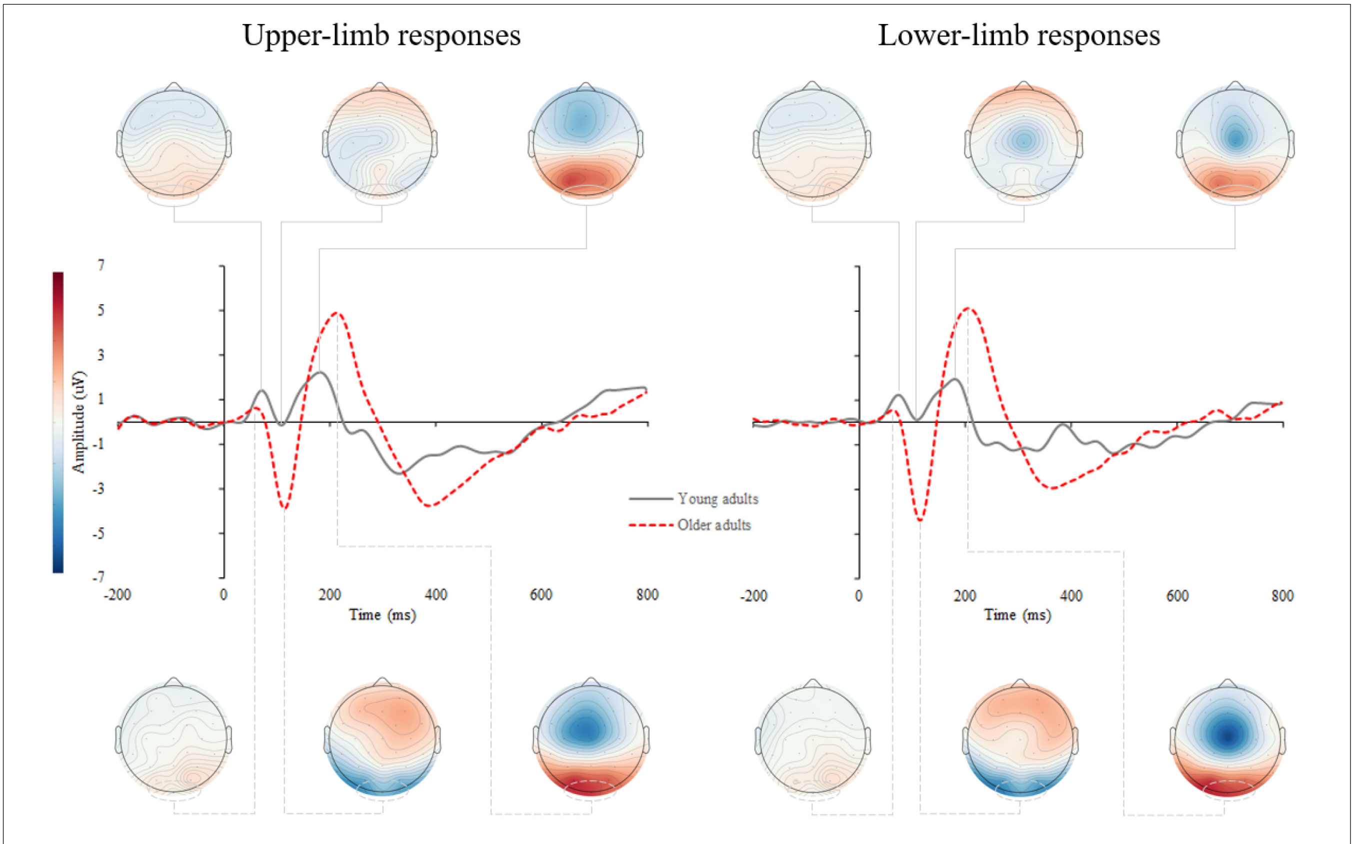

FIGURE 3 | Grand average stimulus-locked event-related potentials (s-ERPs) for upper- (left) and lower-limb RT (right) for younger and older adults. The topographic maps correspond to the individual ERP components: P1, N1, and P2.

interaction effect ($p = 0.426$). Older compared to younger adults had greater negative N1 deflection while responding with upper- ($p = 0.001$) as well as with lower limbs ($p < 0.001$) (**Figure 4**). No significant effect of age ($p = 0.179$), condition ($p = 0.486$) and interaction ($p = 0.719$) was found for N1 latency.

P2 Amplitude and Latency

The P2 amplitude showed a significant age [$F(1,46) = 10.252$, $p = 0.003$, Partial $\eta^2 = 0.249$], but no condition ($p = 0.706$) nor interaction effect ($p = 0.133$). Older compared to younger adults had greater P2 amplitude (**Figure 5**) while responding with both upper- ($p = 0.011$) and lower limbs ($p = 0.001$).

Similarly, for P2 latency a significant age [$F(1,46) = 8.122$, $p = 0.011$, Partial $\eta^2 = 0.208$], but no condition ($p = 0.472$) nor interaction effect ($p = 0.577$) was discovered. Prolonged P2 latency (**Figure 5**) was found in older compared to younger adults for both upper- ($p = 0.011$) and lower limbs ($p = 0.024$).

Motor-Related Cortical Potential

Supplementary Figure 2 shows the response-locked event-related potentials (r-ERPs) on the scalp. Motor response processing was further examined over the contralateral motor cortex for upper-limb responses (C3 and C4 electrodes for the right- and left-handed participants, respectively) and at the vertex (Cz) for lower- limb responses. A grand average of the r-ERP is shown in **Figure 6** with the topographic patterns of onset latency, MRCP peak, and movement-monitoring potential.

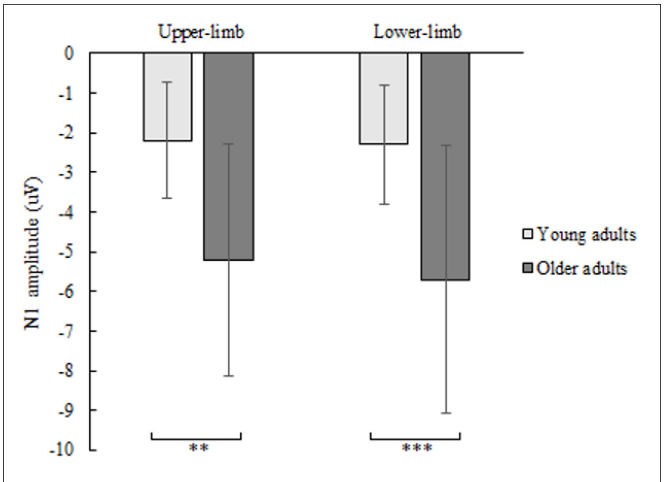

FIGURE 4 | N1 amplitude of younger and older adults for lower- and upper-limb conditions. Error bars reflect one SD. * represents $p < 0.05$; ** represents $p < 0.01$; *** represents $p < 0.001$.

The RM ANOVA for MRCP peak amplitude showed an effect of age [$F(1,42) = 4.914$, $p = 0.030$, Partial $\eta^2 = 0.117$] and

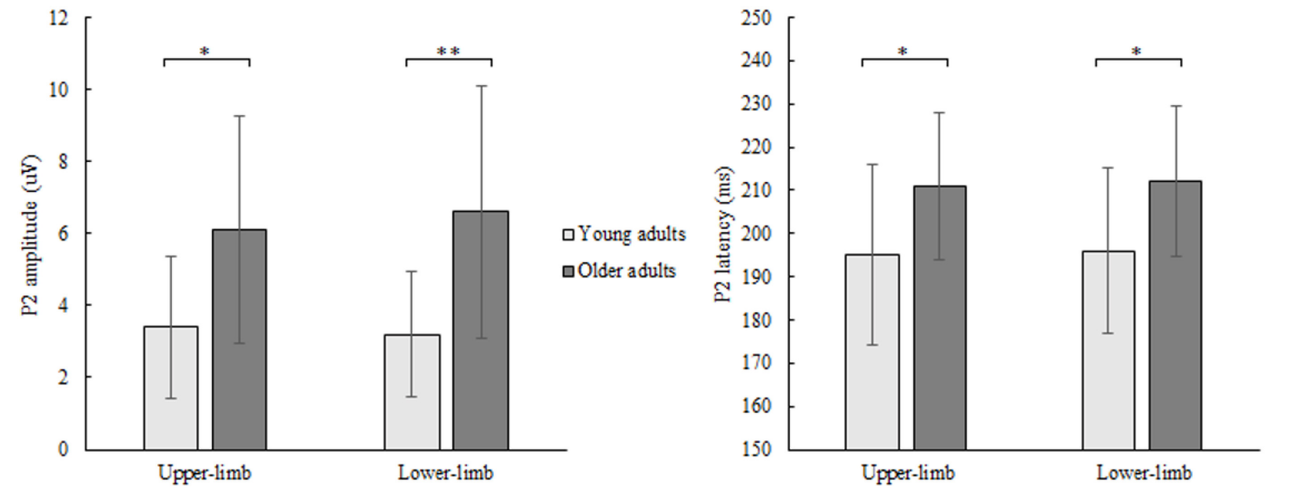

FIGURE 5 | P2 amplitude (left) and latency (right) of younger and older adults for lower- and upper-limb conditions. Error bars reflect one SD. * represents $p < 0.05$; ** represents $p < 0.01$; *** represents $p < 0.001$.

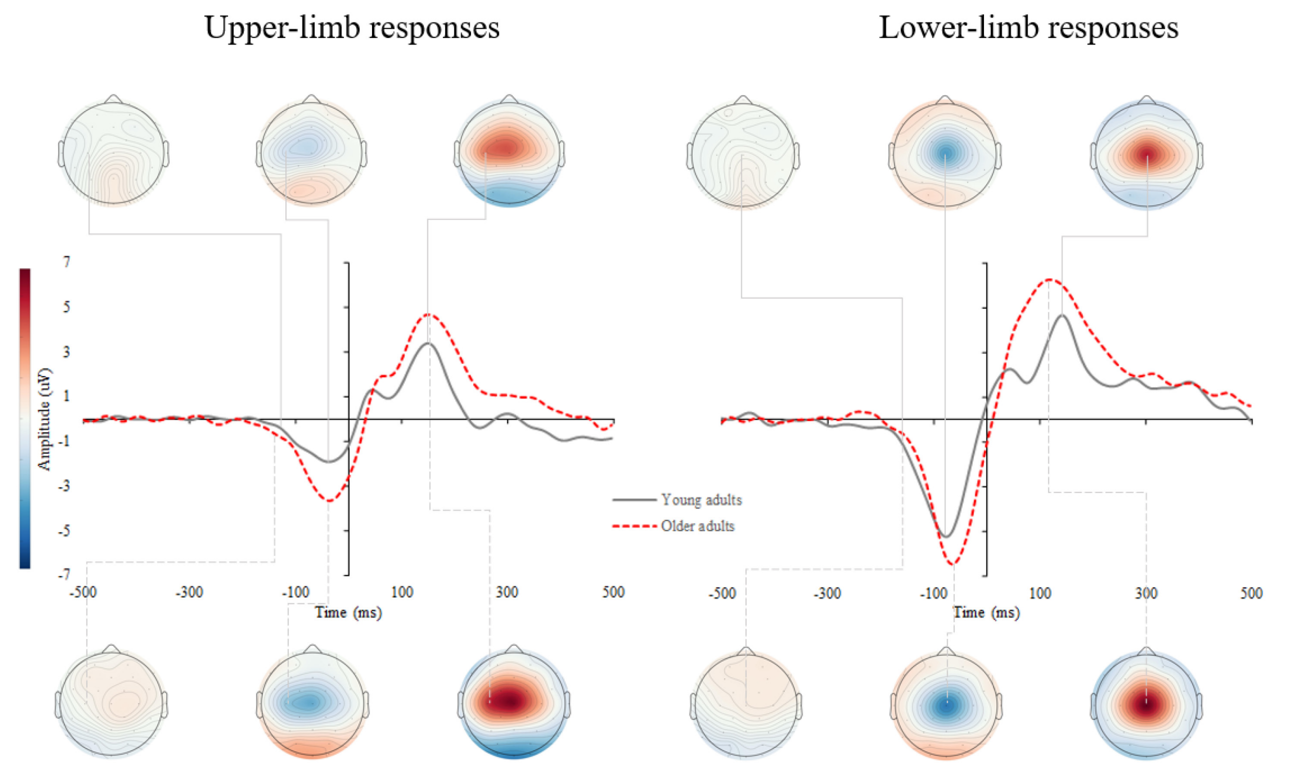

FIGURE 6 | Grand average response-locked event-related potentials (r-ERPs) for upper- (left) and lower-limb RT (right) for younger and older adults. The topographic maps correspond to the individual MRCP components: onset latency, peak amplitude, and movement-monitoring potential.

condition [$F(1,42) = 16.446$, $p < 0.001$, Partial $\eta^2 = 0.586$], while the interaction effect was not significant ($p = 0.868$). A larger MRCP peak amplitude was found in older compared to younger adults for upper- ($p = 0.002$) and a non-significant trend for lower limbs ($p = 0.097$). Although assessed from a different position (upper-limb at C3 or C4, and lower limb at Cz location), the MRCP peak amplitude was larger for lower- compared to upper-limb in younger ($p < 0.001$) and older adults ($p < 0.001$) (**Figure 7A**).

The MRCP peak latency showed a significant condition [$F(1,42) = 62.855$, $p < 0.001$, Partial $\eta^2 = 0.605$] but no age ($p = 0.646$) or interaction effect ($p = 0.132$). The MRCP peak

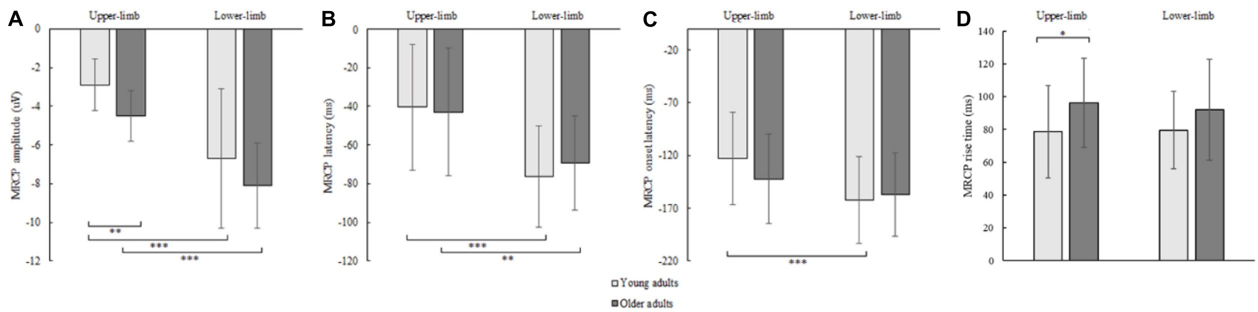

FIGURE 7 | MRCP peak amplitude **(A)**, peak latency **(B)**, onset latency **(C)**, and rise time **(D)** of younger and older adults for lower- and upper-limb conditions. Error bars reflect one SD. * represents $p < 0.05$; ** represents $p < 0.01$; *** represents $p < 0.001$.

latency occurred earlier for lower- compared to upper-limb in younger ($p < 0.001$) and older adults ($p = 0.004$) (**Figure 7B**).

The MRCP onset latency showed a significant condition effect [$F(1,42) = 26.646$, $p < 0.001$, Partial $\eta^2 = 0.477$], but no age ($p = 0.624$) or interaction effect ($p = 0.116$). Longer MRCP onset latencies were found for lower- as compared to upper-limb in younger ($p < 0.001$) and only non-significant trend in older adults ($p = 0.095$) (**Figure 7C**).

The MRCP rise time showed a significant age effect [$F(1,42) = 4.242$, $p = 0.046$, Partial $\eta^2 = 0.192$], but no condition ($p = 0.683$) or interaction effect ($p = 0.526$). Longer MRCP rise times were found in older compared to younger adults for the upper limb ($p = 0.036$), and a non-significant trend for the lower-limb ($p = 0.072$) (**Figure 7D**).

Regression Analyses

A multiple stepwise regression analysis (**Table 2**) revealed that in young adults, upper-limb RTs were significantly predicted by MRCP onset latency [$F(1,22) = 8.398$, $R^2 = 0.39$, $p = 0.017$], while in older adults, the upper-limb RTs were significantly predicted by three parameters, i.e., MRCP onset latency, MRCP rise time, and P2 latency [$F(3,19) = 26.068$, $R^2 = 0.89$, $p < 0.001$]. Lower-limb RTs were significantly predicted by MRCP onset latency parameter in both younger [$F(1,22) = 9.668$, $R^2 = 0.40$, $p = 0.009$] and older adults [$F(1,19) = 4.275$, $R^2 = 0.25$, $p = 0.043$].

DISCUSSION

This study aimed to investigate the age-related slowing of sensorimotor processes while reacting to visual stimuli with the upper and lower extremities. To this end, the EEG/ERP method was used to assess the strength and timing of different ERP components that reflect processing efficiency of the brain. In a sample of forty-eight healthy adults, we found an age-related slowing of simple RTs when responding with the upper- and lower- limbs. Variability was higher in older adults but consistent for both upper- and lower-limb performance. Further examination of s-ERP components revealed overall larger amplitudes with delayed latencies of endogenous potentials in older compared to younger adults. In addition, motor processes in older adults showed age-dependent deflections with higher MRCP amplitude, most likely reflecting less efficient recruitment of neuronal resources required for the execution of the sensorimotor task with the upper and lower limbs. Our study also suggests that specifically for the upper-limb RT in older adults, the P2 component plays an important role in addition to the MRCP parameters.

A general age-related slowing of behavior when responding to a simple visual reaction task was confirmed in our study. Most studies reported delayed upper-limb responses to simple visual stimuli in older compared to younger adults (Inui, 1997; Deary and Der, 2005; Ashoke et al., 2010), while fewer studies focused on lower-limb RTs (Lord and Fitzpatrick, 2001; Cai et al., 2020). In contrast, Yordanova et al. (2004) found no age-related slowing in upper-limb simple RT but confirmed it in choice RT while responding to visual stimuli. Increasing age was also expected to result in greater variability in RTs (for a review see Dykiert et al., 2012), however, inter-limb differences in each age group were not present, implying that all participants were able to maintain the same variability while responding with lower- and upper- limbs.

The origins of age-related behavioral slowing were further analyzed using ERP components reflecting stimulus-related processing. First, the results of our study showed no age-related changes in the early component of P1. Early perceptual processes

TABLE 2 | Results of multiple regression analysis with surviving predictors presented.

Model	*R*	R^2	*B*	Std error	Beta	*p* value
Upper-limb – Young adults						
MRCP onset latency	0.625	0.391	−0.373	0.135	−0.625	0.017
Upper-limb – Older adults						
MRCP onset latency	0.762	0.580	−1.025	0.124	−1.022	<0.001
MRCP rise time	0.891	0.794	−0.750	0.196	−0.475	0.002
P2 latency	0.943	0.890	0.811	0.242	0.325	0.005
Lower-limb – Young adults						
MRCP onset latency	0.630	0.397	−0.493	0.162	−0.630	0.009
Lower-limb – Older adults						
MRCP onset latency	0.496	0.246	−0.508	0.230	−0.496	0.043

All ERP components were entered into a stepwise regression model to predict RTs; R, multiple correlation coefficient; R^2, adjusted coefficient of determination; B, regression coefficient; beta, standardized regression coefficient.

addressed by the P1 (and also N1) component presumably reflect the gain control of sensory processing (Luck et al., 1990; Klimesch et al., 2004, 2007) and, according to previous reports, did not differ between young and old adults (Yordanova et al., 2004; Kavcic et al., 2013). However, other studies reported an age-related enhancement of early components in the processing of visual stimuli that follows the U-shape across the lifespan, with the amplitudes of P1 and N1 being larger in children and the elderly (Reuter et al., 2019). Second, greater negativity in N1 peak amplitude was found in older adults, but no difference in N1 latency. This enhancement (greater negativity) in N1 amplitude could indicate higher attentional resources recruited for the same amount of visual information processed (Hillyard and Anllo-Vento, 1998). If a simple RT task is considered more demanding in advanced age than in younger years, the processes involved in motor preparation and execution must be guided with a stronger reference to external stimuli, and for this reason, more attention is allocated to these stimuli in order to support movement execution (Yordanova et al., 2004). Third, enhanced and delayed P2 responses were observed in old compared with young adults, but there were no differences between the upper- and lower-limbs in any of the age groups. Previous studies examining P2 suggested that this component reflects an index of working memory (Lefebvre et al., 2005; Finnigan et al., 2011), stimulus salience (Riis et al., 2009), and stimulus evaluation (Potts, 2004). It has also been suggested that P2 plays an important role in top-down cognitive control (Karamacoska et al., 2019; Lai et al., 2020). Therefore, together with the significant differences between age groups in the Trail-Making Test (TMT) [indicative of visual scanning ability and working memory (Arbuthnott and Frank, 2020; Ciolek and Lee, 2020)], the age-related increase in P2 amplitude and prolonged P2 latency are indeed indicative of impaired cognitive control.

Here, the P2 latency was found to be a significant predictor of RTs, but only for older adults and the upper limbs. Why P2 latency had no predictive power for lower-limb performance RT, should be further investigated. The overall predictiveness of upper-limb RTs was also not consistent with Yordanova et al. (2004), who reported N1 latency (in addition to the MRCP components discussed below) as a significant predictor of simple RT in both young and older adults. Based on their results, we also hypothesized that N1 latency would be predictive at least for simple RT for upper-limb, however, we did not find any evidence of this. The discrepancy between our results and those of Yordanova et al. (2004) could be due to several factors, including differences in age structure (young 34 year vs. 23 year; older 67 year vs. 58 year, respectively). In the study by Reuter et al. (2019), the N1 component is shown to follow a u-shaped pattern, with the shortest latencies and smallest amplitudes occurring in middle-aged individuals.

The negative potential preceding the movement represents the brain activity that is processed during the planning and preparation of a voluntary movement (Shibasaki and Hallett, 2006). It has been suggested that additional neural resources must be recruited in old age for successful motor performance (Heuninckx et al., 2008), while Yordanova et al. (2004) suggested that greater MRCP deflection was indicative of more extensive depolarization of neurons of the contralateral motor cortex (Yordanova et al., 2004). Similarly, the results of our study showed an age-related stronger MRCP amplitude for upper- and a trend for lower limbs but (although assessed from different positions) the MRCP amplitude was larger for lower- compared to upper-limb in both age groups. The question of why there is less efficient recruitment of neuronal resources required for motor response in the aging brain should be further explored by bringing together different imaging techniques. The review by Seidler et al. (2010) highlighted several factors that contribute to the age-related slowing of movements. Namely, changes in white matter (demyelination) (Zahr et al., 2009), gray matter (atrophy in the prefrontal cortex and also in the primary motor cortex) (Raz et al., 1997; Salat et al., 2004), and biochemical changes [decreased dopamine levels, receptors, transmission, and transporters (Gottfries, 1990; Kaasinen et al., 2000; Yamamoto et al., 2002)]. With respect to cortical motor cortex excitability, some studies suggest that motor cortex oscillations also depend on the inhibitory neurotransmitter γ-aminobutyric acid (GABA) (Gaetz et al., 2011; Burianová et al., 2020). Rossiter et al. (2014) reported that changes in beta oscillations in the motor cortex are associated with changes in GABA. Moreover, the meta-analysis by Porges et al. (2021) reported that GABA levels increase during adolescence and decrease later in adulthood. Thus, we can even speculate that the increased cortical excitability of the motor cortex may be due to the decreased GABA levels in older adults, which leads to decreased inhibitory processes. Further studies should clarify which processes (excitatory or inhibitory) play a greater role in the age-related changes in motor cortex excitability. It may be suggested that there is greater recruitment during planning and preparation of the motor response to the onset of a visual stimulus in the elderly compared to the younger participants. However, in the study by Yordanova et al. (2004), where only the upper limb was examined, similar findings were confirmed for more complex (choice) and not for simple RTs. Some discrepancies between the two studies were listed in the previous paragraph, but regarding MRCPs, our participants responded with the index finger, whereas Yordanova et al. (2004) used the middle finger. In our results, no such clear positivity was found at the ipsilateral site.

Although age-related slowing of simple RT tasks has been previously investigated using the EEG/ERP method for the upper-limb, this study extends knowledge to the lower-limbs. To be able to assess the fundamental responses to random time-locked visual stimuli, the simple RT task was applied. Previous study (Yordanova et al., 2004), however, showed that aging causes a functional dysregulation of the motor cortex that becomes more evident with increased task complexity. Although our study extends the information to the lower limbs, the fact that we do not have a paradigm of choice RT limits our understanding because some motor processes or mechanisms that might be associated with motor slowing in aging, such as response inhibition or mechanisms of limb selection, may not be revealed with the current paradigm. Thus, future studies should expand our protocol with simple RT with more complex cognitive tasks (Yordanova et al., 2004), with possible extension to the lower limbs. Randomizing responses for the upper- and lower limbs within the same block would lead to different results due to inhibitory processes of the brain regions representative of the hand and foot. Participants would have an equal chance of receiving visual stimuli requiring motor execution with the upper- or lower limb, representing a more complex paradigm. Finally, recent advances in Mobile Brain/Body Imaging (MoBI) research allow sensorimotor screening during movement (e.g., walking) in more naturalistic environments (Jungnickel and Gramann, 2016; Olsen et al., 2021; Wunderlich et al., 2021) would provide even more ecologically valid results.

In conclusion, our results to some extent confirm the previous findings showing an age-related slowing of sensorimotor activity occurring at the level of visual input as evidenced by visual-evoked potentials and motor response generation processes of the motor cortex, and further expand the results to the lower limbs. Quick and efficient reactions with upper- as well as lower-limb are needed to react to an unexpected hazard to avoid falls. The simple RT test evaluation is characterized as one of the basic measures that are highly dependent on sensorimotor integration and that estimates an individual's alertness and processing speed. Our aim was to investigate the origin of age-related motor slowing at the neuronal level and to extend it to the lower limbs. Our study shows that age-related slowing already occurs during simple visual RT tasks with the upper and lower extremities and is not influenced by early processes of visual stimulus processing, but has its origin partly in the P2 component in addition to motor efficiency in the motor cortex. Because previous studies have shown that RTs can be improved with different physical (e.g., Fragala et al., 2014; Jehu et al., 2017) and cognitive (for review see Kueider et al., 2012) approaches, it would be important to extend this knowledge from the purely behavioral level to the neural level to explore which components are sensitive to training and to what extent they can be modulated. Such applications may be important not only for the aging population, but also for athletes who want to improve their performance to the millisecond.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the National Medical Ethics Committee (No. KME 57/06/17). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

UM, GD, BR, RP, and VK contributed to conception and design of the study. UM, MP, and NO contributed to data collection and organization of the database. UM, MP, KDP, NO, and VK contributed to data and statistical analysis. UM wrote the first draft of the manuscript. MP, KDP, and VK assisted with the interpretation of results. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.819576/full#supplementary-material

REFERENCES

Amenedo, E., and Díaz, F. (1998). Aging-related changes in processing of non-target and target stimuli during an auditory oddball task. *Biolog. Psychol.* 48, 235–267. doi: 10.1016/S0301-0511(98)00040-4

Arbuthnott, K., and Frank, J. (2020). Trail making test, part B as a measure of executive control: validation using a set-switching paradigm - PubMed. *J. Clin. Exp. Neuropsychol.* 22, 518–528. doi: 10.1076/1380-3395(200008)22:4;1-0;FT518

Ashoke, B., Skikha, D., and Sudarsan, B. (2010). Reaction Time With Respect To the Nature of. *Sport Health* 2, 35–40.

Azim, E., and Kazuhiko, S. (2019). Gain control in the sensorimotor system. *Physiol. Behav.* 8, 177–187. doi: 10.1016/j.cophys.2019.03.005.Gain

Brundle, C., Waterman, H. A., Ballinger, C., Olleveant, N., Skelton, D. A., Stanford, P., et al. (2015). The causes of falls: views of older people with visual impairment. *Health Expect.* 18, 20–21. doi: 10.1111/HEX.12355

Burianová, H., Marstaller, L., Rich, A. N., Williams, M. A., Savage, G., Ryan, M., et al. (2020). Motor neuroplasticity: a MEG-fMRI study of motor imagery and execution in healthy ageing. *Neuropsychologia* 146:107539. doi: 10.1016/j.neuropsychologia.2020.107539

Cai, Y., Hausdorff, J. M., Bean, J. F., Manor, B., You, T., and Leveille, S. G. (2020). Participation in cognitive activities is associated with foot reaction time and gait speed in older adults. *Aging Clin. Exp. Res.* 2020:0123456789. doi: 10.1007/s40520-020-01583-3

Cavazzana, A., Röhrborn, A., Garthus-Niegel, S., Larsson, M., Hummel, T., and Croy, I. (2018). Sensory-specific impairment among older people. An investigation using both sensory thresholds and subjective measures across the five senses. *PLoS One* 13:e0202969. doi: 10.1371/JOURNAL.PONE.0202969

Ciolek, C. H., and Lee, S. Y. (2020). "Cognitive Issues in the Older Adult," in *Guccione's Geriatric Physical Therapy*, eds D. Avers and R. A. Wong (Missouri: Mosby), 425–452. doi: 10.1016/B978-0-323-60912-8.00019-1

Deary, I. J., and Der, G. (2005). Reaction time, age, and cognitive ability: longitudinal findings from age 16 to 63 years in representative population samples. *Aging Neuropsychol. Cogn.* 12, 187–215. doi: 10.1080/13825580590969235

Delorme, A., and Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods* 134, 9–21. doi: 10.1016/J.JNEUMETH.2003.10.009

Dinges, D. F., and Powell, J. W. (1985). Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behav. Res. Methods Instrum. Comp.* 17, 652–655. doi: 10.3758/BF03200977

Dunn, B. R., Dunn, D. A., Languis, M., and Andrews, D. (1998). The relation of ERP components to complex memory processing. *Brain Cogn.* 36, 355–376. doi: 10.1006/brcg.1998.0998

Dykiert, D., Der, G., Starr, J. M., and Deary, I. J. (2012). Age Differences in Intra-Individual Variability in Simple and Choice Reaction Time: Systematic Review and Meta-Analysis. *PLoS One* 7:10. doi: 10.1371/JOURNAL.PONE.0045759

Falkenstein, M., Yordanova, J., and Kolev, V. (2006). Effects of aging on slowing of motor-response generation. *Internat. J. Psychophys.* 59, 22–29. doi: 10.1016/j.ijpsycho.2005.08.004

Finnigan, S., O'Connell, R. G., Cummins, T. D. R., Broughton, M., and Robertson, I. H. (2011). ERP measures indicate both attention and working memory encoding decrements in aging. *Psychophysiology* 48, 601–611. doi: 10.1111/j.1469-8986.2010.01128.x

Fozard, J. L., Vercruyssen, M., Reynolds, S. L., Hancock, P. A., and Quilter, R. E. (1994). Age differences and age changes in reaction times: baltimore longitudinal study of aging. *J. Gerontol.* 49, 179–189. doi: 10.1093/geronb/51B.1.S30

Fragala, M. S., Beyer, K. S., Jajtner, A. R., Townsend, J. R., Pruna, G. J., Boone, C. H., et al. (2014). Resistance exercise may improve spatial awareness and visual reaction in older adults. *J. Strength Cond. Res.* 28:8. doi: 10.1519/JSC.0000000000000520

Freunberger, R., Klimesch, W., Doppelmayr, M., and Höller, Y. (2007). Visual P2 component is related to theta phase-locking. *Neurosci. Lett.* 426, 181–186. doi: 10.1016/j.neulet.2007.08.062

Fries, P. (2015). Rhythms for Cognition: Communication through Coherence. *Neuron* 88, 220–235. doi: 10.1016/j.neuron.2015.09.034

Gaetz, W., Edgar, J. C., Wang, D. J., and Roberts, T. P. (2011). Relating MEG measured motor cortical oscillations to resting γ-aminobutyric acid (GABA) concentration. *Neuroimage* 55, 616–621. doi: 10.1016/j.neuroimage.2010.12.077

Gajewski, P. D., and Falkenstein, M. (2014). Age-Related Effects on ERP and Oscillatory EEG-Dynamics in a 2-Back Task. *J. Psychophys.* 28, 162–177. doi: 10.1027/0269-8803/a000123

Gazzaley, A., Clapp, W., Kelley, J., McEvoy, K., Knight, R. T., and D'Esposito, M. (2008). Age-related top-down suppression deficit in the early stages of cortical visual memory processing. *Proc. Natl. Acad. Sci. U S A* 105, 13122–13126. doi: 10.1073/pnas.0806074105

Gazzaniga, M. S., Ivry, R. B., and Mangun, G. R. (2019). *Cognitive neuroscience: The biology of the mind*, 5th editio Edn. New York, NY: WW Norton & Company.

Gottfries, C. G. (1990). Neurochemical aspects on aging and diseases with cognitive impairment. *J. Neurosci. Res.* 27, 541–547. doi: 10.1002/jnr.490270415

Gottsdanker, R. (1982). Age and simple reaction time. *J. Gerontol.* 37, 342–348. doi: 10.1093/geronj/37.3.342

Heuninckx, S., Wenderoth, N., Debaere, F., Peeters, R., and Swinnen, S. P. (2005). Neural basis of aging: the penetration of cognition into action control. *J. Neurosci.* 25, 6787–6796. doi: 10.1523/JNEUROSCI.1263-05.2005

Heuninckx, S., Wenderoth, N., and Swinnen, S. P. (2008). Systems neuroplasticity in the aging brain: recruiting additional neural resources for successful motor performance in elderly persons. *J. Neurosci.* 28, 91–99. doi: 10.1523/JNEUROSCI.3300-07.2008

Hillyard, S. A., and Anllo-Vento, L. (1998). Event-related brain potentials in the study of visual selective attention. *Proc. Natl. Acad. Sci.* 95, 781–787. doi: 10.1073/PNAS.95.3.781

Inui, N. (1997). Simple reaction times and timing of serial reactions of middle-aged and old men. *Percept. Motor Skills* 84, 219–225. doi: 10.2466/pms.1997.84.1.219

Jehu, D., Paquet, N., and Lajoie, Y. (2017). Balance and mobility training with or without concurrent cognitive training does not improve posture, but improves reaction time in healthy older adults. *Gait Post.* 52, 227–232. doi: 10.1016/j.gaitpost.2016.12.006

Jungnickel, E., and Gramann, K. (2016). Mobile brain/body imaging (MoBI) of physical interaction with dynamically moving objects. *Front. Hum. Neurosci.* 10:306. doi: 10.3389/FNHUM.2016.00306/ABSTRACT

Kaasinen, V., Vilkman, H., Hietala, J., Någren, K., Helenius, H., Olsson, H., et al. (2000). Age-related dopamine D2/D3 receptor loss in extrastriatal regions of the human brain. *Neurobiol. Aging* 21, 683–688. doi: 10.1016/s0197-4580(00)00149-4

Karamacoska, D., Barry, R. J., De Blasio, F. M., and Steiner, G. Z. (2019). EEG-ERP dynamics in a visual Continuous Performance Test. *Facult. Soc. Sci. Papers* 146:260. doi: 10.1016/j.ijpsycho.2019.08.013

Kavcic, V., Martin, T., and Zalar, B. (2013). Aging effects on visual evoked potentials (VEPs) for motion direction discrimination. *Internat. J. Psychophysiol.* 89, 78–87. doi: 10.1016/J.IJPSYCHO.2013.05.012

Klimesch, W., Sauseng, P., Hanslmayr, S., Gruber, W., and Freunberger, R. (2007). Event-related phase reorganization may explain evoked neural dynamics. *Neurosci. Biobehav. Rev.* 31, 1003–1016. doi: 10.1016/j.neubiorev.2007.03.005

Klimesch, W., Schack, B., Schabus, M., Doppelmayr, M., Gruber, W., and Sauseng, P. (2004). Phase-locked alpha and theta oscillations generate the P1-N1 complex and are related to memory performance. *Cogn. Brain Res.* 19, 302–316. doi: 10.1016/j.cogbrainres.2003.11.016

Kropotov, J., Ponomarev, V., Tereshchenko, E. P., Müller, A., and Jäncke, L. (2016). Effect of aging on ERP components of cognitive control. *Front. Aging Neurosci.* 8, 1–15. doi: 10.3389/fnagi.2016.00069

Kueider, A. M., Parisi, J. M., Gross, A. L., and Rebok, G. W. (2012). Computerized cognitive training with older adults: a systematic review. *PLoS One* 2012:e40588. doi: 10.1371/journal.pone.0040588

Lai, L. Y., Fromer, R., Festa, E. K., and Heindel, W. C. (2020). Age-related changes in the neural dynamics of bottom-up and top-down processing during visual object recognition: an electrophysiological investigation. *Neurobiol. Aging* 94, 38–49. doi: 10.1016/J.NEUROBIOLAGING.2020.05.010

Lefebvre, C. D., Marchand, Y., Eskes, G. A., and Connolly, J. F. (2005). Assessment of working memory abilities using an event-related brain potential (ERP)-compatible digit span backward task. *Clin. Neurophys.* 116, 1665–1680. doi: 10.1016/j.clinph.2005.03.015

Lord, S. R., Clark, R. D., and Webster, I. W. (1991). Physiological factors associated with falls in an elderly population. *J. Am. Geriatr. Soc.* 39, 1194–1200. doi: 10.1111/J.1532-5415.1991.TB03574.X

Lord, S. R., and Clark, R. D. (1996). Simple physiological and clinical tests for the accurate prediction of falling in older people. *Gerontology* 42, 199–203. doi: 10.1159/000213793

Lord, S. R., and Fitzpatrick, R. C. (2001). Choice stepping reaction time: a composite measure of falls risk in older people. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* 56, 627–632. doi: 10.1093/gerona/56.10.M627

Lord, S. R., Ward, J. A., Williams, P., and Anstey, K. J. (1994). Physiological factors associated with falls in older community-dwelling women. *J. Am. Geriatr. Soc.* 42, 1110–1117. doi: 10.1111/J.1532-5415.1994.TB06218.X

Luck, S. J., Heinze, H. J., Mangun, G. R., and Hillyard, S. A. (1990). Visual event-related potentials index focused attention within bilateral stimulus arrays. II. Functional dissociation of P1 and N1 components. *Electroencephalogr. Clin. Neurophysiol.* 75, 528–542. doi: 10.1016/0013-4694(90)90139-B

Mattay, V. S., Fera, F., Tessitore, A., Hariri, A. R., Das, S., Callicott, J. H., et al. (2002). Neurophysiological correlates of age-related changes in human motor function. *Neurology* 58, 630–635. doi: 10.1212/WNL.58.4.630

Maver, S. L., Dodd, K., and Menz, H. (2011). Lower limb reaction time discriminates between multiple and single fallers. *Physiother. Theory Pract.* 27, 329–336. doi: 10.3109/09593985.2010.510551

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., et al. (2005). The Montreal Cognitive Assessment, MoCA: a Brief Screening Tool For Mild Cognitive Impairment. *J. Am. Geriat. Soc.* 53, 695–699. doi: 10.1111/J.1532-5415.2005.53221.X

Natale, E., Marzi, C. A., Girelli, M., Pavone, E. F., and Pollmann, S. (2006). ERP and fMRI correlates of endogenous and exogenous focusing of visual-spatial attention. *Eur. J. Neurosci.* 23, 2511–2521. doi: 10.1111/j.1460-9568.2006.04756.x

Olsen, S., Alder, G., Williams, M., Chambers, S., Jochumsen, M., Signal, N., et al. (2021). Electroencephalographic Recording of the Movement-Related Cortical

Potential in Ecologically Valid Movements: a Scoping Review. *Front. Neurosci.* 2021:15. doi: 10.3389/fnins.2021.721387

Pijnappels, M., Delbaere, K., Sturnieks, D. L., and Lord, S. R. (2010). The association between choice stepping reaction time and falls in older adults-a path analysis model. *Age Ageing* 39, 99–104. doi: 10.1093/ageing/afp200

Pion-Tonachini, L., Kreutz-Delgado, K., and Makeig, S. (2019). ICLabel: an automated electroencephalographic independent component classifier, dataset, and website. *NeuroImage* 198, 181–197. doi: 10.1016/J.NEUROIMAGE.2019.05.026

Porges, E. C., Jensen, G., Foster, B., Edden, R. A. E., and Puts, N. A. J. (2021). The trajectory of cortical GABA across the lifespan, an individual participant data meta-analysis of edited MRS studies. *eLife* 10:e62575. doi: 10.7554/ELIFE.62575

Potts, G. F. (2004). An ERP index of task relevance evaluation of visual stimuli. *Brain Cogn.* 56, 5–13. doi: 10.1016/j.bandc.2004.03.006

Raz, N., Gunning, F. M., Head, D., Dupuis, J. H., McQuain, J., Briggs, S. D., et al. (1997). Selective aging of the human cerebral cortex observed *in vivo*: differential vulnerability of the prefrontal gray matter. *Cereb. Cortex* 7, 268–282. doi: 10.1093/cercor/7.3.268

Reitan, R. M. (1958). Validity of the Trail Making Test as an Indicator of Organic Brain Damage. *Percept. Motor Skills* 8, 271–276. doi: 10.2466/PMS.1958.8.3.271

Reuter, E. M., Vieluf, S., Koutsandreou, F., Hübner, L., Budde, H., Godde, B., et al. (2019). A non-linear relationship between selective attention and associated ERP markers across the lifespan. *Front. Psychol.* 10, 1–15. doi: 10.3389/fpsyg.2019.00030

Riis, J. L., Chong, H., McGinnnis, S., Tarbi, E., Sun, X., Holcomb, P. J., et al. (2009). Age-Related Changes in Early Novelty Processing as Measured by ERPs. *Biolog. Psychol.* 82:44. doi: 10.1016/J.BIOPSYCHO.2009.05.003

Rossiter, H. E., Davis, E. M., Clark, E. V., Boudrias, M. H., and Ward, N. S. (2014). Beta oscillations reflect changes in motor cortex inhibition in healthy ageing. *Neuroimage* 91, 360–365. doi: 10.1016/J.NEUROIMAGE.2014.01.012

Salat, D. H., Buckner, R. L., Snyder, A. Z., Greve, D. N., Desikan, R. S., Busa, E., et al. (2004). Thinning of the cerebral cortex in aging. *Cereb. Cortex* 14, 721–730. doi: 10.1093/cercor/bhh032

Salat, D. H. (2011). The Declining Infrastructure of the Aging Brain. *Brain Connect.* 1, 279–293. doi: 10.1089/brain.2011.0056

Seidler, R. D., Bernard, J. A., Burutolu, T. B., Fling, B. W., Gordon, M. T., Gwin, J. T., et al. (2010). Motor control and aging: links to age-related brain structural, functional, and biochemical effects. *Neurosci. Biobehav. Rev.* 34, 721–733. doi: 10.1016/j.neubiorev.2009.10.005

Shakeel, A., Navid, M. S., Anwar, M. N., Mazhar, S., Jochumsen, M., and Niazi, I. K. (2015). A review of techniques for detection of movement intention using movement-related cortical potentials. *Comput. Mathem. Methods Med.* 2015:346217. doi: 10.1155/2015/346217

Shibasaki, H., and Hallett, M. (2006). What is the Bereitschaftspotential? *Clin. Neurophys.* 117, 2341–2356. doi: 10.1016/J.CLINPH.2006.04.025

Stelmach, G. E., and Worringham, C. J. (1985). Sensorimotor deficits related to postural stability. Implications for falling in the elderly. *Clin. Geriatr. Med.* 1, 679–694.

Taniguchi, Y., Burle, B., Vidal, F., and Bonnet, M. (2001). Deficit in motor cortical activity for simultaneous bimanual responses. *Exp. Brain Res.* 137, 259–268. doi: 10.1007/s002210000661

Tombaugh, T. N. (2004). Trail Making Test A and B: normative data stratified by age and education. *Archiv. Clin. Neuropsy.* 19, 203–214. doi: 10.1016/S0887-6177(03)00039-8

Ward, N. S., and Frackowiak, R. S. J. (2003). Age-related changes in the neural correlates of motor performance. *Brain* 126, 873–888. doi: 10.1093/brain/awg071

Wolach, I., and Pratt, H. (2001). The mode of short-term memory encoding as indicated by event-related potentials in a memory scanning task with distractions. *Clin. Neurophys.* 112, 186–197. doi: 10.1016/S1388-2457(00)00501-0

Woodruff, D. S., and Kramer, D. A. (1979). Eeg alpha slowing, refractory period, and reaction time in aging. *Exp. Aging Res.* 5, 279–292. doi: 10.1080/03610737908257205

Woods, D. L., Wyma, J. M., William Yund, E., Herron, T. J., and Reed, B. (2015). Age-related slowing of response selection and production in a visual choice reaction time task. *Front. Hum. Neurosci.* 9, 1–12. doi: 10.3389/fnhum.2015.00193

Wunderlich, A., Vogel, O., Somen, M. M., Peskar, M., Fricke, M., Gramann, K., et al. (2021). Dual-task performance in hearing-impaired older adults–Study protocol for a cross-sectional MoBI-study. *Front. Aging Neurosci.* 2021:778. doi: 10.3389/fnagi.2021.773287

Yamamoto, M., Suhara, T., Okubo, Y., Ichimiya, T., Sudo, Y., Inoue, M., et al. (2002). Age-related decline of serotonin transporters in living human brain of healthy males. *Life Sci.* 71, 751–757. doi: 10.1016/s0024-3205(02)01745-9

Yordanova, J., Kolev, V., Hohnsbein, J., and Falkenstein, M. (2004). Sensorimotor slowing with ageing is mediated by a functional dysregulation of motor-generation processes: Evidence from high-resolution event-related potentials. *Brain* 127, 351–362. doi: 10.1093/brain/awh042

Zalar, B., Martin, T., and Kavcic, V. (2015). Cortical configuration by stimulus onset visual evoked potentials (SO-VEPs) predicts performance on a motion direction discriminationtask. *Internat. J. Psychophysiol.* 96, 125–133. doi: 10.1016/j.ijpsycho.2015.04.004

Zahr, N. M., Rohlfing, T., Pfefferbaum, A., and Sullivan, E. V. (2009). Problem solving, working memory, and motor correlates of association and commissural fiber bundles in normal aging: a quantitative fiber tracking study. *Neuroimage* 44, 1050–1062. doi: 10.1016/j.neuroimage.2008.09.046

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Working-Memory, Alpha-Theta Oscillations and Musical Training in Older Age: Research Perspectives for Speech-on-speech Perception

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During the normal course of aging, perception of speech-on-speech or "cocktail party" speech and use of working memory (WM) abilities change. Musical training, which is a complex activity that integrates multiple sensory modalities and higher-order cognitive functions, reportedly benefits both WM performance and speech-on-speech perception in older adults. This mini-review explores the relationship between musical training, WM and speech-on-speech perception in older age (> 65 years) through the lens of the Ease of Language Understanding (ELU) model. Linking neural-oscillation literature associating speech-on-speech perception and WM with alpha-theta oscillatory activity, we propose that two stages of speech-on-speech processing in the ELU are underpinned by WM-related alpha-theta oscillatory activity, and that effects of musical training on speech-on-speech perception may be reflected in these frequency bands among older adults.

Keywords: older adults, alpha, theta, working memory, musical training, speech-on-speech perception

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INTRODUCTION: THE EASE OF LANGUAGE UNDERSTANDING MODEL AND WORKING MEMORY

Under ideal listening conditions, speech perception is considered automatic (Johnson and Ralston, 1994). With increasing complexity, such as in background noise, it is an active cognitive process (Heald and Nusbaum, 2014; see Mattys et al., 2012), and one's ability to parse information relies on combined sensory and cognitive capacities (van Knijff et al., 2018). When the background masker is non-speech, such as a steady noise, the speech acoustic cues are limited due to direct obliteration from the masker. In such "energetic masking" (Brungart, 2001), speech perception relies on the construction of the speech meaning from the audible temporal and spectral sections of the target speech, using linguistic and semantic constraints, but otherwise no further interference comes from the masker. In contrast, in speech-on-speech perception — a special case of "informational masking" (Pollack, 1975)— where the masker can be a single-talker, multitalker, or babble (gibberish), further interference can occur due to the overlapping temporal and spectral properties of the target and masking speech, and linguistic and semantic content of the masker speech.

During speech-on-speech perception, spectral and temporal components of the speech streams can be used to segregate target and masker streams to better understand a target speaker. For example, increased spatial separation (Viswanathan et al., 2016) and speaker voice differences (Darwin et al., 2003; Başkent and Gaudrain, 2016) seem to improve performance. In segregating target and masker components, the listener also needs to actively inhibit interference from the masker (Tun et al., 2002). Hence, higher-order cognitive functions like selective attention (Oberfeld and Klöckner-Nowotny, 2016) and working memory (WM; Sörqvist and Rönnberg, 2012) are also engaged when speech is attended in the presence of competing speech.

The Ease of Language Understanding (ELU) model (Rönnberg et al., 2013, 2019, 2021) highlights the importance of sensory-cognitive integration in speech-on-speech perception. An initial sensory module that Rapidly, Automatically, and Multimodally Binds Phonological information (RAMBPHO) allows for easy lexical access and understanding of speech. Presbycusis (age-related hearing loss) or interference from background speech can cause a mismatch in phonological binding of input and the representations in long-term memory. The phonological mismatch can result in increased reliance on WM to process degraded speech through an interplay with semantic long-term memory and episodic long-term memory (ELTM) in which linguistic inferences are formed based on prior knowledge.

Working memory is central to goal-directed behaviors where information must be stored and manipulated (Chai et al., 2018), and contains a general executive attention component (Chung et al., 2018) linked to inhibitory control (Getzmann et al., 2018; Tiego et al., 2018). The model's conception of WM also assumes a central pool of cognitive resources that may be allocated to either storage or processing of information. Consequently, increased processing demands lead to reduced storage capacity and vice versa. The ELU emphasizes the integral role of WM during speech perception, especially in the presence of interfering sounds, and posits two distinct functional processes that determine successful comprehension: pre-diction and post-diction. The pre-diction aspect of the ELU suggests that WM is automatically and implicitly involved in the top-down modulation of perceptual processing in terms of priming the cognitive system *via* resource, or attentional allocation and the gating of sensory input. This in turn results in easier RAMBPHO and quicker understanding. Conversely, when a speech-signal is degraded, the post-diction component of WM works to integrate limited perceptual information with accessible representations from semantic long-term memory and ELTM in a more effortful pursuit of understanding (Rönnberg et al., 2021).

Working memory is associated with alpha (8–12 Hz) and theta (4–8 Hz) oscillatory activity (Yurgil et al., 2020) and appears to be underpinned by a fronto-parietal network that incorporates cortical and subcortical regions (Eriksson et al., 2015). In general, alpha-activity underpinned by the prefrontal cortex (PFC) is associated with the gating of sensory information during WM updating (Manza et al., 2014; Misselhorn et al., 2019), and the functional inhibition of activity in brain regions not involved with stimulus processing (Klimesch et al., 2007). Theta-activity is thought to represent interactions between the PFC, posterior regions and hippocampus (Strunk et al., 2017) throughout short-term storage, manipulation and retrieval of information (Hsieh and Ranganath, 2014; Roux and Uhlhaas, 2014). Interestingly, functional differences in WM alpha-theta oscillations reported in the literature seem to coincide with components of the ELU's explicit processing loop —pre-diction and post-diction— that are triggered by phonological mismatch.

We suggest that alpha-activity may govern pre-diction *via* increased listening effort, in which the active inhibition of distractor speech gates relevant information, allowing for more successful binding during RAMBPHO. During speech processing, increases in alpha power are linked to heightened listening effort, particularly in adverse conditions where the auditory signal is degraded (Obleser et al., 2012; Dimitrijevic et al., 2019; Paul et al., 2021). This alpha-activity is related to the gating of lexical integration and selective inhibition of task-irrelevant noise (Strauß et al., 2014a,b), which likely becomes more challenging in the presence of background speech.

Meanwhile, when the speech signal is increasingly degraded, enhanced theta-activity represents the manipulation of limited sensory information to successfully trigger and retrieve appropriate lexical and semantic representations in long term memory stores, which are then integrated to form an understanding. Furthermore, fronto-parietal theta-activity has been implicated in lexical access and retrieval (Meyer et al., 2015; Marko et al., 2019) specifically from ELTM (Roberts et al., 2018; Nyhus et al., 2019), as well as being involved in resolving lexical ambiguity (Strauß et al., 2014a).

In sum, we propose that the dissociable roles of alpha and theta activity, apparent in WM subprocesses and highlighted during speech processing, directly underpin the pre-diction and post-diction components illustrated in the ELU (**Figure 1**), respectively. This pertains especially to speech-on-speech perception, which requires one to process a degraded speech signal and inhibit background speech. While this physiological underpinning seems intuitive and has in part been alluded to in previous ELU publications (Rönnberg et al., 2019), we will show in the coming sections how this phenomenon may be relevant for aging research. Namely, reduced WM-alpha-theta activity that supports pre-diction and post-diction processes after phonological mismatch may explain poorer speech-on-speech perception in older adults. Musical training is suggested in younger adult literature to be associated with increased alpha-theta activity and in older adult literature to enhance working memory. Thus (a background with) musical training in older adults may preserve alpha-theta oscillatory activity associated with working memory longer into older age (i.e., slow the decline). Preserved alpha-theta activity may accordingly preserve the ELU explicit-loop process that can repair phonological mismatch during speech-on-speech perception.

SPEECH ON SPEECH PERCEPTION AND WM IN OLDER AGE

Aging affects sensory and cognitive mechanisms and can make speech-on-speech perception more challenging (Goossens et al., 2017). As the population continues to age and life expectancy becomes longer, addressing these challenges becomes even more relevant. Often these changes occur simultaneously, making it difficult to parse what limitations come from changes in sensory or cognitive mechanisms. On the sensory side, the incidence of hearing loss increases with advanced age (Cunningham and Tucci, 2017). In the population older than 65 years, fewer than

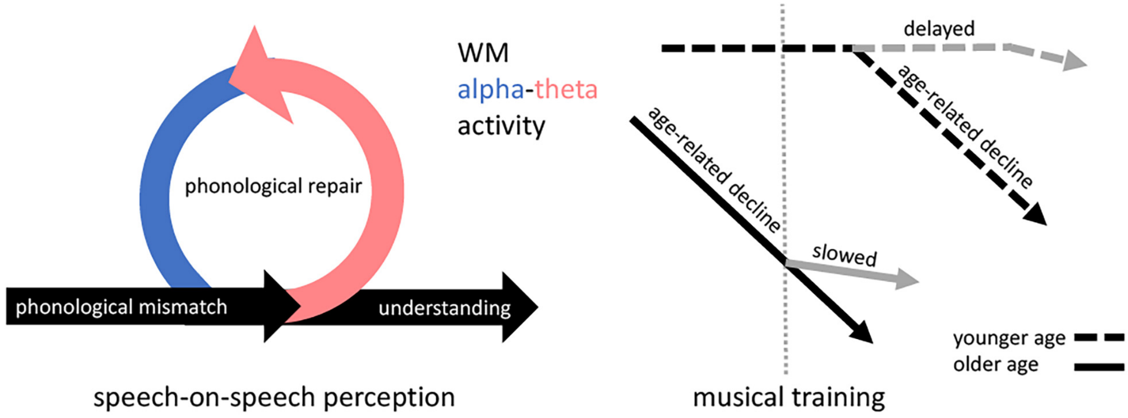

FIGURE 1 | Hypothesized framework. Left, During speech-on-speech perception, the Ease of Language Understanding model (ELU; Rönnberg et al., 2019) describes how mismatch in phonological binding can occur which in turn triggers an explicit processing loop to repair the mismatch. The repair loop is governed by WM, consisting of the subcomponents pre-diction (blue) and post-diction (pink). Post-diction explicitly reevaluates lexical context, and pre-diction informs the (re-)binding of phonological information from the target speech signal in part by inhibiting distractor speech. Here, we suggest that the pre-diction and post-diction subcomponents of the loop are underpinned by alpha- and theta oscillatory activity, respectively. Right, We hypothesize further that any age-related decline in WM-related alpha-theta activity can be delayed if musical training occurred in younger age, or slowed by musical training in older age. In turn, musical training may preserve speech-on-speech perception longer into older age because preserved alpha-theta activity ensures proper repair of mismatched phonological binding. WM = working memory.

50% have normal hearing, which lowers to 10% in those older than 80 (Homans et al., 2017). Since speech-on-speech perception relies in part on parsing target and masker streams based on the spectrotemporal acoustic cues, e.g., pitch contours, common onset and offset, common modulations, voicing, and similar (Bregman, 1990), presbycusis could have a negative effect by potentially altering these cues. However, even when hearing loss is minimized, speech-on-speech perception has been shown to be difficult in middle-aged (Başkent et al., 2014) and older individuals (Zobel et al., 2019).

On the cognitive side, age-related changes have been observed as decline in specific functions such as speed of processing, WM, long and short-term memory (Salthouse, 1996; Deary et al., 2009; Murman, 2015; Pliatsikas et al., 2019), but not in crystallized functions such as verbal knowledge (Park and Gutchess, 2002), which likely contribute to older individuals compensating for other changes when understanding degraded speech (Saija et al., 2014; Başkent et al., 2016). Specifically related to WM, poorer speech perception in older adults has been linked to age-related changes in WM, and particularly poorer attentional control compared to younger adults (Goossens et al., 2017). Likewise, lower WM and inhibitory control performance for normal hearing older adults is associated with more profound difficulties during speech-on-speech (Vermeire et al., 2019), and auditory working memory scores have been observed as the strongest predictor of performance (Anderson et al., 2013). Thus from the perspective of the ELU, one contribution to impoverished speech-on-speech understanding in older adults could be reduced functionality in the WM-governed explicit processing loop consisting of pre-diction and post-diction that occurs after phonological mismatch (RAMBPHO).

Here we suggest a physiological framework for the ELU such that pre-diction and post-diction are underpinned by alpha and theta-oscillatory activity, respectively. This framework is consistent with neurophysiological accounts of WM decline in older adults as well. Working memory decline in older adults is marked by reductions in myelination in the PFC (Schulze et al., 2011), which in turn is associated with WM-related oscillatory activity in alpha- and theta bands (e.g., Strunk et al., 2017; Misselhorn et al., 2019). Accordingly, in older adults, observed decline in WM positively correlates with alpha-theta activity, and is predicted by parahippocampal, striatal, and superior longitudinal fasciculus white matter integrity (Steiger et al., 2019; Kumral et al., 2020). Moreover, where age-related WM decline is observed, associated modulations of alpha-theta activity could explain difficulties in speech-on-speech perception (see Strauß et al., 2014a,b). Slower resting-state alpha and lower alpha-theta power are reported in high WM-load tasks (Rondina et al., 2019), and alpha-power reduction accompanies increased susceptibility to distractions (ElShafei et al., 2020) such as speech maskers (Tun et al., 2002), which increases the likelihood of phonological mismatch during pre-diction. Older adults reputedly sometimes bind information from target and distractor streams, resulting in poorer recall (Strunk et al., 2017), possibly due to deficits in WM maintenance (Jarjat et al., 2019) and ELTM retrieval (Korkki et al., 2020) that are reflected by changes in frontal theta-activity (Tóth et al., 2014).

Taken together, we suggest that within the framework of the ELU, older adults who show signs of WM decline may have a reduced capacity to gate information and inhibit distractor speech due to reductions in alpha-activity, leading to poorer pre-diction. Additionally, declines in WM and subsequent theta-activity result in a lessened ability to maintain and manipulate a degraded speech signal during lexical retrieval, leading to poorer post-diction.

MUSICAL TRAINING AND WM IN OLDER AGE

Musical training is a complex activity that integrates multiple sensory modalities and higher-order cognitive functions (Olszewska and Marchewka, 2021). Musical training studies cannot provide definitive evidence as to whether cognitive benefits are exclusively attained through lifelong musical training, or whether they can be achieved through training once already in older age, due to limitations in both cross-sectional (Schellenberg, 2015; Swaminathan and Schellenberg, 2018; see Hanna-Pladdy and MacKay, 2011) and intervention (Román-Caballero et al., 2018) designs. However, studies with both design types contribute to the overall picture of musical training influencing WM and speech-on-speech perception in older age to some degree.

Though effect sizes vary, cross-sectional evidence has revealed better WM performance in older adult musicians compared to non-musicians (see **Table 1**). In the studies that directly assess WM, several have reported significantly higher digit span (Mansens et al., 2018; Gray and Gow, 2020; Zhang et al., 2021), visuospatial span (Amer et al., 2013) and better performance on measures of WM maintenance and recall with older musicians (Parbery-Clark et al., 2011). There is evidence to also suggest increased efficiency for older musicians in tasks that indirectly measure WM, or in which WM is an important underpinning of task success. Better problem solving and reasoning (Hanna-Pladdy and Gajewski, 2012; Gray and Gow, 2020), faster and more accurate performance during auditory Stroop and reading with distraction tasks (Amer et al., 2013), superior sustained attention (Tierney et al., 2020), as well as advantages in speech-on-speech (Parbery-Clark et al., 2011; Zendel et al., 2019; Zhang et al., 2021) and verbal learning and fluency (Mansens et al., 2018) have all been reported. Additionally, those studies in which no group differences in digit span were found also revealed a musician advantage in short delayed recall tasks and letter-number sequencing in the same population (Hanna-Pladdy and MacKay, 2011; Hanna-Pladdy and Gajewski, 2012). The combined findings could allude to the limitations in relying on span tasks as a measure of WM, given that it is difficult to parse the temporal components of WM processing, within which older musicians may differ depending on the several factors that account for their musical experience and aptitude. This also highlights the difficulties associated with these studies adopting the commonly used "years of experience" (Hanna-Pladdy and MacKay, 2011; Hanna-Pladdy and Gajewski, 2012; Amer et al., 2013; Gray and Gow, 2020), or similarly weak "yes" or "no" musical training survey items (Mansens et al., 2018) as grouping criteria, as studies cannot then draw within-group comparisons between differing engagement in musical training and those temporal components of WM. Nevertheless, the broad cross-sectional data indicates a positive relationship between musical training and components of WM in older age, and studies that included additional grouping criteria based on the age of onset and current musical activity support the findings (Parbery-Clark et al., 2011; Zhang et al., 2021).

Musical intervention studies with older adults often report positive results with regards to WM as well. Following 6 weeks of one-to-one piano lessons combined with 3 h of practice per week, Bugos et al. (2007) reported better digit-span performance for musically trained older adults over controls that was maintained at a 6-month follow-up. Elsewhere, older adults who engaged in 6 months of weekly group piano lessons improved within-group digit-span performance whereas controls did not; there was, however, no between-group difference at post-test (Seinfeld et al., 2013). Although promising in terms of improving WM in older age and maintaining improvements once musical training stopped, more intervention studies are needed to determine causality.

MUSICAL TRAINING AND PRESERVED ALPHA-THETA ACTIVITY IN OLDER AGE?

In older age, benefits in WM related to musical training have been associated with reduced distractor interference and better inhibitory control (Moussard et al., 2016) reputedly originating from the PFC (Alain et al., 2018). As noted, the PFC is thought to underpin alpha recruitment during sensory gating and functional inhibition (Klimesch et al., 2007; Manza et al., 2014; Misselhorn et al., 2019). Beyond this, the relationship between musical training and WM-related alpha-theta activity is still somewhat unclear and to our knowledge, no research has explored musical training-related modulations of alpha recruitment during active inhibition (see Yurgil et al., 2020), especially later in life. However, reported phenomena from younger adults hint that musical training may preserve alpha-theta oscillatory activity. Increased alpha-theta connectivity has been reported in younger adult musicians over non-musicians and is thought to be involved in the propagation of information across long-range brain networks *via* the PFC (Klein et al., 2016). Evidence also suggests a positive effect of musical training on theta-activity specifically related to verbal WM encoding and retrieval. For instance, recent research saw musically trained younger adults outperform non-musicians during a measure of semantic integration and recall of newly learned words, where better performance correlated with increased theta connectivity between ventral and dorsal speech streams (Dittinger et al., 2018). Moreover, increased theta-activity was observed to correlate with the number of years of musical training. Similarly, younger adult musicians performed better than non-musicians in a verbal WM learning and recall task, and increased theta-activity correlated with better performance (Cheung et al., 2017). Next to this oscillation-specific evidence, recent behavioral studies reported positive association between musical training and inhibition (Moreno and Farzan, 2015), as well as musical training benefits in gating information during WM updating (Okada and Slevc, 2018).

The limited literature available from younger adults seems to align with the observed relationship between musical training and WM in older age. Taken together, this supports the idea that musical training may preserve WM-related alpha-theta activity longer into older age. In turn, age-related decline may

TABLE 1 | Overview of selected literature organized by theme.

WM and Musical training		**Total Sample**					**Results**	
Authors	**Year**	**Size**	**Age**	**Sex**	**Groups**	**Criteria**	**Outcome**	**Findings**
Amer et al.	2013	$N = 42$	≥50 years	NA	Musicians ($n = 18$) Non-musicians ($n = 24$)	Years of experience (≥10 years)	-AST -Simon Task -VST -GNG -Reading with Distraction	Musicians outperformed non-musicians on the AST, VST, and reading with distraction. No group differences reported in the Simon Task or GNG
Bugos et al.	2007	$N = 31$	≥60 years	26% Female	Experimental ($n = 15$) Control ($n = 16$)	6-month individualized piano instruction (IPI) program. Participants took part in one 30-min lesson per week and practiced for a minimum of 3 additional hours.	-TMT -DS -TDS -BDI -LNS	Significant improvement for musicians in TMT and DS, as well as better post-test performance than non-musicians. No significant improvement or post-test performance in the TDS, BDI, and LNS
Gray and Gow	2020	$N = 60$	≥60 years	53% Female	Musicians ($n = 30$) Non-musician ($n = 30$)	Years of experience (=10 years)	-CWS -Spatial Reasoning -TMT -Abstract Reasoning -SLCT -TDS	Musicians outperformed non-musicians in measures of CWS, spatial reasoning, abstract reasoning, and SLCT, as well as TDS. No group differences in TMT once scores were adjusted for multiple comparisons.
Hanna-Pladdy and MacKay	2011	$N = 70$	≥60 years	50–60% Female	High-activity musicians ($n = 22$) Low-activity musicians ($n = 27$) Non-musicians (n= 21)	High activity musicians - ≥10 years of experience Low-activity - 5–10 years of experience	-TDS -LNS -WMS -VR -SS -TMT -BNT -L&S fluency -AMNART -CVLT	High-activity musicians performed better than low-activity, and non-musicians in WMS delayed recall, TMT and BNT word retrieval. No group differences in the TDS, LNS, SS, L&S, AMNART and CVLT were reported.
Hanna-Pladdy and Gajewski	2012	$N = 70$	≥59 years	NA	Musicians ($n = 33$) Non-musicians ($n = 37$)	Years of experience (≥10 years)	-LNS -TDS -TMT -L&S fluency -BNT -CVLT-II -WCST -Tower Task -GP	Musicians displayed higher scaled scores in the LNS, which was predicted by earlier age of onset. Musicians also performed better in letter fluency, CVLT short delay and tower task No group differences in the TDS, TMT, BNT and WCST were reported.
Mansens et al.	2018	$N = 1101$	≥55 years	52% Female	Musicians ($n = 277$) Non-musicians ($n = 824$)	Musicians classed as such if they answered 'Yes' to the question 'Do you make music?' in LASA Physical Activity questionnaire	-TDS -Fluency -AVLT	Musical instrumentalists displayed greater TDS than vocalists and non-musicians and better performance in fluency and AVLT, though no difference reported in recall condition of AVLT.
Seinfeld et al.	2013	$N = 41$	≥60 years	NA	Experimental ($n = 25$) Controls ($n = 16$)	4-month group piano intervention. Included one 90-min lesson and an extra 4-h practice per week. Active controls took part in a variety of leisure activities	-TDS -FT -GP -TMT -SDMT -SCWT	Musical group showed improvements in FT, TMT and SCWT, but only outperformed the control in SCWT. Groups did not differ in the TDS, GP, or SDMT
SOS and musical training								

(Continued)

TABLE 1 | (Continued)

SOS and musical training		Total Sample					Results	
Authors	**Year**	**Size**	**Age**	**Sex**	**Groups**	**Criteria**	**Outcome**	**Findings**
Mussoi	2021	*N* = 31	=65 years	NA	Musicians (*n* = 15) Non-musicians (*n* = 16)	(a) Started musical training before the age of 10 (b) At least 5 years formal training (c) Currently practicing at least 3 h per week	-TDS -QuickSIN -HINT -SPIN-R	Musicians and non-musicians did not differ in the QuickSIN, though low WM capacity participants displayed greater SNR loss. No group differences in the TDS, HINT, SPIN-R
Tierney et al.	2020	*N* = 69	16–65 years	46% Female	NA Correlational design	Years of experience used as primary predictor	-AST -SASA -CRM -BAT	Musicians outperformed non-musicians on SASA and BAT, though BAT reliability score was very low and results to be interpreted with caution. Musicians also performed better on CRM and performance correlating with SASA scores.
Parbery-Clark et al.	2011	*N* = 37	45–65	NA	Musicians (*n* = 18) Non-musicians (*n* = 19)	(a) Started musical training before the age of 9 (b) Currently active at least three times per week	-HINT -QuickSIN -WIN -WJ-III -VWM -BM	Musicians outperformed non-musicians on the HINT, QuickSIN WIN, WJ-III, and BM. HINT and QuickSIN performance correlated with better WJ-III scores. No group differences were reported in the VWM
Zendel et al.	2019	*N* = 34	≥55 years	71% Female	Experimental (*n* = 13) Video Game control (*n* = 8) Control (*n* = 13)	6-month piano training intervention in which participants took part in app-based lessons in their own home. Practice took place for 30 min, 5-days a week.	Participants presented with competing multitalker scenarios and asked to recall target words	Behavioral findings revealed the music group outperformed both controls. EEG findings indicated musical training enhanced the N1 component during passive listening. During active listening, authors related enhanced P300 to improved resource allocation.
Zhang et al.	2021	*N* = 77	≥57	51% Female	Musicians (*n* = 48) Non-Musicians (*n* = 29) (Also analyzed a group of younger adults)	Musicians active in conservatories, choirs, and orchestras	-TDS -AST -SIN	Older instrumentalists displayed significantly greater TDS and better SIN than non-musicians and vocalists. Years of experience associated with better TDS, and this correlated with better SIN in older musicians. No group differences in AST were reported

AST, Auditory Stroop task; VST, Visuospatial task; GNG, Go/No Go task; TMT, Trail-Making Task; DS, Digit Symbol task; TDS, Total Digit Span; BDI, Beck Depression Inventory; LNS, Letter Number Sequencing; CWS, Color-Word Stroop Task; SLCT, Single Letter Cancellation Task; WMS-VR, Wechsler Memory Scale – Visual Reproduction; BNT, Boston Naming Test; SS, Spatial Span; L&S fluency, Letter fluency and semantic fluency; AMNART, American Adult Reading Test; CVLT, California Verbal Learning Task; Tower, D-KEFS Tower Task; GP, Grooved pegboard task; WCST, Wisconsin Card Sorting Task; AVLT, Auditory Verbal Learning Test; FT, Finger Tapping test; SDMT, Symbol Digit Modalities test; HINT, Hearing in Noise Task; SPIN-R, Revised Speech Reception in Noise task; SASA, Sustained Auditory Selective Attention Task; CRM, Coordinate Response Measure; VWM, Visual Working Memory; BM, Backwards Masking task; BAT, Beat Alignment Test; WJ-III, Woodcock-Johnson III; RST, Reading Span task; SOS, Speech-on-speech perception.

be delayed from the perspective of the ELU, we suggest that preserved WM-related oscillatory activity in older adults may allow for better explicit repair of mismatched phonological binding during speech-on-speech perception: Preserved alpha-activity may protect from age-related decline in active inhibition of distractor speech during pre-diction. Similarly, we argue that preserved theta-activity in older adults may contribute to more successful post-diction through protection from declines in storage and manipulation of a degraded speech signal, and retrieval of appropriate semantic and lexical representations to understand target speech.

In line with this idea, there is a small body of research reporting improved speech on speech in older adults with musical training compared to adults with no musical training. Improvements in speech-on-speech perception for a group of 69-year-old adults following 6 months of piano lessons were thought to be mediated by benefits in WM (Worschech et al., 2021). Findings that revealed greater post-intervention allocation of attentional resources during speech-on-speech perception for those who underwent musical training, support this view (represented by enhanced attention-related ERP components; Zendel et al., 2019). Better verbal digit-span performance also reputedly mediated better speech-on-speech performance for older musicians in a recent cross-sectional study (Zhang et al., 2021). In Zhang et al. (2021), differences in speech-on-speech were less pronounced in younger musicians, and correlations between WM metrics and improved speech-on-speech perception were more pronounced in older adults compared to younger adults. Given that WM contains a general executive attention component (Chung et al., 2018), WM differences were perhaps reflected in another study when older musicians reportedly outperformed non-musicians during a speech-on-speech perception task, with measures of attentional control accounting for 54% of variance (Tierney et al., 2020). In one recent study where neither musical training nor WM was found to correlate with speech-on-speech (Mussoi, 2021), the author acknowledged that the study was underpowered.

LIMITATIONS

In this mini-review, we do not present comprehensive accounts of speech perception models and make no claims about how the current perspective for the role of WM and related oscillatory activity relates to other models (e.g., Grossberg, 1980; McClelland and Elman, 1986) or neurocognitive frameworks (e.g., Kotz and Schwartze, 2010; Strauß et al., 2014b; Meyer, 2018). We do not fully review all neural mechanisms related to aging (see Cabeza et al., 2018), speech-on-speech processing or hearing loss (e.g., Anderson et al., 2013), nor WM (see Baddeley, 2012; D'Esposito and Postle, 2015; Oberauer, 2019; Xu, 2021). There has been no exhaustive evaluation of WM-related oscillatory activity literature, and the appraisal of the aging, musical training, speech-on-speech, and WM literature is limited to how they intersect. This is in part due to the exploratory nature of this framework, which aims only to provide a direction for future research.

SUMMARY AND RESEARCH PERSPECTIVES

Our mini-review suggests that within the scope of the ELU model, pre-diction and post-diction components may be underpinned by WM-related alpha and theta activity, respectively. As WM function and associated alpha-theta oscillatory activity can decline during normal aging (Rondina et al., 2019), and lower alpha power is related to a lessened ability to inhibit irrelevant information (ElShafei et al., 2020), we argue that musician benefits to WM in older age may relate to preserved top-down modulation of alpha oscillations in sensory regions when understanding speech-on-speech and enhanced theta-activity relating to WM maintenance and retrieval. Specifically, preserved alpha-band activity could thus improve information gating through active inhibition and increased effort during the ELU's pre-diction, while theta activity underpins lexical retrieval and the reconstruction of limited perceptual information during the ELU's post-diction.

Our account highlights the need for further understanding of the relationship between WM, speech-on-speech perception, and musical training in older age. We suggest future musical training paradigms targeting speech-on-speech perception in older adults should not only limit to performance measures of music and speech perception, but also measure WM-related alpha-theta oscillations during speech-on-speech tasks. This will determine whether improvements in WM dictate any observed advantage in older musicians over non-musicians in speech-on-speech perception, and whether improvements in WM dictate this in turn. Additionally, the time course of WM-related alpha-theta oscillatory activity may be able to reflect real-time occurrence of the ELU's pre-diction and post-diction.

Should the positive relationship between musical training, WM and speech-on-speech perception be causal, this would be extremely promising, not only to clarify inconsistencies in the literature, but also at the societal level. With an increasing life expectancy and aging population, the possible benefits of musical training, whether achievable earlier or later in life, are important to society. Future research addressing online recruitment of WM-related neural resources such as alpha-theta activity during speech-on-speech perception tasks could further help to understand this relationship. Causation can be established by musical intervention studies, and musician/non-musician cross-sectional studies should carefully address heterogeneity in WM capabilities and musical backgrounds of older adults. The knowledge of what effects occur due to age-related sensory changes and what effects due to age-related cognitive changes can be gained with experimental designs that utilize different groups of older individuals with varying hearing status, ranging from age minimal to age typical hearing loss. This new information from such studies can lead to better ways of utilizing successful sensory-cognitive integration during speech-on-speech perception in terms of cognitive compensation. This may also provide an avenue for future customized training and rehabilitation tools for older adults with or without presbycusis.

AUTHOR CONTRIBUTIONS

RG, AS, and EH conceived of the research. All authors contributed to the manuscript and contributed to the article and approved the submitted version.

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REFERENCES

Alain, C., Khatamian, Y., He, Y., Lee, Y., Moreno, S., Leung, A. W. S., et al. (2018). Different neural activities support auditory working memory in musicians and bilinguals: neural resources in musicians and bilinguals. *Ann. N. Y. Acad. Sci.* 1423, 435–446. doi: 10.1111/nyas.13717

Amer, T., Kalender, B., Hasher, L., Trehub, S. E., and Wong, Y. (2013). Do Older professional musicians have cognitive advantages? *PLoS One* 8:e71630. doi: 10.1371/journal.pone.0071630

Anderson, S., Parbery-Clark, A., White-Schwoch, T., Drehobl, S., and Kraus, N. (2013). Effects of hearing loss on the subcortical representation of speech cues. *J. Acoust. Soc. Am.* 133, 3030–3038. doi: 10.1121/1.4799804

Baddeley, A. (2012). Working memory: theories, models, and controversies. *Annu. Rev. Psychol.* 63, 1–29. doi: 10.1146/annurev-psych-120710-100422

Başkent, D., and Gaudrain, E. (2016). Musician advantage for speech-on-speech perception. *J. Acoust. Soc. Am.* 139, EL51–EL56. doi: 10.1121/1.4942628

Başkent, D., Clarke, J., Pals, C., Benard, M. R., Bhargava, P., Saija, J., et al. (2016). Cognitive compensation of speech perception with hearing impairment, cochlear implants, and aging: how and to what degree can it be achieved? *Trends Hearing* 20, 1–16.

Başkent, D., van Engelshoven, S., and Galvin, J. J. (2014). Susceptibility to interference by music and speech maskers in middle-aged adults. *J. Acoust. Soc. Am.* 135, EL147–EL153. doi: 10.1121/1.4865261

Bregman, A. S. (1990). *Auditory Scene Analysis: The Perceptual Organization of Sound*. Cambridge, MA: The MIT Press.

Brungart, D. S. (2001). Informational and energetic masking effects in the perception of two simultaneous talkers. *J. Acoust. Soc. Am.* 109, 1101–1109. doi: 10.1121/1.1345696

Bugos, J. A., Perlstein, W. M., McCrae, C. S., Brophy, T. S., and Bedenbaugh, P. H. (2007). Individualized Piano Instruction enhances executive functioning and working memory in older adults. *Aging Mental Health* 11, 464–471. doi: 10.1080/13607860601086504

Cabeza, R., Albert, M., Belleville, S., Craik, F., Duarte, A., Grady, C., et al. (2018). Cognitive neuroscience of healthy aging: maintenance, reserve, and compensation. *Nat. Rev. Neurosci.* 19:701. doi: 10.1038/s41583-018-0068-2

Chai, W. J., Abd Hamid, A. I., and Abdullah, J. M. (2018). Working memory from the psychological and neurosciences perspectives: a review. *Front. Psychol.* 9:401. doi: 10.3389/fpsyg.2018.00401

Cheung, M. C., Chan, A. S., Liu, Y., Law, D., and Wong, C. W. (2017). Music training is associated with cortical synchronization reflected in EEG coherence during verbal memory encoding. *PLoS One* 12:e0174906. doi: 10.1371/journal.pone.0174906

Chung, S., Fieremans, E., Kucukboyaci, N. E., Wang, X., Morton, C. J., Novikov, D. S., et al. (2018). Working memory and brain tissue microstructure: white matter tract integrity based on multi-shell diffusion MRI. *Sci. Rep.* 8:3175. doi: 10.1038/s41598-018-21428-4

Cunningham, L. L., and Tucci, D. L. (2017). Hearing loss in adults. *N. Engl. J. Med.* 377, 2465–2473. doi: 10.1056/NEJMra1616601

Darwin, C. J., Brungart, D. S., and Simpson, B. D. (2003). Effects of fundamental frequency and vocal- tract length changes on attention to one of two simultaneous talkers. *J. Acoust. Soc. Am.* 114, 2913–2922. doi: 10.1121/1.1616924

Deary, I. J., Corley, J., Gow, A. J., Harris, S. E., Houlihan, L. M., Marioni, R. E., et al. (2009). Age-associated cognitive decline. *Br. Med. Bull.* 92, 135–152. doi: 10.1093/bmb/ldp033

D'Esposito, M., and Postle, B. R. (2015). The cognitive neuroscience of working memory. *Annu. Rev. Psychol.* 66, 115–142.

Dimitrijevic, A., Smith, M. L., Kadis, D. S., and Moore, D. R. (2019). Neural indices of listening effort in noisy environments. *Sci. Rep.* 9:11278. doi: 10.1038/s41598-019-47643-1

Dittinger, E., Valizadeh, S. A., Jäncke, L., Besson, M., and Elmer, S. (2018). Increased functional connectivity in the ventral and dorsal streams during retrieval of novel words in professional musicians. *Hum. Brain Mapp.* 39, 722–734. doi: 10.1002/hbm.23877

ElShafei, H. A., Fornoni, L., Masson, R., Bertrand, O., and Bidet-Caulet, A. (2020). Age-related modulations of alpha and gamma brain activities underlying anticipation and distraction. *PLoS One* 15:e0229334. doi: 10.1371/journal.pone.0229334

Eriksson, J., Vogel, E. K., Lansner, A., Bergström, F., and Nyberg, L. (2015). Neurocognitive architecture of working memory. *Neuron* 88, 33–46. doi: 10.1016/j.neuron.2015.09.020

Getzmann, S., Wascher, E., and Schneider, D. (2018). The role of inhibition for working memory processes: ERP evidence from a short-term storage task. *Psychophysiology* 55:e13026. doi: 10.1111/psyp.13026

Goossens, T., Vercammen, C., Wouters, J., and van Wieringen, A. (2017). Masked speech perception across the adult lifespan: impact of age and hearing impairment. *Hear. Res.* 344, 109–124. doi: 10.1016/j.heares.2016.11.004

Gray, R., and Gow, A. J. (2020). How is musical activity associated with cognitive ability in later life? *Aging Neuropsychol. Cogn.* 27, 617–635. doi: 10.1080/13825585.2019.1660300

Grossberg, S. (1980). Intracellular mechanisms of adaptation and self-regulation in self-organizing networks:the role of chemical transducers. *Bull. Math. Biol.* 42, 365–396.

Hanna-Pladdy, B., and Gajewski, B. (2012). Recent and past musical activity predicts cognitive aging variability: direct comparison with general lifestyle activities. *Front. Hum. Neurosci.* 6:198. doi: 10.3389/fnhum.2012.00198

Hanna-Pladdy, B., and MacKay, A. (2011). The relation between instrumental musical activity and cognitive aging. *Neuropsychology* 25, 378–386. doi: 10.1037/a0021895

Heald, S. L. M., and Nusbaum, H. C. (2014). Speech perception as an active cognitive process. *Front. Systems Neurosci.* 8:35. doi: 10.3389/fnsys.2014.00035

Homans, N. C., Metselaar, R. M., Dingemanse, J. G., van der Schroeff, M. P., Brocaar, M. P., Wieringa, M. H., et al. (2017). Prevalence of age-related hearing loss, including sex differences, in older adults in a large cohort study. *Laryngoscope* 127, 725–730. doi: 10.1002/lary.26150

Hsieh, L. T., and Ranganath, C. (2014). Frontal midline theta oscillations during working memory maintenance and episodic encoding and retrieval. *Neuroimage* 85, 721–729.

Jarjat, G., Portrat, S., and Hot, P. (2019). Aging influences the efficiency of attentional maintenance in verbal working memory. *J. Gerontol. Series B* 74, 600–608. doi: 10.1093/geronb/gby067

Johnson, K., and Ralston, J. V. (1994). Automaticity in speech perception: some speech/nonspeech comparisons. *Phonetica* 51, 195–209. doi: 10.1159/000261975

Klein, C., Diaz Hernandez, L., Koenig, T., Kottlow, M., Elmer, S., and Jäncke, L. (2016). The influence of pre-stimulus EEG activity on reaction time during a verbal sternberg task is related to musical expertise. *Brain Topogr.* 29, 67–81. doi: 10.1007/s10548-015-0433-7

Klimesch, W., Sauseng, P., and Hanslmayr, S. (2007). EEG alpha oscillations: the inhibition-timing hypothesis. *Brain Res. Rev.* 53, 63–88. doi: 10.1016/j.brainresrev.2006.06.003

Korkki, S. M., Richter, F. R., Jeyarathnarajah, P., and Simons, J. S. (2020). Healthy ageing reduces the precision of episodic memory retrieval. *Psychol. Aging* 35, 124–142. doi: 10.1037/pag0000432

Kotz, S. A., and Schwartze, M. (2010). Cortical speech processing unplugged: a timely subcortico-cortical framework. *Trends Cogn. Sci.* 14, 392–399. doi: 10.1016/j.tics.2010.06.005

Kumral, D., Cesnaite, E., Beyer, F., Hensch, T., Sander, C., Hegerl, U., et al. (2020). Relationship between regional white matter hyperintensities and alpha oscillations in older adults. *Neurobiol. Aging*. Online ahead of print. doi: 10.1016/j.neurobiolaging.2021.10.006

Mansens, D., Deeg, D. J. H., and Comijs, H. C. (2018). The association between singing and/or playing a musical instrument and cognitive functions in older adults. *Aging Mental Health* 22, 970–977. doi: 10.1080/13607863.2017.1328481

Manza, P., Hau, C. L. V., and Leung, H. C. (2014). Alpha power gates relevant information during working memory updating. *J. Neurosci.* 34, 5998–6002.

Marko, M., Cimrová, B., and Riečanský, I. (2019). Neural theta oscillations support semantic memory retrieval. *Sci. Rep.* 9:17667. doi: 10.1038/s41598-019-53813-y

Mattys, S. L., Davis, M. H., Bradlow, A. R., and Scott, S. K. (2012). Speech recognition in adverse conditions: a review. *Lang. Cogn. Processes* 27, 953–978. doi: 10.1080/01690965.2012.705006

McClelland, J. L., and Elman, J. L. (1986). The TRACE model of speech perception. *Cognit. Psychol.* 18, 1–86. doi: 10.1016/0010-0285(86)90015-0

Meyer, L. (2018). The neural oscillations of speech processing and language comprehension: state of the art and emerging mechanisms. *Eur. J. Neurosci.* 48, 2609–2621. doi: 10.1111/ejn.13748

Meyer, L., Grigutsch, M., Schmuck, N., Gaston, P., and Friederici, A. D. (2015). Frontal-posterior theta oscillations reflect memory retrieval during sentence comprehension. *Cortex* 71, 205–218. doi: 10.1016/j.cortex.2015.06.027

Misselhorn, J., Friese, U., and Engel, A. K. (2019). Frontal and parietal alpha oscillations reflect attentional modulation of cross-modal matching. *Sci. Rep.* 9:5030. doi: 10.1038/s41598-019-41636-w

Moreno, S., and Farzan, F. (2015). Music training and inhibitory control: a multidimensional model. *Ann. N. Y. Acad. Sci.* 1337, 147–152. doi: 10.1111/nyas.12674

Moussard, A., Bermudez, P., Alain, C., Tays, W., and Moreno, S. (2016). Life-long music practice and executive control in older adults: an event-related potential study. *Brain Res.* 1642, 146–153. doi: 10.1016/j.brainres.2016.03.028

Murman, D. (2015). The impact of age on cognition. *Sem. Hearing* 36, 111–121. doi: 10.1055/s-0035-1555115

Mussoi, B. S. (2021). The impact of music training and working memory on speech recognition in older age. *J. Speech Lang. Hear Res.* 64, 4524–4534. doi: 10.1044/2021_JSLHR-20-00426

Nyhus, E., Engel, W. A., Pitfield, T. D., and Vakkur, I. M. W. (2019). Increases in theta oscillatory activity during episodic memory retrieval following mindfulness meditation training. *Front. Hum. Neurosci.* 13:311. doi: 10.3389/fnhum.2019.00311

Oberauer, K. (2019). Working memory and attention - a conceptual analysis and review. *J. Cogn.* 2:36. doi: 10.5334/joc.58

Oberfeld, D., and Klöckner-Nowotny, F. (2016). Individual differences in selective attention predict speech identification at a cocktail party. *eLife* 5:e16747. doi: 10.7554/eLife.16747

Obleser, J., Wöstmann, M., Hellbernd, N., Wilsch, A., and Maess, B. (2012). Adverse listening conditions and memory load drive a common α oscillatory network. *J. Neurosci.* 32, 12376–12383. doi: 10.1523/JNEUROSCI.4908-11.2012

Okada, B. M., and Slevc, L. R. (2018). Individual differences in musical training and executive functions: a latent variable approach. *Mem. Cogn.* 46, 1076–1092. doi: 10.3758/s13421-018-0822-8

Olszewska, A. M., and Marchewka, A. (2021). How musical training shapes the adult brain: predispositions and neuroplasticity. *Front. Neurosci.* 15:630829. doi: 10.3389/fnins.2021.630829

Parbery-Clark, A., Strait, D. L., Anderson, S., Hittner, E., and Kraus, N. (2011). Musical experience and the aging auditory system: implications for cognitive abilities and hearing speech in noise. *PLoS One* 6:e18082. doi: 10.1371/journal.pone.0018082

Park, D. C., and Gutchess, A. H. (2002). Aging, cognition, and culture: a neuroscientific perspective. *Neurosci. Biobehav. Rev.* 26, 859–867. doi: 10.1016/s0149-7634(02)00072-6

Paul, B. T., Chen, J., Le, T., Lin, V., and Dimitrijevic, A. (2021). Cortical alpha oscillations in cochlear implant users reflect subjective listening effort during speech-in-noise perception. *PLoS One* 16:e0254162. doi: 10.1371/journal.pone.0254162

Pliatsikas, C., Veríssimo, J., Babcock, L., Pullman, M. Y., Glei, D. A., Weinstein, M., et al. (2019). Working memory in older adults declines with age, but is modulated by sex and education. *Quarterly J. Exp. Psychol.* 72, 1308–1327. doi: 10.1177/1747021818791994

Pollack, I. (1975). Auditory informational masking. *J. Acoust. Soc. Am.* 57:S5.

Roberts, B. M., Clarke, A., Addante, R. J., and Ranganath, C. (2018). Entrainment enhances theta oscillations and improves episodic memory. *Cogn. Neurosci.* 9, 181–193. doi: 10.1080/17588928.2018.1521386

Román-Caballero, R., Arnedo, M., Triviño, M., and Lupiáñez, J. (2018). Musical practice as an enhancer of cognitive function in healthy aging—a systematic review and meta-analysis. *PLoS One* 13:e0207957. doi: 10.1371/journal.pone.0207957

Rondina, R. II, Olsen, R. K., Li, L., Meltzer, J. A., and Ryan, J. D. (2019). Age-related changes to oscillatory dynamics during maintenance and retrieval in a relational memory task. *PLoS One* 14:e0211851. doi: 10.1371/journal.pone.0211851

Rönnberg, J., Holmer, E., and Rudner, M. (2019). Cognitive hearing science and ease of language understanding. *Int. J. Audiol.* 58, 247–261. doi: 10.1080/14992027.2018.1551631

Rönnberg, J., Holmer, E., and Rudner, M. (2021). Cognitive hearing science: three memory systems, two approaches, and the ease of language understanding model. *J. Speech Lang. Hear Res.* 64, 359–370. doi: 10.1044/2020_JSLHR-20-00007

Rönnberg, J., Lunner, T., Zekveld, A., Sörqvist, P., Danielsson, H., Lyxell, B., et al. (2013). The Ease of Language Understanding (ELU) model: theoretical, empirical, and clinical advances. *Front. Systems Neurosci.* 7:31. doi: 10.3389/fnsys.2013.00031

Roux, F., and Uhlhaas, P. J. (2014). Working memory and neural oscillations: Alpha-gamma versus theta-gamma codes for distinct WM information? *Trends Cogn. Sci.* 18, 16–25. doi: 10.1016/j.tics.2013.10.010

Saija, J. D., Akyürek, E. G., Andringa, T. C., and Başkent, D. (2014). Perceptual restoration of degraded speech is preserved with advancing age. *J. Assoc. Res. Otolaryngol.* 15, 139–148. doi: 10.1007/s10162-013-0422-z

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychol. Rev.* 103, 403–428. doi: 10.1037/0033-295X.103.3.403

Schellenberg, E. G. (2015). Music training and speech perception: a gene-environment interaction: music training and speech perception. *Ann. N. Y. Acad. Sci.* 1337, 170–177. doi: 10.1111/nyas.12627

Schulze, E. T., Geary, E. K., Susmaras, T. M., Paliga, J. T., Maki, P. M., and Little, D. M. (2011). Anatomical correlates of age-related working memory declines. *J. Aging Res.* 2011:606871. doi: 10.4061/2011/606871

Seinfeld, S., Figueroa, H., Ortiz-Gil, J., and Sanchez-Vives, M. V. (2013). Effects of music learning and piano practice on cognitive function, mood and quality of life in older adults. *Front. Psychol.* 4:810. doi: 10.3389/fpsyg.2013.00810

Sörqvist, P., and Rönnberg, J. (2012). Episodic long-term memory of spoken discourse masked by speech: what is the role for working memory capacity? *J. Speech Lang. Hear. Res.* 55, 210–218. doi: 10.1044/1092-4388(2011/10-0353)

Steiger, T. K., Herweg, N. A., Menz, M. M., and Bunzeck, N. (2019). Working memory performance in the elderly relates to theta-alpha oscillations and is predicted by parahippocampal and striatal integrity. *Sci. Rep.* 9:706. doi: 10.1038/s41598-018-36793-3

Strauß, A., Kotz, S. A., Scharinger, M., and Obleser, J. (2014a). Alpha and theta brain oscillations index dissociable processes in spoken word recognition. *Neuroimage* 97, 387–395. doi: 10.1016/j.neuroimage.2014.04.005

Strauß, A., Wöstmann, M., and Obleser, J. (2014b). Cortical alpha oscillations as a tool for auditory selective inhibition. *Front. Hum. Neurosci.* 8:350. doi: 10.3389/fnhum.2014.00350

Strunk, J., James, T., Arndt, J., and Duarte, A. (2017). Age-related changes in neural oscillations supporting context memory retrieval. *Cortex* 91, 40–55. doi: 10.1016/j.cortex.2017.01.020

Swaminathan, S., and Schellenberg, E. G. (2018). Musical competence is predicted by music training. cognitive abilities, and personality. *Sci. Rep.* 8:9223. doi: 10.1038/s41598-018-27571-2

Tiego, J., Testa, R., Bellgrove, M. A., Pantelis, C., and Whittle, S. (2018). A hierarchical model of inhibitory control. *Front. Psychol.* 9:1339. doi: 10.3389/fpsyg.2018.01339

Tierney, A., Rosen, S., and Dick, F. (2020). Speech-in-speech perception, non-verbal selective attention, and musical training. *J. Exp. Psychol. Learn. Mem. Cogn.* 46, 968–979. doi: 10.1037/xlm0000767

Tóth, B., Kardos, Z., File, B., Boha, R., Stam, C. J., and Molnár, M. (2014). Frontal midline theta connectivity is related to efficiency of WM maintenance and is affected by aging. *Neurobiol. Learn. Mem.* 114, 58–69. doi: 10.1016/j.nlm.2014.04.009

Tun, P., O'Kane, G., and Wingfield, A. (2002). Distraction by competing speech in young and older adult listeners. *Psychol. Aging* 17, 453–467. doi: 10.1037//0882-7974.17.3.453

van Knijff, E. C., Coene, M., and Govaerts, P. J. (2018). Speech understanding in noise in elderly adults: the effect of inhibitory control and syntactic complexity: speech in noise understanding in elderly adults. *Int. J. Lang. Commun. Disord.* 53, 628–642. doi: 10.1111/1460-6984.12376

Vermeire, K., Knoop, A., De Sloovere, M., Bosch, P., and van den Noort, M. (2019). Relationship between working memory and speech-in-noise recognition in young and older adult listeners with age-appropriate hearing. *J. Speech Lang. Hear. Res.* 62, 3545–3553. doi: 10.1044/2019_JSLHR-H-18-0307

Viswanathan, N., Kokkinakis, K., and Williams, B. T. (2016). Spatially separating language masker from target results in spatial and linguistic masking release. *J. Acoust. Soc. Am.* 140, EL465–EL470. doi: 10.1121/1.4968034

Worschech, F., Marie, D., Jünemann, K., Sinke, C., Krüger, T. H. C., Großbach, M., et al. (2021). Improved speech in noise perception in the elderly after 6 months of musical instruction. *Front. Neurosci.* 15:696240. doi: 10.3389/fnins.2021.696240

Xu, Y. (2021). Towards a better understanding of information storage in visual working memory. *Visual Cogn.* 29, 437–445. doi: 10.1080/13506285.2021.1946230

Yurgil, K. A., Velasquez, M. A., Winston, J. L., Reichman, N. B., and Colombo, P. J. (2020). Music training, working memory, and neural oscillations: a review. *Front. Psychol.* 11:266. doi: 10.3389/fpsyg.2020.00266

Zendel, B. R., West, G. L., Belleville, S., and Peretz, I. (2019). Musical training improves the ability to understand speech-in-noise in older adults. *Neurobiol. Aging* 81, 102–115. doi: 10.1016/j.neurobiolaging.2019.05.015

Zhang, L., Fu, X., Luo, D., Xing, L., and Du, Y. (2021). Musical experience offsets age-related decline in understanding speech-in-noise: type of training does not matter. working memory is the key. *Ear Hear.* 42, 258–270. doi: 10.1097/AUD.0000000000000921

Zobel, B. H., Wagner, A., Sanders, L. D., and Başkent, D. (2019). Spatial release from informational masking declines with age: evidence from a detection task in a virtual separation paradigm. *J. Acoust. Soc. Am.* 146, 548–566. doi: 10.1121/1.5118240

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Does Cognitive Training Improve Mobility, Enhance Cognition, and Promote Neural Activation?

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A close inter-relationship between mobility and cognition is reported in older adults, with improvements in gait performance noticeable after cognitive remediation in frail individuals. The aim of this study was to evaluate the efficacy of computerized cognitive training (CCT) on mobility in healthy, independently living older adults, and to determine whether CCT is associated with changes in neural activation for mobility-related brain processes. Using a randomized single-blind control design, sixty-three non-demented adults age 60 y and older (mean age = 67 y; 76% female, mean Montreal Cognitive Assessment [MoCA] score = 27) were recruited from a local Senior Activity Center. Participants were randomly assigned to either a 2-month CCT program (8 weeks, 3x/week, 40 min/session) or a wait-list control group. Primary outcome was self-selected gait speed during single- and dual-task walking. Secondary outcome was executive function on Trail Making Test (TMT), Part B. Neural activity was assessed *via* electroencephalography/event-related potentials (EEG/ERPs) targeting lower-limb performance. Results from a linear mixed effect model, adjusted for baseline MoCA score, age, gender, and study completion revealed that compared to controls, CCT improved gait speed during the dual-task ($p = 0.008$) but not during the single-task walking condition ($p = 0.057$). CCT also improved executive function ($p = 0.024$). Further, shorter foot reaction time responses ($p = 0.019$) were found with enhanced neural activation over sensorimotor areas, with shorter ERP latencies during the P2 component ($p = 0.008$) and enhanced motor responses ($p = 0.009$) also evident in the CCT group after the intervention. Overall, the electrophysiological findings suggest possible neural adaptations that could explain improvements in mobility and executive functions associated with CCT in healthy older adults.

Keywords: visual evoked potentials (VEP), motor-related cortical potentials (MRCP), executive control, cognitive-motor brain networks, healthy aging, sensorimotor integration, functional mobility

INTRODUCTION

Walking difficulties are widespread among older adults, and are associated with restricted activities of daily living, mobility disability and death (Hirvensalo et al., 2000; Rosano et al., 2008). While exercise is recommended to improve mobility (Urzi et al., 2019), only 16% of U.S. seniors exercise at the recommended level and 33% remain inactive (Lee et al., 2017). Sedentary behavior or inactivity is related to increased risk of disability within all levels of physical activity (DiPietro et al., 2018).

Among non-pharmacological interventions, cognitive training has been shown to stabilize or even improve cognitive performance of healthy older adults (Tardif and Simard, 2011; Simons et al., 2016). Gait and cognitive functions are interrelated in older adults. Previous studies have revealed that the prefrontal cortex (PFC) plays a critical role in successful gait and cognition (Beauchet et al., 2016) and have linked gait to structural changes in cerebellar, precuneus, supplementary motor, insular, and PFC brain regions (Blumen et al., 2019). These findings support the notion that cognitive training could improve both cognitive and motor functions. Additionally, previous experiments have shown that cognitive training can improve response times, with improvements seen in multiple ERP components in healthy young (Olfers and Band, 2018) and old adults (Gajewski and Falkenstein, 2012, 2018; Pergher et al., 2018), promoting neural enhancements in aging (Nguyen et al., 2019).

Impairments in cognitive processes are associated with slower gait and gait instability (Montero-Odasso et al., 2012). Successful mobility performance is dependent on intact cognitive function (Montero-Odasso et al., 2012). Hence, recent research has focused on ways to improve cognitive function as a means to improve mobility. In a pilot study with sedentary seniors, Verghese et al. (2010) reported a far transfer computerized cognitive training (CCT) effect to mobility. A recent meta-analysis of 10 trials with 351 participants reported that cognitive training interventions can improve mobility-related outcomes, especially during challenging walking conditions requiring higher-order executive functions (Marusic et al., 2018a,b). More recently, computerized cognitive remediation improved walking and executive functions in older adults aged 70 years and above at high-risk for mobility disability, but not compared to an active control that included low level cognitive remediation training (Verghese et al., 2021).

Most studies examining the effect of CCT on mobility-related outcomes enrolled sedentary or frail older adults (Verghese et al., 2010; Smith-Ray et al., 2013; Ng et al., 2015; Azadian et al., 2018), and demonstrate significant CCT effects on mobility outcomes. Although the association between brain health, cognition and mobility has been demonstrated even in non-clinical populations (Cohen et al., 2016; Demnitz et al., 2017), the effect of CCT in healthy active older adults has not been established. Moreover, the underlying neural mechanisms of enhanced gait control after cognitive remediation programs have not been well investigated (Marusic et al., 2018b).

To address these knowledge gaps, we conducted a randomized single-blind control trial in 63 healthy active older adults. Our hypotheses were based on our previous work (Marusic et al., 2018a,b), which indicated that CCT would lead to improvements in executive functions and gait performance, particularly during challenging walking while talking conditions. We also hypothesized that CCT-related enhancements would be evident in pre-post assessments using electroencephalography (EEG)/event-related potentials (ERPs) over sensorimotor regions. This was guided by our recent investigation of the efficiency of recruitment of neuronal resources for the upper and lower extremity response task in young and old adults (Marusic et al., 2022), thus sparking an interest in investigating CCT related changes in neural activation.

METHODS

Study Design

The current study employed a single-blind randomized control trial design to investigate the efficacy of computerized cognitive training (CCT) on gait in healthy older adults recruited from a local adult activity center in Koper, Slovenia (EU). The inclusion criteria were: active and healthy older adults (defined according to self-reported questionnaires), normal or corrected normal vision, and no self-reported history of cardiovascular, neurological, or psychiatric conditions. The exclusion criteria were: symptoms of cognitive decline or evidence of cognitive impairment on the Montreal cognitive assessment (MoCA; score < 25), history of falls in the past 12 months, regular heavy alcohol consumption, or presence of acute or chronic skeletal, neuromuscular, metabolic and/or cardiovascular disease conditions that may limit mobility. All procedures were carried out in accordance with the ethical standards of the 1964 Declaration of Helsinki and were approved by the Republic of Slovenia National Medical Ethics Committee (KME57/06/17). Written informed consent was obtained from all participants prior to study enrollment. The trial was registered at ClinicalTrials.gov (NCT03860441).

Participants

Figure 1 presents the study flow. From the initial 77 participants who were assessed for eligibility, 63 were randomized to either the intervention or the wait-list control group. Fourteen participants were excluded because they either did not meet study criteria or were unwilling to participate in the study. Sixty-three older participants (67.5 ± 5.9 years; MoCA score: 27.2 ± 1.7) were enrolled and included in the intention to treat analyses (see **Figure 1**). A subsample of 45 participants agreed to complete an EEG / ERPs study before and after the CCT intervention.

Clinical Assessments

Prior to the intervention, all participants were screened and interviewed by the research team. We asked participants to rate their general health on a 5-point Likert scale ranging from 1 (worst possible) to 5 (best). As previously mentioned, the MoCA (Nasreddine et al., 2005) was used to determine inclusion eligibility and also served as a covariate in the statistical models.

Computerized Cognitive Training Intervention

A commercially available internet-based cognitive training software CogniFit (CogniFit INC; San Francisco, CA, USA) was used for training. CogniFit software provides participants' with individualized training programs based on the results of their baseline cognitive performance evaluation. Difficulty of each cognitive task or game is systematically increased by the software in order to gradually increase the difficulty of each subsequent task, while ensuring that all abilities are trained. As well, this methodology is intended to provide personalized programs

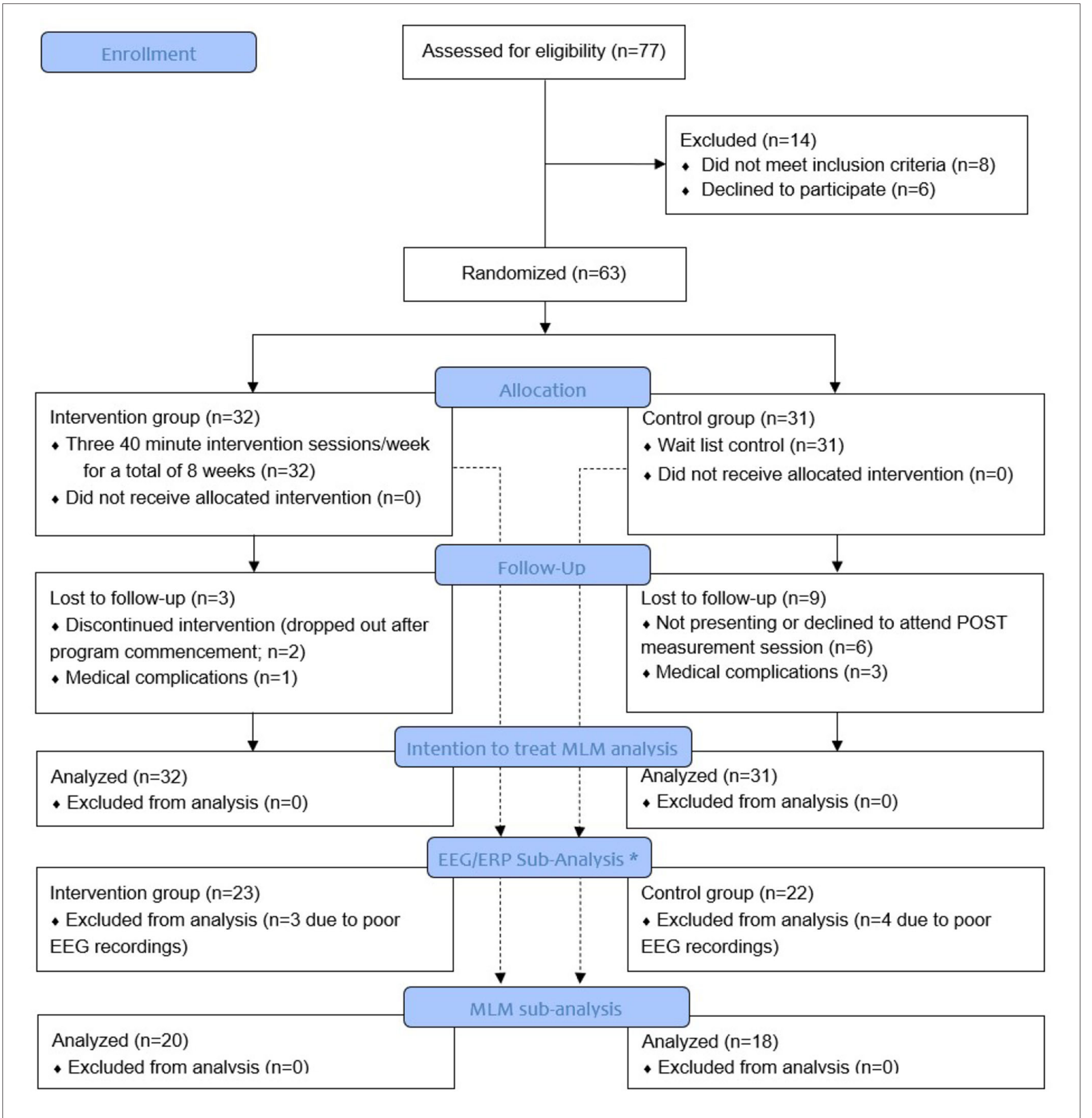

FIGURE 1 | Study flow diagram. *A mixed linear model (MLM) analysis of variance was used for EEG sub-analysis when EEG data were of good quality and a merged pre-post EEG decomposition was acceptable. Poor quality of pre- or post-EEG data resulted in elimination of both datasets.

that strategically strengthen the individual's weakest cognitive abilities by emphasizing cognitive strengths in a manner that keeps participants within their comfort zone. The CCT training software in this study (CogniFit) is identical to that employed by Verghese et al. (2010, 2016, 2021) in their previous cognitive remediation trials.

Participants in the CCT group attended 40 mins training sessions three times weekly for a total of 8 weeks (24 sessions). The length of each daily session was set according to optimal duration determined in our systematic review (Marusic et al., 2018b). Sessions were administered at the activity center. CCT sessions included a maximum of eight participants and a minimum of two research assistants who aided with software initiation and insured participants' comprehension of each CCT task instruction set.

Wait-List Control

Participants randomly allocated to the control group were informed that upon conclusion of baseline measurements, their name would be added to a wait-list for future studies at our center. They received a lecture detailing the importance of maintaining a healthy lifestyle. Research assistants contacted control participants weekly *via* telephone to maintain interest and adherence in the trial as well as to match for study contacts in the intervention arm. Participants in the wait-list group were not revealed to the intervention group participants, and vice versa as members of each group were invited to the activity center on different days and/or times.

Outcome Measures

Our primary outcome measure was gait speed (m/s) during single- and dual-task walking conditions. Our secondary outcomes included executive function performance as assessed with the Trail making test (TMT); a simple visual reaction time task with lower limb as part of the EEG study; as well as sensory and motor ERPs. Research assistants assessed all outcome measures blinded to study group allocation at baseline and immediately following the conclusion of the 8-week study period for both the intervention and control groups.

Single- and Dual-Task Walking

Gait speed in single and dual task conditions was selected as our primary outcome as it is the most widely used metric to characterize mobility, and it was demonstrated to be sensitive to CCT effects (Verghese et al., 2010). Participants were instructed to "walk as if they were going to the nearest store and they were not in any hurry." Gait speed was acquired with the 2D OptoGait system (Microgate, Bolzano, Italy); a valid and reliable measure of gait (Lienhard et al., 2013). To measure steady-state gait, all participants started at a marked point on the floor 2 meters before the 5-meter OptoGait recording area, and then walked until they reached a marked point 2 meters beyond the recording area.

To study cognitive-motor interactions, participants were instructed to walk at their preferred speed, while performing a cognitive interference task, which required them to recite alternate letters of the alphabet starting with the letter "A" (Verghese et al., 2010, 2016). They were instructed to pay equal attention to walking and talking to minimize task prioritization effects (Verghese et al., 2007). The number of errors and correctly recited alternate letters were recorded by the research assistants. Each participant completed a baseline practice trial of reciting alternate letters of the alphabet while standing prior to the dual-task walking.

Cognitive Measures

Executive function and attention are two essential cognitive resources required for normal walking (Montero-Odasso et al., 2012). The Trail Making Test (TMT) is divided into two parts and provides general information on visual search, scanning, speed of processing, mental flexibility, and executive function (Tombaugh, 2004). Part A assesses simple visual attention and sequencing (Reitan and Wolfson, 1985), while Part B assesses executive functions linked to prefrontal cortex activity (Kubo et al., 2008). Part B was strategically included to detect CCT-related transfer of learning (Marusic et al., 2018a).

Electrophysiological and Psychophysical Measures

Scalp electroencephalographic (EEG) activity was recorded using g.tec medical engineering equipment (Schiedlberg, Austria, EU), with 32 Ag/AgCl electrodes, arranged according to the International 10–20 System. The sampling rate was 512 Hz with 32-bit resolution.

Due to time- and study resource-constrains, only a sub-group of 23 intervention and 22 control participants were randomly selected and measured before and after the 2-month study period (see **Figure 1**). Participants were assessed while seated in a neutral position. After collection of baseline measurements with eyes open and closed, participants were instructed to perform a simple reaction time test in response to 70 visual stimuli presented with a random inter-stimulus interval between 2 and 5 secs on a 17.0-inch flat panel LCD monitor (120-Hz refresh rate) situated ∼50 centimeters in front of them. Their task was to press the response button as quickly as possible with the bottom of the right foot (which rested on the response pad). The response pad was connected to a trigger box (g.tec TRIGbox). The visual stimuli were presented in the center of a monitor (circular disc with a 5 cm radius was presented against a black background at the center of the display, duration 150 ms, intensity 50 cd/m^2) placed directly in front of the participant's field of view. Stimulus-locked ERPs (s-ERPs; also known as visual-evoked potentials VEPs) and response-locked ERPs (r-ERP; for the lower limb, also known as motor-related cortical potentials MRCPs) were extracted as described in Yordanova et al. (2004). The s-ERPs correspond to occipital electrodes (averaged across O1, Oz, and O2) and show visual components P1, N1, and P2 after the visual stimuli occurrence while the r-ERPs (MRCP) correspond to central electrode Cz and show the peak latency and amplitude of the most negative displacement of the MRCP, prior to or at the time of response execution. Details about sensorimotor task and EEG/ERP processing can be found in manuscript of Marusic et al. (2022).

Statistical Analyses

Data were analyzed in SPSS software version 26.0 (IBM, Chicago, IL). An examination for normal distribution was conducted using the Shapiro-Wilk's test and visual inspection (histogram and Q-Q plot). To examine potential group differences in demographic and clinical outcome measures at baseline, an independent-sample *t*-test was performed. The difference between groups in attrition rate was assessed using chi-square statistics. A mixed linear model (MLM) analysis of variance was used to test the effect of the 2-month CCT intervention on the outcome measures in comparison with the control group. Groups were compared using the intention-to-treat principle with MLM adjusted for confounders (baseline MoCA score, age, and gender). While the MLM can handle missing data due to dropout missing at random (Laird and Ware, 1982), the analysis controlled for attrition

TABLE 1 | Table of baseline characteristics for intervention and control group (intention to treat).

Variables	Intervention	Control	*p* value
N	32	31	
Age (years)	67.7 ± 5.8	67.2 ± 6.0	0.757
Women (*n*)	25	23	
BMI (kg/m^2)	25.4 ± 5.3	25.8 ± 4.4	0.725
Education (years)	13.4 ± 2.1	12.9 ± 2.1	0.294
MoCA score (0–30)	27.4 ± 1.7	27.0 ± 1.7	0.353
General health status (1–5)*	3.6 ± 0.6	3.7 ± 0.7	0.736
Self-selected gait speed ST(m/s)	1.14 ± 0.21	1.18 ± 0.22	0.356
Self-selected gait speed DT (m/s)	0.93 ± 0.25	0.95 ± 0.23	0.873
TMT A (sec)	41.8 ± 19.7	46.6 ± 23.5	0.425
TMT B (sec)	98.9 ± 50.1	99.2 ± 52.4	0.987

**1, minimal; 5, best; BMI, body mass index; MoCA, Montreal Cognitive Assessment; TMT, Trail Making Test.*

in both arms by including a dichotomous 'study completion' variable as a covariate in the model. More specifically, *Group* (experimental *vs.* control), *time* (pre- *vs.* post-intervention), and *group × time interaction* terms were treated as fixed effects and *participants* as a random effect. Maximum Likelihood (ML) was used to produce parameter estimates. The alpha level was set to 0.05.

RESULTS

Group Characteristics

Of the 63 participants, 32 were randomized to the CCT and 31 to the control group. **Table 1** represents the baseline characteristics of the final sample. The majority of participants were women (78% in CCT and 74% in control group); however, the two groups did not demonstrate significant differences across any key demographic variables suggesting adequate randomization. The sub-sample of 45 participants for EEG/ERP analysis also did not show any group differences in baseline characteristics (all *p*s ≥ 0.125).

The attrition in the control group ($n = 9$) was significantly higher than the attrition in the intervention group ($n = 3$; ($\chi_{(1)} = 3.946$, $p = 0.047$). In the control group, 3 participants were lost due to medical issues and 6 participants did not show up for the POST measurement session. In the intervention group, 1 participant was lost due to medical issues and 2 participants discontinued the intervention program (see also **Figure 1**). There were no significant differences in baseline characteristics parameters between those who dropped vs. those who completed the study ($p \geq 0.217$); however, we included study completeness as a covariate in the MLM. In the intervention group, the CCT adherence was high (87.3%). When queried about self-reported daily computer exposure, eight CCT participants (25.0%) reported daily computer exposure prior to the study, 12 (37.5%) reported moderate exposure, while the remaining 12 (37.5%) reported minimal to no computer exposure.

Primary Outcomes

Primary outcome results are presented in **Table 2**.

Self-Selected Single-Task Gait Speed

At baseline, no difference between group was observed for the self-selected single-task gait speed ($p = 0.226$). However, there was a non-significant group × time interaction trend ($p = 0.057$; **Table 2**). *Post-hoc* analyses revealed that self-selected gait speed significantly increased within the intervention group (+17.0 ± 21.3%; $p<0.001$), while there was a lesser within group improvement for the control group (+7.2 ± 15.4%; $p = 0.096$). Comparison of speed in the self-selected single-task gait speed condition showed that older adults in the intervention group walked 0.16 m/s faster at the end of the CCT intervention, whereas participants in the control group increased their speed by 0.07 m/s from baseline.

Self-Selected Dual-Task Gait Speed

At baseline, no difference between group was observed for the self-selected dual-task gait speed ($p = 0.901$). The MLM revealed a significant group × time interaction ($p = 0.008$) indicating that CCT improved dual-task performance in the intervention compared to the control group. *Post-hoc* analyses revealed that self-selected dual-task gait speed significantly increased within the intervention group (+20.6 ± 24.8%; $p < 0.001$), while there were no within group changes pre- to post-intervention for the control group (+3.0 ± 13.8%; $p = 0.467$). Older adults in the intervention group walked 0.13 m/s faster in self-selected dual-task gait speed condition at the end of the CCT intervention, whereas participants in the control group increased their speed by 0.02 m/s from baseline.

Secondary Outcomes

Secondary outcome results are presented in **Table 3**. We had reported blood draws as secondary outcomes in the clinicaltrials.gov registration form, but these are not included in this manuscript due to their complexity.

TMT A

At baseline, no difference between groups was observed in TMT A test ($p = 0.397$). The MLM revealed no significant group × time interaction ($p = 0.137$). Delta values showed that post-CCT, older adults in the intervention group solved TMT A, on the average, 9.8 s faster compared to older adults in the control group who solved TMT A, on the average, 2.5 s faster.

TMT B

At baseline, no difference between groups was observed in TMT B test ($p = 0.948$). The MLM revealed a significant group × time interaction ($p = 0.024$). *Post-hoc* analyses revealed that time to complete the TMT B was significantly reduced in the intervention group (−21.1 ± 31.1%; $p = 0.002$), while there were no changes pre- to post-intervention for the control group (+2.9 ± 33.0%; $p = 0.855$). Delta values showed that older adults in the intervention group solved TMT B on average 31.9 s faster at the end of the CCT intervention, whereas participants in the control group reduced solving time by 1.3 s.

TABLE 2 | Mixed-effect linear model results for primary outcome measures revealing Group, Time, and Group × time interactions as well as adjustments.

Parameter	Estimate	Std. error	df	*t*	Sig.	95% confidence interval	
						Lower bound	Upper bound
Self-selected single-task gait speed							
Group * Time	−0.098	0.050	48.222	−1.949	0.057	−0.199	0.003
Gender	−0.001	0.058	47.871	−0.016	0.987	−0.118	0.116
Age	−0.002	0.005	46.995	−0.332	0.741	−0.011	0.008
MoCA total score	0.008	0.015	47.122	0.529	0.599	−0.023	0.039
Study completion	−0.036	0.072	54.746	−0.500	0.619	−0.179	0.108
Self-selected dual-task gait speed							
Group * Time	−0.130	0.046	45.127	−2.790	**0.008**	−0.223	−0.036
Gender	0.016	0.076	47.156	0.212	0.833	−0.136	0.168
Age	−0.007	0.006	46.625	−1.124	0.267	−0.019	0.005
MoCA total score	−0.006	0.020	46.516	−0.315	0.754	−0.046	0.034
Study completion	−0.065	0.091	51.444	−0.714	0.479	−0.248	0.118

Significant group × time interactions are signed with bold.

Foot Reaction Time Test

At baseline, no difference between groups was observed in simple reaction time using lower limbs ($p = 0.932$). However, the MLM revealed a significant group × time interaction ($p = 0.019$). *Post-hoc* analyses revealed that simple reaction time was significantly reduced in the intervention group (−5.0 ± 9.9%; $p = 0.040$), however remained unchanged in the control group (+2.7 ± 9.4%; $p = 0.222$) during the pre- to post-intervention period. Delta values showed that older adults in the intervention group had on average foot reaction time 9.5 ms faster at the end of the CCT intervention, whereas participants in the control group prolonged their foot reaction time on average by 6.8 ms.

ERPs

Results for the ERP components are summarized in **Figures 2**, **3** and **Table 2**. A significant interaction between *group* and *time* was found for the P2 latency component ($p = 0.008$). *Post-hoc* analyses revealed that P2 latency was significantly reduced in the intervention group (−6.6 ± 5.7%; $p < 0.001$; **Figure 2** left), there were no changes pre- to post-intervention for the control group (+1.8 ± 9.1%; $p = 0.500$). Delta values revealed that older adults in the intervention group reduced their P2 latency on average for 14.6 ms at the end of the CCT intervention, whereas participants in the control group prolonged their P2 latency by 4.0 ms.

Similarly, a significant interaction was found for the peak amplitude in motor-related processes ($p = 0.009$). *Post-hoc* analyses revealed that MRCP peak amplitude was significantly reduced in the intervention group (−14.5 ± 23.3%; $p = 0.029$; **Figure 3** left), though there were no changes pre- to post-intervention for the control group (+22.6 ± 47.7%; $p = 0.154$). Delta values indicated that older adults in the intervention group reduced their MRCP peak amplitude on average for 1.1 uV at the end of the CCT intervention, whereas participants in the control group increased their MRCP peak amplitude by 0.2 uV. No other significant interactions were found for the remaining ERP components (see **Table 3**).

Correlation Analyses

There were significant correlations found only in the Intervention group between delta scores on TMT B and self-selected dual-task gait speed (r = −0.42; $p = 0.041$), TMT B and P2 latency (r = 0.62; $p = 0.025$), and self-selected dual-task gait speed and P2 latency (r = −0.68; $p = 0.006$).

DISCUSSION

The findings from this single-blind randomized controlled trial reveal that CCT was effective in improving not only gait but also executive function in active, healthy and independently living older adults. At the conclusion of this structured 2-month cognitive training program (24 sessions of CCT), the intervention group exhibited improved gait performance, especially during challenging walking conditions, relative to the control group. Enhanced primary/gait outcome measures were accompanied with enhanced performance on a test of executive function (TMT) as well as on a sensorimotor task for lower limbs. This was also evident from a correlation analysis showing that improvements in motor and cognitive functions were related to a shortening of the P2 component of visual processing. To our knowledge, this is the first study to reveal that CCT alone can improve complex mobility performance in active, healthy older adults. These results extend previous behavioral reports of the impact of CCT on both cognitive and motor performance in less healthy populations (Mewborn et al., 2017; Marusic et al., 2018b), as well as provide preliminary support for neural enhancements in the aging brain.

The improvement in executive functions in the intervention group supports near transfer of training effects of CCT as demonstrated in previous studies (Klusmann et al., 2010; Heinzel et al., 2014; Marusic et al., 2018a). Compared to the controls, participants in the intervention group required less time to complete the TMT B task - a test of executive functioning that was not used for training purposes in the CogniFit software.

TABLE 3 | Mixed-effect linear model results for secondary outcome measures revealing Group, Time and Group × time interactions as well as covariates.

Parameter	Estimate	Std. error	df	*t*	Sig.	95% confidence interval	
						Lower bound	Upper bound
TMT A							
Group * Time	6.999	4.625	44.007	1.513	0.137	−2.322	16.320
Gender	−6.746	5.808	48.420	−1.161	0.251	−18.422	4.930
Age	−0.109	0.484	50.718	−0.225	0.823	−1.082	0.864
MoCA total score	−0.986	1.510	47.039	−0.653	0.517	−4.024	2.052
Study completion	2.269	7.295	61.307	0.311	0.757	−12.317	16.855
TMT B							
Group * Time	28.063	11.981	42.796	2.342	**0.024**	3.898	52.227
Gender	−19.074	12.426	46.818	−1.535	0.132	−44.075	5.926
Age	0.628	1.042	49.984	0.603	0.550	−1.465	2.720
MoCA total score	−8.219	3.220	45.026	−2.552	0.014	−14.705	−1.733
Study completion	8.984	16.053	65.965	0.560	0.578	−23.067	41.034
Foot reaction times							
Group * Time	27.685	11.034	25.641	2.509	**0.019**	4.988	50.382
Gender	17.642	14.572	33.320	1.211	0.235	−11.994	47.277
Age	1.399	1.100	31.922	1.272	0.213	−0.842	3.639
MoCA total score	−1.408	3.991	33.024	−0.353	0.727	−9.528	6.713
Study completion	4.755	15.369	38.974	0.309	0.759	−26.332	35.841
Stimulus processing P1 amplitude							
Group * Time	1.301	1.069	18.550	1.218	0.239	−0.939	3.542
Gender	1.604	0.817	22.222	1.962	0.062	−0.090	3.298
Age	0.135	0.073	26.747	1.849	0.076	−0.015	0.285
MoCA total score	−0.556	0.223	21.098	−2.493	0.021	−1.020	−0.092
Study completion	−0.311	1.194	33.987	−0.260	0.796	−2.736	2.115
Stimulus processing P1 latency							
Group * Time	6.558	9.866	17.900	0.665	0.515	−14.177	27.294
Gender	−11.821	8.788	23.016	−1.345	0.192	−30.000	6.357
Age	0.652	0.772	26.575	0.845	0.406	−0.932	2.236
MoCA total score	2.947	2.408	22.256	1.224	0.234	−2.044	7.938
Study completion	1.557	11.839	31.465	0.132	0.896	−22.574	25.689
Stimulus processing N1 amplitude							
Group * Time	−1.112	1.073	16.109	−1.036	0.315	−3.385	1.161
Gender	−1.666	1.329	23.356	−1.253	0.223	−4.414	1.082
Age	−0.089	0.114	25.436	−0.782	0.441	−0.323	0.145
MoCA total score	0.578	0.366	23.007	1.578	0.128	−0.180	1.335
Study completion	−1.160	1.420	22.980	−0.817	0.423	−4.097	1.778
Stimulus processing N1 latency							
Group * Time	12.160	12.512	18.091	0.972	0.344	−14.117	38.438
Gender	−11.126	10.145	22.389	−1.097	0.284	−32.144	9.892
Age	0.166	0.900	26.572	0.185	0.855	−1.681	2.014
MoCA total score	2.400	2.774	21.415	0.865	0.397	−3.362	8.161
Study completion	6.386	14.400	33.431	0.443	0.660	−22.896	35.668
Stimulus processing P2 amplitude							
Group * Time	−0.899	1.218	14.437	−0.738	0.472	−3.505	1.706
Gender	2.330	1.497	21.813	1.556	0.134	−0.777	5.437
Age	−0.039	0.128	24.097	−0.302	0.765	−0.303	0.226
MoCA total score	−0.328	0.412	21.433	−0.795	0.435	−1.184	0.528
Study completion	1.374	1.610	21.597	0.854	0.403	−1.968	4.716

(Continued)

TABLE 3 | Continued

Parameter	Estimate	Std. error	df	*t*	Sig.	95% confidence interval	
						Lower bound	Upper bound
Stimulus processing P2 latency							
Group * Time	27.012	8.656	13.046	3.121	**0.008**	8.320	45.704
Gender	−0.851	13.851	21.462	−0.061	0.952	−29.619	27.917
Age	−1.726	1.173	22.911	−1.471	0.155	−4.153	0.702
MoCA total score	−1.234	3.821	21.246	−0.323	0.750	−9.174	6.707
Study completion	16.787	11.944	16.752	1.405	0.178	−8.442	42.016
Motor-related processes: peak amplitude							
Group * Time	−3.501	1.207	18.500	−2.901	**0.009**	−6.032	−0.971
Gender	1.380	1.279	24.186	1.079	0.291	−1.259	4.018
Age	0.006	0.109	23.468	0.059	0.953	−0.219	0.232
MoCA total score	−0.097	0.342	24.113	−0.283	0.780	−0.802	0.609
Study completion	1.924	1.596	30.938	1.206	0.237	−1.330	5.178
Motor-related processes: peak latency							
Group * Time	−0.549	13.023	14.251	−0.042	0.967	−28.435	27.337
Gender	−3.477	13.640	20.750	−0.255	0.801	−31.864	24.909
Age	−2.026	1.642	19.614	−1.233	0.232	−5.456	1.405
MoCA total score	−2.971	3.669	20.245	−0.810	0.428	−10.618	4.677
Study completion	−7.629	17.608	15.684	−0.433	0.671	−45.017	29.759
Motor-related processes: onset latency							
Group * Time	−19.049	21.215	14.570	−0.898	0.384	−64.385	26.287
Gender	5.535	16.212	17.792	0.341	0.737	−28.555	39.624
Age	−1.108	1.986	16.088	−0.558	0.584	−5.316	3.099
MoCA total score	−5.727	4.368	17.060	−1.311	0.207	−14.941	3.488
Study completion	9.188	25.816	16.683	0.356	0.726	−45.358	63.735

Significant group × time interactions are signed with bold.

Also, the TMT was administered only twice (both pre- and post- study) to both the intervention and control groups, so practice effects across both groups cannot explain enhancements in performance solely for the intervention group. Traditionally, training interventions have only evaluated cognitive training-related improvements in the directly trained cognitive domain (Butler et al., 2018), although some initial cognitive interventions report potential transfer effects to other domains like driving performance and daily functioning (Ball et al., 2002; Willis et al., 2006).

Far transfer, to a distal untrained domain, such as mobility was reported in the present trial in a sample of asymptomatic older adults where self-selected dual-task gait speed was significantly increased (0.13 m/s = 21% intervention *vs.* 0.02 m/s = 3% control improvement) in the intervention compared to control group. Moreover, there was a trend toward improved walking speed during the single-task (0.16m/s = 17% intervention *vs.* 0.07m/s = 7% control improvement). Similar findings were obtained in a pilot study of sedentary older adults (Verghese et al., 2010) and latter summarized in our meta-analytical review (Marusic et al., 2018b) that highlighted larger cognitive training-related improvements during challenging walking conditions given their reliance on higher-order executive functions. From the perspective of clinically meaningful change, both gait speeds were increased by more than 0.08 m/s in the intervention group, which was considered a meaningful change in physical performance (Kwon et al., 2009). Recently, a larger CCT study of 383 non-demented seniors at high risk for mobility disability was completed (Verghese et al., 2021). The authors reported an improvement in walking, but this was no greater than in the active control group, who also completed the same amount of CCT but with no progress in the difficulty of the games performed (Verghese et al., 2021). Here, the authors report that practice effects might explain the improvements seen in both arms and the lack of between-group differences; however, the investigators also discuss an alternate hypothesis that the more robust effect on executive function tests in the cognitive remediation arm compared to the active control may indicate a true training effect, and raises the possibility that even low levels of cognitive remediation (as in their active control arm) lead to cognitive benefits (Verghese et al., 2021). Nevertheless, the current study differed in several ways that might explain the discrepancy in results including, smaller sample size, use of healthy elderly population, wait list control, and the inclusion of neurophysiological measures that were lacking in the previous trial.

The near and far transfer improvements in the current experiment suggest that common brain substrates involving

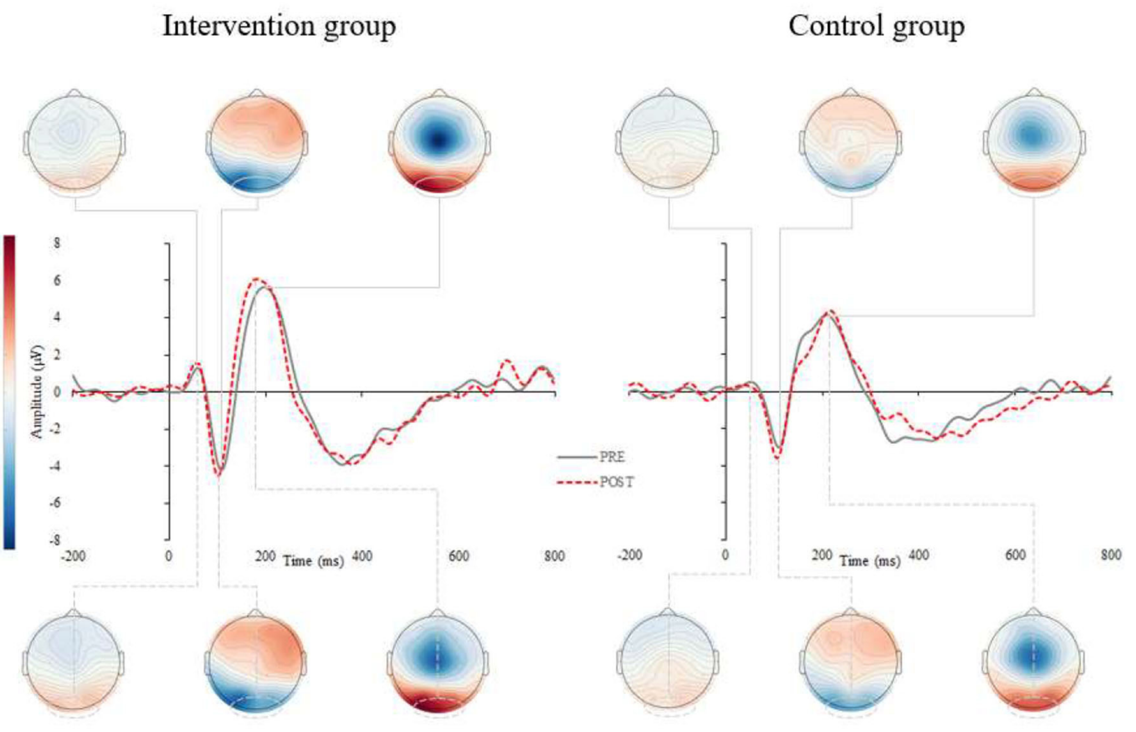

FIGURE 2 | Grand average stimulus-locked event-related potentials (s-ERPs) for the intervention (left) and control (right) group. Figure represents the grand averaged ERPs for pre- (gray, solid) and post-assessments (red, dashed) for intervention (left) and control group (right). The s-ERPs correspond to occipital electrodes (averaged across O1, Oz, and O2) and show visual components P1, N1 and P2 after the visual stimuli occurrence.

cognitive and mobility processes were strengthened by the CCT. The electrophysiological study in a subgroup of our participants provides further insights into the observed benefits. That is, the intervention group manifested shortened foot reaction times to visual stimuli after 2 months of CCT with concomitant P2 latency reduction over occipital regions as well as decreased MRCP amplitudes over motor cortex region. The former likely reflects enhancements in executive attention processes and sensory encoding (Finnigan et al., 2011), while the latter points toward the optimization in response generation and efficiency in depolarization of motor cortex neurons (Yordanova et al., 2004). While slower foot reaction times have been associated with falls (Lord et al., 2003), a recent study revealed a link between participation in cognitive activities and neuromotor performance (Cai et al., 2020). Although using a cross-sectional design, the latter study showed the participation in cognitively stimulating activities is associated with shorter foot reaction times and faster gait speed (Cai et al., 2020), which is consistent with our longitudinal observations.

Enhancing neural substrates and consequently (sub)components of executive functions [i.e., cognitive flexibility; for details see (Diamond, 2013)] seems like a plausible explanation for improvements in gait (Marusic et al., 2018b), as well as sensory functioning. Previous EEG/ERP studies typically report a u-shape pattern in ERP components (Reuter et al., 2019), and more specifically increased P2 component latencies in older as compared to younger adults (Goodin et al., 1978; Iragui et al., 1993). Our recent study found overall larger amplitudes with delayed latencies of endogenous potentials in older compared to younger adults (Marusic et al., 2022), which is consistent with our recent findings in which P2 latency was significantly reduced after CCT. Moreover, the lower MRCP amplitude during sensorimotor task performed with the lower limbs may indicate less intense depolarization of motor cortex neurons or more efficient recruitment of neuronal resources required for the lower extremity response task after CCT (Yordanova et al., 2004; Marusic et al., 2022).

It is well-documented that walking, a rhythmic motor task, involves complex motor, sensory and cognitive processes (Holtzer et al., 2006; Scherder et al., 2007; Al-Yahya et al., 2011). It is also known that older adults require more attentional demands for motor control while walking, indicating the compounded involvement of attentional resources during gait (Kressig, 2010). Moreover, the association of multisensory integration processes with attention-based performance (Mahoney and Verghese, 2020) and measures of mobility including balance, falls and gait (Mahoney et al., 2019) have been well established. Findings reveal that better performance on a visual-somatosensory simple RT test requiring lower limb responses was associated with better cognitive and motor outcomes in healthy older adults. The authors present a potential overlapping neural circuit which emphasizes the critical role of the prefrontal cortex for

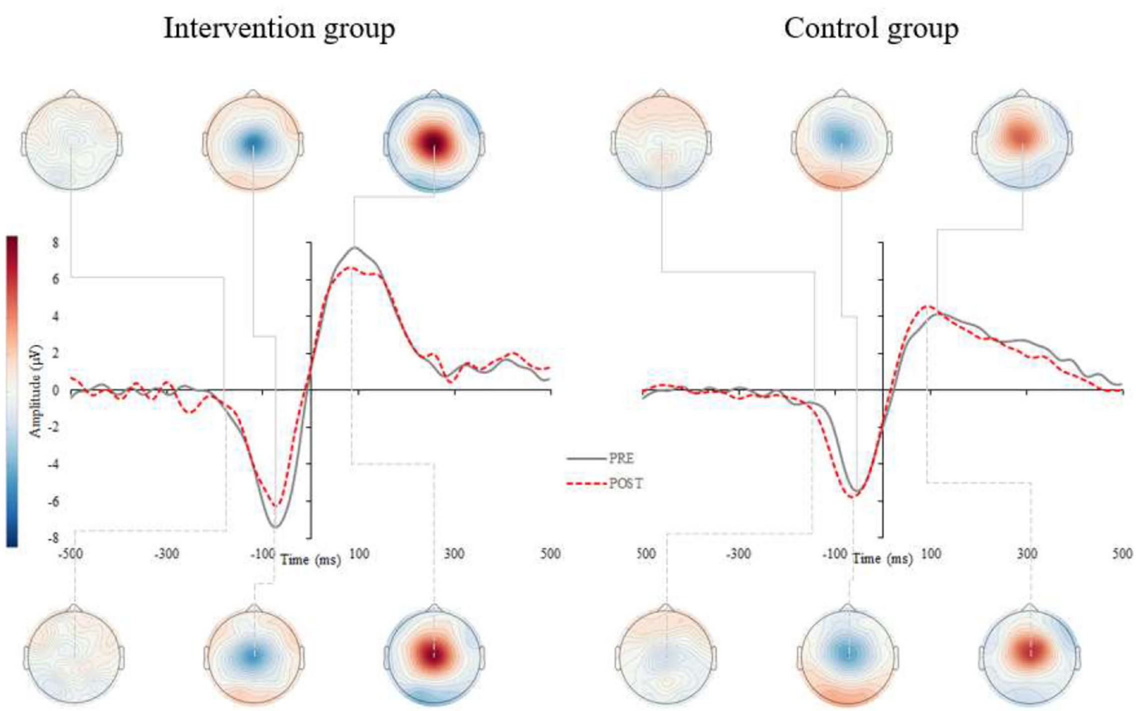

FIGURE 3 | Grand average response-locked event-related potentials (r-ERPs) for the intervention (left) and control (right) group. Figure represents the grand averaged ERPs for pre- (gray, solid) and post-assessments (red, dashed) for intervention (left) and control group (right). The r-ERPs (MRCP) correspond to central electrode Cz and show the peak latency and amplitude of the most negative displacement of the MRCP, prior to or at the time of response execution.

intact multisensory, motor and cognitive performance (Mahoney and Verghese, 2020). However, further studies are needed to determine whether CCT simultaneously improves sensory, cognitive, and motor functioning by targeting neural networks with connections to prefrontal cortex.

The main strength of the current study is the application of a randomized control design for examining the effect of CCT. The current study replicates previous studies addressing mobility-related improvements after non-physical training, while revealing the potential of CCT in asymptomatic older adults and highlighting for the first time associated neural alterations.

This study is not without limitations. The sample size was determined by convenience in which we targeted recruitment of older adults attending the Center for daily activities for the elderly. There was a relatively high attrition rate, particularly in the control group, but similar to other cognitive training studies (Ballesteros et al., 2014; Maffei et al., 2017). Attrition rates could likely be improved by including an active control group and/or compensating participants for their time and effort (Verghese et al., 2016). Recent findings by Verghese et al. (2021) in which the active control group showed cognitive and motoric benefits point to the possibility that even low levels of cognitive training have cognitive benefits (Verghese et al., 2021). We were unable to assess durability effects of CCT over time on our outcome measures. Future studies should explore monitoring brain activity directly during actual locomotion through a Mobile Brain/Body Imaging (MoBI) setup for example, to gain further insights into neuroplasticity in ecologically valid environments (Wunderlich et al., 2021).

CONCLUSIONS AND IMPLICATIONS

Overall, results from the current study provide evidence that CCT improves mobility in a population of active, healthy and independently living older adults, and is associated with enhancements in cognitive performance. Enhanced executive functions together with optimization of sensorimotor processing that contributes to shorter lower-limb response times after CCT may play a role in enhanced mobility but requires further validation. Our correlational analyses suggest that neurophysiological findings support alterations in neural activity that may contribute to the reported enhancements in cognitive and motor performance. Understanding the underlying mechanisms of how non-physical interventions can improve mobility could guide future research in situations where physical exercise is limited or not possible such as before or after surgery or during periods of immobilization as in hospital stays. There is a need for well-designed large-scale clinical trials with active controls to identify neuronal substrates that are susceptible to CCT enhancement to improve current multimodal interventions to prevent cognitive and motoric declines in aging.

DATA AVAILABILITY STATEMENT

Raw data supporting the results of this study are available from the corresponding author, upon reasonable request.

ETHICS STATEMENT

All procedures were carried out in accordance with the ethical standards of the 1964 Declaration of Helsinki and were approved by the Republic of Slovenia National Medical Ethics Committee (KME57/06/17).

AUTHOR CONTRIBUTIONS

UM: concept creation, project holder, data acquisition monitoring, data processing, data analysis, interpretation of data, and drafted manuscript. JV and JRM: concept creation, interpretation of data, critically reading, and proof-reading the manuscript. All authors read and approved the final manuscript.

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REFERENCES

Al-Yahya, E., Dawes, H., Smith, L., Dennis, A., Howells, K., and Cockburn, J. (2011). Cognitive motor interference while walking: a systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* 35, 715–728. doi: 10.1016/j.neubiorev.2010.08.008

Azadian, E., Majlesi, M., and Jafarnezhadgero, A. A. (2018). The effect of working memory intervention on the gait patterns of the elderly. *J. Bodywork Move. Therap.* 22, 881–887. doi: 10.1016/j.jbmt.2017.08.008

Ball, K., Berch, D. B., Helmers, K. F., Jobe, J. B., Leveck, M. D., Marsiske, M., et al. (2002). Effects of cognitive training interventions with older adults - A randomized controlled trial. *Jama-J. Am. Med. Assoc.* 288, 2271–2281. doi: 10.1001/jama.288.18.2271

Ballesteros, S., Prieto, A., Mayas, J., Toril, P., Pita, C., Ponce de León, L., et al. (2014). Brain training with non-action video games enhances aspects of cognition in older adults: a randomized controlled trial. *Front. Aging Neurosci.* 6, 277. doi: 10.3389/fnagi.2014.00277

Beauchet, O., Allali, G., Annweiler, C., and Verghese, J. (2016). Association of motoric cognitive risk syndrome with brain volumes: results from the GAIT study. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences.* 71, 1081–1088.

Blumen, H. M., Brown, L. L., Habeck, C., Allali, G., Ayers, E., Beauchet, O., et al. (2019). Gray matter volume covariance patterns associated with gait speed in older adults: a multi-cohort MRI study. *Brain Imaging and Behavior.* 13, 446–460.

Butler, M., McCreedy, E., Nelson, V. A., Desai, P., Ratner, E., Fink, H. A., et al. (2018). Does cognitive training prevent cognitive decline?: a systematic review. *Ann. Intern. Med.* 168, 63–68. doi: 10.7326/M17-1531

Cai, Y., Hausdorff, J. M., Bean, J. F., Manor, B., You, T., and Leveille, S. G. (2020). Participation in cognitive activities is associated with foot reaction time and gait speed in older adults. *Aging Clin. Exp. Res.* 3, 1583. doi: 10.1007/s40520-020-01583-3

Cohen, R. G., Vasavada, A. N., Wiest, M. M., and Schmitter-Edgecombe, M. (2016). Mobility and upright posture are associated with different aspects of cognition in older adults. *Front. Aging Neurosci.* 8, 257. doi: 10.3389/fnagi.2016.00257

Demnitz, N., Zsoldos, E., Mahmood, A., Mackay, C. E., Kivimäki, M., Singh-Manoux, A., et al. (2017). Associations between mobility, cognition, and brain structure in healthy older adults. *Front. Aging Neurosci.* 9, 155. doi: 10.3389/fnagi.2017.00155

Diamond, A. (2013). Executive functions. *Ann. Rev. Psychol.* 64, 135–168. doi: 10.1146/annurev-psych-113011-143750

DiPietro, L., Jin, Y., Talegawkar, S., and Matthews, C. E. (2018). The joint associations of sedentary time and physical activity with mobility disability in older people: the NIH-AARP diet and health study. *J. Gerontol. Series A* 73, 532–538. doi: 10.1093/gerona/glx122

Finnigan, S., O'Connell, R. G., Cummins, T. D., Broughton, M., and Robertson, I. H. (2011). ERP measures indicate both attention and working memory encoding decrements in aging. *Psychophysiology* 48, 601–611. doi: 10.1111/j.1469-8986.2010.01128.x

Gajewski, P. D., and Falkenstein, M. (2012). Training-induced improvement of response selection and error detection in aging assessed by task switching: effects of cognitive, physical, and relaxation training. *Front. Hum. Neurosci.* 6, 130. doi: 10.3389/fnhum.2012.00130

Gajewski, P. D., and Falkenstein, M. (2018). ERP and behavioral effects of physical and cognitive training on working memory in aging: a randomized controlled study. *Neural Plasticity* 2018, 835. doi: 10.1155/2018/3454835

Goodin, D. S., Squires, K. C., Henderson, B. H., and Starr, A. (1978). Age-related variations in evoked potentials to auditory stimuli in normal human subjects. *Electroencephalogr. Clin. Neurophysiol.* 44, 447–458. doi: 10.1016/0013-4694(78)90029-9

Heinzel, S., Schulte, S., Onken, J., Duong, Q.-L., Riemer, T. G., Heinz, A., et al. (2014). Working memory training improvements and gains in non-trained cognitive tasks in young and older adults. *Aging Neuropsychol. Cogn.* 21, 146–173. doi: 10.1080/13825585.2013.790338

Hirvensalo, M., Rantanen, T., and Heikkinen, E. (2000). Mobility difficulties and physical activity as predictors of mortality and loss of independence in the community-living older population. *J. Am. Geriatric. Soc.* 48, 493–498. doi: 10.1111/j.1532-5415.2000.tb04994.x

Holtzer, R., Verghese, J., Xue, X., and Lipton, R. B. (2006). Cognitive processes related to gait velocity: results from the Einstein Aging Study. *Neuropsychology* 20, 215. doi: 10.1037/0894-4105.20.2.215

Iragui, V. J., Kutas, M., Mitchiner, M. R., and Hillyard, S. A. (1993). Effects of aging on event-related brain potentials and reaction times in an auditory oddball task. *Psychophysiology* 30, 10–22. doi: 10.1111/j.1469-8986.1993.tb03200.x

Klusmann, V., Evers, A., Schwarzer, R., Schlattmann, P., Reischies, F. M., Heuser, I., et al. (2010). Complex mental and physical activity in older women and cognitive performance: a 6-month randomized controlled trial. *J. Gerontol. Series a-Biologic. Sci. Med. Sci.* 65, 680–688. doi: 10.1093/gerona/glq053

Kressig, S. A. B. R. W. (2010). *Laboratory Review: The Role of Gait Analysis in Seniors' Mobility and Fall Prevention.*

Kubo, M., Shoshi, C., Kitawaki, T., Takemoto, R., Kinugasa, K., Yoshida, H., et al. (2008). Increase in prefrontal cortex blood flow during the computer version trail making test. *Neuropsychobiology* 58, 200–210. doi: 10.1159/000201717

Kwon, S., Perera, S., Pahor, M., Katula, J. A., King, A. C., Groessl, E. J., et al. (2009). What is a meaningful change in physical performance? findings from a clinical trial in older adults (the LIFE-P study). *J. Nutr. Health Aging* 13, 538–544. doi: 10.1007/s12603-009-0104-z

Laird, N. M., and Ware, J. H. (1982). Random-effects models for longitudinal data. *Biometrics* 963–974. doi: 10.2307/2529876

Lee, P. G., Jackson, E. A., and Richardson, C. R. (2017). Exercise prescriptions in older adults. *Am. Fam. Physic.* 95, 425–432.

Lienhard, K., Schneider, D., and Maffiuletti, N. A. (2013). Validity of the Optogait photoelectric system for the assessment of spatiotemporal gait parameters. *Med. Eng. Physic.* 35, 500–504. doi: 10.1016/j.medengphy.2012.06.015

Lord, S. R., Menz, H. B., and Tiedemann, A. (2003). A physiological profile approach to falls risk assessment and prevention. *Phys. Ther.* 83, 237–252. doi: 10.1093/ptj/83.3.237

Maffei, L., Picano, E., Andreassi, M., Angelucci, A., Baldacci, F., Baroncelli, L., et al. (2017). Randomized trial on the effects of a combined physical/cognitive training in aged MCI subjects: the Train the Brain study. *Sci. Rep.* 7, 39471. doi: 10.1038/srep39471

Mahoney, J. R., Cotton, K., and Verghese, J. (2019). Multisensory integration predicts balance and falls in older adults. *J. Gerontol. Series A* 74, 1429–1435. doi: 10.1093/gerona/gly245

Mahoney, J. R., and Verghese, J. (2020). Does cognitive impairment influence visual-somatosensory integration and mobility in older adults? *J. Gerontol. Series A* 75, 581–588. doi: 10.1093/gerona/glz117

Marusic, U., Giordani, B., Moffat, S. D., Petrič, M., Dolenc, P., Pišot, R., et al. (2018a). Computerized cognitive training during physical inactivity improves executive functioning in older adults. *Aging Neuropsychol. Cogn.* 25, 49–69. doi: 10.1080/13825585.2016.1263724

Marusic, U., Peskar, M., De Pauw, K., Omejc, N., Drevensek, G., Rojc, B., et al. (2022). Neural bases of age-related sensorimotor slowing in the upper and lower limbs. *Frontiers in Aging Neuroscience.* 355. doi: 10.3389/fnagi.2022.819576

Marusic, U., Verghese, J., and Mahoney, J. R. (2018b). Cognitive-based interventions to improve mobility: a systematic review and meta-analysis. *J. Am. Med. Direct. Assoc.* 18, 2. doi: 10.1016/j.jamda.2018.02.002

Mewborn, C. M., Lindbergh, C. A., and Miller, L. S. (2017). Cognitive interventions for cognitively healthy, mildly impaired, and mixed samples of older adults: a systematic review and meta-analysis of randomized-controlled trials. *Neuropsychol. Rev.* 27, 403–439. doi: 10.1007/s11065-017-9350-8

Montero-Odasso, M., Verghese, J., Beauchet, O., and Hausdorff, J. M. (2012). Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *J. Am. Geriatr. Soc.* 60, 2127–2136. doi: 10.1111/j.1532-5415.2012.04209.x

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., et al. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* 53, 695–699. doi: 10.1111/j.1532-5415.2005.53221.x

Ng, T. P., Feng, L., Nyunt, M. S. Z., Feng, L., Niti, M., Tan, B. Y., et al. (2015). Nutritional, physical, cognitive, and combination interventions and frailty reversal among older adults: a randomized controlled trial. *Am. J. Med.* 128, 1225–1236. doi: 10.1016/j.amjmed.2015.06.017

Nguyen, L., Murphy, K., and Andrews, G. (2019). Cognitive and neural plasticity in old age: a systematic review of evidence from executive functions cognitive training. *Ageing Res. Rev.* 53, 100912. doi: 10.1016/j.arr.2019.100912

Olfers, K. J., and Band, G. P. (2018). Game-based training of flexibility and attention improves task-switch performance: near and far transfer of cognitive training in an EEG study. *Psychol. Res.* 82, 186–202. doi: 10.1007/s00426-017-0933-z

Pergher, V., Wittevrongel, B., Tournoy, J., Schoenmakers, B., and Van Hulle, M. M. (2018). N-back training and transfer effects revealed by behavioral responses and EEG. *Brain Behav.* 8, e01136. doi: 10.1002/brb3.1136

Reitan, R. M., and Wolfson, D. (1985). *The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation.* Tucson, Ariz.: Neuropsychology Press.

Reuter, E.-M., Vieluf, S., Koutsandreou, F., Hübner, L., Budde, H., Godde, B., et al. (2019). A Non-linear relationship between selective attention and associated ERP markers across the lifespan. *Front. Psychol.* 10, 30. doi: 10.3389/fpsyg.2019.00030

Rosano, C., Newman, A. B., Katz, R., Hirsch, C. H., and Kuller, L. H. (2008). Association between lower digit symbol substitution test score and slower gait and greater risk of mortality and of developing incident disability in well-functioning older adults. *J. Am. Geriatric. Soc.* 56, 1618–1625. doi: 10.1111/j.1532-5415.2008.01856.x

Scherder, E., Eggermont, L., Swaab, D., van Heuvelen, M., Kamsma, Y., de Greef, M., et al. (2007). Gait in ageing and associated dementias; its relationship with cognition. *Neurosci. Biobehav. Rev.* 31, 485–497. doi: 10.1016/j.neubiorev.2006.11.007

Simons, D. J., Boot, W. R., Charness, N., Gathercole, S. E., Chabris, C. F., Hambrick, D. Z., et al. (2016). Do "brain-training" programs work? *Psychol. Sci. Public Inter.* 17, 103–186. doi: 10.1177/1529100616661983

Smith-Ray, R. L., Hughes, S. L., Prohaska, T. R., Little, D. M., Jurivich, D. A., and Hedeker, D. (2013). Impact of cognitive training on balance and gait in older adults. *J. Gerontol. Series B: Psychol. Sci. Soc. Sci.* 13, 97. doi: 10.1093/geronb/gbt097

Tardif, S., and Simard, M. (2011). Cognitive stimulation programs in healthy elderly: a review. *Int. J. Alzheimers Dis.* 2011, 378934. doi: 10.4061/2011/378934

Tombaugh, T. N. (2004). Trail making Test A and B: normative data stratified by age and education. *Archiv. Clinic. Neuropsychol.* 19, 203–214. doi: 10.1016/S0887-6177(03)00039-8

Urzi, F., Marusic, U., Ličen, S., and Buzan, E. (2019). Effects of elastic resistance training on functional performance and myokines in older women—a randomized controlled trial. *J. Am. Med. Direct. Assoc.* 20, 830–834. doi: 10.1016/j.jamda.2019.01.151

Verghese, E., Mahoney, J. R., Ambrose, A., Wang, C., and Holtzer, R. (2016). Cognitive remediation to enhance mobility in older adults: the CREM study. *Neurodegenerat. Dis. Manage.* 6, 457–466. doi: 10.2217/nmt-2016-0034

Verghese, G., Holtzer, R., Katz, M., Xue, X., Buschke, H., and Pahor, M. (2007). Walking while talking: effect of task prioritization in the elderly. *Arch Phys Med Rehabil* 88, 50–53. doi: 10.1016/j.apmr.2006.10.007

Verghese, J., Mahoney, J., Ambrose, A. F., Wang, C. L., and Holtzer, R. (2010). Effect of cognitive remediation on gait in sedentary seniors. *J. Gerontol. Series a-Biologic. Sci. Med. Sci.* 65, 1338–1343. doi: 10.1093/gerona/glq127

Verghese, J. R., Ayers, E., Ambrose, A. F., Wang, C., and Holtzer, R. (2021). Computerised cognitive remediation to enhance mobility in older adults: a single-blind, single-centre, randomised trial. *Lancet Healthy Longev.* 2, e571–e579. doi: 10.1016/S2666-7568(21)00173-2

Willis, S. L., Tennstedt, S. L., Marsiske, M., Ball, K., Elias, J., Koepke, K. M., et al. (2006). Long-term effects of cognitive training on everyday functional outcomes in older adults. *JAMA* 296, 2805–2814. doi: 10.1001/jama.296.23.2805

Wunderlich, A., Vogel, O., Šömen, M. M., Peskar, M., Fricke, M., Gramann, K., et al. (2021). Dual-Task Performance in Hearing-Impaired Older Adults-Study Protocol for a Cross-Sectional Mobile Brain/Body Imaging Study. *Front. Aging Neurosci.* 13, 773287. doi: 10.3389/fnagi.2021.773287

Yordanova, J., Kolev, V., Hohnsbein, J., and Falkenstein, M. (2004). Sensorimotor slowing with ageing is mediated by a functional dysregulation of motor-generation processes: evidence from high-resolution event-related potentials. *Brain* 127, 351–362. doi: 10.1093/brain/awh042

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The remaining 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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Multisensory visual-vestibular training improves visual heading estimation in younger and older adults

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Self-motion perception (e.g., when walking/driving) relies on the integration of multiple sensory cues including visual, vestibular, and proprioceptive signals. Changes in the efficacy of multisensory integration have been observed in older adults (OA), which can sometimes lead to errors in perceptual judgments and have been associated with functional declines such as increased falls risk. The objectives of this study were to determine whether passive, visual-vestibular self-motion heading perception could be improved by providing feedback during multisensory training, and whether training-related effects might be more apparent in OAs vs. younger adults (YA). We also investigated the extent to which training might transfer to improved standing-balance. OAs and YAs were passively translated and asked to judge their direction of heading relative to straight-ahead (left/right). Each participant completed three conditions: (1) vestibular-only (passive physical motion in the dark), (2) visual-only (cloud-of-dots display), and (3) bimodal (congruent vestibular and visual stimulation). Measures of heading precision and bias were obtained for each condition. Over the course of 3 days, participants were asked to make bimodal heading judgments and were provided with feedback ("correct"/"incorrect") on 900 training trials. Post-training, participants' biases, and precision in all three sensory conditions (vestibular, visual, bimodal), and their standing-balance performance, were assessed. Results demonstrated improved overall precision (i.e., reduced JNDs) in heading perception after training. Pre- vs. post-training difference scores showed that improvements in JNDs were only found in the visual-only condition. Particularly notable is that 27% of OAs initially could not discriminate their heading at all in the visual-only condition pre-training, but subsequently obtained thresholds in the visual-only condition post-training that were similar to those of the other participants. While OAs seemed to show optimal integration pre- and post-training (i.e., did not show significant differences between predicted and observed JNDs), YAs only showed optimal integration post-training. There were no significant effects of training for bimodal or vestibular-only heading estimates, nor standing-balance performance. These results indicate that it may be possible to improve unimodal (visual) heading perception using a multisensory (visual-vestibular) training paradigm. The results may also help to inform interventions targeting tasks for which effective self-motion perception is important.

KEYWORDS

heading estimation, postural control, straight-ahead perception, training, aging, bimodal perception, self-motion, multisensory integration (MSI)

Introduction

Accurately and precisely perceiving our own movements through space is important for safely navigating our environment. During tasks such as walking, driving, and standing, we receive dynamic information from several different sensory systems that our brains must quickly and efficiently integrate to coherently perceive self-motion. In real-world environments these individual sensory inputs are rarely experienced in isolation and integrating them typically improves perceptual precision (Meredith and Stein, 1986; Ernst and Banks, 2002; Angelaki et al., 2009; Fetsch et al., 2009; Butler et al., 2010, 2015; Gu et al., 2013). The greatest benefits of multisensory integration are often observed when sensory estimates are less reliable (The Principle of Inverse Effectiveness; Meredith and Stein, 1986), and older age is often associated with sensory decline. This suggests that older adults may particularly benefit from multisensory stimulation.

Two of the most important cues to self-motion perception are visual cues (e.g., optic flow; Gibson, 1950) and vestibular cues (Angelaki and Cullen, 2008). In younger and older adults, visual and vestibular cues are often weighted and integrated in an optimal manner that minimizes variability to inform self-motion perception (Fetsch et al., 2009, 2010; Butler et al., 2010, 2015; Angelaki et al., 2011; Karmali et al., 2014; Greenlee et al., 2016; Ramkhalawansingh et al., 2017, 2018). When visual and vestibular cues are congruent and redundant (as is typically the case during most everyday experiences), integrating these inputs improves the precision of perceptual estimates (Ernst and Bülthoff, 2004; Fetsch et al., 2010; Butler et al., 2015).

Aging is associated with changes in individual sensory functioning, such as vestibular perception (Roditi and Crane, 2012; Bermúdez Rey et al., 2016; Karmali et al., 2017; Beylergil et al., 2019; Kobel et al., 2021; Gabriel et al., 2022a) and visual perception (Owsley, 2011). In terms of self-motion perception specifically, relative to younger adults, healthy older adults are worse at perceiving the direction of visual motion (Bennett et al., 2007) and self-motion perception in particular (e.g., egomotion simulated with an optic flow field) (Warren et al., 1989; Mapstone et al., 2006; Snowden and Kavanagh, 2006; Billino et al., 2008; Duffy, 2009; Mapstone and Duffy, 2010; Kavcic et al., 2011; Velarde et al., 2013; Lich and Bremmer, 2014; Ramkhalawansingh et al., 2017, 2018), with some evidence indicating that a subset of healthy older adults are completely unable to estimate their heading direction using optic flow alone (Warren et al., 1989; Ramkhalawansingh et al., 2018). With regards to vestibular self-motion perception (passive movements in the dark), older adults demonstrate larger perceptual detection and discrimination thresholds relative to younger adults across most axes and directions (Roditi and Crane, 2012; Bermúdez Rey et al., 2016; Karmali et al., 2017, 2018; Beylergil et al., 2019; Gabriel et al., 2022a), except for in the yaw axis (Chang et al., 2014; Roditi and Crane, 2012; but see Bermúdez Rey et al., 2016). They do not, however, show differences relative to younger adults in discriminating forward linear heading direction using only vestibular inputs (Ramkhalawansingh et al., 2018). These results suggest that while certain aspects of vestibular perception decline with older age, other aspects may not (e.g., heading discrimination).

In addition to these unimodal changes, aging is also associated with changes in multisensory integration, which may become heightened with older age (Laurienti et al., 2006; Mahoney et al., 2011; Mozolic et al., 2012; Diaconescu et al., 2013; Freiherr et al., 2013; McGovern et al., 2014; de Dieuleveult et al., 2017), including heightened visual-vestibular integration (Ramkhalawansingh et al., 2017, 2018; Nestmann et al., 2020; Kenney et al., 2021). In other words, when multiple sensory inputs are congruent and redundant, older adults may experience greater perceptual benefits from integrating these sensory inputs compared to younger adults (Hughes et al., 1994; Cienkowski and Carney, 2002; Laurienti et al., 2006; Peiffer et al., 2007; Tye-Murray et al., 2010; Mozolic et al., 2011; McGovern et al., 2014; Ramkhalawansingh et al., 2016, 2018; de Dieuleveult et al., 2017). However, heightened integration can also lead to performance decrements when sensory inputs are in conflict. For instance, older adults are more susceptible to integrating incongruent sensory cues (e.g., visual and vestibular heading directions that differ) than younger adults, and they weight the less reliable sensory cue higher than is optimal (Ramkhalawansingh et al., 2018; Nestmann et al., 2020). These age-related changes in unisensory and multisensory processes may partially explain why older adults are particularly vulnerable to injury during tasks requiring accurate self-motion perception, such as when driving and walking (Public Health Agency of Canada, 2014; Center for Disease Control, 2018a,b). Therefore, improving self-motion perception might help protect against adverse outcomes, such as injuries due to falls or collisions, in the older adult population.

Very few studies have investigated whether heading perception (i.e., self-motion perception) can be improved through training. Recently, Klaus et al. (2020). found that younger adults' perception of self-motion in the dark improved following training (i.e., feedback) when the trained motion type was a combination of roll and tilt (i.e., stimulating both the vestibular semicircular canals and otoliths simultaneously). However, Hartmann et al. (2013). showed that training was not effective when participants were moved exclusively in yaw (rotation around an Earth-vertical axis) or sway (linear motion from side to side) stimulating only the canals or otoliths, respectively. They also found that training was effective in improving sway (but not yaw) motion perception if vision was also provided during training (i.e., if training was multisensory).

With regards to visual-only training, Kuang et al. (2020) showed that younger adults can improve their visual estimates of left/right heading direction from optic flow fields through feedback-based training, and Gibson et al. (2020) also showed that training could improve vertical heading accuracy (e.g., down-and-forward vs. down-and-backward). But no studies have yet evaluated whether vestibular and/or visual self-motion training can improve heading perception in older adults. This present study therefore investigates the effects of multisensory training on heading perception [biases and just-noticeable differences (JNDs)] and assesses whether any benefits of perceptual training might transfer to other performance-related domains such as improving standing-balance. We also examine whether potential training-related improvements may be more apparent in older relative to younger adults.

Here, we trained older and younger adults in a passive visual-vestibular heading discrimination task (forward left/right judgments). Participants' heading estimation biases and JNDs were measured both pre- and post-training for three different sensory conditions: (1) visual-only (they were visually moved through a virtual starfield using a head-mounted display), (2) vestibular-only (they were physically moved on a six-degree-of-freedom motion platform in the dark), and (3) bimodal (visual and vestibular cues combined). We also assessed potential far-transfer-of-training effects by collecting pre- and post-training posturography measures during a quiet standing balance task under full and reduced sensory conditions.

Materials and methods

Participants

Participants were screened over the phone and were invited to participate only if they reported no history of stroke, seizures, diagnosed vestibular disorder, disabling musculoskeletal disorder, acute psychiatric disorder, eye disease (e.g., glaucoma or cataracts), diagnosed mild cognitive impairment, dementia, or hearing loss. Ultimately, 14 older adults and 13 younger adults met the screening-eligibility criteria and were invited to participate in the study. The sample size was based on (and/or exceeded) previous visual-vestibular training studies (Hartmann et al., 2013). Older adult participants completed an in-lab baseline assessment session (see below), which consisted of a battery of sensory, cognitive, and mobility tests, a sub-set of which were used to ensure that certain eligibility criteria were met (visual acuity, pure tone audiometry, cognitive impairment). Data from three older adult participants were excluded due to an inability to understand task instructions ($n = 1$) or because they did not have their prescription glasses for both pre-training and post-training sessions ($n = 2$). Data from two younger adults were also excluded due to not completing the post-training session. Thus, the data from 11 older adults (M_{age} = 71.54 years, SD = 6.70, females = 9, males = 2) and 11 younger adults (M_{age} = 23.73 years, SD = 5.18, females = 8, males = 3) were included in the analyses. Participants provided written informed consent and were compensated $20/h for their participation. This study was approved by the Research Ethics Boards of the University Health Network (Protocol Number: 18-5331.0) and the University of Toronto (Protocol number: 00037394).

Baseline assessment session

Older adult participants completed a series of sensory, cognitive, and mobility assessments. Both age groups completed the visual assessments. If participants wore corrective lenses during the experimental procedure, they were required to wear those same corrective lenses during the baseline assessment testing. Results of these assessments are given in **Table 1**.

Vision screening

Visual acuity

To measure visual acuity, participants stood 4 m away from an ETDRS (Early Treatment Diabetic Retinopathy Study Research Group, 1985) visual acuity chart and were asked to read the letters on the chart. They were instructed to read the chart from left-to-right for their left eye, and right-to-left for their right eye, beginning with their better-seeing eye. When participants could not read a letter, they were asked to guess. Testing stopped once the participant made three errors on one line. For each eye, the last line read with at least three correct letters was recorded and later converted into a LogMAR score. All participants had a LogMAR score which was less (i.e., better) than 0.5 (see **Table 1**), indicating visual acuity in the normal or near-normal range (Colenbrander, 2002, 2010).

Pelli-robson contrast sensitivity

To measure contrast sensitivity, participants stood 1 m from a Pelli-Robson contrast sensitivity chart (Pelli et al., 1988) and were instructed to read the letters from left-to-right for each eye, beginning with their better-seeing eye and then with both eyes. Testing continued until participants reported two out of three letters in a triplet incorrectly. Participants' log contrast sensitivity score was recorded as the last triplet for which they had correctly read at least two out of the three letters (**Table 1**), and all participants obtained scores within the range of normal (or better) for their age-group (Mäntyjärvi and Laitinen, 2001).

Randot stereo test

The Randot Stereo test (12%; Stereo Optical Company)[1] was used to assess stereovision (**Table 1**). The test booklet was held by the experimenter 16 inches from the participant. Participants were instructed to wear polarizing viewers (over their prescription glasses, if necessary) and report the forms or images displayed in the booklet. Seconds of arc at 16 inches were recorded for each subtest.

Auditory screening

Pure-tone audiometry

Given that declines in vestibular functioning may be associated with age-related hearing loss (Viljanen et al., 2009; Lin and Ferrucci, 2012; Zuniga et al., 2012; Campos et al., 2018; Carpenter and Campos, 2020; Lubetzky et al., 2020; Gabriel et al., 2022b) all older adult participants were screened to ensure normal hearing. Audiometric testing was completed as per the guidelines established by the International Organization of Standardization (ISO; ISO 8253-1, 1989). Pure-tone audiometry was used to determine audiometric hearing thresholds using a Grason-Stadler 61 Clinical Audiometer (GSI-61; Grason-Stadler Inc., Eden Prairie, MN) and Telephonics TDH-50P headphones (Telephonics Corporation, Farmingdale, NY). Testing was performed in a double-walled, sound-attenuating

1 https://www.stereooptical.com/

TABLE 1 Summary of baseline assessment measures.

	Older adults	Younger adults	*P*-value
Age	71.55 (6.70)	23.72 (5.18)	<0.001
Sex (*n*) (Female : Male)	9:2	8:3	–
ETDRS[a] (logMAR)			
Right	0.13 (0.06)	0.07 (0.15)	0.36
Left	0.21 (0.18)	0.10 (0.20)	0.26
Pelli-Robson (log-CS)			
Right	1.50 (0.14)	1.78 (0.13)	<0.001
Left	1.54 (0.13)	1.82 (0.20)	<0.001
Binocular	1.63 (0.05)	1.95 (0.09)	<0.001
Randot stereo test (Arcsec)			
Circles	36.82 (15.70)	30 (7.75)	0.22
Forms	340.91 (126.13)	250 (0)	0.04
Animals	140.91 (70.06)	113.64 (25.23)	0.29
PTA[b]	21.00 (14.43)	–	–
Speech Spatial, spatial and qualities hearing scale	7.76 (1.28)	–	–
MoCA[c]	28.30 (1.95)	–	–
TUG[d]	8.71 (1.42)	–	–

p-values represent the results of independent samples, two-tailed t-tests between the two groups.
With the exception of "Sex" which is reported as sample size (n), all scores and values are reported as averages with standard deviations in parentheses.
[a]ETDRS = Early Treatment Diabetic Retinopathy Study visual acuity test.
[b]PTA = Binaural Pure Tone Average; frequencies tested: 500, 1,000, 2,000, and 4,000 Hz, inclusive.
[c]MoCA, Montreal Cognitive Assessment.
[d]TUG, Timed-Up and Go Task.

booth (Industrial Acoustics Company, Inc., New York, NY). Frequencies tested were from 250 to 8,000 Hz, inclusive. Binaural pure-tone audiometric (PTA) thresholds were averaged across 500, 1,000, 2,000, and 4,000 Hz (**Table 1**). All but $n = 3$ older adult participants had an average binaural (and better ear) PTA average below the 25 dB HL cut-off for hearing loss (World Health Organization, 1991).

Speech, spatial and qualities of hearing scale

The Speech, Spatial and Qualities of Hearing Scale comprises three separate scales that measure subjective abilities to hear spoken language in day-to-day settings ("Speech"), to accurately perceive the direction or location of a sound source ("Spatial"), and to perceive the clarity of a given real-world auditory stimulus ("Qualities") (Gatehouse and Noble, 2004). The maximum average test score is 10 points, which is the total combined average of all tested items and indicates that the participant reported no hearing difficulties. All but 2 older adults completed this assessment (**Table 1**).

Cognition

Mild cognitive impairment was screened for using the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). The test assesses general cognitive abilities by examining several domains of cognitive functioning including attention, executive function, memory, and language and is scored out of a total of 30 points. In this study, level-of-education adjusted scores are reported and all participants obtained a score of 26 or higher (the common cut-off for mild cognitive impairment).

Mobility

Walking, balance, and mobility impairments were assessed using the Timed-Up-and-Go (TUG) task. Four older adults did not complete this task. For each trial, participants were seated in a chair with armrests and instructed to stand and walk at a comfortable pace to a clearly delineated point 3 m away, turn around, and sit back down again. Participants completed this task twice while the experimenter timed each trial. The cut-off time for community-dwelling older adults who are not at risk of falling is 12s or less (Shumway-Cook et al., 2000; Bischoff et al., 2003). All older adults who were tested met this criterion.

Experimental sessions

The combined experimental sessions for this study were roughly 7 h in duration per participant spread across three separate days within a 2-week span (see **Figure 1**): Day 1 (pre-training psychophysical heading judgments and posturography tasks followed by the first 250 training trials: 2.5 h), Day 2 (400 training trials: 2 h), Day 3 (250 training trials, post-training psychophysical heading judgments and posturography tasks: 2.5 h). The psychophysical tasks consisted of three conditions: visual-only, vestibular-only, visual-vestibular (combined and congruent; bimodal). Training trials were bimodal visual-vestibular trials with feedback provided.

Psychophysical heading judgment task

Stimuli and apparatus

Visual condition. Visual stimuli were rendered using the platform *Unity* version 2019.2.2f1 by Unity Technologies Inc. (Unity, 2019). The visual display consisted of a 120 × 120 × 50 m virtual space, presented through a stereoscopic head-mounted display (HMD; HTC Vive, 2016) whose AMOLED (active-matrix organic light-emitting diode) screen resolution was 1,080 × 1,200 pixels per eye, with a 90 Hz refresh rate, and 110° diagonal field of view. The virtual space was populated with 2,000 white spheres with a visual angle of 0.1° at its furthest distance (i.e., smallest size; **Figure 2A**). Forward visual self-motion was simulated by moving the spheres toward and past the viewer. The size of the spheres increased as their distance to the viewer decreased within the virtual space. The movement of the starfield followed a smooth sinusoidal acceleration and deceleration profile, beginning at 0 m/s and reaching a peak velocity of 0.4 m/s after 1 s with a peak acceleration of 0.628 m/s^2. The motion then decelerated to 0 m/s for another 1 s (**Figure 2C**). As such, each trial lasted 2 s, allowing participants to visually travel 0.4 m through the virtual starfield. At the start of each condition, participants were moved toward a point 25° to the left or right of straight ahead. This heading angle then widened or narrowed as a function of an adaptive staircase, described in more detail below. Participants remained securely seated within the laboratory for the duration of the experiment and used a videogame controller to submit their direction-discrimination responses ("left" or "right").

Vestibular condition. The experiment took place in one of the KITE-Research Institute's 8 m^3 fiberglass laboratories, which was mounted on a 6-degree-of-freedom hydraulic hexapod motion platform (Bosch-Rexroth HyMotion 11000; **Figure 2B**). Participants were seated on a specially constructed bucket-seat and secured with a four-point harness to reduce torso, head, and limb movement. The seat was cushioned to reduce vibrotactile cues to the body. Participants also rested their feet on a foam mat and wore an inflatable neck-pillow to further reduce movement of, and vibrotactile cues to, the neck and legs, thereby limiting the availability of extra-vestibular cues to motion. To reduce visual-input, and for consistency, participants continued to wear the head-mounted display that they wore during the visual-only condition, but the screen was dark (black) for the duration of each 2 s trial.

Motions were applied through movements of the motion platform, which used a smooth, sinusoidal acceleration and deceleration profile. The maximum acceleration and peak velocity were identical to those of the visual stimuli (i.e., ± 0.628

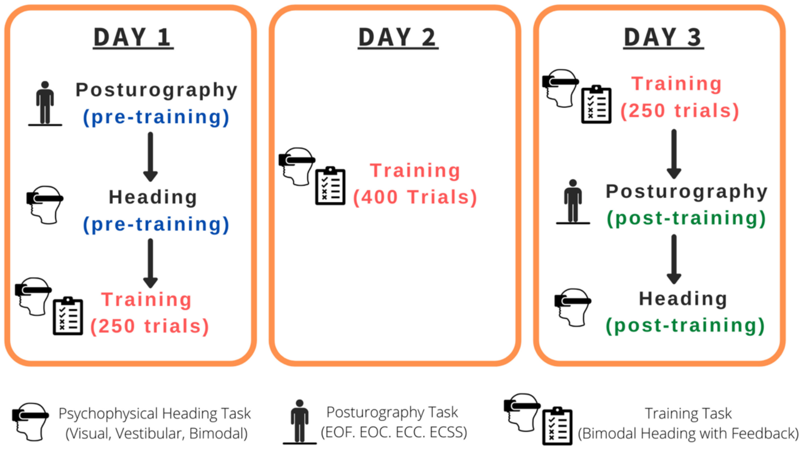

FIGURE 1
Order of the tasks completed for each participant. EOF, Eyes-open on a firm surface; EOC, Eyes-open on a compliant surface; ECC, Eyes-closed on a compliant surface; ECSS, Eyes-closed on a compliant surface, wearing passive sound-suppressing headphones.

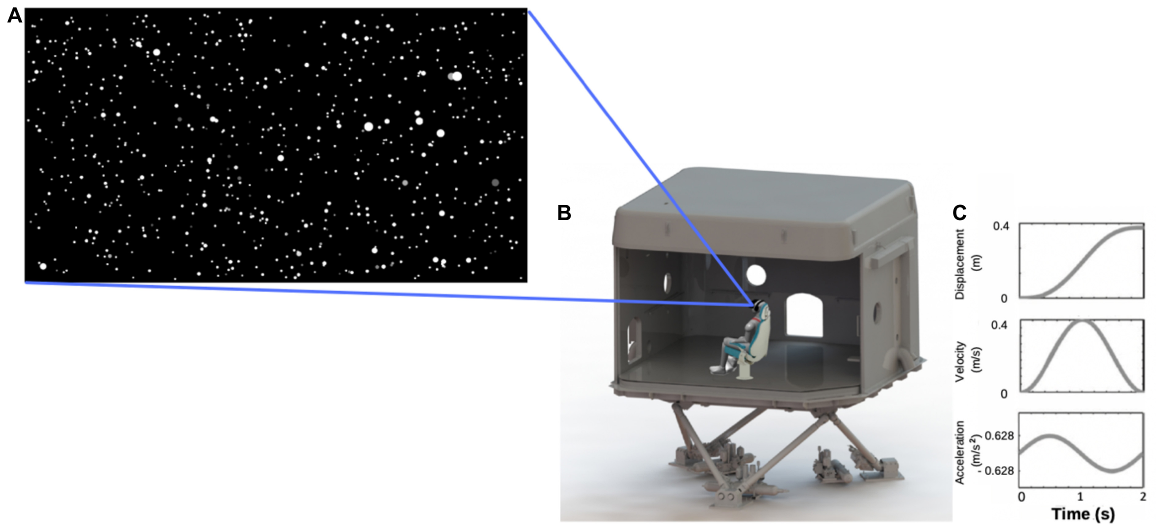

FIGURE 2
(A) Screen capture of the starfield viewed by participants; **(B)** illustration of a participant wearing a head-mounted display, seated in a chair located within the laboratory that was mounted on top of the 6-degree-of-freedom hydraulic hexapod motion platform; **(C)** motion profile for one trial.

m/s^2 and peak velocity of 0.4 m/s), meaning that the lab moved 0.4 m during every 2 s trial (see Figure 2C). This motion profile was similar to that used by Ramkhalawansingh et al. (2018) and is well above human acceleration detection thresholds. Again, this condition started with movement direction displaced 25° to the left or right of straight ahead, with the angle changing as a function of an adaptive staircase procedure throughout the trials, as described below.

Visual-vestibular (bimodal) condition. During the bimodal visual-vestibular condition, participants were presented with simultaneous, congruent visual and vestibular input, with the same motion profiles described above.

Procedure

Every participant completed, (1) pre-training psychophysical tasks (visual-only, vestibular-only, bimodal) and pre-training posturography tasks, (2) training task, and (3) post-training posturography tasks and post-training psychophysical tasks (visual-only, vestibular-only, bimodal), across 3 days (see Figure 1 for a summary of the timeline).

Psychophysical heading task

On Day 1 (pre-training) and Day 3 (post-training) we used two, randomly interleaved Parametric Estimation by Sequential Testing (PEST) staircases (Taylor and Creelman, 1967) for each of the three condition (visual-only, vestibular-only, and bimodal) separately to assess the bias and JND of participants' heading percepts. Each trial began with a yellow fixation cross in the VR display, followed by a movement. After each movement, a white fixation cross was presented straight ahead of the participant and the participant was instructed to indicate whether they had been moved to the left or right of straight ahead. Participants responded using a videogame controller by pressing and holding the joystick to the left or right for 2 s. The 2 s period was indicated by a green bar that grew to full size in 2 s (see **Figure 3**).

Conventional PEST rules were used to determine the next heading angle to be presented in each staircase (Taylor and Creelman, 1967; see **Figure 4A** for an example). The initial step size was 45° and the initial focus of expansion (FOE) of the headings were 25° to the left of straight ahead for one staircase, and 25° to the right of straight ahead for the other. The largest angle that could be presented was 50°. Each staircase terminated after 15 reversals. MATLAB was used to fit the data to a logistic function, where the 50% point represented participants' perceptual bias—the heading where they were equally likely to choose left or right of straight ahead (**Figure 4B**). The slope of that function (defined as ±23.1% of the bias) was used to represent the JND of their heading judgments. Each condition took approximately 20 min to complete and the order in which the three conditions were tested was randomized across the participants.

Training task

During the second half of the Day 1 session, during the full session on Day 2, and during the first half of the Day 3 session (see **Figure 1** for a timeline), participants completed 900 bimodal training trials total. During each training trial, participants were physically and visually moved (congruent and bimodal) in a direction either to the right or left of straight-ahead and asked to judge their heading direction relative to straight-ahead. Following their "left" or "right" responses they received feedback of either "Correct" in green, or "Incorrect" in red on the visual display. The heading angles were chosen randomly from a range centered around true straight-ahead (0°), ±67% of their angular bias from the pre-training bimodal psychophysical heading estimation task. Specifically, we took 67% of each participant's bias and presented them with values chosen randomly from the range of plus and minus this value (e.g., a participant with a perceptual bias of +10 would be presented with heading angles between −6.7 and +6.7° from true straight-ahead). The training range was chosen to ensure that the deviations from true straight-ahead were not too easy (in which case there would be no added value from receiving feedback) or too difficult (i.e., imperceptible). Guidance for these values was also provided by the training range selected by Hartmann et al. (2013).

Posturography task

Immediately before the pre-training and post-training psychophysical heading task on Days 1 and 3, participants completed a posturography task. Participants were asked to stand on a force plate (AMTI MSA-6 MiniAmp strain gage amplifier) for 30 s (Scoppa et al., 2013). The center of pressure (COP) path length (cm), velocity (cm/s), and velocity root-mean-square (RMS; cm/s) were measured during quiet standing. Participants stood with feet parallel and wore a loose harness throughout the procedure to protect against a potential loss of balance. This posturography task was completed under four counterbalanced conditions. Participants either stood (1) directly on the forceplate with their eyes open on a firm surface (EOF; "firm surface"), (2) with their eyes open while standing on a piece of high-density, compliant foam placed directly on the forceplate (EOC; "compliant surface"; AIREX, Balance-Pad; 50 × 41 × 6 cm; density = 55 kg/m^2), (3) with their eyes closed on the compliant surface (ECC), or (4) with their eyes closed on the compliant surface, while wearing sound-suppressing headphones (ECSS).

The forceplate data were collected at a sampling rate of 1,000 Hz. The first 5 s of the data were removed for each condition and the remaining data were passed through a 2nd order zero-lag dual-pass Butterworth filter with a 6 Hz cut-off frequency. MATLAB was used to extract mean COP path lengths, velocity, and velocity-RMS. Path length was defined as the absolute total length of sway in centimeters recorded in each condition, average velocity as the COP excursion divided by trial time, and velocity-RMS as the square-root of the mean of squares of the velocity measures. Longer path lengths, and higher velocities and velocity-RMS indicated more variable postural sway.

Data analysis

All analyses were run using the biases and JNDs obtained as described above in R 3.6.0 (R Core Team, 2017). While the analyses presented below use raw, unwinsorized data, analyses with winsorized data can be found in **Supplementary material 1**. Two separate mixed-factorial ANOVAs, 2 (Age Group; younger, older) × 3 (Psychophysical Condition; visual-only, vestibular-only, bimodal) × 2 (Session; pre-training, post-training), were conducted to evaluate the extent to which participants' perceptual biases and JNDs (dependent variables) changed in the older and younger groups following training, for each of the three psychophysical conditions (visual-only, vestibular-only, bimodal). Post-hoc *t*-tests were Tukey-corrected for

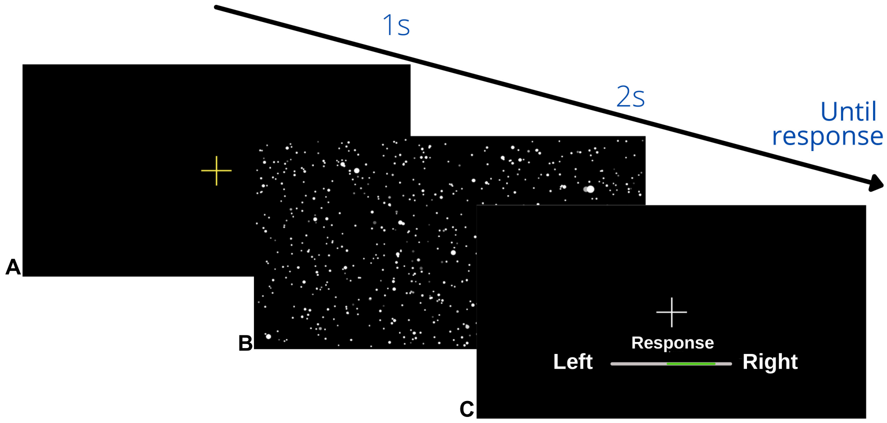

FIGURE 3
Schematic overview of visual display during the psychophysical heading task: **(A)** initial yellow fixation cross to signal the start of the trial, **(B)** heading movement: the starfield was present for the visual, bimodal and training trials, but during the vestibular condition the display was black, **(C)** response screen: participants pressed and held their response until the bar on the display was filled in green in the direction of their heading judgment (left/right) (2 s). This sequence repeated until the end of the block.

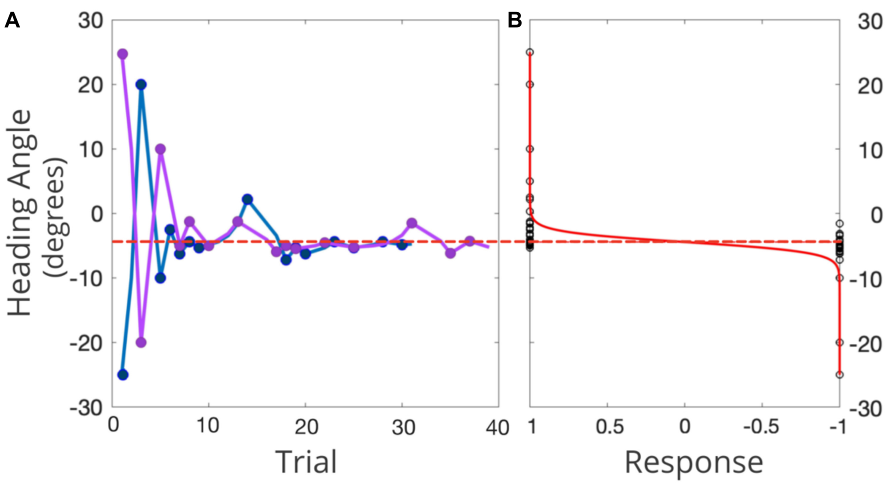

FIGURE 4
(A) Example of two interleaved PEST staircases for one representative participant in one condition. The right-starting PEST is plotted in pink and the left-starting PEST in blue. 0° represents straight-ahead, with positive values representing rightward angles, and negative values leftward angles. The red dashed line represents the participants' bias as inferred from the logistic function. **(B)** Black circles represent the participant's response (1 = right, −1 = left) for each presented heading angle, in the solid red line is the fitted psychometric function. The dotted red line represents the midpoint of this function (i.e., participant's perception of straight ahead).

multiple comparisons. We also examined the magnitude of change in biases and JNDs for these participants, which we calculated using difference scores pre- vs. post-training. Specifically, we took the absolute value obtained post-training and subtracted it from the absolute value obtained pre-training [$Bias_{DifferenceScore} = abs\,(Bias_{Session1}) - abs\,(Bias_{Session3})$; $JND_{DifferenceScore} = abs\,(JND_{Session1}) - abs\,(JND_{Session3})$]. Positive scores indicated an improvement (biases or JNDs larger in Session 1 than in Session 3), while negative values indicate the opposite. We conducted two different 2 (Age Group) by 3 (Psychophysical Condition Difference Score) mixed-factorial ANOVAs with bias or precision as the dependent variable.

Importantly, three out of 11 older adults in this study were unable to complete the visual-only condition during the pre-training session. Specifically, the data obtained from the left- and right-starting PESTs in these three older adult participants for the visual-only condition did not converge due to essentially random responding (see Supplementary material 2 for their raw data). The experimenter re-explained the task to them numerous times to ensure that it was not a problem of task comprehension. They were also able to do the other two pre-training conditions (vestibular and bimodal). As such, we have omitted these participants' heading data from the group analysis, and instead report their data separately.

We conducted pairwise *t*-tests to assess whether the difference scores, when collapsing across Age Groups, were significantly different from zero (i.e., no training effect). We also report the number of participants who demonstrated numeric post-training improvements, both including and excluding the three older adults who were unable to complete the visual-only condition pre-training (see **Supplementary material 3**).

Using a Maximum Likelihood Estimation (MLE) model we calculated the predicted optimal JNDs and biases for each condition and compared these predictions to the observed values using paired-sample *t*-tests.

For the training data, each of the 900 trials were coded as "1" for correct, and "0" for incorrect. This classification allowed us to calculate the number of correct responses obtained by participants within a given bin. Specifically, the percent correct for every 50 trials was calculated creating 18 bins of 50 trials where larger values indicated a greater percentage of correct responses than smaller values. Average of percent correct responses were computed for each of the 3 days separately (i.e., Day 1 was 250 trials, Day 2 was 400 trials, and Day 3 was 250 trials). A 2 (Age Group; younger, older) × 3 (Days; 1, 2, 3) mixed-factorial ANOVA was conducted to examine the extent to which performance changed over the course of training and whether there were any age-related differences.

With respect to the posturography measures, three mixed-factorial ANOVAs, 2 (Age Group; younger, older) × 4 (Posturography Condition; EOF, EOC, ECF, ECSS) × 2 (Session; pre-training, post-training) were conducted for COP (1) path length, (2) velocity, and (3) velocity-RMS. Post-hoc *t*-tests used were Tukey-corrected for multiple comparisons. Posturography data from three younger adults were excluded from all analyses due to a technical error during Session 1.

Results

Heading

Just-noticeable difference values

The pre-and post-training JNDs are shown in **Figure 5**. The 2 (Age Group) × 3 (Psychophysical Condition) × 2 (Session) mixed-factorial ANOVA on JND values revealed a main effect of Session [$F(1, 17) = 9.45$, $p = 0.007$], indicating that pre-training JNDs were significantly larger (i.e., worse) than post-training JNDs. It also showed a main effect of Condition [$F(1.48, 25.14) = 5.89$, $p = 0.013$], with *post-hoc t*-tests revealing that JNDs in the vestibular-only condition were significantly smaller than the JNDs in the visual-only condition [$t(17) = -2.72$, $p = 0.037$], and results trending to suggest that JNDs in the bimodal condition were significantly smaller than those in the visual-only condition [$t(17) = -2.54$, $p = 0.053$] (**Figure 5**).

No other main effects or interactions were significant. This includes the Session × Condition interaction which was only trending, [$F(1.45, 24.65) = 3.04$, $p = 0.080$], with *post-hoc t*-tests showing this trend to be driven by the visual-only data, [$t(17) = 2.56$, $p = 0.020$].

Just-noticeable differences: Absolute difference scores

For each of the conditions, we took the absolute value of the post-training JND and subtracted it from the absolute pre-training JND (i.e., Session 1 minus Session 3). Positive scores thus indicate improvement (JNDs being larger, or worse, in Session 1 than Session 3), while negative values indicate the opposite. A 2 (Age Group) × 3 (Condition Difference Score) mixed-factorial ANOVA showed a significant main effect of Condition, [$F(1.36, 27.14) = 4.43$, $p = 0.034$]. Tukey-corrected *post-hoc t*-tests showed the visual condition to be driving this effect—with larger difference scores (improvement) for the visual condition compared to the bimodal condition [$t(40) = -2.74$, $p = 0.024$], and trending significance for the vestibular condition [$t(40) = -2.38$, $p = 0.057$], indicating significantly greater precision for the visual condition following training (**Figure 6**).

We then conducted three separate pairwise *t*-tests to compare each condition's JND difference scores (visual, vestibular, bimodal) with "0," in order to assess whether the changes in JNDs following training differed significantly from zero. The results showed that the post-training reduction in JNDs in the visual condition was significantly different from 0, [$t(21) = -2.728$, $p = 0.012$] but the vestibular-only and bimodal conditions were not significantly different from 0 ($p > 0.05$).

We also tallied the number of participants who demonstrated numeric post-training improvements (lower JND) for each of the three sensory conditions (see **Supplementary material 3**). Notably, while 75% of older adults (or 82% if including the three older adults who could not complete the visual-only heading task) demonstrated lower visual-only JNDs post-training, only 64% of younger adults demonstrated lower visual-only JNDs post-training.

Bias values

The pre-and post-training bias values are shown in **Figure 7**. A 2 (Age Group) × 3 (Condition) × 2 (Session) mixed-factorial ANOVA on perceptual biases showed a significant main effect of Condition [$F(1.44, 24.41) = 5.58$, $p = 0.017$], with *post-hoc t*-tests revealing significantly larger biases for the bimodal condition relative to the vestibular only condition [$t(40) = -3.324$, $p = 0.011$], but no significant differences for the bimodal condition relative to the visual-only condition, or the bimodal condition compared to the vestibular-only condition (p's both > 0.05). There were no other

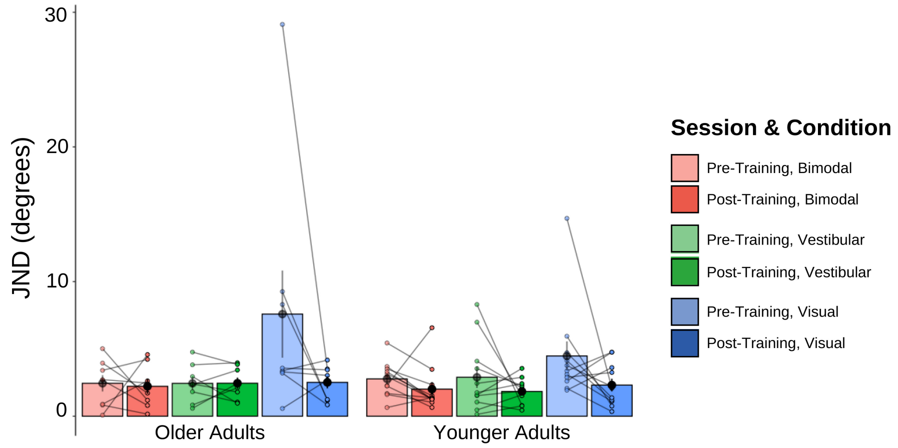

FIGURE 5
Mean and individual JND values plotted for each Age Group and sensory condition, pre-training (lighter shades) and post-training (darker shades). Individual data points are also plotted, with lines connecting each participant's pre-training JND to their post-training JND for each of the three sensory conditions (visual-only, vestibular-only, bimodal). Black dots represent means, plotted with standard error bars.

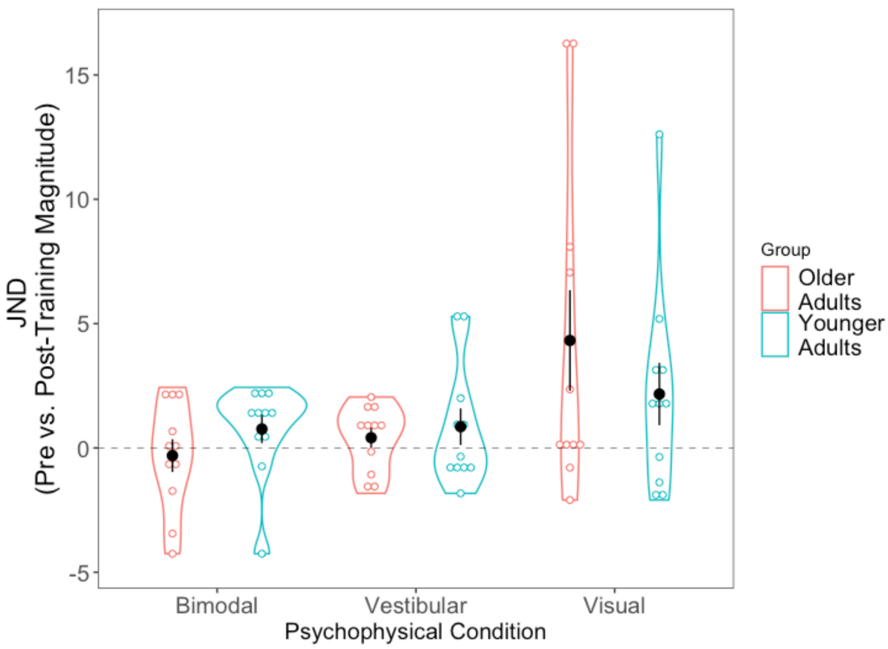

FIGURE 6
Difference scores for JNDs, across all three psychophysical conditions, for each of the two age groups. Black dots represent means, and error bars represent standard error. Individual data points are represented by the blue (younger adults) and red (older adults) circles. Positive values indicate improvement. Black dashed line represents "0" (i.e., no change after training).

significant main effects or interactions (i.e., no other effects of training).

Bias: Absolute difference scores

Absolute difference scores (pre-post) were calculated for the biases in the same way that they were for the JNDs. Getting closer to true straight ahead after training would result in a positive score. The 2 (Age Group) × 3 (Condition Difference Score) mixed-factorial ANOVA on perceptual biases did not show any significant main effects or interactions. We then conducted three separate pairwise *t*-tests to compare each condition's difference bias scores (visual, vestibular, bimodal) with "0," in order to assess whether changes in pre- and post-training biases differed significantly from zero. The results

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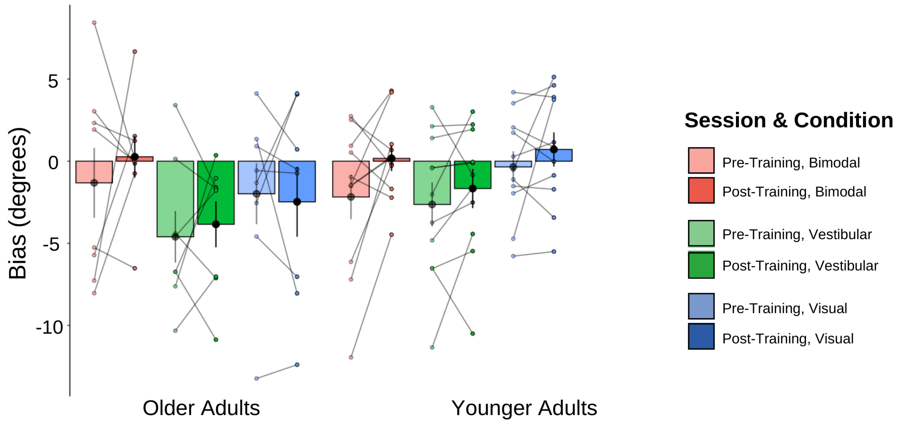

FIGURE 7
Biases plotted for each Age Group and sensory condition. Pre-training values (lighter shades) and post-training (darker shades). Individual data points are also plotted, with lines connecting each participant's pre-training bias to their post-training bias, for each of the three sensory conditions (visual-only, vestibular-only, bimodal). Black dots represent means, plotted with standard error bars.

(**Figure 8**) showed that only the bimodal bias was significantly greater than 0 (i.e., closer to true straight ahead) following training, [$t(21) = -2.149$, $p = 0.043$].

As with the JNDs, we tallied the number of participants who demonstrated numeric post-training improvements in bias and report them for each sensory condition in **Supplementary material 3**.

Maximum likelihood estimation

We calculated predicted optimal JNDs for both older and younger adults using an MLE model:

$$JND_{Bimodal} = \sqrt{\frac{JND^2_{Visual} + JND^2_{Vestibular}}{JND^2_{Visual} \times JND^2_{Vestibular}}} \quad \ldots\ldots\ldots \quad (1)$$

These were calculated for the pre-training and post-training bimodal session values separately (**Figure 9**). Paired sample t-tests revealed that older adults' predicted JNDs did not differ significantly from their observed JNDs for either the pre-training session [$t(7) = 0.776$, $p = 0.463$] or the post-training session [$t(7) = -1.855$ $p = 0.986$]. For the younger adults, while predicted JNDs were significantly smaller (i.e., more precise) than their observed JNDs for the pre-training session [$t(10) = -2.97$, $p = 0.014$], we did not observe a significant difference in the post-training session [$t(10) = -2.08$ $p = 0.064$].

Older adults who were unable to estimate visual heading pre-training

Importantly, three of our older adult participants were not able to judge their heading in the visual-only condition before training and provided "left" and "right" responses essentially randomly during the task, despite understanding the instructions. Thus, their left- and right-starting PESTs for the visual-only condition did not converge, and we could not obtain meaningful JND or bias values for these participants. As such, they were removed from the group-level analyses described above. They were, however, able to perform the visual-only heading task following the training, indicating a profound improvement as a result of training. We report their individual data here in **Tables 2A,B**. Further details of their performance can be found in **Supplementary material 2**.

Training data

A 2 (Age Group) × 3 (Days) mixed-factorial ANOVA did not reveal any significant main effects of Days [$F(1.41, 21.13) = 0.12$, $p = 0.82$], Age Group [$F(1, 15) = 0.11$, $p = 0.74$], or interaction effects [$F(1.41, 21.13) = 2.15$, $p = 0.15$] (**Figure 10**).

Posturography task

A 2 (Age Group) × 4 (Posturography Condition) × 2 (Session) mixed-factorial ANOVA, with COP path length as the dependent variable was conducted (**Figure 11**). Data from the three older adults who could not estimate their visual pre-training heading were removed from these analyses. There was a main effect of Age Group [$F(1,14) = 5.41$, $p = 0.036$], indicating that older adults had significantly longer COP path lengths (M = 69.7 cm, SD = 42.3) than younger adults (M = 53.6 cm, SD = 30.2). There was also a main effect of Posturography Condition $F(1.54, 21.50) = 48.87$, $p < 0.001$], with pairwise comparisons showing that more difficult postural conditions produced significantly longer COP path lengths than each of the easier conditions ($p < 0.05$ between all conditions), with the exception of ECC compared to ECSS conditions ($p >= 0.999$). No other main effects or interactions were significant.

We conducted two additional mixed-factorial ANOVAs [2 (Age Group) × 4 (Posturography Condition) × 2

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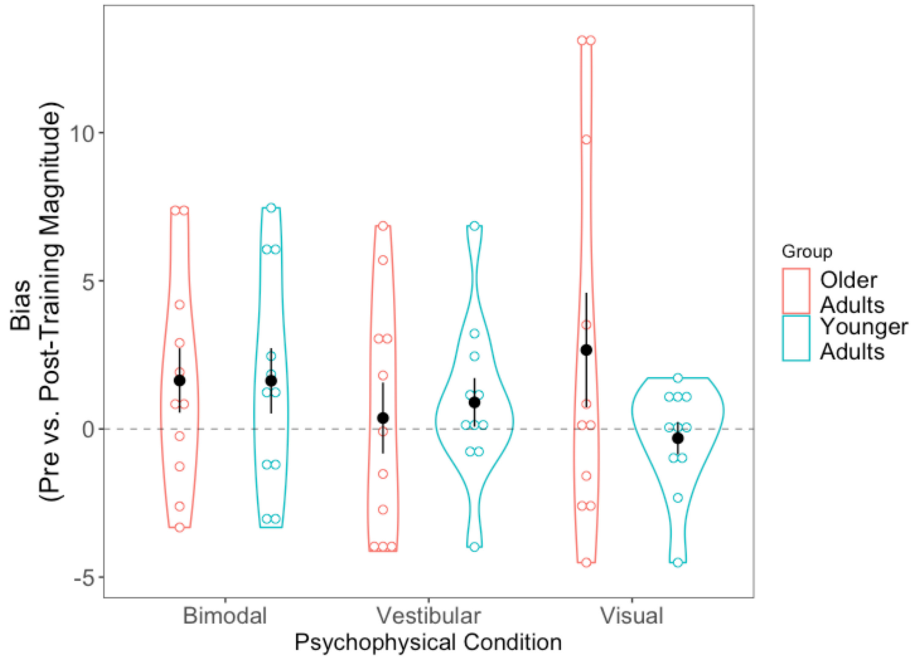

FIGURE 8
Difference scores for bias, across all three psychophysical conditions, for each of the two age groups. Black dots represent means, and error bars represent standard error. Individual data points are represented by the blue (younger adults) and red (older adults) circles. Black dashed line indicates a bias no closer to true straight ahead following training.

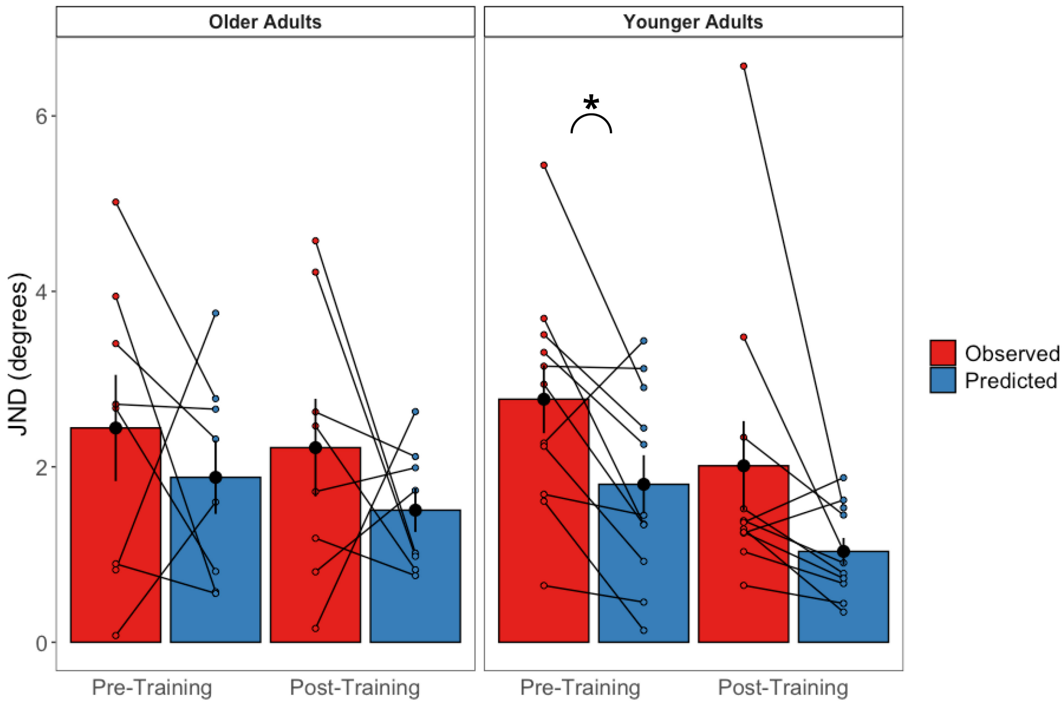

FIGURE 9
Observed bimodal JNDs relative to predicted bimodal JNDs in older (left panel) and younger (right panel) adults. Black dots represent the averages and error bars represent standard errors. Colored dots represent individual participant's scores. *$p < 0.05$.

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TABLE 2A JNDs for the three older adults who could not perform the visual-only heading task pre-training, as well as the group average and standard deviations for the rest of the older adult group.

JNDs	Pre-training			Post-training		
	Visual	Vestibular	Bimodal	Visual	Vestibular	Bimodal
Older Adult 1	–	2.14	0.48	36.16	0.93	0.97
Older Adult 2	–	1.68	0.25	25.10	0.37	3.69
Older Adult 3	–	5.85	1.20	3.54	3.80	1.29
Average of other older adults (*n* = 8)	10.14 (8.18)	2.65 (1.61)	1.95 (1.67)	5.79 (7.11)	2.24 (1.34)	2.15 (1.48)

JNDs are given in degrees. The averages of the other older adults' data are presented in the last row along with the corresponding standard deviations.

TABLE 2B Biases for the three older adults who could not perform the visual-only heading task pre-training, as well as the group average and standard deviations for the rest of the older adult group.

Biases	Pre-training			Post-training		
	Visual	Vestibular	Bimodal	Visual	Vestibular	Bimodal
Older Adult 1	–	−1.68	−1.44	1.24	−6.00	−4.89
Older Adult 2	–	−0.67	1.51	6.71	−4.47	−4.12
Older Adult 3	–	1.86	−0.94	−7.03	−1.03	−0.75
Average of other older adults (*n* = 8)	−1.97 (5.27)	−4.60 (4.34)	−1.32 (6.02)	−2.47 (6.02)	−3.84 (3.96)	0.27 (3.61)

Biases are given in degrees. The averages of the other older adults' data are presented in the last row along with the corresponding standard deviations.

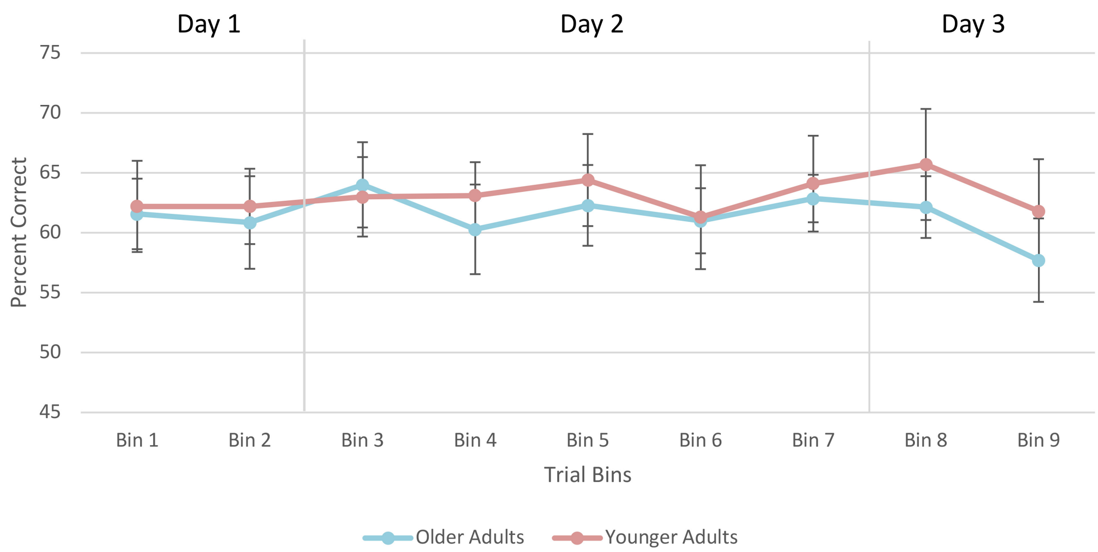

FIGURE 10
Average percent correct on the training trials for older and younger adults. Values for each bin represent the average percent correct for each 100 trials. Error bars represent standard error. Participants completed 250 trials on Day 1, 400 trials on Day 2, and 250 trials on Day 3. Older adult data are plotted in blue, and younger adult data in orange.

(Session)] with COP velocity and velocity-RMS as the dependent variables. Like the results of COP path length, older adults had larger velocity and velocity-RMS, compared to younger adults, with a similar main effect of Posturography Condition as described above, but no effect of training.

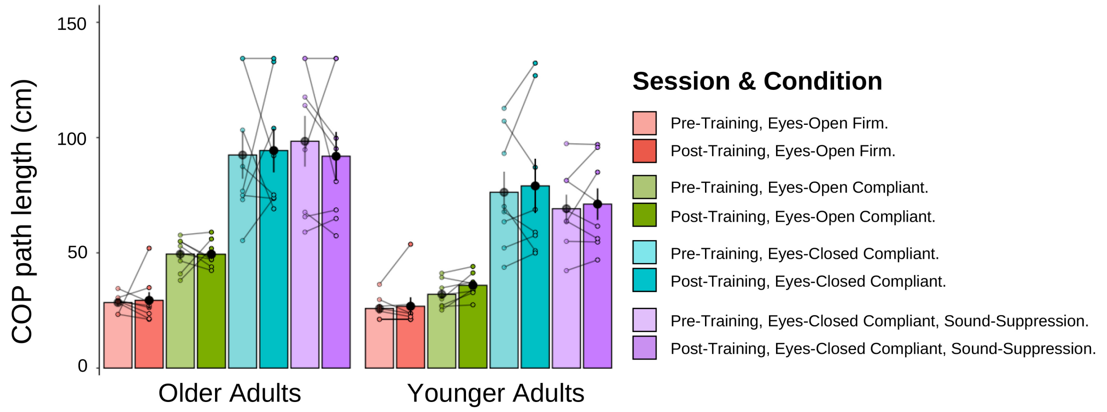

FIGURE 11
Mean COP path length (cm) for older and younger adults, pre-training (lighter shades) and post-training (darker shades). The individual data points are plotted for all four posturography conditions, with lines connecting each participant's pre-training COP path length to their post-training COP path length. Black dots represent means, plotted with standard error bars.

Discussion

In this study, we examined whether older and younger adults would show reduced biases and/or smaller JNDs (i.e., increased precision) in their heading estimates following a visual-vestibular heading training task. Overall, we found a main effect of training for JND values (increased precision post-training relative to pre-training). Using difference scores, we observed that these training-related effects were only found in the visual-only condition and not in the bimodal or vestibular-only conditions. In line with previous studies investigating visual heading perception in older adults (Warren et al., 1989; Ramkhalawansingh et al., 2018) we found that three of our older adult participants (27% of our sample) were unable to perform the visual-only heading discrimination task in the pre-training phase of our study (Warren et al., 1989; Ramkhalawansingh et al., 2018). Importantly, however, all three of these participants were able to complete the visual-only heading task successfully after training (**Table 2**). We did not find improvements during the around-threshold training sessions, nor were there any changes in participants' postural stability following training. Only the older (not younger) adults demonstrated a non-significant difference between predicted and obtained pre-training JNDs, which suggests optimal integration, in line with MLE model predictions. Both groups, however, showed optimal integration following training.

Effects of training

Based on previous training studies (Hartmann et al., 2013; Fitzpatrick et al., 2015; Klaus et al., 2020; Diaz-Artiles and Karmali, 2021), we expected that we would observe improvements in heading perception following training. In support of these hypotheses, we did observe a main effect of training indicating that JNDs were reduced post-training compared to pre-training, with these training effects being mainly attributed to improvements in the vision-only condition. Following training, we also noted a profound improvement in the performance of three older adults who originally could not perform the visual-only task at all pre-training. This pronounced training effect for the visual-only condition could suggest that the sensory system with the poorest pre-training precision, in this case vision, benefited significantly from training with a bimodal input that included an additional, more precise sensory input (vestibular). While a unimodal training study would be needed to confirm this speculation, this interpretation is consistent with recent, mounting evidence demonstrating that multisensory training can facilitate perceptual improvements for unisensory tasks (Seitz et al., 2006; Von Kriegstein and Giraud, 2006; Shams and Seitz, 2008; Shams et al., 2011). Specifically, previous studies have shown that the benefits observed for unisensory tasks following multisensory training tend to exceed those obtained following unisensory training. For instance, in a recent audio-visual training study (Seitz et al., 2006), participants were provided with trial-by-trial feedback on a motion direction-detection task (i.e., "which of two intervals contained directional rather than random motion"). Participants who were trained on the audio-visual task demonstrated greater and faster improvements when tested on the visual-only motion task, relative to participants who were trained with only visual input. These results suggest that multisensory training might promote better learning for unisensory tasks than unisensory training alone.

Part of the reason we may have observed improvements during the post-training phase (relative to pre-training) but not during the training trials themselves may be because the training trials provided participants with subthreshold stimuli (i.e., ±67% of each participants' bias). This method is consistent with previous multisensory training literature which found that sub-threshold, but not at-threshold or suprathreshold training, is associated with perceptual improvements.

While it is unclear why multisensory training may promote greater training benefits than unisensory training, it has been suggested that while unisensory training engages only primary sensory regions, multisensory learning engages several primary sensory regions (e.g., both auditory and visual cortices), as well as multisensory regions (e.g., parietal cortex), and functional as well as structural connections among these regions (Shams and Seitz, 2008). Such additional activation could account for some of the benefits observed from multisensory training, especially as it compares to unisensory training. In the present study, training would likely have recruited visual, vestibular, and bimodal regions (e.g., VIP, MSTd, insula; Fasold et al., 2002; Angelaki and Cullen, 2008; Lopez and Blanke, 2011) as well as connections among those regions. Furthermore, compared to training with only individual sensory inputs, multisensory inputs provide more information about a given object or event which could then be used to increase perceptual precision (Burr and Gori, 2011) and allow for calibration among the senses during training. This would be particularly beneficial for a sensory input that has a lower reliability when combined with a sensory input that has higher reliability, as was the case in the current study: visual-only heading perception was less precise than vestibular-only heading perception, especially for many of our older participants. In the present study, participants may have demonstrated greater post-training improvements in the visual-only condition (i.e., the least reliable pre-training condition), since this sensory condition was paired with redundant and congruent information from a more reliable sensory cue (i.e., vestibular) during training. Future studies could add a unisensory training condition (i.e., visual alone or vestibular alone) to examine whether multisensory training is indeed more effective than unisensory training in the visual-vestibular domain.

In the context of aging, very little is currently understood about whether older adults can benefit to the same or even greater extent from multisensory training as younger adults, given their often poorer overall precision and their heightened sensory integration (Ramkhalawansingh et al., 2018). This study is the first, to our knowledge, to show that self-motion perception, specifically in the context of visual-vestibular integration, can be improved following training. Interestingly, on average, the effects were not statistically different between age groups but most notable for three older adults who were initially completely unable to estimate their heading in the visual-only heading task pre-training, but were able to perform this task well post-training. Likewise, when examining difference scores, we found that participants showed improved (i.e., lower) JNDs for the visual-only condition relative to the bimodal after training, with results trending to suggest they were also lower than the JNDs in the vestibular condition ($p = 0.057$). The visual-only condition was also the only condition for which the training-related effects (difference scores) were significantly greater than zero.

Transfer of training to standing balance stability

We also assessed the extent to which multisensory heading perception training might lead to changes in a standing balance task, given that both tasks rely on the precise integration of visual and vestibular cues. We did not, however, find any significant effects of bimodal heading training on balance performance. To our knowledge, there are no studies that have considered the effects of multisensory perceptual training on postural control. It has been shown, however, that poorer standing balance in older adults is associated with an increased susceptibility to the sound-induced flash illusion (Stapleton et al., 2014) and that training postural stability reduces susceptibility to such illusions (Merriman et al., 2015), suggesting that multisensory processing abilities may underlie both types of tasks.

One possible reason why effects of training did not transfer to postural control could be that our static posturography task may have been too easy and participants may have been able to take sufficient advantage of other, non-trained sensory inputs to successfully complete the tasks (e.g., proprioceptive/tactile). As such, using a more complex test of postural stability that would further challenge visual and/or vestibular abilities, such as dynamic posturography following a balance perturbation, might reveal some effects of visual-vestibular training (Baloh et al., 1998; Prosperini and Pozzilli, 2013).

Conclusion

This study examined whether younger and older adults could be trained to better perceive self-motion (heading) after completing a multisensory training paradigm. We found that both younger and older adults became more precise in their visual-only performance following bimodal training. This improvement did not transfer to a static posturography task. Our results may have implications for mobility rehabilitation strategies, particularly in contexts when some sensory cues to self-motion are poor while others remain reliable.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the University Health Network Research Ethics Board (Protocol Number: 18-5331.0) and University of Toronto Research Ethics Board (Protocol number: 00037394). The patients/participants provided their written informed consent to participate in this study.

Author contributions

LH, DH, and JC conceived the study. GG, LH, DH, and JC helped design the study. GG and MP collected the data. GG, LH, and JC analyzed and interpreted the data. GG and JC drafted the manuscript. All authors contributed to critically revising the manuscript.

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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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.816512/full#supplementary-material

References

Angelaki, D. E., and Cullen, K. E. (2008). Vestibular system: the many facets of a multimodal sense. *Ann. Rev. Neurosci.* 31, 125–150. doi: 10.1146/annurev.neuro.31.060407.125555

Angelaki, D. E., Gu, Y., and DeAngelis, G. C. (2009). Multisensory integration: psychophysics, neurophysiology, and computation. *Curr. Opin. Neurobiol.* 19, 452–458. doi: 10.1016/j.conb.2009.06.008

Angelaki, D. E., Gu, Y., and DeAngelis, G. C. (2011). Visual and vestibular cue integration for heading perception in extrastriate visual cortex. *J. Physiol.* 589, 825–833. doi: 10.1113/jphysiol.2010.194720

Baloh, R. W., Jacobson, K. M., Beykirch, K., and Honrubia, V. (1998). Static and dynamic posturography in patients with vestibular and cerebellar lesions. *Arch. Neurol.* 55, 649–654. doi: 10.1001/archneur.55.5.649

Bennett, P. J., Sekuler, R., and Sekuler, A. B. (2007). The effects of aging on motion detection and direction identification. *Vis. Res.* 47, 799–809. doi: 10.1016/j.visres.2007.01.001

Bermúdez Rey, M. C., Clark, T. K., Wang, W., Leeder, T., Bian, Y., and Merfeld, D. M. (2016). Vestibular perceptual thresholds increase above the age of 40. *Front. Neurol.* 7:162. doi: 10.3389/fneur.2016.00162

Beylergil, S. B., Karmali, F., Wang, W., Bermúdez Rey, M. C., and Merfeld, D. M. (2019). Vestibular roll tilt thresholds partially mediate age-related effects on balance. *Prog. Brain Res.* 248, 249–267. doi: 10.1016/bs.pbr.2019.04.019

Billino, J., Bremmer, F., and Gegenfurtner, K. R. (2008). Differential aging of motion processing mechanisms: Evidence against general perceptual decline. *Vis. Res.* 48, 1254–1261. doi: 10.1016/j.visres.2008.02.014

Bischoff, H. A., Stähelin, H. B., Monsch, A. U., Iversen, M. D., Weyh, A., von Dechend, M., et al. (2003). Identifying a cut-off point for normal mobility: a comparison of the timed "up and go" test in community-dwelling and institutionalised elderly women. *Age Ageing* 32, 315–320. doi: 10.1093/ageing/32.3.315

Burr, D., and Gori, M. (2011). "Multisensory integration develops late in humans," in *The Neural Bases of Multisensory Processes*, eds M. M. Murray and M. T. Wallace (Boca Raton, FL: CRC Press), 345–362. doi: 10.1201/b110 92-23

Butler, J. S., Campos, J. L., and Bülthoff, H. H. (2015). Optimal visual–vestibular integration under conditions of conflicting intersensory motion profiles. *Exp. Brain Res.* 233, 587–597. doi: 10.1007/s00221-014-4136-1

Butler, J. S., Smith, S. T., Campos, J. L., and Bülthoff, H. H. (2010). Bayesian integration of visual and vestibular signals for heading. *J. Vis.* 10, 23–23. doi: 10.1167/10.11.23

Campos, J. L., Ramkhalawansingh, R., and Pichora-Fuller, M. K. (2018). Hearing, self-motion perception, mobility, and aging. *Hear. Res.* 369, 42–55. doi: 10.1016/j.heares.2018.03.025

Carpenter, M. G., and Campos, J. L. (2020). The effects of hearing loss on balance: a critical review. *Ear Hear.* 41, 107S–119S.

Center for Disease Control (2018a). *10 Leading Causes of Injury Deaths by Age Group Highlighting Unintentional Injury Deaths, United States*. Atlanta: Center for Disease Control.

Center for Disease Control (2018b). *Leading Causes of Nonfatal Injury Reports*. Atlana: Center for Disease Control.

Cienkowski, K. M., and Carney, A. E. (2002). Auditory-visual speech perception and aging. *Ear Hear.* 23, 439–449. doi: 10.1097/00003446-200210000-00006

Colenbrander, A. (2002). "Aspects and ranges of vision loss," in *Proceedings of the internacional council of ophthalmology* at the 29th international congress of ophthalmology, Sydney, NSW.

Colenbrander, A. (2010). Assessment of functional vision and its rehabilitation. *Acta Ophthalmol.* 88, 163–173.

de Dieuleveult, A. L., Siemonsma, P. C., van Erp, J. B. F., and Brouwer, A.-M. (2017). Effects of aging in multisensory integration: a systematic review. *Front Aging Neurosci.* 9:80. doi: 10.3389/fnagi.2017.00080

Diaconescu, A. O., Hasher, L., and McIntosh, A. R. (2013). Visual dominance and multisensory integration changes with age. *NeuroImage* 65, 152–166. doi: 10.1016/j.neuroimage.2012.09.057

Diaz-Artiles, A., and Karmali, F. (2021). Vestibular precision at the level of perception, eye movements, posture, and neurons. *Neuroscience* 468, 282–320. doi: 10.1016/J.NEUROSCIENCE.2021.05.028

Duffy, C. J. (2009). Visual motion processing in aging and Alzheimer's disease: Neuronal mechanisms and behaviorfrom monkeys to man. *Ann. New York Acad. Sci.* 1170, 736–744. doi: 10.1111/j.1749-6632.2009.04021.x

Early Treatment Diabetic Retinopathy Study Research Group (1985). Photocoagulation for diabetic macular edema: early treatment diabetic retinopathy study report number 1 early treatment diabetic retinopathy study research group. *Arch. Ophthalmol.* 103, 1796–1806. doi: 10.1001/archopht.1985.01050120030015

Ernst, M. O., and Banks, M. S. (2002). Humans integrate visual and haptic information in a statistically optimal fashion. *Nature* 415, 429–433. doi: 10.1038/415429a

Ernst, M. O., and Bülthoff, H. H. (2004). Merging the senses into a robust percept. *Trends Cogn. Sci.* 8, 162–169. doi: 10.1016/j.tics.2004.02.002

Fasold, O., Von Brevern, M., Kuhberg, M., Ploner, C. J., Villringer, A., Lempert, T., et al. (2002). Human vestibular cortex as identified with caloric stimulation in functional magnetic resonance imaging. *NeuroImage* 17, 1384–1393. doi: 10.1006/NIMG.2002.1241

Fetsch, C. R., Deangelis, G. C., and Angelaki, D. E. (2010). Visual-vestibular cue integration for heading perception: applications of optimal cue integration theory. *Eur. J. Neurosci.* 31, 1721–1729. doi: 10.1111/j.1460-9568.2010.07207.x

Fetsch, C. R., Turner, A. H., DeAngelis, G. C., and Angelaki, D. E. (2009). Dynamic reweighting of visual and vestibular cues during self-motion perception. *J. Neurosci.* 29, 15601–15612. doi: 10.1523/JNEUROSCI.2574-09.2009

Fitzpatrick, R. C., Watson, S. R. D., Fitzpatrick, R. C., and Watson, S. R. D. (2015). Passive motion reduces vestibular balance and perceptual responses. *J. Physiol.* 593, 2389–2398. doi: 10.1113/JP270334

Freiherr, J., Lundström, J. N., Habel, U., and Reetz, K. (2013). Multisensory integration mechanisms during aging. *Front. Hum. Neurosci.* 7:863. doi: 10.3389/fnhum.2013.00863

Gabriel, G. A., Harris, L. R., Gnanasegaram, J. J., Cushing, S. L., Gordon, K. A., Haycock, B. C., et al. (2022a). Age-related changes to vestibular heave and pitch perception and associations with postural control. *Sci. Rep.* 12:6426. doi: 10.1038/s41598-022-09807-4

Gabriel, G. A., Harris, L. R., Gnanasegaram, J. J., Cushing, S. L., Gordon, K. A., Haycock, B. C., et al. (2022b). Vestibular perceptual thresholds in older adults with and without age-related hearing loss. *Ear Hear.* 43, 420–435. doi: 10.1097/AUD.0000000000001118

Gatehouse, S., and Noble, I. (2004). The speech, spatial and qualities of hearing scale (SSQ). *Int. J. Audiol.* 43, 85–99. doi: 10.1080/14992020400050014

Gibson, J. J. (1950). "The perception of the visual world," in *The Perception of the Visual World*, ed. L. Carmichael (Boston, MA: Houghton Mifflin).

Gibson, M. E., Kim, J. J.-J., McManus, M., and Harris, L. R. (2020). The effect of training on the perceived approach angle in visual vertical heading judgements in a virtual environment. *Exp. Brain Res.* 238, 1861–1869. doi: 10.1007/s00221-020-05841-8

Greenlee, M. W., Frank, S. M., Kaliuzhna, M., Blanke, O., Bremmer, F., Churan, J., et al. (2016). Multisensory Integration in Self Motion Perception. *Multisensory Res.* 29, 525–556. doi: 10.1163/22134808-00002527

Gu, Y., Angelaki, D. E., and DeAngelis, G. C. (2013). Neural correlates of multi-sensory cue integration in macaque area MSTd. *Nat. Neurosci.* 13, 83–96. doi: 10.1002/ana.22528.Toll-like

Hartmann, M., Furrer, S., Herzog, M. H., Merfeld, D. M., and Mast, F. W. (2013). Self-motion perception training: thresholds improve in the light but not in the dark. *Exp. Brain Res.* 226, 231–240. doi: 10.1007/s00221-013-3428-1

HTC Vive (2016). *Virtual reality device. [Apparatus and software]*. Available online at: https://www.vive.com

Hughes, H. C., Reuter-Lorenz, P. A., Nozawa, G., and Fendrich, R. (1994). Visual-auditory interactions in sensorimotor processing: saccades versus manual responses. *J. Exp. Psychol. Hum. Percept. Perform.* 20, 131–153. doi: 10.1037/0096-1523.20.1.131

ISO 8253-1 (1989). *Acoustics-Audiometric Test methods-Part 1: Basic pure tone air and bone conduction threshold audiometry*. Geneva: International Organization for Standardization.

Karmali, F., Lim, K., and Merfeld, D. M. (2014). Visual and vestibular perceptual thresholds each demonstrate better precision at specific frequencies and also exhibit optimal integration. *J. Neurophysiol.* 111, 2393–2403. doi: 10.1152/JN.00332.2013/ASSET/IMAGES/LARGE/Z9K0061423470010.JPEG

Karmali, F., Rey, M. C. B., Clark, T. K., Wang, W., and Merfeld, D. M. (2017). Multivariate analyses of balance test performance,vestibular thresholds, and age. *Front. Neurol.* 8:578. doi: 10.3389/fneur.2017.00578

Karmali, F., Whitman, G. T., and Lewis, R. F. (2018). Bayesian optimal adaptation explains age-related human sensorimotor changes. *J. Neurophysiol.* 119, 509–520. doi: 10.1152/JN.00710.2017/SUPPL_FILE/MATLAB_CODE3.TXT

Kavcic, V., Vaughn, W., and Duffy, C. J. (2011). Distinct visual motion processing impairments in aging and Alzheimer's disease. *Vis. Res.* 51, 386–395. doi: 10.1016/j.visres.2010.12.004

Kenney, D. M., Jabbari, Y., von Mohrenschildt, M., and Shedden, J. M. (2021). Visual-vestibular integration is preserved with healthy aging in a simple acceleration detection task. *Neurobiol. Aging* 104, 71–81. doi: 10.1016/j.neurobiolaging.2021.03.017

Klaus, M. P., Schöne, C. G., Hartmann, M., Merfeld, D. M., Schubert, M. C., and Mast, F. W. (2020). Roll tilt self-motion direction discrimination training: first evidence for perceptual learning. *Attent. Percept. Psychophys.* 82, 1987–1999. doi: 10.3758/s13414-019-01967-2

Kobel, M. J., Wagner, A. R., Merfeld, D. M., and Mattingly, J. K. (2021). Vestibular thresholds: a review of advances and challenges in clinical applications. *Front. Neurol.* 12:643634. doi: 10.3389/fneur.2021.643634

Kuang, S., Deng, H., and Zhang, T. (2020). Adaptive heading performance during self-motion perception. *PsyCh J.* 9, 295–305. doi: 10.1002/pchj.330

Laurienti, P. J., Burdette, J. H., Maldjian, J. A., and Wallace, M. T. (2006). Enhanced multisensory integration in older adults. *Neurobiol. Aging* 27, 1155–1163. doi: 10.1016/j.neurobiolaging.2005.05.024

Lich, M., and Bremmer, F. (2014). Self-motion perception in the elderly. *Front. Hum. Neurosci.* 8:681. doi: 10.3389/fnhum.2014.00681

Lin, F. R., and Ferrucci, L. (2012). Hearing loss and falls among older adults in the United States. *Arch. Int. Med.* 172, 369–371. doi: 10.1001/archinternmed.2011.728

Lopez, C., and Blanke, O. (2011). The thalamocortical vestibular system in animals and humans. *Brain Res. Rev.* 67, 119–146. doi: 10.1016/J.BRAINRESREV.2010.12.002

Lubetzky, A. V., Gospodarek, M., Arie, L., Kelly, J., Roginska, A., and Cosetti, M. (2020). Auditory input and postural control in adults: a narrative review. *JAMA Otolaryngol. Head Neck Surg.* 146, 480–487. doi: 10.1001/jamaoto.2020.0032

Mahoney, J. R., Li, P. C. C., Oh-Park, M., Verghese, J., and Holtzer, R. (2011). Multisensory integration across the senses in young and old adults. *Brain Res.* 1426, 43–53. doi: 10.1016/j.brainres.2011.09.017

Mäntyjärvi, M., and Laitinen, T. (2001). Normal values for the Pelli-Robson contrast sensitivity test. *J. Cataract Refract. Surg.* 27, 261–266. doi: 10.1016/S0886-3350(00)00562-9

Mapstone, M., and Duffy, C. J. (2010). Approaching objects cause confusion in patients with Alzheimer's disease regarding their direction of self-movement. *Brain* 133, 2690–2701. doi: 10.1093/brain/awq140

Mapstone, M., Logan, D., and Duffy, C. J. (2006). Cue integration for the perception and control of self-movement in ageing and Alzheimer's disease. *Brain* 129, 2931–2944. doi: 10.1093/brain/awl201

McGovern, D. P., Roudaia, E., Stapleton, J., McGinnity, T. M., and Newell, F. N. (2014). The sound-induced flash illusion reveals dissociable age-related effects in multisensory integration. *Front. Aging Neurosci.* 6:250. doi: 10.3389/fnagi.2014.00250

Meredith, M. A., and Stein, B. E. (1986). Visual, auditory, and somatosensory convergence on cells in superior colliculus results in multisensory integration. *J. Neurophysiol.* 56, 640–662. doi: 10.1152/jn.1986.56.3.640

Merriman, N. A., Whyatt, C., Setti, A., Craig, C., and Newell, F. N. (2015). Successful balance training is associated with improved multisensory function in fall-prone older adults. *Comput. Hum. Behav.* 45, 192–203. doi: 10.1016/j.chb.2014.12.017

Mozolic, J. L., Hugenschmidt, C. E., Peiffer, A. M., and Laurienti, P. J. (2011). "Multisensory integration and aging," in *The Neural Bases of Multisensory Processes*, eds M. M. Murray and M. T. Wallace (Boston, FL: CRC Press), 381–392. doi: 10.1201/b11092-25

Mozolic, J. L., Hugenschmidt, C. E., Peiffer, A. M., and Laurienti, P. J. (2012). Multisensory integration and aging. *Neural Bases Multisensory Proc.* 2008, 1–9. doi: 10.1201/b11092

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., et al. (2005). The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J. Am. Geriat. Soc.* 53, 695–699. doi: 10.1111/j.1532-5415.2005.53221.x

Nestmann, S., Karnath, H.-O. O., Bülthoff, H. H., and de Winkel, K. N. (2020). Changes in the perception of upright body orientation with age. *PLoS One* 15:e0233160. doi: 10.1371/journal.pone.0233160

Owsley, C. (2011). Aging and vision. *Vis. Res.* 51, 1610–1622. doi: 10.1016/j.visres.2010.10.020

Peiffer, A. M., Mozolic, J. L., Hugenschmidt, C. E., and Laurienti, P. J. (2007). Age-related multisensory enhancement in a simple audiovisual detection task. *NeuroReport* 18, 1077–1081. doi: 10.1097/WNR.0b013e3281e72ae7

Pelli, D. G., Pelli, D. G., Robson, J. G., and Wilkins, A. J. (1988). The design of a new letter chart for measuring contrast sensitivity. *Clin. Vis. Sci.* 2, 187—-199.

Prosperini, L., and Pozzilli, C. (2013). The clinical relevance of force platform measures in multiple sclerosis: a review. *Mult. Scler. Int.* 2013, 1–9. doi: 10.1155/2013/756564

Public Health Agency of Canada (2014). "Seniors' Falls in Canada," in *Chronic Diseases and Injuries in Canada*, V34, (Ottawa, ON: Statistics Canada).

R Core Team (2017). *A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing, 2017.

Ramkhalawansingh, R., Butler, J. S., and Campos, J. L. (2018). Visual-vestibular integration during self-motion perception in younger and older adults. *Psychol. Aging* 33, 798–813. doi: 10.1037/pag0000271

Ramkhalawansingh, R., Keshavarz, B., Haycock, B., Shahab, S., and Campos, J. L. (2016). Age differences in visual-auditory self-motion perception during a simulated driving task. *Front. Psychol.* 7:595. doi: 10.3389/fpsyg.2016.00595

Ramkhalawansingh, R., Keshavarz, B., Haycock, B., Shahab, S., and Campos, J. L. (2017). Examining the effect of age on visual–vestibular self-motion perception using a driving paradigm. *Perception* 46, 566–585. doi: 10.1177/0301006616675883

Roditi, R. E., and Crane, B. T. (2012). Directional asymmetries and age effects in human self-motion perception. *JARO J. Assoc. Res. Otolaryngol.* 13, 381–401. doi: 10.1007/s10162-012-0318-3

Scoppa, F., Capra, R., Gallamini, M., and Shiffer, R. (2013). Clinical stabilometry standardization. basic definitions - acquisition interval - sampling frequency. *Gait Post.* 37, 290–292. doi: 10.1016/j.gaitpost.2012.07.009

Seitz, A. R., Kim, R., and Shams, L. (2006). Sound facilitates visual learning. *Curr. Biol.* 16, 1422–1427. doi: 10.1016/j.cub.2006.05.048

Shams, L., and Seitz, A. R. (2008). Benefits of multisensory learning. *Trends Cogn. Sci.* 12, 411–417. doi: 10.1016/j.tics.2008.07.006

Shams, L., Wozny, D. R., Kim, R., and Seitz, A. (2011). Influences of multisensory experience on subsequent unisensory processing. *Front. Psychol.* 2:264. doi: 10.3389/fpsyg.2011.00264

Shumway-Cook, A., Brauer, S., and Woollacott, M. H. (2000). Predicting the probability for falls in community-dwelling older adults using the timed up and go test. *Phys. Therapy* 80, 896–903. doi: 10.1093/ptj/80.9.896

Snowden, R. J., and Kavanagh, E. (2006). Motion perception in the ageing visual system: Minimum motion, motion coherence, and speed discrimination thresholds. *Perception* 35, 9–24. doi: 10.1068/p5399

Stapleton, J., Setti, A., Doheny, E. P., Kenny, R. A., and Newell, F. N. (2014). A standing posture is associated with increased susceptibility to the sound-induced flash illusion in fall-prone older adults. *Exp. Brain Res.* 232, 423–434. doi: 10.1007/s00221-013-3750-7

Taylor, M. M., and Creelman, C. D. (1967). PEST: efficient estimates on probability functions. *J. Acoust. Soc. Am.* 41, 782–787. doi: 10.1121/1.1910407

Tye-Murray, N., Sommers, M., Spehar, B., Myerson, J., and Hale, S. (2010). Aging, audiovisual integration, and the principle of inverse effectiveness. *Ear Hear.* 31, 636–644. doi: 10.1097/AUD.0b013e3181ddf7ff

Unity (2019). *Unity [Computer software] Version 2019.2.2f1*

Velarde, C., Perelstein, E., Ressmann, W., and Duffy, C. J. (2013). Independent deficits of visual word and motion processing in aging and early Alzheimer's Disease. *J. Alzheimers Dis.* 31, 613–621. doi: 10.3233/JAD-2012-112201. Independent

Viljanen, A., Kaprio, J., Pyykkö, I., Sorri, M., Pajala, S., Kauppinen, M., et al. (2009). Hearing as a predictor of falls and postural balance in older female twins. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* 64, 312–317. doi: 10.1093/gerona/gln015

Von Kriegstein, K., and Giraud, A. L. (2006). Implicit multisensory associations influence voice recognition. *PLoS Biol.* 4:1809–1820. doi: 10.1371/journal.pbio.0040326

Warren, W. H., Blackwell, A. W., and Morris, M. W. (1989). Age differences in perceiving the direction of self-motion from optical flow. *J. Gerontol.* 44, 147–153. doi: 10.1093/geronj/44.5.P147

World Health Organization (1991). *Report of the Informal Working Group on Prevention of Deafness and Hearing Impairment Programme Planning*, Vol. 18-21. Geneva: World Health Organization, 1991.

Zuniga, M. G., Dinkes, R. E., Davalos-Bichara, M., Carey, J. P., Schubert, M. C., King, W. M., et al. (2012). Association between hearing loss and saccular dysfunction in older individuals. *Otol. Neurotol.* 33, 1586–1592. doi: 10.1097/MAO.0b013e31826bedbc

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