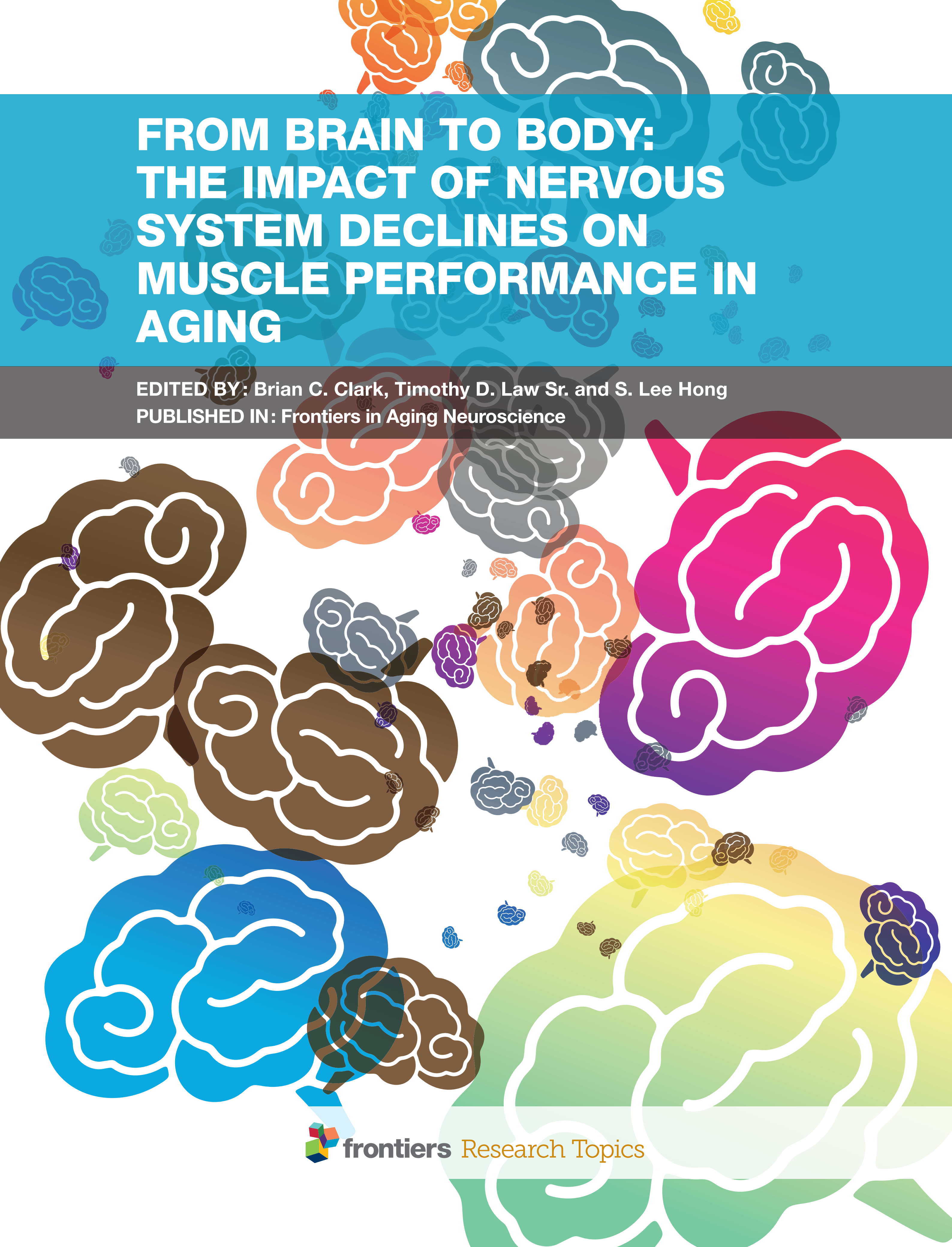


FROM BRAIN TO BODY: THE IMPACT OF NERVOUS SYSTEM DECLINES ON MUSCLE PERFORMANCE IN AGING

EDITED BY: Brian C. Clark, Timothy D. Law Sr. and S. Lee Hong
PUBLISHED IN: Frontiers in Aging Neuroscience

frontiers Research Topics

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.

Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view.

By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

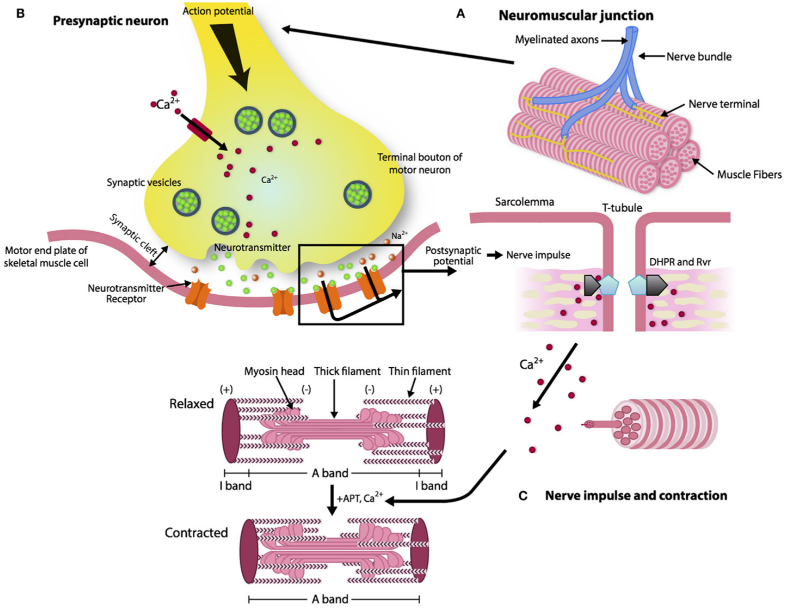
What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: **researchtopics@frontiersin.org**

ISSN 1664-8714
ISBN 978-2-88919-686-9
DOI 10.3389/978-2-88919-686-9

FROM BRAIN TO BODY: THE IMPACT OF NERVOUS SYSTEM DECLINES ON MUSCLE PERFORMANCE IN AGING

Topic Editors:
Brian C. Clark, Ohio University, USA
Timothy D. Law Sr., Ohio University, USA
S. Lee Hong, Ohio University, USA



The architecture of a neuromuscular junction (NMJ). (A, B) The NMJ is composed of three elements: pre-synaptic (motor nerve terminal), intrasynaptic (synaptic basal lamina), and post-synaptic component (muscle fiber and muscle membrane) (Punga and Ruegg, 2012). When the action potential reaches the motor nerve terminal the calcium channels open and the calcium enters in the neuron and delivers ACh in the synaptic cleft. (C) AChR activates the DHPRs located in the sarcolemma and by induction the RyRs. Calcium released from the sarcoplasmic reticulum through the RyRs binds to troponin C and allows cross-bridge cycling and force production.

Figure taken from: Gonzalez-Freire M, de Cabo R, Studenski SA and Ferrucci L (2014) The neuromuscular junction: aging at the crossroad between nerves and muscle. Front. Aging Neurosci. 6:208. doi: 10.3389/fnagi.2014.00208

The deterioration of skeletal muscle performance (e.g., declines in muscle strength and motor performance) with advancing age has long been anecdotally recognized as Shakespeare pointed out nearly a half millennium ago in his monologue. The Seven Ages of Man, and has been of scientific interest for well over a century. Over the past several decades the scientific and medical communities have recognized that reduced skeletal muscle performance is a debilitating and life threatening condition in the elderly. For example, the age-associated loss of muscle strength, as well as impairment in the ability to finely control movement, is highly associated with physical disability and difficulty performing activities of daily living.

While the nervous system is widely recognized for its role in controlling skeletal muscle during motor function, its role in determining the performance characteristics of aged skeletal muscle has largely been understudied. Historically, it was believed that these reductions in muscle performance were primarily resultant of age-associated adaptations in skeletal muscle (e.g., muscle atrophy). However, aging is associated with widespread qualitative and quantitative changes in both the central and peripheral nervous systems that are likely to influence numerous aspects of muscle performance, such as muscle strength, fatigue, and motor control, as well as mobility.

In this research topic, we sought to examine a broad range of issues surrounding: 1) the age-related changes in nervous system anatomical, physiological, and biochemical changes in the central and/or peripheral nervous systems; 2) the functional role of these nervous system changes in contributing to altered skeletal muscle performance and/or mobility; and 3) physical and pharmacologic interventions that act via the nervous system to enhance muscle performance and/or mobility. Researchers and academicians engaged in aging, neuroscience, and/or applied physiology research focused within the scope of this research topic, were encouraged to contribute an original research article, review article, clinical case study, hypothesis and theory article, method article, opinion article, or technology report to this research topic. Herein, we present a series of outstanding articles within this scope of work, including a last minute addition article from Wiesmeier, Dalin and Maurer that is not mentioned in the editorial, that we hope will help to vertically advance the intersecting fields of aging/geriatrics and neuroscience.

Lastly, as the editors, we wish to thank all article contributors and peer reviewers for their efforts in contributing to this Research Topic journal issue/book. Additionally, we would like to thank people everywhere who volunteer their time and body for human subjects research studies, such that are presented herein. It is the wonderful individuals who are willing to participate in experiments that make scientific exploration and health and medical advancements possible.

Citation: Clark, B. C., Law Sr., T., D., Hong, S. L., eds. (2015). From Brain to Body: The Impact of Nervous System Declines on Muscle Performance in Aging. Lausanne: Frontiers Media. doi: 10.3389/978-2-88919-686-9

Table of Contents

frontiers
in Aging Neuroscience

EDITORIAL
published: 30 April 2015
doi: 10.3389/fnagi.2015.00066

Editorial: “From brain to body: the impact of nervous system declines on muscle performance in aging”

Brian C. Clark[1, 2, 3]*, **Timothy D. Law**[1, 3, 4] and **S. Lee Hong**[1, 2]

[1] Ohio Musculoskeletal and Neurological Institute, Ohio University, Athens, OH, USA, [2] Department of Biomedical Sciences, Ohio University, Athens, OH, USA, [3] Department of Geriatric Medicine, Ohio University, Athens, OH, USA, [4] Department of Family Medicine, Ohio University, Athens, OH, USA

Keywords: muscle, sarcopenia, dynapenia, aging, frailty, weakness, motor control

Edited and reviewed by:
Rodrigo Orlando Kuljiš,
Zdrav Mozak Limitada, Chile

Correspondence:
Brian C. Clark,
clarkb2@ohio.edu

Received: *06 January 2015*
Accepted: *14 April 2015*
Published: *30 April 2015*

Citation:
Clark BC, Law TD and Hong SL (2015) Editorial: “From brain to body: the impact of nervous system declines on muscle performance in aging.” Front. Aging Neurosci. 7:66. doi: 10.3389/fnagi.2015.00066

Around 30% of women and 15% of men in the United States over 60 years self-report that they are unable to lift or carry 10 pounds, and ∼50% of women and 40% of men report difficulty in stooping, crouching, or kneeling (Louie and Ward, 2010). Further, more than 40% of seniors have limitations in performing one or more daily tasks (e.g., walking two to three blocks, transferring from sitting to standing) that are essential for maintaining physical independence (Louie and Ward, 2010). While many factors contribute to reductions in physical function, one contributor is skeletal muscle impairments (e.g., muscle weakness) (Manini et al., 2007). While the nervous system is widely recognized for its role in coordination, its role in determining the performance characteristics of aged skeletal muscle has largely been understudied.

Historically, it was believed that the reductions in muscle performance were primarily resultant of age-associated adaptations in skeletal muscle (e.g., muscle atrophy). However, the vast range of motions and forces that humans can achieve arises from the activity of more than 600 skeletal muscles, which are under the control of the nervous system. As such, the nervous system is in all likelihood a critical contributor to all aspects of aged-related changes in muscle performance, and as a consequence, motor behavior (Rosso et al., 2013). Indeed a growing body of research indicates that a good predictor of impending cognitive decline in older adults is a slowed and stooped gait, which has been assigned the term “motoric cognitive risk syndrome” (Verghese et al., 2013, 2014a,b). In this *Frontiers in Aging Neuroscience* research topic, we solicited articles on a broad range of issues surrounding: (1) the age-related changes in nervous system anatomical, physiological, and biochemical changes in the central and/or peripheral nervous systems; (2) the functional role of these nervous system changes in contributing to altered skeletal muscle performance and/or mobility; and (3) the physical and pharmacologic interventions that act via the nervous system to enhance muscle performance and/or mobility. We invited individuals, both *via* invitation and an open call for manuscripts, engaged in aging, neuroscience, and/or applied physiology research focused within the scope of this research topic, to contribute an original research article, review article, clinical case study, hypothesis and theory article, method article, opinion article, or technology report.

In this issue we present 12 articles within this scope. Specifically, in this issue we present 2 review articles, 1 theory article, and 9 original research articles. Below we highlight some of the most notable findings from this research topic issue:

- A general theme at the level of brain activation that arises is the dedifferentiation and compensatory activation. Coppi et al. (2014) and McGregor et al. (2013) both found increased interhemispheric interactions and decreased interhemispheric inhibition in older adults. Similarly, Heetkamp et al. (2014) found older adults to exhibit more diffuse, bilateral brain activation patterns during unilateral motor tasks. In the theory and hypothesis paper by Sleimen-Malkoun et al. (2014), the concept of differentiation in aging is co-constructed with the loss of complexity framework, presenting an argument that these patterns of decline are inherent at the level of brain, muscle, and behavior. In a similar vein, Berchicci et al. (2014) showed that exercise reduces the amount of brain activation needed to perform cognitive tasks in older adults, and Yao et al. (2014) reports that older adults require greater activation in higher-order cortical fields for controlling eccentric muscle contractions.

- Another general theme that arises in the Vanden Noven et al. (2014) and Hasson and Sternad (2014) original articles is that increasing task complexity in older people results in increased motor variability. Of particular interest was the finding from Vanden Noven et al. (2014) indicating that motor performance was dramatically impaired when a high demand cognitive task was performed concomitant with the motor function task. Findings of this nature have implications for injury risk reduction approaches as well as ergonomic applications.
- Two original articles by scientists from the University of Florida examined the neural contributors to mobility in older people. The first of these, from Cruz-Almeida et al. (2014) indicates that sensory tactile perception at the first metatarsal head was associated with both usual and maximal walking speed, while the second article by Clark et al. (2014) observed that the changes in activity of the prefrontal cortex during performance of complex walking tasks were linked to the quality of gait in older adults. Additionally, one of the review articles from Iosa et al. (2014) discusses mobility issues associated with aging, specifically the decline in upright gait stability. They point out that the loss of skeletal muscle with aging, even in healthy older adults, contributes to the inability to maintain an upright posture during walking along with decreased sensory and cognitive declines. A confluence of these declines, they argue, contributes to increased instability and risk of falls.
- The last of the articles, a review by Gonzalez-Freire et al. (2014), points out that aging and its associated loss of muscle mass and strength, are related to neuromuscular junction dysfunction. As a result, they postulate that interventions such as exercise and calorie restriction can positively affect the neuromuscular junction.

Overall, the articles within this Research Topic point to an intimate relationship between brain and nervous system function and its impact of muscle activation, and consequently, motor behavior. Physical fitness and exercise seem to be a central component in maintaining both brain and nervous system health, as well as motor function, against the effects of aging.

Funding

NIH R01AG044424 to BC Clark.

References

Berchicci, M., Lucci, G., Perri, R. L., Spinelli, D., and Di Russo, F. (2014). Benefits of physical exercise on basic visuo-motor functions across age. *Front. Aging Neurosci.* 6:48. doi: 10.3389/fnagi.2014.00048

Clark, D. J., Rose, D. K., Ring, S. A., and Porges, E. C. (2014). Utilization of central nervous system resources for preparation and performance of complex walking tasks in older adults. *Front. Aging Neurosci.* 6:217. doi: 10.3389/fnagi.2014.00217

Coppi, E., Houdayer, E., Chieffo, R., Spagnolo, F., Inuggi, A., Straffi, L., et al. (2014). Age-related changes in motor cortical representation and interhemispheric interactions: a transcranial magnetic stimulation study. *Front. Aging Neurosci.* 6:209. doi: 10.3389/fnagi.2014.00209

Cruz-Almeida, Y., Black, M. L., Christou, E. A., and Clark, D. J. (2014). Site-specific differences in the association between plantar tactile perception and mobility function in older adults. *Front. Aging Neurosci.* 6:68. doi: 10.3389/fnagi.2014.00068

Gonzalez-Freire, M., de Cabo, R., Studenski, S. A., and Ferrucci, L. (2014). The neuromuscular junction: aging at the crossroad between nerves and muscle. *Front. Aging Neurosci.* 6:208. doi: 10.3389/fnagi.2014.00208

Hasson, C. J., and Sternad, D. (2014). Safety margins in older adults increase with improved control of a dynamic object. *Front. Aging Neurosci.* 6:158. doi: 10.3389/fnagi.2014.00158

Heetkamp, J., Hortobagyi, T., and Zijdewind, I. (2014). Increased bilateral interactions in middle-aged subjects. *Front. Aging Neurosci.* 6:5. doi: 10.3389/fnagi.2014.00005

Iosa, M., Fusco, A., Morone, G., and Paolucci, S. (2014). Development and decline of upright gait stability. *Front. Aging Neurosci.* 6:14. doi: 10.3389/fnagi.2014.00014

Louie, G. H., and Ward, M. M. (2010). Sex disparities in self-reported physical functioning: true differences, reporting bias, or incomplete adjustment for confounding? *J. Am. Geriatr. Soc.* 58, 1117–1122. doi: 10.1111/j.1532-5415.2010.02858.x

Manini, T. M., Visser, M., Won-Park, S., Patel, K. V., Strotmeyer, E. S., Chen, H., et al. (2007). Knee extension strength cutpoints for maintaining mobility. *J. Am. Geriatr. Soc.* 55, 451–457. doi: 10.1111/j.1532-5415.2007.01087.x

McGregor, K. M., Nocera, J. R., Sudhyadhom, A., Patten, C., Manini, T. M., Kleim, J. A., et al. (2013). Effects of aerobic fitness on aging-related changes of interhemispheric inhibition and motor performance. *Front. Aging Neurosci.* 5, 66. doi: 10.3389/fnagi.2013.00066

Rosso, A. L., Studenski, S. A., Chen, W. G., Aizenstein, H. J., Alexander, N. B., Bennett, D. A., et al. (2013). Aging, the central nervous system, and mobility. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* 68, 1379–1386. doi: 10.1093/gerona/glt089

Sleimen-Malkoun, R., Temprado, J. J., and Hong, S. L. (2014). Aging induced loss of complexity and dedifferentiation: consequences for coordination dynamics within and between brain, muscular and behavioral levels. *Front. Aging Neurosci.* 6:140. doi: 10.3389/fnagi.2014.00140

Vanden Noven, M. L., Pereira, H. M., Yoon, T., Stevens, A. A., Nielson, K. A., and Hunter, S. K. (2014). Motor variability during sustained contractions increases with cognitive demand in older adults. *Front. Aging Neurosci.* 6:97. doi: 10.3389/fnagi.2014.00097

Verghese, J., Annweiler, C., Ayers, E., Barzilai, N., Beauchet, O., Bennett, D. A., et al. (2014a). Motoric cognitive risk syndrome: multicountry prevalence and dementia risk. *Neurology* 83, 718–726. doi: 10.1212/WNL.0000000000000717

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

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

Yao, W. X., Li, J., Jiang, Z., Gao, J. H., Franklin, C. G., Huang, Y., et al. (2014). Aging interferes central control mechanism for eccentric muscle contraction. *Front. Aging Neurosci.* 6:86. doi: 10.3389/fnagi.2014.00086

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

frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 11 August 2014
doi: 10.3389/fnagi.2014.00209

Age-related changes in motor cortical representation and interhemispheric interactions: a transcranial magnetic stimulation study

Elisabetta Coppi, Elise Houdayer, Raffaella Chieffo, Francesca Spagnolo, Alberto Inuggi, Laura Straffi, Giancarlo Comi and Letizia Leocani*

Neurological Department and Experimental Neurophysiology Unit, Institute of Experimental Neurology (INSPE), University Hospital-IRCCS San Raffaele, Milan, Italy

Edited by:
Brian C. Clark, Ohio University, USA

Reviewed by:
Martin Lotze, University of Greifswald, Germany
Ashleigh Elizabeth Smith, University of South Australia, Australia

****Correspondence:***
Letizia Leocani, Experimental Neurophysiology Unit, INSPE-Institute of Experimental Neurology, Hospital San Raffaele, Via Olgettina 60, 20132, Milan, Italy
e-mail: letizia.leocani@hsr.it

To better understand the physiological mechanisms responsible for the differential motor cortex functioning in aging, we used transcranial magnetic stimulation to investigate interhemispheric interactions and cortical representation of hand muscles in the early phase of physiological aging, correlating these data with participants' motor abilities. Right-handed healthy subjects were divided into a younger group ($n = 15$, mean age 25.4 ± 1.9 years old) and an older group ($n = 16$, mean age 61.1 ± 5.1 years old). Activity of the bilateral abductor pollicis brevis (APB) and abductor digiti minimi (ADM) was recorded. Ipsilateral silent period (ISP) was measured in both APBs. Cortical maps of APB and ADM were measured bilaterally. Mirror movements (MM) were recorded during thumb abductions. Motor abilities were tested using Nine Hole Peg Test, finger tapping, and grip strength. ISP was reduced in the older group on both sides, in terms of duration ($p = 0.025$), onset ($p = 0.029$), and area ($p = 0.008$). Resting motor threshold did not differ between groups. APB and ADM maps were symmetrical in the younger group, but were reduced on the right compared to the left hemisphere in the older group ($p = 0.008$). The APB map of the right hemisphere was reduced in the older group compared to the younger ($p = 0.021$). Older subjects showed higher frequency of MM and worse motor abilities ($p < 0.001$). The reduction of right ISP area correlated significantly with the worsening of motor performances. Our results showed decreased interhemispheric interactions in the early processes of physiological aging and decreased cortical muscles representation over the non-dominant hemisphere. The decreased ISP and increased frequency of MM suggest a reduction of transcallosal inhibition. These data demonstrate that early processes of normal aging are marked by a dissociation of motor cortices, characterized, at least, by a decline of the non-dominant hemisphere, reinforcing the hypothesis of the right hemi-aging model.

Keywords: physiological aging, transcranial magnetic stimulation, ipsilateral silent period, muscle cortical maps, motor performances

INTRODUCTION

During physiological aging, the human brain undergoes a series of morphological and functional changes. In healthy aging, cognitive and simple motor tasks produce more symmetrical and widespread cortical activation compared to young adults, due to a higher recruitment of cortical areas of both hemispheres, as supported by functional neuroimaging (Hutchinson et al., 2002; Mattay et al., 2002; Riecker et al., 2006; Ward et al., 2007) and electroencephalographic (EEG) studies (Sailer et al., 2000; Labyt et al., 2006; Vallesi et al., 2010).

In cognitive processes, this greater bilateral cortical activation seems to reflect compensatory mechanisms, in order to support cognitive abilities in healthy older people (Cabeza et al., 2002; Dolcos et al., 2002). Conversely, evidence for a positive effect of this cortical hyperactivation on motor functions is less clear. Functional neuroimaging (Riecker et al., 2006) and EEG (Inuggi et al., 2011) studies demonstrated that this bilateral cortical activation was still characterized by reduced motor abilities in aging. These results suggest that the more symmetrical motor cortex activity observed in physiological aging would not be due to a compensatory mechanism (Inuggi et al., 2011). Therefore, the functional modulations revealed in motor cortices during physiological aging are likely to be related to a loss of balance between excitatory and inhibitory circuits.

A major hypothesis is that this could be related to changes in interhemispheric connections between motor cortices (Talelli et al., 2008), due to either a loss of transcallosal fibers or to a decreased excitability of interhemispheric connections. Transcranial magnetic stimulation (TMS) has been used to investigate the effects of aging on interhemispheric inhibition (IHI). A paired-pulse TMS study, with conditioning stimulus on the hemisphere ipsilateral to the moving hand and a contralateral test stimulus, showed no age-related differences in IHI at rest, but demonstrated an enhanced IHI in young subjects during unilateral movements (from the activated hemisphere to the resting one) (Talelli et al., 2008). This IHI modulation during movement was absent in the older group, showing functional alteration of the IHI in physiological aging.

More recently, single-pulse TMS was used to study IHI in aging using the ipsilateral silent period (ISP) (Davidson and Tremblay, 2013; Petitjean and Ko, 2013). These studies demonstrated a reduction in ISP in terms of duration (Petitjean and Ko, 2013) and area (Davidson and Tremblay, 2013) in older subjects compared to younger participants. The ISP consists in stimulating one motor cortex during maximal voluntary contraction of the ipsilateral hand (Ferbert et al., 1992). The stimulated motor cortex would induce a transcallosal IHI of the opposite motor cortex (Meyer et al., 1995). This inhibition is detectable as a pause in the ipsilateral electromyographic (EMG) trace (ISP). Although both IHI and ISP represent a phenomenon of IHI, they are due to different neuronal mechanisms (Chen et al., 2003). The advantage of studying ISP is that, unlike IHI, representing a reduction of motor evoked potential (MEP) amplitude, ISP represents a direct measure of the interhemispheric control of voluntary cortical motor output (Giovannelli et al., 2009).

In line with decreased interhemispheric interactions, physiological aging can be accompanied by an increased in mirror movements (MM), or more generally motor overflow (MO), reflecting all kinds of involuntary movements that appear in other muscular districts during the execution of a voluntary muscle contraction (Hoy et al., 2004). MM are due to an impaired transcallosal inhibition (Bodwell et al., 2003) and are generally observed in neurological disorders involving the corpus callosum, such as complex congenital syndromes (Galléa et al., 2011) or also post-stroke (Chieffo et al., 2013).

The increased symmetrical motor cortex activation observed in aging could also be due to an increased cortical representation of the different muscles involved in the movement, or to an increased excitability of these motor representations. Regarding the excitability of the motor cortex in physiological aging, no consensus has been found since some authors found no significant differences in resting motor threshold (RMT) between young and older people (Pitcher et al., 2003; Oliviero et al., 2006; Fujiyama et al., 2012), while others revealed a significant increase in RMT (indicating a lower excitability) in older subjects (Rossini et al., 1992; Petitjean and Ko, 2013). Peinemann et al. (2001) found only a trend toward a slightly lower RMT in younger compared with older subjects.

Thus, in order to better understand the physiological mechanisms responsible for this differential motor cortex functioning in aging, it is necessary to provide complementary data on the different aspects of motor control. To this aim, we investigated interhemispheric interactions (using ISP) in physiological aging and correlated this functional data with cortical representation of various hand muscles (using TMS mapping) and with participants' motor performance (using hand motor function tests). Moreover, in order to better understand the mechanisms of physiological aging, we decided to focus on the early phase of aging and included healthy people in the age-range 50–70 years old.

MATERIALS AND METHODS

POPULATION

Thirty-one healthy volunteers were included in this study and divided into two groups: younger (15 subjects, 6 females, mean age ± SD: 25.4 ± 1.9 years, range 21–28 years old) and older (16 subjects, 7 females, mean age ± SD: 61.1 ± 5.1 years, range 51–72 years old). All subjects were fully right-handed, having obtained the maximal score at a translated modified version of the Edinburgh Handedness Inventory (Oldfield, 1971). Participants had no history of neurologic or psychiatric disorders, drug abuse, current use of psychoactive medications, neurosurgery, and metal/electronic implants or other contraindications for the use of TMS (Rossi et al., 2009). Subjects gave their written informed consent before participating in the study, which was approved by the Institutional Ethics Committee.

TRANSCRANIAL MAGNETIC STIMULATION

Transcranial magnetic stimulation was delivered by a Magstim 200 simulator (Magstim Company, Ltd., Whitland, Dyfed, UK) connected to a figure-of-eight coil (Magstim second generation, 70 mm of external diameter). EMG activity of the bilateral abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscles were recorded using surface Ag/AgCl electrodes in a belly tendon montage. The coil was positioned over the best scalp location (hotspot, marked on a fitting polyester cap that subjects were wearing) for optimal MEPs over the contralateral target muscle (APB or ADM). RMT was defined as the lowest intensity that could induce a 50 μV peak-to-peak amplitude MEP in at least 5 out of 10 trials (Rossi et al., 2009). RMTs were measured on each side. For ISPs measurements, 15 stimuli were applied at an intensity of 90% of the stimulator output (Chen et al., 2003; Trompetto et al., 2004; Spagnolo et al., 2013) while subjects were performing a voluntary maximal contraction of the ipsilateral APB muscle. In between the TMS pulses, subjects were instructed to relax for 4–8 s. Both hemispheres were tested.

For the cortical maps registration, a grid centered on the vertex was placed on the polyester cap. Intersection points of the grid lines were spaced 1 cm apart and served as visual references for coil positioning. Over each hemisphere, a total of 144 intersection points were drawn. TMS pulses were delivered at 115% RMT, starting from point 1, placed 6 cm laterally to the vertex. Then, the coil was moved following growing clockwise (for the right hemisphere) or anticlockwise (left hemisphere) spirals, from one point to another until no MEP could be evoked. Four TMS pulses were applied over each stimulating point. At the end of the session, each stimulating point as well as anatomical references (nasion, vertex, left, and right tragus) were digitized (Polhemus©, FastTrak, Colchester, VT, USA).

Electromyographic signals were sampled at 2 kHz, amplified and bandpass filtered (30–1000 Hz). Impedances were kept below 5 kΩ. Data were acquired using the SynAmp/SCAN 4.3 system (Compumedics Germany GmbH, Singen, Germany) and stored on a computer for off-line analyses.

HAND MOTOR PERFORMANCE

Mirror movements

Participants were comfortably seated on an armchair, their forearms and pronated hands resting on a table in front of them. They performed voluntary phasic ("brief and brisk") thumb abductions in response to a verbal "go" command (10 trials at inter-trial interval of 4 s). EMG was recorded bilaterally. The occurrence of MM in the opposite muscles was inspected off-line. For each trial, the single rectified EMG traces were averaged. If EMG average showed an involuntary activity in the contralateral homologous muscle, MM was considered positive (MM score = 1), otherwise MM score was considered as 0 (Spagnolo et al., 2013).

Nine Hole Peg Test

Nine Hole Peg Test (NHPT) score (Oxford Grice et al., 2003) consisted of the time taken by the subject to insert every peg in the empty holes and then remove them and place them back in the shallow container, as quickly as possible. The test was performed twice. The fastest speed among the two trials was kept for further analyses.

Finger tapping

Subjects were comfortably seated on a chair, their forearm and hands resting on a table placed in front of them. Participants were instructed to press on a left-button mouse as fast as possible during 10 s with their index finger. The test was performed three times, with both hands, in random sequence. Tapping frequency was calculated using STIM software (Compumedics Germany GmbH, Singen, Germany). The mean frequency of the three trials, for each hand, was kept for analyses.

Martin's vigorimeter

Grip strength was measured using the Martin's dynamometer (Martin's Vigorimeter; BCB Ltd., Cardiff, Wales, UK). Subjects were comfortably seated on a chair, their back leaning against the back of the chair and their feet fully resting on the floor. They were asked to grab the dynamometer with their elbow flexed at 90° and their wrist extended between 0° and 30° and squeeze as hard as they could for a few seconds. Three trials per side were recorded for each subject, and the averages of the three scores were kept for further analyses.

Hand motor function scores asymmetry was calculated by subtracting left hand (L) from the right (R) values, and normalizing by their sum:

$$\mathrm{Asym} = \frac{\mathrm{R} - \mathrm{L}}{\mathrm{R} + \mathrm{L}}$$

TMS DATA ANALYSES

Ipsilateral silent period durations were determined by rectifying the EMG traces before average. ISP onset was defined as the latency at which the averaged EMG activity became constantly (for at least 10 ms) smaller than the averaged baseline contraction level (between −60 and −10 ms before stimulus; Spagnolo et al., 2013). ISP offset was set at the first point after ISP onset at which the EMG activity regained the baseline activity for at least 10 ms. ISP duration was defined as:

$$\mathrm{ISP}_{\mathrm{duration}} = \mathrm{ISP}_{\mathrm{offset}} - \mathrm{ISP}_{\mathrm{onset}}$$

We also measured the $\mathrm{ISP}_{\mathrm{area}}$, which was normalized according to the degree of muscle contraction pre-trigger, in order to correct for intersubject variability. The $\mathrm{ISP}_{\mathrm{area}}$ (in mV × s), was calculated as $[\mathrm{ISP}_{\mathrm{amplitude}} \times \mathrm{ISP}_{\mathrm{duration}}]$, and then normalized according to the pre-trigger EMG amplitude as follows: [(ISP area − baseline area)/(baseline area × 100)]. $\mathrm{ISP}_{\mathrm{duration}}$ and normalized $\mathrm{ISP}_{\mathrm{area}}$ asymmetry were calculated by subtracting L from R-hand values, and normalizing by their sum:

$$\mathrm{Asym} = \frac{\mathrm{R} - \mathrm{L}}{\mathrm{R} + \mathrm{L}}$$

To analyze the cortical maps, the four MEPs obtained at each stimulating point were averaged, and the mean peak-to-peak amplitude was measured. Then, the following parameters were calculated for each considered muscle (APB and ADM):

(1) maximal MEP amplitude;
(2) map area (total number of stimulating sites in which the mean MEP was at least 50 μV of amplitude).

STATISTICAL ANALYSES

All statistical analyses were performed with SPSS/PC+ 13.0 (SPSS, Inc., Chicago, IL, USA). Normality of the data was assessed using the Kolmogorov–Smirnov test. For each variable, outliers were identified according to Tukey's method, implemented in SPSS, and excluded from the corresponding statistical analyses. Hand motor performance scores, RMTs, ISPs, and map parameters were analyzed either with an ANOVA for repeated measures, or the Conover's free distribution method, a non-parametric ANOVA based on ranks, depending on the data normality (Conover and Iman, 1982). For the ISP and motor performance analyses the two main factors were SIDE (two levels: right and left) and GROUP (two levels: younger and older). For the cortical maps analyses, the main factors were MUSCLE (two levels: APB and ADM) and HEMISPHERE (two levels: right and left). If a main effect or an interaction between the main factors was found, t-tests, Mann–Whitney, or Wilcoxon tests (for unpaired or paired data) were used for *post hoc* analyses. Asymmetry values were compared between groups using Mann–Whitney or t-tests, depending on the normality of the data. MM frequency was compared between groups using Chi-square analyses. After having subdivided subjects according to the occurrence of MM (including both younger and older subjects), we used non-parametric Mann–Whitney tests to confront ISP parameters between these latter subgroups (group 1: presence of MM, group 2: no MM). Cross-sectional and longitudinal correlations between TMS and behavioral data were assessed using Pearson or Spearman tests, according to the data distribution. Data were considered significant when $p \leq 0.05$.

RESULTS

Eight participants (four older subjects) did not tolerate the high intensity used during ISP measurements and were thus excluded from the ISP analyses, leading thus to $n = 12$ in the older group, and $n = 11$ in the younger group for ISP and correlation analyses. However, these subjects were kept for hand motor performance and cortical map analyses.

TMS DATA

Conover analysis showed no group differences in terms of RMT, but showed a significant SIDE effect ($F_{1,29} = 13.931$; $p = 0.001$), left hemisphere RMTs being lower than right hemisphere [mean

RMT ± SD (% stimulator output); older group: left hemisphere = 50.9 ± 8.4, right hemisphere = 58.1 ± 12.1; younger group: left hemisphere = 48 ± 4.9, right hemisphere = 53.4 ± 11.1].

The ANOVA for repeated measures showed a significant SIDE effect ($F_{1,18} = 9.841$; $p = 0.006$) and a significant GROUP effect ($F_{1,18} = 5.614$; $p = 0.029$) for the $\text{ISP}_{\text{onset}}$ (one upper outlier for right $\text{ISP}_{\text{onset}}$ in the older group and two lower outliers for right $\text{ISP}_{\text{onset}}$ in the older group). $\text{ISP}_{\text{duration}}$ showed a significant SIDE effect ($F_{1,21} = 5.047$; $p = 0.036$) as well as a significant GROUP effect ($F_{1,21} = 5.798$; $p = 0.025$). In ISP_{area} analyses, the ANOVA demonstrated also a significant GROUP effect ($F_{1,19} = 8.82$; $p = 0.008$), and a trend for a SIDE effect ($F_{1,19} = 3.567$; $p = 0.074$) (one upper outlier for right ISP_{area} in the older group and one lower outlier for right ISP_{area} in the younger group). Thus, in the older group $\text{ISP}_{\text{onset}}$ was delayed, $\text{ISP}_{\text{duration}}$ and ISP_{area} were reduced on both sides (see **Figure 1**). Moreover, in both groups, left hand ISP was significantly greater than right hand ISP (except for ISP_{area} where only a trend was observed). It is noteworthy that pre-trigger EMG levels were similar in both groups ($p > 0.05$). ISP data are presented in **Table 1**.

Regarding the map areas (**Figure 2**), in the younger group the repeated measures ANOVA showed a significant main effect of MUSCLE ($F_{1,28} = 4.460$; $p = 0.04$) and no significant main effect of HEMISPHERE ($F_{1,28} = 1.219$; $p = 0.279$), demonstrating that APB had a greater cortical representation than ADM on both hemispheres.

The older group showed no significant effect of MUSCLE ($F_{1,30} = 0.327$; $p = 0.572$), but a significant main effect of HEMISPHERE ($F_{1,30} = 8.085$; $p = 0.008$), showing that APB and ADM maps had similar areas and were reduced on the right hemisphere compared with the left hemisphere. *Post hoc* between-group t-test comparisons within the right hemisphere confirmed a significant

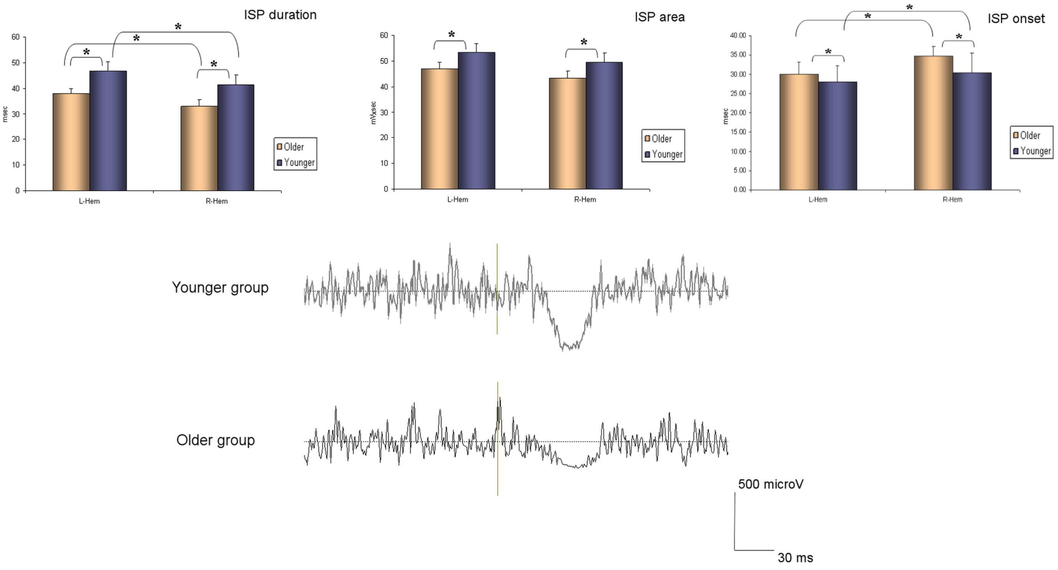


FIGURE 1 | Ipsilateral silent period parameters (duration, area, and onset) according to group and side (average ± SD). L-Hem, left hemisphere; R-Hem, right hemisphere. *$p < 0.05$. Examples of ISP traces in one older and one younger subject are exposed on the lower part of the figure.

Table 1 | ISP parameters (onset, area, duration, and offset) are shown in both groups of participants (younger and older).

ISP parameters	Younger Average ± SD	*p*-Value R vs. L	Older group Average ± SD	*p*-Value R vs. L	*p*-Value Younger vs. older
Onset (ms)	**L** 27.95 ± 4.34	$p = 0.006$*	**L** 30.99 ± 3.01	$p = 0.006$*	$p = 0.029$*
	R 30.38 ± 5.01		**R** 35.41 ± 11.69		$p = 0.029$*
Area (mV × s)	**L** 53.28 ± 13.28	ns	**L** 46.93 ± 13.03	ns	$p = 0.008$*
	R 49.62 ± 11.88		**R** 43.42 ± 9.43		$p = 0.008$*
Duration (ms)	**L** 46.48 ± 11.39	$p = 0.036$*	**L** 38.05 ± 6.59	$p = 0.036$*	$p = 0.025$*
	R 41.5 ± 12.3		**R** 32.89 ± 9.88		$p = 0.025$*
Offset (ms)	**L** 74.63 ± 11.34	ns	**L** 69.04 ± 5.68	ns	ns
	R 71.88 ± 11.34		**R** 68.3 ± 11.89		ns

L, left; R, right; SD, standard deviation; ns, non-significant.

**Statistically significant differences.*

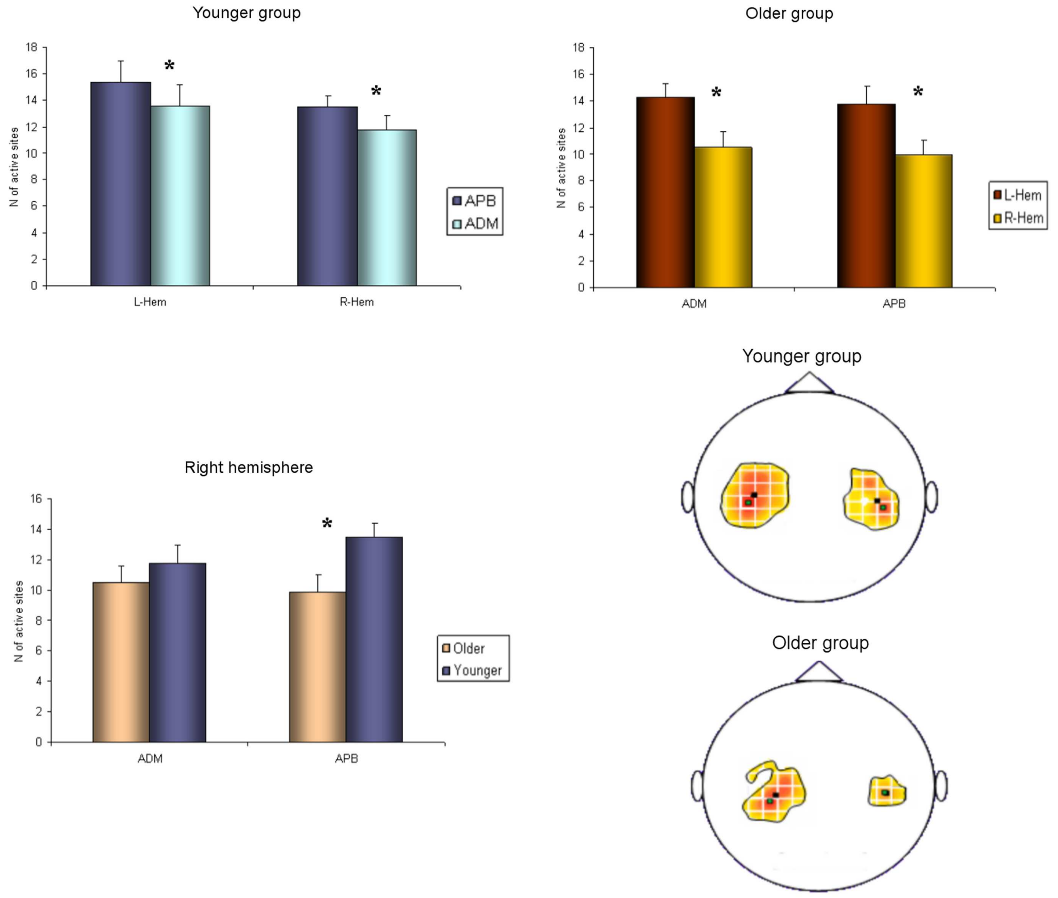


FIGURE 2 | Cortical maps of APB and ADM muscles in the younger and older groups. Upper left graph shows representations of APB and ADM muscles in the younger group, demonstrating a significantly reduced ADM map compared to the APB, on both hemispheres. Upper right graph illustrates the significant reduction of the right hemisphere maps of both APB and ADM muscles, respected to the left hemisphere, in the older group. The lower part of Figure 2 represents the significant reduction of the APB map over the right hemisphere in the older group, compared to the younger group. $^*p < 0.05$.

reduction of APB map in the older compared to the younger group ($p = 0.021$). No such differences were observed on the left hemisphere ($p = 0.269$). For ADM maps no significant differences were found between older and younger subjects, on both hemispheres.

Conversely, the analyses of the maximal MEP amplitude (concerning both APB and ADM) did not demonstrate any significant differences, either between groups or between hemispheres ($p > 0.05$). The analyses of the asymmetry confirmed this latter result ($p = 0.774$). Cortical maps data are presented in **Tables 2** and **3**.

HAND MOTOR PERFORMANCE

Brisk thumb movements induced significantly more MM in the older than in the younger group (in 9 older subjects and 1 younger subject for right finger movements, $p < 0.001$; and in 13 older subjects and 5 younger subjects for left thumb extension, $p = 0.001$) (see **Figure 3**). Subjects showing MM did not have significantly different ISP parameters compared to subjects without MM ($p > 0.05$).

Regarding the NHPT analyses, the repeated measures ANOVA showed a significant main effect of SIDE ($F_{1,26} = 17.219$; $p < 0.001$) and GROUP ($F_{1,26} = 29.742$; $p < 0.001$), as the younger had faster scores than the older group, and the right hand scores were better than the left hand, in both groups (one upper outlier for right NHPT in the younger group, one upper outlier for left NHPT in the younger group, and one upper outlier for left NHPT in the older group). The same results were obtained for the finger tapping (FT) frequency (one upper outlier for left FT in the younger group): the younger group was faster than the older group ($F_{1,28} = 30.337$; $p < 0.001$), and performances were faster on the right compared with the left hand ($F_{1,28} = 60.681$; $p < 0.001$). The ANOVA for repeated measures showed greater grip strength in the younger group ($F_{1,29} = 6.545$; $p = 0.016$), and a strong trend for better scores with the right hand in both groups (although non-significant, $F_{1,29} = 4.189$; $p = 0.051$). The paired t-tests demonstrated that the asymmetrical hand motor performances (right better than left) did not differ between groups. Motor performances data are presented in **Table 4**.

CORRELATIONS

We found that hand motor performances (NHPT, FT, and grip strength) of both hands correlated significantly with the

Table 2 | Maps parameters for APB muscles are shown in both group of participants (younger and older).

APB MAPS parameters	Younger group Average ± SD	*p*-Value R vs. L	Older group Average ± SD	*p*-Value R vs. L	*p*-Value Younger vs. older
Map area (*N* of active sites)	**L** 15.4 ± 6.17	ns	**L** 13.87 ± 5.27	$p = 0.008$*	ns
	R 13.53 ± 3.37		**R** 9.93 ± 4.69		$p = 0.021$*
MEP amplitude (μV)	**L** 798.77 ± 546.29	ns	**L** 819.19 ± 948.7	ns	ns
	R 589.18 ± 345.83		**R** 583.06 ± 652.87		ns

APB, abductor pollicis brevis; L-Hem, left hemisphere (dominant); R-Hem, right hemisphere (non-dominant); MEP, motor evoked potential; SD, standard deviation; ns, non-significant; L, Left; R, Right.

**Statistically significant differences.*

Table 3 | Maps parameters for ADM muscles are shown in both group of participants (younger and older).

ADM MAPS parameters	Younger group Average ± SD	*p*-Value R vs. L	Older group Average ± SD	*p*-Value R vs. L	*p*-Value Younger vs. older
Map area (*N* of active sites)	**L** 13.66 ± 6.18	ns	**L** 14.37 ± 4.16	$p = 0.008$*	ns
	R 11.8 ± 4.26		**R** 10.56 ± 4.81		ns
MEP amplitude (μV)	**L** 705.38 ± 527.19	ns	**L** 1299.85 ± 1256.05	Ns	ns
	R 554.63 ± 330.29		**R** 631.55 ± 623.91		ns

ADM, abductor digiti minimi; L-Hem, left hemisphere (dominant); R-Hem, right hemisphere (non-dominant); MEP, motor evoked potential; SD, standard deviation; ns, non-significant; L, Left; R, Right.

**Statistically significant differences.*

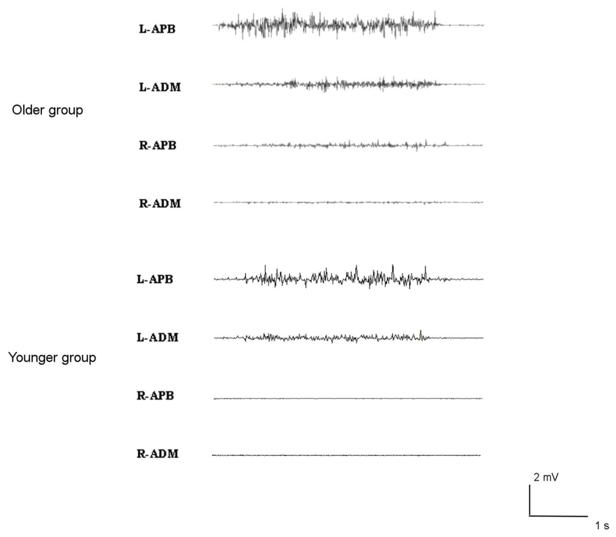


FIGURE 3 | Examples of mirror movements in an older subject (upper traces), compared to a young subject (lower traces).

right ISP_{area}: a smaller right ISP_{area} is associated with worse motor performances with both upper limbs in NHPT (for right NHPT $p = 0.021$, $\rho = 0.499$; for left NHPT $p = 0.006$, $\rho = 0.576$), FT (for right FT $p = 0.009$, $\rho = -0.555$; for left FT $p = 0.027$, $\rho = -0.483$), and grip strength (R: $p = 0.024$, $\rho = -0.492$; L: $p = 0.049$, $\rho = -0.435$). There were no further significant correlations with the other variables analyzed.

DISCUSSION

Our data are consistent with the fact that physiological aging is characterized by a deterioration of interhemispheric inhibition, as previously reported in recent TMS studies (Davidson and Tremblay, 2013; Petitjean and Ko, 2013). The present results bring further details on these abnormal interactions by reporting all components of ISP (duration, onset, and area) and correlating them with other measurements of motor control.

The reduction of all ISP parameters, bilaterally, reflects a declined efficiency of interhemispheric interactions, most probably due to a decreased transcallosal inhibition (Bodwell et al., 2003). Indeed, physiological aging is accompanied by a progressive degeneration of the cerebral tissue as demonstrated by the reduction in fractional anisotropy in the cerebral white matter (Pfefferbaum et al., 2000; Pfefferbaum and Sullivan, 2003; Rovaris et al., 2003; Head et al., 2004). This progressive degeneration involves also the corpus callosum, especially in its anterior portions (Abe et al., 2002; Head et al., 2004; Ota et al., 2006) that connects bilateral motor cortices (Zarei et al., 2006). The defective interhemispheric communication might thus be responsible for the more symmetrical cerebral activity observed in EEG or fMRI studies (Sailer et al., 2000; Hutchinson et al., 2002; Mattay et al., 2002; Labyt et al., 2006; Riecker et al., 2006; Ward et al., 2007; Vallesi et al., 2010) and might also be responsible for the increased frequency of MM, as previously shown in patients with agenesis of the corpus callosum (Mayston et al., 1999; Galléa et al., 2011). Indeed, our older group showed an increase in MM frequency, as the expression of a reduced ability to inhibit the tendency to activate bilateral motor cortices during a simple unimanual motor task (Cincotta and Ziemann, 2008). Thus, our results support the

Table 4 | Hand motor performances are shown in both groups of participants (younger and older).

Hand motor performances	**Younger group Average ± SD**	***p*-Value R vs. L**	**Older group Average ± SD**	***p*-Value R vs. L**	***p*-Value Younger vs. older**
FT (Hz)	**L** 4.9 ± 0.79	$p < 0.001$*	**L** 3.65 ± 0.55	$p < 0.001$*	$p < 0.001$*
	R 6.44 ± 1.13		**R** 4.51 ± 0.68		$p < 0.001$*
Grip strength (kg)	**L** 0.92 ± 0.24	$p = 0.051$	**L** 0.71 ± 0.18	$p = 0.051$	$p = 0.016$*
	R 0.96 ± 0.26		**R** 0.73 ± 0.22		$p = 0.016$*
NHPT (s)	**L** 17.05 ± 1.62	$p < 0.001$*	**L** 20.69 ± 3.06	$p < 0.001$*	$p < 0.001$*
	R 15.82 ± 1.6		**R** 18.87 ± 2.14		$p < 0.001$*

FT, finger tapping; NHPT, Nine Hole Peg Test; R-Hand, right hand; L-Hand, left hand; SD, standard deviation; L, Left; R, Right.

**Statistically significant differences.*

hypothesis of an abnormal bilateral cortical activation in the early processes of physiological aging, as described in the literature during the execution of unilateral simple motor tasks, probably due to a disruption of inter-cortical inhibitory circuits.

In our older group, the declined IHI was associated with a reduction of the cortical representation of hand muscle on the right (non-dominant) hemisphere. More specifically, while in the younger group APB and ADM muscles were symmetrically represented on the two motor cortices, in our older subjects the cortical maps resulted smaller on the right hemisphere compared with the left (dominant) one. Moreover, in older subjects, APB cortical representation on the right hemisphere was significantly reduced compared with the younger ones. No significant differences were found between groups for ADM map on the right hemisphere, probably because ADM muscle is physiologically poorly represented on motor cortices even in young people (Menon et al., 2014). As a consequence, physiological changes in hand muscles representations would be more apparent on the APB map.

This finding of a reduced cortical hand muscles representation on the right hemisphere in older subjects recalls the "right hemi-aging model" (Dolcos et al., 2002). This model is based on some evidence, especially in cognitive functions, of a progressive involution of the right cerebral hemisphere during physiological aging, but has never been demonstrated through neurophysiological studies, so far. Moreover, the hypothesis of a right hemisphere involution could explain previous findings of strong hand-dominance with a reduction of the prevalence of left-handedness in older subjects (Gilbert and Wysocki, 1992). Indeed, the progressive decline in left hand muscle representation at the cortical level could lead aging subjects to use preferentially their right hand.

We did not find significant differences in RMTs between the two groups, confirming the results of previous studies (Peinemann et al., 2001; Pitcher et al., 2003; Oliviero et al., 2006; Fujiyama et al., 2012). Thus, it seems that normal aging would not be accompanied by a change in the excitability of the pyramidal cells membrane, suggesting that Na+ and Ca2+ channels of the pyramidal cells' axons are not modified by physiological aging (Ziemann et al., 1996). A previous study showed increased RMTs in older subjects (Rossini et al., 1992). This divergence could be explained by the higher age of the subjects (age-range 51–86 years) and the use of a different (circular) coil. Interestingly, Petitjean and Ko (2013) also found an increased RMT in the older group, but only on the right hemisphere (Petitjean and Ko, 2013). This latter result could be compatible with the "right hemi-aging model."

As expected, the older group had slower hand motor performances. One could attribute such decline to the loss of muscle mass and strength primarily due to the loss of alpha motoneurons and the subsequent denervation of muscle fibers in aging (Doherty et al., 1993). However, these motoneuron losses are seen only after the seventh or eighth decade of age (Tomlinson and Irving, 1997). Thus, earlier changes may be attributable to supraspinal mechanisms. Indeed, Pitcher et al. (2003) demonstrated a greater trial-to-trial variability in MEP amplitudes in older subjects, attributed to a reduced synchronization of I waves in the descending volleys. Moreover, aging is associated with changes in NMDA-receptors function, in particular at the striatal level (Landfield and Pitler, 1984; Disterhoft et al., 1996; Thibault et al., 2001), leading to less efficient striatal processing of cortical information. Akopian and Walsh (2006) demonstrated age-related differences in long-term potentiation, associated with reduced sensitivity to block NMDA receptors. These modulations of corticostriatal functioning in normal aging might thus contribute to age-related deficits in striatum control of movement. These data suggest that normal aging is accompanied by impaired glutamatergic (excitatory) transmission. Moreover, inhibitory circuits would also be involved in the mechanisms of physiological aging since TMS studies demonstrated a reduced efficacy of intra-cortical inhibitory interneurons in older people. Indeed, apart from IHI deficits, age-related decreased short-interval intra-cortical inhibition (SICI) and cortical silent period durations have been shown, illustrating deficits in GABAergic (a and b) transmission (Peinemann et al., 2001; Oliviero et al., 2006; Fujiyama et al., 2012). Thus, all these previous data combined with ours suggest that early processes of physiological aging are accompanied by an imbalance in the regulation of inhibitory and excitatory circuits that might participate to the age-related worsening of motor abilities.

Degradation of motor performance in normal aging would also be related to several other factors, such as corpus callosum functions. Even unilateral movements require the functional integrity of the corpus callosum. Indeed, lesions of the corpus callosum increase the incidence of MM (Cox et al., 2012), which are also often observed in young children who have an immature corpus callosum (Mayston et al., 1999). It is thus not surprising that motor performances and ISP were significantly correlated in our study. This result might be an indirect correlation reflecting deficient corpus callosum connections and/or intrahemispheric inhibition. Indeed, ISP measurements reflect bilateral mechanisms involving activation of transcallosal fibers from one hemisphere to the other and local intra-cortical inhibitory interneurons. Thus, an ISP reduction could be due to dysfunction of one or both of these components. This could explain why right ISP area reduction correlated significantly with motor performance of both hands. If the functional decline within the right hemisphere tends to appear earlier than the left hemisphere, we may hypothesize that the right ISP measurements might be more sensitive to highlight correlations between motor performances and interhemispheric interactions. It would now be of great interest to study older aging populations in order to determine how these intra- and interhemispheric interactions evolve with time.

To conclude, our present findings suggest that early processes of physiological aging are marked by interhemispheric dissociation of motor cortices, characterized, at least in right-handed subjects, by a decline of the non-dominant hemisphere and of transcallosal interactions. In order to better qualify these early age-related changes in motor control, it would be of great interest to explore the dynamics of such changes during skilled motor behavior.

ACKNOWLEDGMENTS

This study was partly supported by the Joint Italian-Israeli laboratory San Raffaele-Weizmann (Italian Ministry of Foreign Affairs).

REFERENCES

Abe, O., Aoki, S., Hayashi, N., Yamada, H., Kunimatsu, A., Mori, H., et al. (2002). Normal aging in the central nervous system: quantitative MR diffusion-tensor analysis. *Neurobiol. Aging* 23, 433–441. doi:10.1016/S0197-4580(01)00318-9

Akopian, G., and Walsh, J. P. (2006). Pre- and postsynaptic contributions to age-related alterations in corticostriatal synaptic plasticity. *Synapse* 60, 223–238. doi:10.1002/syn.20289

Bodwell, J. A., Mahurin, R. K., Waddle, S., Price, R., and Cramer, S. C. (2003). Age and features of movement influence motor overflow. *J. Am. Geriatr. Soc.* 51, 1735–1739. doi:10.1046/j.1532-5415.2003.51557.x

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

Chen, R., Yung, D., and Li, J. Y. (2003). Organization of ipsilateral excitatory and inhibitory pathways in the human motor cortex. *J. Neurophysiol.* 89, 1256–1264. doi:10.1152/jn.00950.2002

Chieffo, R., Inuggi, A., Straffi, L., Coppi, E., Gonzalez-Rosa, J., Spagnolo, F., et al. (2013). Mapping early changes of cortical motor output after subcortical stroke: a transcranial magnetic stimulation study. *Brain Stimul.* 6, 322–329. doi:10.1016/j.brs.2012.06.003

Cincotta, M., and Ziemann, U. (2008). Neurophysiology of unimanual motor control and mirror movements. *Clin. Neurophysiol.* 119, 744–762. doi:10.1016/j.clinph.2007.11.047

Conover, W. J., and Iman, L. (1982). Analysis of covariance using the rank transformation. *Biometrics* 38, 715–724. doi:10.2307/2530051

Cox, B. C., Cincotta, M., and Espay, A. J. (2012). Mirror movements in movement disorders: a review. *Tremor Other Hyperkinet. Mov. (N. Y.)* 2, tre-02-59-398-1.

Davidson, T., and Tremblay, F. (2013). Age and hemispheric differences in transcallosal inhibition between motor cortices: an ispsilateral silent period study. *BMC Neurosci.* 14:62. doi:10.1186/1471-2202-14-62

Disterhoft, J. F., Thompson, L. T., Moyer, J. R. Jr., and Mogul, D. J. (1996). Calcium-dependent afterhyperpolarization and learning in young and aging hippocampus. *Life Sci.* 59, 413–420. doi:10.1016/0024-3205(96)00320-7

Doherty, T. J., Vandervoort, A. A., and Brown, W. F. (1993). Effects of ageing on the motor unit: a brief review. *Can. J. Appl. Physiol.* 18, 331–358. doi:10.1139/h93-029

Dolcos, F., Rice, H. J., and Cabeza, R. (2002). Hemispheric asymmetry and aging: right hemisphere decline or asymmetry reduction. *Neurosci. Biobehav. Rev.* 26, 819–825. doi:10.1016/S0149-7634(02)00068-4

Ferbert, A., Priori, A., Rothwell, J. C., Day, B. L., Colebatch, J. G., and Marsden, C. D. (1992). Interhemispheric inhibition of the human motor cortex. *J. Physiol.* 453, 525–546.

Fujiyama, H., Hinder, M. R., Schmidt, M. W., Tandonnet, C., Garry, M. I., and Summers, J. J. (2012). Age-related differences in corticomotor excitability and inhibitory processes during a visuomotor RT task. *J. Cogn. Neurosci.* 24, 1253–1263. doi:10.1162/jocn_a_00201

Galléa, C., Popa, T., Billot, S., Méneret, A., Depienne, C., and Roze, E. (2011). Congenital mirror movements: a clue to understanding bimanual motor control. *J. Neurol.* 258, 1911–1919. doi:10.1007/s00415-011-6107-9

Gilbert, A. N., and Wysocki, C. J. (1992). Hand preference and age in the United States. *Neuropsychologia* 30, 601–608. doi:10.1016/0028-3932(92)90065-T

Giovannelli, F., Borgheresi, A., Balestrieri, F., Zaccara, G., Viggiano, M. P., Cincotta, M., et al. (2009). Modulation of interhemispheric inhibition by volitional motor activity: an ipsilateral silent period study. *J. Physiol.* 587, 5393–5410. doi:10.1113/jphysiol.2009.175885

Head, D., Buckner, R. L., Shimony, J. S., Williams, L. E., Akbudak, E., Conturo, T. E., et al. (2004). Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: evidence from diffusion tensor imaging. *Cereb. Cortex* 14, 410–423. doi:10.1093/cercor/bhh003

Hoy, K. E., Fitzgerald, P. B., Bradshaw, J. L., Armatas, C. A., and Georgiou-Karistianis, N. (2004). Investigating the cortical origins of motor overflow. *Brain Res. Rev.* 46, 315–327. doi:10.1016/j.brainresrev.2004.07.013

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

Inuggi, A., Amato, N., Magnani, G., González-Rosa, J. J., Chieffo, R., Comi, G., et al. (2011). Cortical control of unilateral simple movement in healthy aging. *Neurobiol. Aging* 32, 524–538. doi:10.1016/j.neurobiolaging.2009.02.020

Labyt, E., Cassim, F., Szurhaj, W., Bourriez, J. L., and Derambure, P. (2006). Oscillatory cortical activity related to voluntary muscle relaxation: influence of normal aging. *Clin. Neurophysiol.* 117, 1922–1930. doi:10.1016/j.clinph.2006.05.017

Landfield, P. W., and Pitler, T. A. (1984). Prolonged Ca2+-dependent afterhyperpolarizations in hippocampal neurons of aged rats. *Science* 226, 1089–1092. doi:10.1126/science.6494926

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

Mayston, M. J., Harrison, L. M., and Stephens, J. A. (1999). A neurophysiological study of mirror movements in adults and children. *Ann. Neurol.* 45, 583–594. doi:10.1002/1531-8249(199905)45:5<583::AID-ANA6>3.0.CO;2-W

Menon, P., Kiernan, M. C., and Vucic, S. (2014). Cortical excitability differences in hand muscles follow a split-hand pattern in healthy controls. *Muscle Nerve* 49, 836–844. doi:10.1002/mus.24072

Meyer, B. U., Röricht, S., Gräfin von Einsiedel, H., Kruggel, F., and Weindl, A. (1995). Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum. *Brain* 118(Pt 2), 429–440. doi:10.1093/brain/118.2.429

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

Oliviero, A., Profice, P., Tonali, P. A., Pilato, F., Saturno, E., Dileone, M., et al. (2006). Effects of aging on motor cortex excitability. *Neurosci. Res.* 55, 74–77. doi:10.1016/j.neures.2006.02.002

Ota, M., Obata, T., Akine, Y., Ito, H., Ikehira, H., Asada, T., et al. (2006). Age-related degeneration of corpus callosum measured with diffusion tensor imaging. *Neuroimage* 31, 1445–1452. doi:10.1016/j.neuroimage.2006.02.008

Oxford Grice, K., Vogel, K. A., Le, V., Mitchell, A., Muniz, S., and Vollmer, M. A. (2003). Adult norms for a commercially available Nine Hole Peg Test for finger dexterity. *Am. J. Occup. Ther.* 57, 570–573. doi:10.5014/ajot.57.5.570

Peinemann, A., Lehner, C., Conrad, B., and Siebner, H. R. (2001). Age-related decrease in paired-pulse intracortical inhibition in the human primary motor cortex. *Neurosci. Lett.* 313, 33–36. doi:10.1016/S0304-3940(01)02239-X

Petitjean, M., and Ko, J. Y. (2013). An age-related change in the ipsilateral silent period of a small hand muscle. *Clin. Neurophysiol.* 124, 346–353. doi:10.1016/j.clinph.2012.07.006

Pfefferbaum, A., and Sullivan, E. V. (2003). Increased brain white matter diffusivity in normal adult aging: relationship to anisotropy and partial voluming. *Magn. Reson. Med.* 49, 953–961. doi:10.1002/mrm.10452

Pfefferbaum, A., Sullivan, E. V., Hedehus, M., Lim, K. O., Adalsteinsson, E., and Moseley, M. (2000). Age-related decline in brain white matter anisotropy measured with spatially corrected echo-planar diffusion tensor imaging. *Magn. Reson. Med.* 44, 259–268. doi:10.1002/1522-2594(200008)44:2<259::AID-MRM13>3.0.CO;2-6

Pitcher, J. B., Ogston, K. M., and Miles, T. S. (2003). Age and sex differences in human motor cortex input-output characteristics. *J. Physiol.* 546, 605–613. doi:10.1113/jphysiol.2002.029454

Riecker, A., Groschel, K., Ackermann, H., Steinbrink, C., Witte, O., and Kastrup, A. (2006). Functional significance of age-related differences in motor activation patterns. *Neuroimage* 32, 1345–1354. doi:10.1016/j.neuroimage.2006.05.021

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., and Safety of TMS Consensus Group. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin. Neurophysiol.* 120, 2008–2039. doi:10.1016/j.clinph.2009.08.016

Rossini, P. M., Desiato, M. T., and Caramia, M. D. (1992). Age-related changes of motor evoked potentials in healthy humans: non-invasive evaluation of central and peripheral motor tracts excitability and conductivity. *Brain Res.* 593, 14–19. doi:10.1016/0006-8993(92)91256-E

Rovaris, M., Iannucci, G., Cercignani, M., Sormani, M. P., De Stefano, N., Gerevini, S., et al. (2003). Age-related changes in conventional, magnetization transfer, and diffusion-tensor MR imaging findings: study with whole-brain tissue histogram analysis. *Radiology* 227, 731–738. doi:10.1148/radiol.2273020721

Sailer, A., Dichgans, J., and Gerloff, C. (2000). The influence of normal aging on the cortical processing of a simple motor task. *Neurology* 55, 979–985. doi:10.1212/WNL.55.7.979

Spagnolo, F., Coppi, E., Chieffo, R., Straffi, L., Fichera, M., Nuara, A., et al. (2013). Interhemispheric balance in Parkinson's disease: a transcranial magnetic stimulation study. *Brain Stimul.* 6, 892–897. doi:10.1016/j.brs.2013.05.004

Talelli, P., Waddingham, W., Ewas, A., Rothwell, J. C., and Ward, N. S. (2008). The effect of age on task-related modulation of interhemispheric balance. *Exp. Brain Res.* 186, 59–66. doi:10.1007/s00221-007-1205-8

Thibault, O., Hadley, R., and Landfield, P. W. (2001). Elevated postsynaptic [Ca2+]i and L-type calcium channel activity in aged hippocampal neurons: relationship to impaired synaptic plasticity. *J. Neurosci.* 15, 9744–9756.

Tomlinson, B. E., and Irving, D. (1997). The numbers of limb motor neurons in the human lumbosacral cord throughout life. *J. Neurol. Sci.* 34, 213–219. doi:10.1016/0022-510X(77)90069-7

Trompetto, C., Bove, M., Marinelli, L., Avanzino, L., Buccolieri, A., and Abbruzzese, G. (2004). Suppression of the transcallosal motor output: a transcranial magnetic stimulation study in healthy subjects. *Exp. Brain Res.* 158, 133–140. doi:10.1007/s00221-004-1881-6

Vallesi, A., McIntosh, A. R., Kovacevic, N., Chan, S. C., and Stuss, D. T. (2010). Age effects on the asymmetry of the motor system: evidence from cortical oscillatory activity. *Biol. Psychol.* 85, 213–218. doi:10.1016/j.biopsycho.2010.07.003

Ward, N. S., Swayne, O. B., and Newton, J. M. (2007). Age-dependent changes in the neural correlates of force modulation: an fMRI study. *Neurobiol. Aging* 29, 1434–1446. doi:10.1016/j.neurobiolaging.2007.04.017

Zarei, M., Johansen-Berg, H., Smith, S., Ciccarelli, O., Thompson, A. J., and Matthews, P. M. (2006). Functional anatomy of interhemispheric cortical connections in the human brain. *J. Anat.* 209, 311–320. doi:10.1111/j.1469-7580.2006.00615.x

Ziemann, U., Lonnecker, S., Steinhoff, B. J., and Paulus, W. (1996). Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. *Ann. Neurol.* 40, 367–378. doi:10.1002/ana.410400306

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

Received: 30 May 2014; accepted: 25 July 2014; published online: 11 August 2014.
Citation: Coppi E, Houdayer E, Chieffo R, Spagnolo F, Inuggi A, Straffi L, Comi G and Leocani L (2014) Age-related changes in motor cortical representation and interhemispheric interactions: a transcranial magnetic stimulation study. Front. Aging Neurosci. ***6****:209. doi: 10.3389/fnagi.2014.00209*
This article was submitted to the journal Frontiers in Aging Neuroscience.

frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 30 October 2013
doi: 10.3389/fnagi.2013.00066

Effects of aerobic fitness on aging-related changes of interhemispheric inhibition and motor performance

Keith M. McGregor[1,2]*, **Joe R. Nocera**[1,2], **Atchar Sudhyadhom**[3,4], **Carolynn Patten**[3,5], **Todd M. Manini**[6], **Jeffrey A. Kleim**[7], **Bruce Crosson**[1,2] **and Andrew J. Butler**[1,8]

[1] *Center for Visual and Neurocognitive Rehabilitation, U.S. Department of Veterans Affairs, Decatur, GA, USA*
[2] *Department of Neurology, Emory University, Atlanta, GA, USA*
[3] *VA Center of Excellence, Gainesville, FL, USA*
[4] *Department of Neurosurgery, University of Florida, Gainesville, FL, USA*
[5] *Department of Physical Therapy, University of Florida, Gainesville, FL, USA*
[6] *Department of Geriatrics, University of Florida, Gainesville, FL, USA*
[7] *School of Biological and Health Systems Engineering, Arizona State University, Tempe, AZ, USA*
[8] *Department of Physical Therapy, Georgia State University, Atlanta, GA, USA*

Edited by:
Timothy D. Law, Ohio University Heritage College of Osteopathic Medicine, USA

Reviewed by:
Heather Allyson Bimonte-Nelson, Arizona State University, USA
Marcia Chaves, Federal University of Rio Grande do Sul, Brazil

***Correspondence:**
Keith M. McGregor, Department of Neurology; Emory University, 1518 Clifton Road NE, Decatur, GA 30033, USA
e-mail: keith.mcgregor@emory.edu

Physical fitness has been long associated with maintenance and improvement of motor performance as we age. In particular, measures of psychomotor speed and motor dexterity tend to be higher in physically fit aging adults as compared to their sedentary counterparts. Using functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS), we explored the patterns of neural activity that may, in part, account for differences between individuals of varying physical fitness levels. In this study, we enrolled both sedentary and physically fit middle age (40–60) and younger (18–30) adults and measured upper extremity motor performance during behavioral testing. In a follow-up session, we employed TMS and fMRI to assess levels of interhemispheric communication during unimanual tasks. Results show that increased physical fitness is associated with better upper extremity motor performance on distal dexterity assessments and increased levels of interhemispheric inhibition in middle age adults. Further, the functional correlates of changes of ipsilateral activity appears to be restricted to the aging process as younger adults of varying fitness levels do not differ in hemispheric patterns of activity or motor performance. We conclude that sedentary aging confers a loss of interhemispheric inhibition that is deleterious to some aspects of motor function, as early as midlife, but these changes can be mediated by chronic engagement in aerobic exercise.

Keywords: aging neuroscience, aging, fMRI, TMS, physical fitness, interhemispheric communication, negative BOLD, dexterity

INTRODUCTION

As we age, manual dexterity and upper extremity motor performance begins to decline. While there are many factors that are implicated in this process from a mechanical level (e.g., rheumatism, decreased muscle mass, increased rigidity of connective tissues) the predominant factor for aging-related decreases in hand motor function is most likely caused by alteration of neural function within the central nervous system (Cole et al., 1998; Latash and Zatsiorsky, 2009; Christou, 2011). There is long-standing evidence that indicates that the continuous engagement in aerobic activity throughout the lifespan helps maintain dexterity and coordinated hand function (Spirduso, 1975, 1980; Spirduso et al., 1988). However, the link between neural function, aerobic activity, and measures of motor performance in aging has only recently been approached. Application of functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) to address this problem has discerned that aging-related changes in patterns of cortical activity predicts changes in motor function associated with aging (Fling et al., 2011a; McGregor et al., 2011, 2012a; Bernard and Seidler, 2012). Moreover, these aging-related changes in activity may be altered by the regular engagement in aerobic exercise, which may explain the maintenance of hand dexterity in exercising aging adults (McGregor et al., 2011, 2012b; Davidson and Tremblay, 2013).

An increasing body of literature indicates that as we age, we experience a decrease in the level of interhemispheric inhibition in primary sensorimotor areas particularly during execution of motor tasks in the upper extremity (Sale and Semmler, 2005; Riecker et al., 2006; Fujiyama et al., 2009; Seidler et al., 2010; McGregor et al., 2011; Petitjean and Ko, 2012; Davidson and Tremblay, 2013). During unimanual hand movements the contralateral (to the moving hand) primary motor cortex results in increased metabolic activity and increased activity relative to baseline resting conditions (Rao et al., 1993; Allison et al., 2000; Newton et al., 2005). However, recent evidence has revealed that activity of the ipsilateral cortex during such movements may vary according to one's chronological age or level of physical conditioning (McGregor et al., 2011, 2012a; Davidson and Tremblay, 2013). The presence of interhemispheric inhibition can be measured using fMRI, where during unimanual tasks, activity in the ipsilateral primary motor cortex (iM1) is suppressed or deactivated, as indicated by a negative BOLD response (decreased T2* signal to levels below that of resting baseline conditions) in this area (Allison et al., 2000; Stefanovic et al., 2004; Newton et al., 2005; Riecker et al., 2006; McGregor et al., 2009, 2011). This signal pattern is most prevalent in younger adults (18–20 years) (Riecker et al., 2006). In contrast, during similar movements, elderly adults (60+ years) appear to recruit the ipsilateral motor (iM1) cortex, indicated by the presence of a positive BOLD response in this area (Hlushchuk and Hari, 2006; Naccarato et al., 2006; Riecker et al., 2006; Ward et al., 2008; McGregor et al., 2009, 2011; Langan et al., 2010).

However, the recruitment of the ipsilateral cortex in elderly adults may vary as a function of their physical fitness level. Recently, Voelcker-Rehage et al. (2010) reported that elderly adults (mean: 68 years) with higher levels of motor (muscle strength and coordination) and physical fitness, evidenced decreases in ipsilateral BA4 activity relative to baseline during a unimanual button response task. In our own lab, we compared elderly adults (60+ years) who regularly engaged in aerobic physical activity against a relatively sedentary elderly cohort using both fMRI and TMS to assess interhemispheric inhibition. The results showed that not only were the aerobically active elderly adults more likely to show a negative BOLD in fMRI in the ipsilateral motor cortex, but these individuals also evidenced significantly longer ipsilateral silent periods (iSPs) (a measure of interhemispheric inhibition), as assessed by TMS (McGregor et al., 2011). A recent study with elderly adults by Davidson and Tremblay (2013) also yielded similar findings respective of TMS in that the most physically fit individuals showed the longest iSPs. Based on the above evidence, there is sufficient support to contend that as we enter sedentary senescence (60+ years), interhemispheric inhibition decreases and may be correlated to changes in motor function.

However, aging is not a discrete process and the selection of only extreme age cohorts (18–30 or 60+ years) represents a challenge for cross-sectional investigation relating to neural control of movement. What happens in middle age strongly informs on the processes of change that appear in senescence. To address this concern, the present investigation enrolled middle age adults (40–60 years) of varying fitness levels for assessment of interhemispheric communication. We contrast this age cohort with younger adults (18–30 years), also of varying fitness level. As such, the present study is a cross-section of middle age ($N = 38$) and younger adults ($N = 21$), each grouped by their self-reported (validated by a direct aerobic assessment) aerobic activity. We employed both fMRI and TMS with these individuals to evaluate levels of interhemispheric inhibition using each modality in addition to examining each participant's performance on a battery of motor assessments. In fMRI, participants engaged in a simple unimanual tapping sequence previously shown to evoke differential BOLD response across age group comparisons (McGregor et al., 2011). For TMS, we assessed each participant's iSP, which is an index of interhemispheric inhibition (Meyer et al., 1995). An additional focus of the present study was to investigate the relationship of motor function tests to BOLD and TMS indices of interhemispheric inhibition. We hypothesized that more physically active individuals would show greater levels of interhemispheric inhibition and better motor performance. Further, we hypothesized this trend would be exacerbated in comparisons of middle age adults. We believe this project is the first study to apply both neuroimaging and neurophysiological techniques to probe the effects of cardiovascular fitness on the relationship between motor function and aging in midlife.

MATERIALS AND METHODS

PARTICIPANTS

Of 240 screened candidates we enrolled 38 middle aged (ages 40–60) and 21 (ages 19–32) younger adults in the current study who were reportedly healthy at the time of screening and study participation. Individuals were screened into one of two categories, either sedentary or physically active, based on self-reported exercise activity (Physical Activity Readiness Questionnaire – PARQ) and performance on a submaximal cardiovascular fitness assessment (YMCA Cycling Protocol). Eight additional participants (not included in the above total) were removed from study consideration due to mismatch fitness screen and self-report, scheduling difficulties, or reported discomfort in a mock MRI environment. Included participant characteristics are summarized in **Table 1**. All participants were right handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). Participants qualifying for the sedentary group were comprised of reportedly healthy individuals that engaged in voluntary cardiovascular exercise for fewer than 90 total minutes per week and had an assessed VO_2max estimate of <35. This group was termed the "sedentary group" for each age cohort. The second group of adults was comprised of healthy individuals who reportedly engaged in bouts of medium to vigorous voluntary aerobic (swimming, bicycling, jogging, etc.) exercise lasting at least 45 min at least three times per week and an assessed estimate of VO_2max of >35. As such, there were four groups in the current study: physically active middle age adults, sedentary middle age adults, physically active younger adults, and sedentary younger adults. Of the physically active middle age adults, 12 individuals reported they engaged in physically active professions (e.g., personal trainer, aerobic fitness instructor).

We excluded individuals with cardiac history (angina, prior cardiac arrest, uncontrolled hypertension) contraindicating tests of aerobic fitness. We also excluded individuals with contraindications to MRI including metal implants, alcohol, or drug abuse, neurological disorder (tremor, stroke, motor disorders, multiple

Table 1 | Overall participant characteristics.

	Middle age	Younger
Age*	52.1 (6.44) (41–60)*	22.1 (3.41) (19–29)*
N/gender	38/21 Female	21/12 Female
Education	16.1 (2.33)	15.6 (1.9)
BMI*	24.4 (3.9)	24.36 (5.11)
VO_2max	38.76 (14.1)	40.25 (11.37)
Weekly activity (min)*	76 (33.4)	64.7 (32.5)

*BMI, body mass index. Cell values denote group means. Parentheses indicate standard deviation within cell. Bracket indicates range. Student's t-test contrast significance at *$p < 0.05$.*

sclerosis), major psychological disorder, or hearing difficulties. A recent medication history was taken for each participant. Persons on medications that were contraindicated for fitness testing (beta blockers) were also disqualified from the study. Cortical activation characteristics in primary motor cortex may be altered by skilled (Jancke et al., 2000; Krampe et al., 2002) or repeated digit movement practice (Gordon et al., 2008) so we excluded participants if they reported upon inquiry that they engaged in repeated skilled finger practice (musical instruments, expert typing, etc.) with practice specified as at least three 1-h training sessions performed on a weekly basis. Study personnel completed the informed consent process with each participant following protocols approved by the University of Florida's Institutional Review Board (IRB).

SESSIONS AND PROCEDURES

Participation for the study occurred over two sessions separated by at least five, but no more than 21 calendar days. We attempted to schedule both sessions at the same time of day to avert potential differences due to circadian cycles. Participants were asked to refrain from drinking caffeinated beverages at least 3 h prior to each session to prevent potential signal alteration in imaging. **Figure 1** presents a flowchart of study participation.

FIRST SESSION: MOTOR ASSESSMENT AND FITNESS MEASURES

Motor assessment

Participants completed motor assessments of the dominant hand including: hand and pinch grip strength, the Halstead Finger Tapping task, simple reaction time assessment, Purdue pegboard (pin placement and assembly tasks), Poffenberger Crossed-Uncrossed difference test, hand steadiness test (Lafayette Instruments, Lafayette, IN, USA), and the Nine-Hole Pegboard task. Additionally, to test distal motor dexterity, participants engaged in a coin-rotation task with two conditions. In the first condition, the participant rotated a coin (U.S. nickel) 20 times as quickly as possible using the index finger, middle finger, and thumb, with time to completion as the outcome measure. An assessment of motor dysfunction in neurological practice, the coin-rotation test has been shown to be diagnostic of distal motor function both in cases of suspected pathology and aging in the absence of pathology (Hanna-Pladdy et al., 2002; Mendoza et al., 2009). In the second coin-rotation condition, the participant maintained an isometric pinch force of 25–35% of maximum voluntary force with a pinch grip dynamometer using a lateral grip. Coin-rotation tasks were performed with both the left and right hands. Both the hand used for coin-rotation and trial condition (unimanual or bimanual task) were pseudo-randomized and counter-balanced across participants to account for potential order effects. Accidental coin drops were excluded from consideration and the participant repeated the trial if a drop occurred. Participants were allowed three to five practice trials to acclimate to the rotation task in each task condition. The difference score between the bimanual and unimanual task conditions was calculated to assess the effect of bimanual activity. Grip force was measured in lateral pinch, precision pinch, and power grip using Jamar brand dynamometers. For the simple reaction time test and crossed-uncrossed difference test, E-Prime software (PST Software, Pittsburgh, PA, USA) was used to present a target stimulus on a computer screen situated 60 cm away from the participant's chin. In both paradigms, participant maintained surface contact with the hand and depressed a computer keypad button as quickly as possible in response to the visual stimulus. Inter-stimulus intervals were pseudo-randomized between 250 and 1000 ms. The simple reaction time task involved the presentation of a stimulus in the center of the screen and the participant response only with the right hand for 50 trials. The Poffenberger Crossed-Uncrossed difference test required the participant to visually fixate at a centered fixation cross and make an immediate keyboard response when a small circle was presented offset 3° either to the right or left of the fixation cross (Marzi, 1999). This was done in consecutive blocks of 100 trials for the right and left hand, respectively. The uncrossed response was the time required to press the button when the circle was presented in the same visual hemifield as the hand responding (e.g., right side stimulus with right-hand response). The crossed response condition was the time required to press the button when the stimulus was in the opposite visual hemifield (e.g., left side stimulus with right-hand response). The difference score between the two conditions has been shown to describe potential alteration of callosal function across age groups in previous work (Schulte et al., 2005), see also (Bernard et al., 2011).

Biometrics

After behavioral testing, the participant was brought to a physical assessment facility. There we compiled a list of physical function

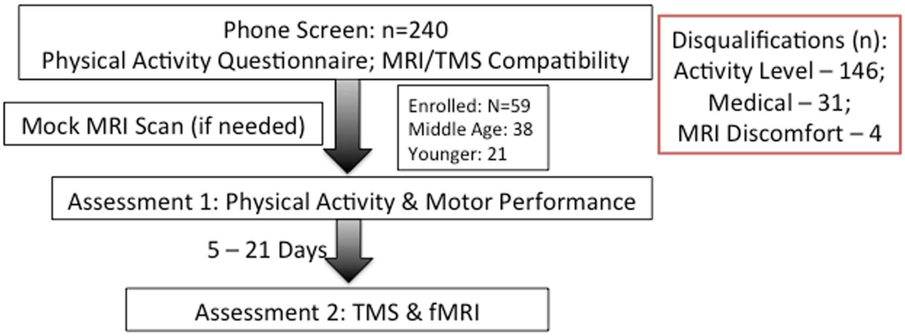


FIGURE 1 | Flowchart of study. Category and number of screen-outs are listed on right.

measures for each individual. These included height, weight, blood pressure, resting heart rate, and a simple test of balance (sitting at rest on the bicycle ergometer) to ensure compatibility with a cycle-based fitness assessment.

Aerobic endurance

To assess aerobic fitness level, we employed the cycle-based YMCA submaximal VO_2 cardiovascular fitness assessment. This test is an accurate method to assess aerobic fitness level without placing maximal strain on the participant (Garatachea et al., 2007). In the YMCA test, heart rate workload values are obtained at two to four points and extrapolated to predict workload at the estimated maximum heart rate (MHR) (e.g., 220-age). VO_2max is then calculated from the predicted maximum workload. Participants rode a stationary bicycle for two to four 3-min stages. The first stage was a warm-up at 50 revolutions per minute (RPM) at a power level of 25 W. During all testing stages, heart rate was continuously monitored to ensure the participant did not exceed 85% of age-predicted MHR, at which point the exam would be stopped. For the analysis, average heart rate during the final 30 s of the second and third minutes was plotted against workload for each stage. Three-minute trial workloads below were chosen based on the participants' heart rate at the end of the warm-up period. The fourth 3-min stage was a cool-down period added to the end of the test. Outcome measures for the YMCA test were estimated VO_2max and estimated liters of oxygen consumed per minute.

SECOND SESSION: TRANSCRANIAL MAGNETIC STIMULATION AND FUNCTIONAL MRI

After at least five calendar days, the participant was scheduled for the second and final participation session. This session lasted for about 3 h and involved single-pulse TMS followed by fMRI.

SINGLE-PULSE TRANSCRANIAL MAGNETIC STIMULATION

For the TMS procedure, participants sat in a comfortable chair within the confines of a stereotactic positioning frame. Full procedural details have been described in another article (Kleim et al., 2007). Electromyography (EMG) was taken from the first dorsal interosseous (FDI) muscle on both hands. Muscle activation was monitored with a real-time oscilloscope software package (LabChart 7.0, ADInstruments Ltd., Colorado Springs, CO, USA). A Magstim 200^2 magnetic stimulator (The Magstim Company Ltd., Carmarthenshire, UK) with a 70-mm figure-of-eight coil was used to stimulate the left primary motor cortex during all TMS procedures. Navigation of the stimulator coil to target cortex was accomplished using coil registration to a standardized brain image provided by BrainSight software (Rogue-Research, Montreal, QC, Canada). During stimulation, the coil was placed tangential to the scalp with the handle pointing backwards and 45° away from the midline. The scalp site ("hotspot") corresponding to the lowest stimulator output sufficient to generate a magnetic evoked potential (MEP) of at least 50 mV in 6 out of 10 trials was defined as the site of lowest motor threshold (LMT). This hotspot was the site of stimulation for all measures in the current investigation, which are described below.

Two single-pulse TMS measures were considered for the current study: LMT value and iSP. LMT value simply represents the stimulator output value as a percentage of maximum stimulator output. For the iSP assessment, the left FDI muscle was contracted via pinch grip at 20–30% maximal voluntary contraction (MVC), determined by pinch dynamometer, and a 150% LMT stimulus was delivered to the left primary motor area FDI hotspot. Twenty consecutive trials were performed for iSP assessments. Participants were allowed a brief (1–2 min) rest after every five trials to allay potential fatigue. Prior to silent period assessment, the participant was instructed to maintain the non-active hand in a prone, resting position. EMG of the contralateral hand was monitored for mirror activity and the trial was discarded and repeated if such activity was observed.

FUNCTIONAL IMAGING

After the TMS session, participants were given a rest of ∼30 min during which time they were instructed on the procedures to be carried out during MRI. After acknowledging understanding of the tasks, the participant was brought to the imaging facility.

Parameters

Magnetic resonance images were acquired on a 3-T Achieva Whole-Body Scanner (Philips) using a 32-channel SENSE head coil. Head motion was minimized using foam padding and laser grid alignment. Before functional imaging sequences, structural images were acquired [$160\,\text{mm} \times 1.0\,\text{mm}$ thick sagittal slices, using a 3D T1-weighted sequence: time of echo (TE) = 8.057 ms; time of repetition (TR) = 3.685 ms; flip angle (FA) = 8]. Whole-brain high-resolution echo planar functional images (EPI) were acquired using $57\,\text{mm} \times 2\,\text{mm}$ thick axial slices and the following parameters: TE = 30 ms; TR = 4000 ms; FA = 87; FOV = $192\,\text{mm} \times 192\,\text{mm} \times 114\text{mm}$; Matrix = 96×96; SENSE factor = 1.5. Two dummy EPI acquisitions were acquired and discarded to allow for signal equilibration.

Stimuli were presented on a first surface mirror presentation system situated at the rear bore aperture of the magnet. Stimuli were sent via personal computer (PC) to a 30″ high-resolution (2560×1600 pixels) MR-compatible LCD display (Philips *in vivo* Systems) via fiber optic connection. A large mirror reflected the LCD display into the bore of the magnet. A mirror situated on the head coil then reversed the mirror image for presentation to the participant.

fMRI task

A block-design, right-hand motor task was used to evaluate interhemispheric cortical activation patterns. Blocks consisted of seven images (28 s) for both rest and active conditions. Six cycles (alternating between seven rest images and seven active images) comprised each run (5 min 36 s). In the scanner, participants engaged in two runs of the motor task and all performance data (accuracy, reaction times) was saved for later analysis. Participants were trained on the task inside the scanner prior to data acquisition. Between runs, participants again verified their understanding of the task via verbal report.

The motor task was a block presentation of a repeated button squeeze using an index finger to thumb opposition ("button tapping"). This task has been shown to exhibit a negative BOLD response in ipsilateral primary motor cortex (M1) in young adults

(Allison et al., 2000; Riecker et al., 2006; McGregor et al., 2011). Performance of similar tasks in sedentary elderly samples, however, shows positive BOLD responses in ipsilateral M1 (McGregor et al., 2009, 2011). Stimuli were presented using E-Prime software (PST Software, Pittsburgh, PA, USA). Button responses were made on a RP04U button response unit (BRU) manufactured by MagConcept (Sunnyvale, CA, USA) connected to the presentation computer. Researchers positioned the participants' fingers in the correct posture on the BRU prior to acquisition and instructed on target force output. The participant was asked to use the index finger-thumb squeeze to depress a button for each trial press with only as much force as required to generate a tactile "click" on the response device (equivalent to roughly 3N). The participants' left (non-active) hand was placed in a prone, resting position along the side of the body. Participants were visually monitored for movements of this hand during active task blocks. Consistent overt mirrored movement was used as a criterion for exclusion.

During the functional run, participants fixated gaze on a central fixation cross of a computer screen throughout each of two runs. Blocks were cued by the change of fixation cross varying between the word "Squeeze" (movement condition) or the word "Rest" (rest condition). During the movement condition, participants were instructed to time button presses with the flashing visual stimulus (2 Hz). Trials were briefly practiced in the scanner prior to image acquisition. Researchers in the scanner operation room monitored subject performance during the task.

ANALYSIS

Behavioral measures

Motor performance. Group data for behavioral measures were compared using between-subjects Student's t-test and p-values ≤ 0.05 were considered statistically significant. Statistical analyses were completed using the application JMP 9.0 (SAS Institute, Cary, NC, USA), unless otherwise specified.

Physical activity. We measured physical activity based on estimated VO_2max and self-reported weekly activity surveys. All individuals in the aerobically fit group had to exhibit a VO_2max of 35 ml/min/kg or greater and report a weekly engagement in aerobic activity of over 135 min. Sedentary individuals had to exhibit an assessed VO_2max of 34 ml/min/kg or lower and <90 min of physical activity per week. **Tables 2–4** present group data of physical attributes.

Mirror movements. As a criterion for data exclusion, we also included the presence of mirror movements during unimanual muscle contraction at the TMS session. We assessed such movements during 20 unimanual contractions each of both the left FDI muscle (via submaximal force pinch grip) using EMG. A mirror score for each hand was calculated for each trial by taking the root mean square of the EMG in the mirror hand and dividing by the median EMG root mean square value (over the 20 contractions) in the voluntary hand. This procedure was adapted from previously reported work (Hermsdorfer et al., 1995; Verstynen et al., 2007; McGregor et al., 2011). The mirror scores for the trials were then averaged within each hand squeeze condition. Individuals exhibiting a mirror score >0.20 were to be removed from study consideration. No participants evidenced significant mirror scores over threshold, however.

Table 2 | Aerobically fit participant characteristics.

	Active middle age	Active younger
Age*	51.3 (5.9) (41–60)*	23.1 (3.8) (19–29)*
N/gender	17/6 Female	12/6 Female
Education	16.1 (2.25)	16.4 (2.38)
BMI	22.1 (2.5)*	22.3 (3.5)
VO_2max	49.8 (12.7)*	47.3 (9.8)
Weekly activity (min)	146 (23.4)*	126.7 (22.5)

*BMI, body mass index. Cell values denote group means. Parentheses indicate standard deviation within cell. Bracket indicates range. Student's t-test contrast significance at *p < 0.05.*

Table 3 | Sedentary participant characteristics.

	Sedentary middle age	Sedentary younger
Age	51.3 (5.9) (41–60)	22.4 (2.9) (19–28)
N/Gender	21/12 Female	9/6 Female
Education	16.1 (2.25)	14.4 (3.38)
BMI	26.1 (3.95)*	28 (5.65)
VO_2max	29.8 (12.7)	30.8 (3.77)
Weekly activity (min)	36.7 (12.5)	40.3 (22.5)

*BMI, body mass index. Cell values denote group means. Parentheses indicate standard deviation within cell. Bracket indicates range. Student's t-test contrast significance at *p < 0.05.*

Table 4 | Fitness group differences.

	Middle age fit vs. sed	Younger fit vs. sed
Age	$t(36) = 0.64$, ns	$t(19) = 0.4$, ns
Education	$t(36) = 1.47$, ns	$t(19) = 1.4$, ns
BMI	$t(36) = 3.51$, $p < 0.01$*	$t(19) = 2.7$ $p = 0.01$
VO_2max	$t(36) = 6.22$, $p < 0.01$*	$t(19) = 5.3$ $p < 0.01$
Weekly activity (min)	$t(36) = 7.4$, $p < 0.01$*	$t(19) = 4.9$ $p < 0.01$

*BMI, body mass index. Cell values denote group means. Parentheses indicate standard deviation within cell. Bracket indicates range. Student's t-test contrast significance at *p < 0.05.*

Transcranial magnetic stimulation

Two measures were analyzed from TMS: LMT, duration of iSP. LabChart 7.0, JMP 9.0, and Microsoft Excel 2007 software were used to complete this analysis. The analysis of silent period duration was adapted from (Garvey et al., 2001). All EMG data was rectified and normalized to baseline of pre-stimulus EMG prior to analysis. EMG baseline was taken as mean of the 20-ms pre-stimulus waveform during pinchgrip. The latency of MEPs was measured from the onset of the stimulus presentation to the onset of the MEP. The first of five consecutive datapoints after MEP that evidenced a minimum decrease of 80% from mean EMG values from the 20-ms pre-stimulus recording period were taken as the silent period onset. Conversely,

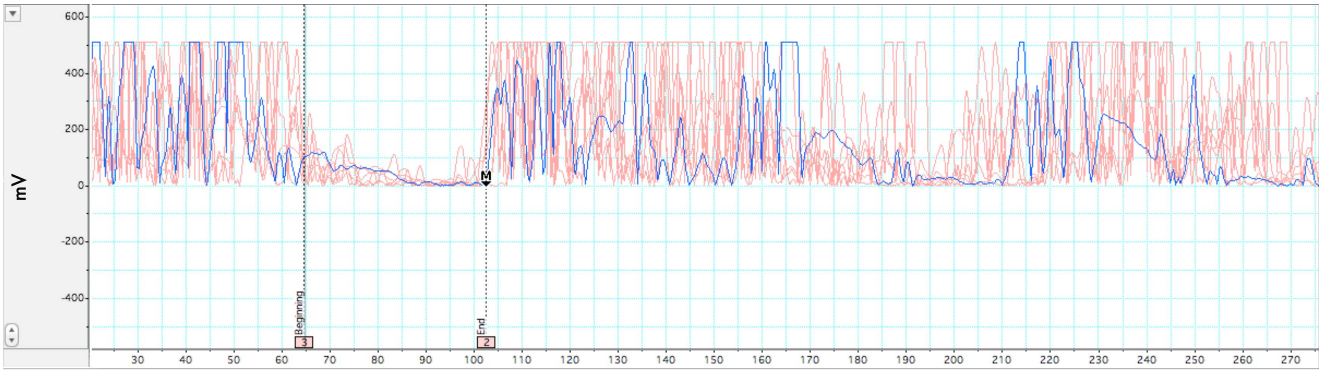


FIGURE 2 | Illustration of ipsilateral silent period. Rectified EMG across multiple trials within a single participant while holding isometric force at 35–50% MVC. In-graphic lines represent beginning and end of EMG depression for the iSP. A pre-stimulus acquisition of 20 ms was acquired for baseline comparison. Motor evoked potential and subsequent silent period occurs at ∼38 ms. iSP duration for this participant was 42 ms.

the first of five consecutive data points evidencing a return to >20% of pre-stimulus mean levels was set as the point of termination of the silent period. A sample silent period grouping for a subject session is presented in **Figure 2**. Group comparisons of TMS measures were analyzed using between-subjects Student's t-test and p-values < 0.05 were considered statistically significant.

Functional magnetic resonance imaging

Functional images were analyzed and overlaid onto structural images with the Analysis of Functional Neuroimaging (AFNI) program (Cox, 1996). To mitigate spatial deviation from the structural to functional images, a local Pearson correlation registration procedure was implemented with AFNI's 3dAllineate program (Saad et al., 2009). To minimize the effects of head motion, time series images were spatially registered in three-dimensional space to the first functional image using a linear rigid-body transform as implemented by AFNI's 3dvolreg. A subject's data was excluded from further analyses if any time series of a subject is judged, from visual inspection, to contain a significant number of images with gross artifacts or residual motion. However, sub-threshold (over 3 mm gross movement) motion parameters $(x, y, z) + (\text{yaw, pitch, roll})$ were added as nuisance regressors for deconvolution analysis. To control for multiple comparisons, a False Discovery Rate correction (Genovese et al., 2002) procedure was utilized on fMRI statistical maps using AFNI's 3dFDR program with a q-value set to 0.05.

fMRI within-group analyses. We hypothesized that sedentary middle age adults would show more positive BOLD voxels in their right sensorimotor cortex (rM1S1), while young adults and physically active middle age adults would show a greater number of negative BOLD voxels in this region. To assess this hypothesis, we performed a within-group analysis of suprathreshold voxels ($q < 0.05$) in primary motor cortex. For this procedure, functional images were spatially smoothed using a 5-mm full-width half-maximum (FWHM) Gaussian filter to compensate for variability in structural and functional anatomy across participants. Anatomic and functional images were then interpolated to volumes with 2 mm^3 voxels and converted to MNI152 standard space as implemented by AFNI. Estimates of hemodynamic response functions (HRF) were generated from a block regressor deconvolution procedure, as implemented by AFNI's 3dDeconvolve (Ward, 2002), for each participant. We then summed the values of the impulse response function to get the area-under-the-curve (AUC) of each voxel. These values were then tested against baseline activity using AFNI's 3dttest++.

fMRI between group analyses. Comparisons were made between groups of estimates of HRF derived from the above-described deconvolution analysis. Each MNI152 transformed voxel's estimated M1 activity proportion was entered into a voxel-wise between-subjects t-test (using AFNI's 3dttest++) for each pairwise comparison of the four groups for each functional task.

Correlation analyses

Estimated VO$_2$max with iSP and AUC fMRI data. This study was primarily interested in investigating the relationship of physical activity to neural correlates of aging-related changes in activity in the ipsilateral motor cortex. To test this relationship of physical fitness and fMRI amplitude change in BOLD response and the iSP, we completed a correlational analysis for: (a) all subjects and (b) within fitness groups. AUC measures were derived using the same M1 region of interest mask used for the impulse response analysis.

Motor performance measures with VO$_2$max. To assess the relationship of physical fitness with respect to motor hand function, we also tested the correlation of our behavioral motor performance assessments with the estimated VO$_2$max assessment. The behavioral measures included strength (hand grip, pinch grip), psychomotor speed (simple visuomotor reaction time, motor tapping), dexterity (9-hole pegboard, Purdue pegboard, coin-rotation task), and interhemispheric transfer (Poffenberger).

Motor performance measures with iSP and AUC fMRI data. We hypothesized a strong relationship between loss of interhemispheric inhibition with sedentary aging and subsequent loss of motor function. To test relationship, we correlated behavioral motor performance assessments (listed in above paragraph) with TMS and fMRI findings of aging-related change in iM1S1 activity.

RESULTS

BEHAVIORAL MEASURES

Behavioral data for the motor assessments are detailed in **Table 5**. Physically fit middle age adults showed better performance on measures of hand strength, dexterity, and psychomotor speed, as compared to their sedentary age cohort. There were no statistically significant differences in behavioral tests of motor performance between fit and sedentary younger adults. Respective of this, we collapsed this group to a "young adult" group consisting of $n = 21$ for contrast to sedentary and fit middle age adults.

MIRROR MOVEMENT ASSESSMENT

Mirror movements above EMG threshold (EMG signal in ipsilateral hand $\geq$20% of active pinch squeeze) were not present in any of the assessed individuals during TMS. No liminal mirror movements were detected during fMRI during the motor tapping condition.

TRANSCRANIAL MAGNETIC STIMULATION

Presented in **Table 6** are group data from TMS with associated t-tests and significance. There were no significant differences between fit and sedentary younger group on TMS measures, as such, we collapsed across these groups to compare a "young adult" group to the sedentary and fit middle age groups. Sedentary middle age adults had significantly shorter silent periods as compared to fit middle age and younger adults. LMT value did not significantly differ between any subject groups.

FUNCTIONAL MAGNETIC RESONANCE IMAGING

Task-to-baseline comparisons

We were interested in the qualitative difference in response of the hemodynamic response (HDR) respective of grouping having hypothesized that cardiovascular fitness maintains negative BOLD in aging adults. **Figure 3** presents comparisons of AUC values depicting whole-brain t-test comparisons (3dttest++) of activity to baseline within each grouping. Color-coding indicates direction of BOLD response with orange indicating positive AUC values relative to baseline and blue indicating negative AUC values. As shown in **Figure 3** (middle row), physically fit middle age adults showed negative BOLD in right (ipsilateral) M1S1 cortex, as compared to sedentary middle age adults (**Figure 3** – middle row) who showed positive BOLD in rM1S1. Younger adults showed negative BOLD in ipsilateral M1S1 regardless of group (**Figure 3** – bottom row).

Group comparisons

Direct group comparisons on AUC (3dttest++) of estimated HDR profiles (quantitatively described by the area-the-curve of the HDR) during motor tapping tasks are presented in **Figure 4**. Hue in the figure indicates minimum significance at $p < 0.05$, False Discovery Rate corrected. **Figure 4** (in axial presentation of supra-callosal slices) indicates comparison of sedentary middle age against physically fit middle age adults (orange indicates higher AUC in sedentary). As compared to sedentary middle age adults, both physically active middle age adults and young adults evidenced significantly lower values of AUC relative to baseline in the hand knob of right motor cortex during the tapping task.

Table 5 | Behavioral measures.

	Sedentary middle age	Fit middle age	Younger
HAND STRENGTH (PSI)			
Hand grip left	63.47 (22.25)	75.5 (18.9)	63.1 (18.9)
Hand grip right	66.95 (21.5)	78.47 (19.1)	69.42 (20.9)
Pinch grip left	11.85 (2.97)[a]	14.23 (3.66)[a]	13.1 (3.91)
Pinch grip right	12.67 (3.03)[a]	15.4 (3.55)[a]	14.25 (3.5)
DEXTERITY			
9-Hole pegboard (s)	18.79 (3.03)[a,b]	16.21 (1.76)[a]	16.72 (1.94)[b]
Purdue (pegs)	15.85 (2.5)	16.23 (1.25)	16.47 (2.3)
Purdue (assembly)	9.93 (1.55)	9.68 (1.01)	10.28 (0.9)
Coin-rotation L (uni)	15.34 (3.37)	13.05 (2.18)	13.74 (3.3)
Coin-rotation R (uni)	14.99 (3.77)[b]	13.28 (2.89)	12.1 (2.7)[b]
Coin-rotation L (bi)	12.60 (2.3)	12.73 (1.4)	13.44 (2.96)
Coin-rotation R (bi)	12.95 (2.41)	13.16 (2.72)	12.18 (2.42)
Coin-rotation diff L	2.74 (2.03)[a,b]	0.31 (2.01)	0.29 (1.98)[b]
Coin-rotation diff R	2.03 (3.24)[a,b]	0.09 (1.83)	−0.04 (2.32)[b]
PSYCHOMOTOR SPEED			
Reaction time (ms)	289.2 (32.2)[b]	269.3 (32.3)	252.05 (27.8)[b]
Halstead finger tap	43.86 (8.7)[a]	52.29 (7.26)[a]	47.90 (8.7)
Poffenberger CUD (ms)	3.1 (0.5)	3.1 (0.9)	3.2 (0.3)

Coin rotation (uni) indicates unimanual coin-rotation score. Coin rotation (bi) indicates bimanual coin-rotation score. Coin-rotation diff (L/R) represents difference between unimanual and bimanual coin rotation task conditions (Left and right, respectively). Poffenberger CUD represents difference between crossed and uncrossed conditions. Cell values denote group means. Parentheses indicate standard deviation within cell. Student's t-test contrast significance at $p < 0.05$ denoted by:

[a] *For sedentary vs. fit middle age.*

[b] *For sedentary vs. younger.*

Table 6 | Transcranial magnetic stimulation measures.

	Sedentary middle age	Fit middle age	Younger
iSP duration (ms)	43.9 (6.5)[a,b]	51.4 (7.4)[a]	50.14 (6.5)[b]
Lowest motor threshold (%)	46.3 (18.25)	41.4 (19.5)	40.5 (15.9)

Cell values denote group means. Parentheses indicate standard deviation within cell. Student's t-test contrast significance at $p < 0.05$ denoted by:

[a] *For sedentary vs. fit middle age.*

[b] *For sedentary vs. younger.*

CORRELATION ANALYSES

Correlation analysis of VO_2max estimate with iSP and AUC fMRI data

We hypothesized that physical fitness level would be correlated with measures of interhemispheric inhibition. **Figure 5**

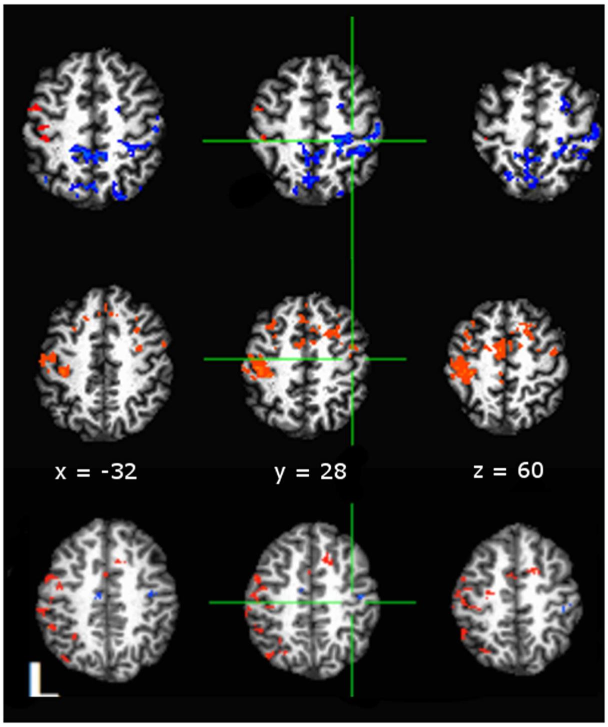


FIGURE 3 | Comparisons of area-under-curve (AUC) of the deconvolved hemodynamic response during performance of a tapping task taken against a null baseline condition with significance set to $p < 0.05$, False Discovery Rate corrected (Hues: orange indicates positive *t*-statistic, blue indicates negative *t*-statistic). Data shown for: top row, active middle age adults; middle row, sedentary middle age adults; bottom row, younger adults. Both middle age adults and young adults showed a negative to baseline pattern of activity in rM1, while sedentary middle age adults showed positive to baseline activity in rM1. Anatomical underlay is a skull-stripped standardized (MNI152) T1 image.

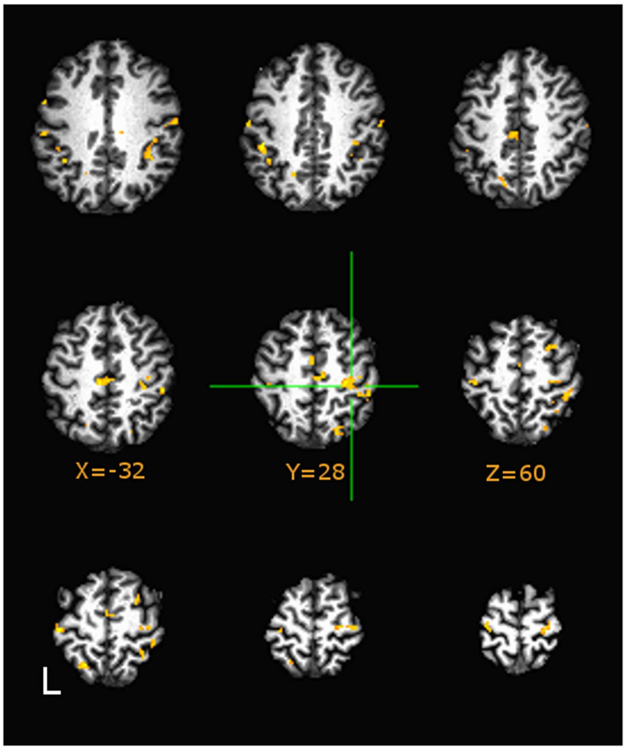


FIGURE 4 | Group differences in area-under-curve (AUC) group comparisons between Sedentary and Fit middle age adults on tapping task at $p < 0.05$, Image montage is in axial presentation of supra-callosal MNI152 registered slices separated by 6 mm. False Discovery Rate ($q < 0.05$) corrected comparisons are presented in color (Hues: orange indicates more positive values in Sedentary adults, blue indicates vice-versa). Sedentary middle age adults showed significantly higher values of AUC (corresponding to positive BOLD) in right sensorimotor areas.

presents correlational data across all participants between estimated VO_2max against iSP and area under curve of right sensorimotor areas from fMRI across all participants. VO_2max was strongly positively correlated with iSP and strongly negatively correlated with AUC of the right (ipsilateral) sensorimotor cortex. Within age-groupings, middle age adults showed a significantly positive correlation [$r(36) = 0.56$, $p < 0.01$] of VO_2max with iSP duration and significantly negative correlation [$r(36) = -0.60$, $p < 0.01$] of VO_2max with AUC of right sensorimotor cortex. Interestingly, within younger adults, there were no significant correlations between VO_2max and either iSP duration or fMRI data.

As shown in **Table 7**, iSP duration was negatively correlated with AUC of the right (ipsilateral sensorimotor cortex) in middle age adults: $r(36) = -0.46$, $p < 0.03$. These measures did not show significant correlation in younger adults.

In summary, across participants, physical fitness was significantly correlated with measures of interhemispheric inhibition. However, when we analyzed within each participant grouping, the results indicated that these effects were restricted to middle age adults.

Motor performance measures with VO_2max

Across participants, there were significant correlations between estimated VO_2max and the following motor assessments: Halstead finger tapping [$r(57) = 0.39$, $p < 0.01$]; 9-hole pegboard test [$r(57) = -0.35$, $p < 0.01$]; Simple Reaction Time [$r(57) = -0.31$, $p = 0.02$]. Within age groups, middle aged adults (**Table 6**) also showed significant correlations between VO_2max and the same motor measures: Halstead [$r(36) = 0.42$, $p < 0.01$]; 9-Hole pegboard [$r(36) = -0.36$, $p = 0.02$]; Simple Reaction Time [$r(36) = -0.37$, $p = 0.02$]. No significant correlations between VO_2max and motor performance metrics were evident across younger adults.

In summary, measures of physical fitness were significantly correlated with motor performance. However, these correlations were restricted to middle age groups underscoring that alteration of motor function respective of physical fitness is an aging-related phenomenon.

Motor performance measures with iSP and AUC fMRI data

Table 7 presents significant correlations in middle age adults of motor measures with both silent period and fMRI activity

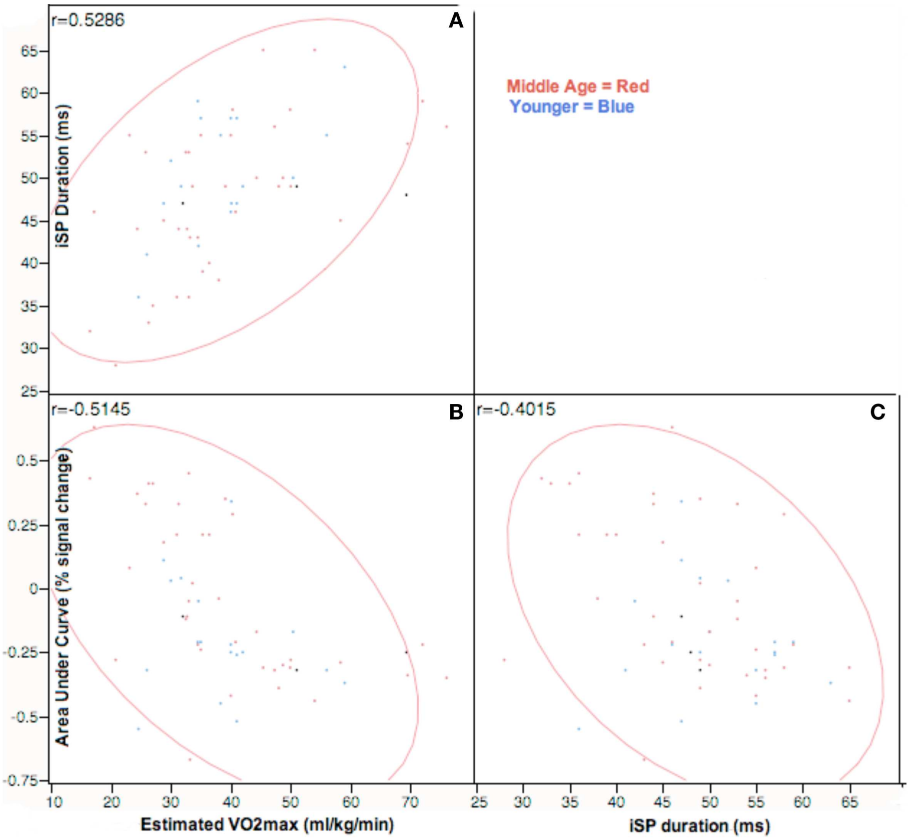


FIGURE 5 | Correlation analysis of VO_2max assessments against ipsilateral silent period and area-under-curve values on tapping task at $p < 0.05$, Across participants, VO_2max estimates are positively correlated with both iSP duration and negatively correlated with AUC estimates in rM1S1. Right M1S1 AUC values are negatively correlated to duration of ipsilateral silent period. Correlations are represented in the top left corner for comparisons of: **(A)** iSP duration and estimated VO_2max; **(B)** fMRI AUC of right M1S1 and VO_2max; **(C)** iSP duration and fMRI AUC of right M1S1.

Table 7 | Significant pair-wise correlations of measures showing across middle age adults.

Variable	Variable	Correlation	Count	Significant prob
fMRI_RM1S1	VO_2max	−0.6147	38	<0.0001[a]
iSP duration	VO_2max	0.5676	38	0.0002[a]
fMRI_RM1S1	Reaction time	0.507	38	0.0012[a]
iSP duration	fMRI_RM1S1	−0.4622	38	0.0035[a]
Halstead	VO_2max	0.412	38	0.0102[a]
iSP duration	Reaction time	−0.376	38	0.02[a]
Reaction time	VO_2max	−0.371	38	0.0218[a]
Halstead	9-hole	−0.3724	38	0.0213[a]
9-Hole	fMRI_RM1S1	0.3719	38	0.0215[a]
9-Hole	VO_2max	−0.3692	38	0.0226[a]

fMRI_RM1S1, fMRI area under curve of right sensorimotor cortex; iSP duration, duration of ipsilateral silent period; Halstead, Halstead finger tapping; 9-hole, 9-hole pegboard test.

[a] *Indicates significant Pearson correlation.*

in M1S1. Dexterity (9-Hole pegboard) and psychomotor speed (Reaction time, finger tapping) showed significant correlations with both iSP and fMRI. In younger adults, a trend $[r(19) = -0.31, p = 0.07]$ existed between silent period duration and reaction time. No other significant relationships between motor measures and TMS or fMRI were found within younger adults.

Importantly, the significant correlations in middle age adults provide a link between aging-related changes in interhemispheric inhibition and alteration of motor performance. Interestingly, though we had hypothesized this effect would be present regardless of age group; we did not find a relationship between level of interhemispheric inhibition and motor performance in younger adults. This, again, may indicate that the aging-related alteration of interhemispheric communication is the strong driver of behavioral change in motor performance.

DISCUSSION

The current study investigated the effects of physical fitness on interhemispheric inhibition and motor performance previously shown to differ across elderly and younger groups. The study extends the previous findings across the lifespan and shows that changes in interhemispheric activity occur within middle age (40–60), as well as in elderly (60+) populations (McGregor et al., 2011). Importantly, loss of interhemispheric inhibition appears to have deleterious effects on motor function. That is, sedentary middle age adults showed larger levels of positive BOLD activity in ipsilateral cortex and short iSPs with coincident decreased motor performance (psychomotor speed and dexterity). Further, the alterations of cortical activity and performance deficits respective of fitness level appear to be aging-related, as comparisons of physically fit and sedentary younger adults did not show such differences. To the best of our knowledge, this is the first study to show that sedentary aging, even in middle age, confers a loss of interhemispheric inhibition with negative effects on motor function, but cardiovascular fitness may mitigate these losses.

There is a growing body of evidence that has shown that the aging process is associated with altered communication in the primary motor cortices (Sale and Semmler, 2005; Riecker et al., 2006; Fujiyama et al., 2009, 2012; Langan et al., 2010; Davidson and Tremblay, 2013). The functional relevance of such changes to motor performance has been a matter of debate, however. The neurophysiological and imaging studies to date have bred essentially three lines of thought. The first of which is that aging-related alteration of patterns of cortical activity may be epiphenomenological and not interact with the function of the motor system. A wealth of evidence, however, has shown that alteration of motor function are associated with changes in levels interhemispheric inhibition (Talelli et al., 2008a,b; Giovannelli et al., 2009; Langan et al., 2010; Fling and Seidler, 2011; Fling et al., 2011a; McGregor et al., 2011, 2012a; Bernard and Seidler, 2012). Interestingly, the same interaction of function and alteration of interhemispheric inhibition has been reported in investigations of the sensorimotor cortex using median nerve stimulation during fMRI. In a series of studies, one lab has systematically shown that the levels of ipsilateral negative BOLD in primary sensory cortex (S1) are modified by varying the level of median nerve stimulation (Kastrup et al., 2008; Klingner et al., 2010, 2011). Moreover, this lab has shown evidence that the amount of ipsilateral S1 BOLD response during median nerve stimulation varies as a function of age with older adults (55+ years) showing lower levels of interhemispheric S1 inhibition (Gröschel et al., 2013).

A second interpretation of aging-related loss of inhibition in M1S1 involves the notion of aging-related cortical compensation. Largely driven by reports using fMRI, this view argues that increased bilateral positive BOLD of motor cortex in aging adults acts in a compensatory function to assist task completion (Mattay et al., 2002; Heuninckx et al., 2005; Wu and Hallett, 2005; Zimerman et al., in press). The critical assumption in this opinion is that the aging brain loses the capacity (via gray or white matter dysfunction) to complete tasks without the intervention of additional neural substrates. This, in turn, argues for a hierarchical pattern of activity across hemispheres whereby more difficult tasks require the intervention of the ipsilateral cortex. While related literature has shown some support for this hierarchical recruitment hypothesis (Hutchinson et al., 2002; Verstynen et al., 2005; Stippich et al., 2007), it is challenged by other studies that do not show increased bilaterality of M1 recruitment with greater task demands (Wu and Hallett, 2005; Riecker et al., 2006; McGregor et al., 2009; Van Impe et al., 2009). In large part, the idea of increased activation in ipsilateral cortex as a compensatory function is derived from models of alteration in cognitive functions more specific to the prefrontal cortex. Perhaps the most noteworthy model is the hemispheric asymmetry reduction in older adults (HAROLD) model posited by Cabeza (2002). However, work in the field has evolved to refine our understanding of aging-related changes in laterality of recruitment that is more domain-specific (e.g., the compensation related utilization of neural circuits – CRUNCH). However, the core assumption of compensation still remains.

The third interpretation of aging-related change in interhemispheric inhibition and motor function is that increased recruitment of the ipsilateral cortex during unimanual movements exacts a deleterious effect on motor performance. The current manuscript lends support to this, as sedentary middle age adults who had less interhemispheric inhibition during unimanual tasks performed worse on tests of psychomotor speed and dexterity. Further, as described in McGregor et al. (2012a), the engagement (pinch squeeze) of the ipsilateral motor cortex during a bimanual task (coin rotation), eliminates the dexterity advantage enjoyed by individuals with intact interhemispheric inhibition. It is likely that transcallosal communication during unimanual tasks is inhibitory in nature (Meyer et al., 1998; Stefanovic et al., 2004; Manson et al., 2006, 2008; Lenzi et al., 2007; Giovannelli et al., 2009; Llufriu et al., 2012) within healthy individuals and its reduction in older adults (and in instances of frank pathology) hinders proper task performance. There are numerous studies that have shown that increasing excitability in the contralateral motor cortex via anodal transcranial direct stimulation results in improved motor learning capacity and better motor performance (Hummel et al., 2010; Furuya et al., 2013; Saucedo Marquez et al., 2013; Zimerman et al., 2013). Corollary findings exist in different cognitive domains, as well. An interesting recent study combining tDCS and fMRI by Meinzer et al. (2013), investigated word production in aging and noted that the more likely older adults were to activate Broca's homolog (right frontal operculum) in fMRI, the worse was their language performance. However, when anodal tDCS was applied to Broca's area (left frontal operculum) in older adults, fMRI activity during word production remained lateralized to the left hemisphere and performance was markedly improved (Meinzer et al., 2013).

As the current study is one of the first to examine the functional implications of aging-related loss of interhemispheric inhibition on upper extremity motor performance using a multi-modality approach, additional research is required to explore the implications of these findings. It is important to state however, that the authors of this work do not intend to argue that aging-related change in patterns of activity in the primary motor cortex subsume all aspects of motor function be they unimanual or bimanual. Clearly, the alteration of functional networks of activity involving motor planning centers (SMA/PreSMA) and prefrontal executive areas is a driving factor in much of the changes reported in the current manuscript (Voelcker-Rehage et al., 2010; Fling and Seidler, 2011, 2012; Fling et al., 2011b; Bernard and Seidler, 2012). One structure of clear importance in the modulation of interhemispheric and network communication is the corpus callosum. Recent findings have pointed that alteration of the density of the corpus callosum is strongly implicated in the change of both resting state and functional connectivity of the motor cortices (Fling et al., 2011a; Bernard and Seidler, 2012). We approached callosal function in the current work using a crossed-uncrossed difference test (Poffenberger paradigm). Surprisingly, we found no differences between groups regardless of age or fitness level in contrast to Bernard and Seidler (2012). It may be that this assessment is not sensitive enough to differentiate functional change at the currently tested age ranges. Further work using more sensitive behavioral metrics of callosal function is needed to explore this critical anatomic structure in light of past and present findings.

Perhaps the most important finding within the current study is that even in middle age, sedentary aging confers a loss of interhemispheric inhibition with negative effects on motor function, but having higher levels of cardiovascular fitness may mitigate these losses. The current study extends and refines previous reports by our lab (McGregor et al., 2011, 2012a) and others (Marks et al., 2007; Voelcker-Rehage et al., 2010) that cardiovascular fitness is a strong driver of neuroplasticity in the motor system. A great deal of attention has been focused on the effects of cardiovascular fitness on the human neural system with respect to aging and cognition, and rightfully so (Colcombe et al., 2003, 2004a,b, 2006; Voelcker-Rehage et al., 2010, 2011; Erickson et al., 2011a,b; Prakash et al., 2011; Voss et al., 2011; Szabo et al., 2012). While it is, of course, impossible to dissociate cognition from motor control, the present findings indicate that physical fitness has a large impact on even very simple motor processes. This suggests that increased cardiovascular fitness over time may exert a core prophylactic effect to central nervous system changes that occur due to the aging process.

There are two notable findings involving the methodologies used within this study. The first of which is that the present study replicates previous findings (McGregor et al., 2011) of the strong relationship between BOLD activity in the ipsilateral motor cortex and the duration of the iSP. The relationship between neurophysiological measures of inhibition and BOLD imaging (negative BOLD in particular) has been an area of active study (Hayes and Huxtable, 2012; Muthukumaraswamy et al., 2012; Zeharia et al., 2012). Previous work has shown that areas of the motor cortex exhibiting negative BOLD during unimanual tasks have decreased blood flow using arterial spin labeling techniques (Stefanovic et al., 2004). However, the correspondence of negative BOLD in sensorimotor cortex to EMG or electrophysiology has only recently been explored (Yuan et al., 2011; Sarfeld et al., 2012). A recent study by Sarfeld et al. (2012) with younger adults using neuronavigated TMS tested the iSP in conjunction with the peak activity within the contralateral primary motor cortex. The results showed that the individuals with the highest peak contralateral BOLD activity showed the longest iSPs. The authors interpreted the results to indicate that the larger the inhibitory transcallosal transfer (due to increased BOLD signal in contralateral cortex) in these subjects was the likely driver of the longer silent period tested with TMS. (The authors did not report about negative BOLD response and used a unidirectional test to evaluate HDR.) The Sarfeld et al. (2012) findings relate to the current project in that individuals with longer iSPs also showed larger negative BOLD response in ipsilateral cortex. Interestingly, in the present study we did not see differences in contralateral motor cortex activity between groups. Further study is needed to investigate the interaction of cortical recruitment patterns in fMRI with electro and neurophysiological measures.

Secondly, the present study, we believe, is the first of its kind to differentiate both middle age and younger adults into fitness levels to assess the effects of physical fitness level on motor cortical function. Within our younger samples, we found no assessments (apart from BMI, fitness level, and reported activity level) that showed significant differences between fitness levels. This finding is perhaps limited due to the rather low sample size ($n = 21$), however, the results were highly systematic across TMS, imaging, and behavioral motor assessments. We interpret these results to support the contention that the alteration of interhemispheric communication reported in the current project is largely due to the aging process. However, a great deal of additional study is required to explore the effects of cardiovascular fitness across the lifespan.

There are some limitations that should be noted about the current work. First, we would like to point out that our physically fit middle age adults were well above the normative values (and even ACSM recommendations) for physical activity in this age group. Many of these individuals engaged in physical exercise as part of their profession (trainers, fitness instructors, exercise scientists). This was an intended outcome as we strived to study a clear stratification between the fitness levels of the two groups from the outset of the study. While we acknowledge that this may somewhat limit how accurately we can infer these findings to the general population, our present results indicate the strong effect of physical activity level on the motor system of middle aged adults and far outweigh the potential limitations. Secondly, the small sample size in younger adults and relatively high level of assessed fitness across all groups (e.g., sedentary young adults reported a VO_2max of ~30 ml/min/kg) may introduce floor effects with respect to differences in physical fitness level. With a larger and more diverse sample size, detection of motor and neurological functioning differences between fit and sedentary younger groups may be possible. Finally, cross-sectional studies such as the current one, while instructive, are not as convincing as a direct interventional approach. Future work should involve recruiting sedentary individuals into both a short and long-term exercise program to test the plasticity of patterns cortical activity in response to a regimented fitness intervention.

In conclusion, we believe the present work represents the first report using both fMRI and TMS to assess the relationship of physical activity, interhemispheric inhibition, and upper extremity motor performance across middle age adults. A major implication of the study is that the long-standing relationship between physical fitness and upper extremity motor performance (Spirduso, 1975) in aging is influenced by changes in interhemispheric communication within the cerebral cortex.

REFERENCES

Allison, J. D., Meador, K. J., Loring, D. W., Figueroa, R. E., and Wright, J. C. (2000). Functional MRI cerebral activation and deactivation during finger movement. *Neurology* 54, 135–142. doi:10.1212/WNL.54.1.135

Bernard, J. A., and Seidler, R. D. (2012). Evidence for motor cortex dedifferentiation in older adults. *Neurobiol. Aging* 33, 1890–1899. doi:10.1016/j.neurobiolaging.2011.06.021

Bernard, J. A., Taylor, S. F., and Seidler, R. D. (2011). Handedness, dexterity, and motor cortical representations. *J. Neurophysiol.* 105, 88–99. doi:10.1152/jn.00512.2010

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

Christou, E. A. (2011). Aging and variability of voluntary contractions. *Exerc. Sport Sci. Rev.* 39, 77–84. doi:10.1097/JES.0b013e31820b85ab

Colcombe, S. J., Erickson, K. I., Raz, N., Webb, A. G., Cohen, N. J., McAuley, E., et al. (2003). Aerobic fitness reduces brain tissue loss in aging humans. *J. Gerontol. A Biol. Sci. Med. Sci.* 58, 176–180. doi:10.1093/gerona/58.2.M176

Colcombe, S. J., Erickson, K. I., Scalf, P. E., Kim, J. S., Prakash, R., McAuley, E., et al. (2006). Aerobic exercise training increases brain volume in aging humans. *J. Gerontol. A Biol. Sci. Med. Sci.* 61, 1166–1170. doi:10.1093/gerona/61.11.1166

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

Colcombe, S. J., Kramer, A. F., McAuley, E., Erickson, K. I., and Scalf, P. (2004b). Neurocognitive aging and cardiovascular fitness: recent findings and future directions. *J. Mol. Neurosci.* 24, 9–14. doi:10.1385/JMN:24:1:009

Cole, K. J., Rotella, D. L., and Harper, J. G. (1998). Tactile impairments cannot explain the effect of age on a grasp and lift task. *Exp. Brain Res.* 121, 263–269. doi:10.1007/s002210050459

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput. Biomed. Res.* 29, 162–173. doi:10.1006/cbmr.1996.0014

Davidson, T., and Tremblay, F. (2013). Age and hemispheric differences in transcallosal inhibition between motor cortices: an ispsilateral silent period study. *BMC Neurosci.* 14:62. doi:10.1186/1471-2202-14-62

Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Heo, S., McLaren, M., et al. (2011a). Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. *J. Neurosci.* 30, 5368–5375. doi:10.1523/JNEUROSCI.6251-09.2010

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., et al. (2011b). Exercise training increases size of hippocampus and improves memory. *Proc. Natl. Acad. Sci U.S.A.* 108, 3017–3022. doi:10.1073/pnas.1015950108

Fling, B. W., Benson, B. L., and Seidler, R. D. (2011a). Transcallosal sensorimotor fiber tract structure-function relationships. *Hum. Brain Mapp.* 34, 384–395. doi:10.1002/hbm.21437

Fling, B. W., Peltier, S. J., Bo, J., Welsh, R. C., and Seidler, R. D. (2011b). Age differences in interhemispheric interactions: callosal structure, physiological function, and behavior. *Front. Neurosci.* 5:38. doi:10.3389/fnins.2011.00038

Fling, B. W., and Seidler, R. D. (2011). Fundamental differences in callosal structure, neurophysiologic function, and bimanual control in young and older adults. *Cereb. Cortex* 22, 2643–2652. doi:10.1093/cercor/bhr349

Fling, B. W., and Seidler, R. D. (2012). Task-dependent effects of interhemispheric inhibition on motor control. *Behav. Brain Res.* 226, 211–217. doi:10.1016/j.bbr.2011.09.018

Fujiyama, H., Garry, M. I., Levin, O., Swinnen, S. P., and Summers, J. J. (2009). Age-related differences in inhibitory processes during interlimb coordination. *Brain Res.* 1262, 38–47. doi:10.1016/j.brainres.2009.01.023

Fujiyama, H., Hinder, M. R., Schmidt, M. W., Garry, M. I., and Summers, J. J. (2012). Age-related differences in corticospinal excitability and inhibition during coordination of upper and lower limbs. *Neurobiol. Aging* 33, e1–e14. doi:10.1016/j.neurobiolaging.2011.12.019

Furuya, S., Nitsche, M. A., Paulus, W., and Altenmuller, E. (2013). Early optimization in finger dexterity of skilled pianists: implication of transcranial stimulation. *BMC Neurosci.* 14:35. doi:10.1186/1471-2202-14-35

Garatachea, N., Cavalcanti, E., Garcia-Lopez, D., Gonzalez-Gallego, J., and de Paz, J. A. (2007). Estimation of energy expenditure in healthy adults from the YMCA submaximal cycle ergometer test. *Eval. Health Prof.* 30, 138–149. doi:10.1177/0163278707300628

Garvey, M. A., Ziemann, U., Becker, D. A., Barker, C. A., and Bartko, J. J. (2001). New graphical method to measure silent periods evoked by transcranial magnetic stimulation. *Clin. Neurophysiol.* 112, 1451–1460. doi:10.1016/S1388-2457(01)00581-8

Genovese, C. R., Lazar, N. A., and Nichols, T. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage* 15, 870–878. doi:10.1006/nimg.2001.1037

Giovannelli, F., Borgheresi, A., Balestrieri, F., Zaccara, G., Viggiano, M. P., Cincotta, M., et al. (2009). Modulation of interhemispheric inhibition by volitional motor activity: an ipsilateral silent period study. *J. Physiol.* 587, 5393–5410. doi:10.1113/jphysiol.2009.175885

Gordon, B. A., Rykhlevskaia, E. I., Brumback, C. R., Lee, Y., Elavsky, S., Konopack, J. F., et al. (2008). Neuroanatomical correlates of aging, cardiopulmonary fitness level, and education. *Psychophysiology* 45, 825–838. doi:10.1111/j.1469-8986.2008.00676.x

Gröschel, S., Sohns, J. M., Schmidt-Samoa, C., Baudewig, J., Becker, L., Dechent, P., et al. (2013). Effects of age on negative BOLD signal changes in the primary somatosensory cortex. *NeuroImage* 71, 10–18. doi:10.1016/j.neuroimage.2012.12.039

Hanna-Pladdy, B., Mendoza, J. E., Apostolos, G. T., and Heilman, K. M. (2002). Lateralised motor control: hemispheric damage and the loss of deftness. *J. Neurol. Neurosurg. Psychiatry* 73, 574–577. doi:10.1136/jnnp.73.5.574

Hayes, D. J., and Huxtable, A. G. (2012). Interpreting deactivations in neuroimaging. *Front. Psychol.* 3:27. doi:10.3389/fpsyg.2012.00027

Hermsdorfer, J., Danek, A., Winter, T., Marquardt, C., and Mai, N. (1995). Persistent mirror movements: force and timing of "mirroring" are task-dependent. *Exp. Brain Res.* 104, 126–134. doi:10.1007/BF00229862

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

Hlushchuk, Y., and Hari, R. (2006). Transient suppression of ipsilateral primary somatosensory cortex during tactile finger stimulation. *J. Neurosci.* 26, 5819–5824. doi:10.1523/JNEUROSCI.5536-05.2006

Hummel, F. C., Heise, K., Celnik, P., Floel, A., Gerloff, C., and Cohen, L. G. (2010). Facilitating skilled right hand motor function in older subjects by anodal polarization over the left primary motor cortex. *Neurobiol. Aging* 31, 2160–2168. doi:10.1016/j.neurobiolaging.2008.12.008

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

Jancke, L., Shah, N. J., and Peters, M. (2000). Cortical activations in primary and secondary motor areas for complex bimanual movements in professional pianists. *Brain Res. Cogn. Brain Res.* 10, 177–183. doi:10.1016/S0926-6410(00)00028-8

Kastrup, A., Baudewig, J., Schnaudigel, S., Huonker, R., Becker, L., Sohns, J. M., et al. (2008). Behavioral correlates of negative BOLD signal changes in the primary somatosensory cortex. *Neuroimage* 41, 1364–1371. doi:10.1016/j.neuroimage.2008.03.049

Kleim, J. A., Kleim, E. D., and Cramer, S. C. (2007). Systematic assessment of training-induced changes in corticospinal output to hand using frameless stereotaxic transcranial magnetic stimulation. *Nat. Protoc.* 2, 1675–1684. doi:10.1038/nprot.2007.206

Klingner, C. M., Hasler, C., Brodoehl, S., and Witte, O. W. (2010). Dependence of the negative BOLD response on somatosensory stimulus intensity. *Neuroimage* 53, 189–195. doi:10.1016/j.neuroimage.2010.05.087

Klingner, C. M., Huonker, R., Flemming, S., Hasler, C., Brodoehl, S., Preul, C., et al. (2011). Functional deactivations: multiple ipsilateral brain areas engaged in the processing of somatosensory information. *Hum. Brain Mapp.* 32, 127–140. doi:10.1002/hbm.21006

Krampe, R. T., Engbert, R., and Kliegl, R. (2002). The effects of expertise and age on rhythm production: adaptations to timing and sequencing constraints. *Brain Cogn.*

48, 179–194. doi:10.1006/brcg.2001.1312

Langan, J., Peltier, S. J., Bo, J., Fling, B. W., Welsh, R. C., and Seidler, R. D. (2010). Functional implications of age differences in motor system connectivity. *Front. Syst. Neurosci.* 4:17. doi:10.3389/fnsys.2010.00017

Latash, M. L., and Zatsiorsky, V. M. (2009). Multi-finger prehension: control of a redundant mechanical system. *Adv. Exp. Med. Biol.* 629, 597–618. doi:10.1007/978-0-387-77064-2_32

Lenzi, D., Conte, A., Mainero, C., Frasca, V., Fubelli, F., Totaro, P., et al. (2007). Effect of corpus callosum damage on ipsilateral motor activation in patients with multiple sclerosis: a functional and anatomical study. *Hum. Brain Mapp.* 28, 636–644. doi:10.1002/hbm.20305

Llufriu, S., Blanco, Y., Martinez-Heras, E., Casanova-Molla, J., Gabilondo, I., Sepulveda, M., et al. (2012). Influence of corpus callosum damage on cognition and physical disability in multiple sclerosis: a multimodal study. *PLoS ONE* 7:e37167. doi:10.1371/journal.pone.0037167

Manson, S. C., Palace, J., Frank, J. A., and Matthews, P. M. (2006). Loss of interhemispheric inhibition in patients with multiple sclerosis is related to corpus callosum atrophy. *Exp. Brain Res.* 174, 728–733. doi:10.1007/s00221-006-0517-4

Manson, S. C., Wegner, C., Filippi, M., Barkhof, F., Beckmann, C., Ciccarelli, O., et al. (2008). Impairment of movement-associated brain deactivation in multiple sclerosis: further evidence for a functional pathology of interhemispheric neuronal inhibition. *Exp. Brain Res.* 187, 25–31. doi:10.1007/s00221-008-1276-1

Marks, B. L., Madden, D. J., Bucur, B., Provenzale, J. M., White, L. E., Cabeza, R., et al. (2007). Role of aerobic fitness and aging on cerebral white matter integrity. *Ann. N. Y. Acad. Sci.* 1097, 171–174. doi:10.1196/annals.1379.022

Marzi, C. A. (1999). The Poffenberger paradigm: a first, simple, behavioural tool to study interhemispheric transmission in humans. *Brain Res. Bull.* 50, 421–422. doi:10.1016/S0361-9230(99)00174-4

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

McGregor, K., Craggs, J., Benjamin, M., Crosson, B., and White, K. (2009). Age-related changes in motor control during unimanual movements. *Brain Imaging Behav.* 3, 317–331. doi:10.1007/s11682-009-9074-3

McGregor, K., Heilman, K., Nocera, J., Patten, C., Manini, T., Crosson, B., et al. (2012a). Aging, aerobic activity and interhemispheric communication. *Brain Sci.* 2, 634–648. doi:10.3390/brainsci2040634

McGregor, K. M., Carpenter, H., Kleim, E., Sudhyadhom, A., White, K. D., Butler, A. J., et al. (2012b). Motor map reliability and aging: a TMS/fMRI study. *Exp. Brain Res.* 219, 97–106. doi:10.1007/s00221-012-3070-3

McGregor, K. M., Zlatar, Z., Kleim, E., Sudhyadhom, A., Bauer, A., Phan, S., et al. (2011). Physical activity and neural correlates of aging: a combined TMS/fMRI study. *Behav. Brain Res.* 222, 158–168. doi:10.1016/j.bbr.2011.03.042

Meinzer, M., Lindenberg, R., Antonenko, D., Flaisch, T., and Floel, A. (2013). Anodal transcranial direct current stimulation temporarily reverses age-associated cognitive decline and functional brain activity changes. *J. Neurosci.* 33, 12470–12478. doi:10.1523/JNEUROSCI.5743-12.2013

Mendoza, J. E., Apostolos, G. T., Humphreys, J. D., Hanna-Pladdy, B., and O'Bryant, S. E. (2009). Coin rotation task (CRT): a new test of motor dexterity. *Arch. Clin. Neuropsychol.* 24, 287–292. doi:10.1093/arclin/acp030

Meyer, B. U., Röricht, S., Gräfin von Einsiedel, H., Kruggel, F., and Weindl, A. (1995) Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum. *Brain* 118(Pt 2), 429–440. doi:10.1093/brain/118.2.429

Meyer, B. U., Roricht, S., and Woiciechowsky, C. (1998). Topography of fibers in the human corpus callosum mediating interhemispheric inhibition between the motor cortices. *Ann. Neurol.* 43, 360–369. doi:10.1002/ana.410430314

Muthukumaraswamy, S. D., Evans, C. J., Edden, R. A., Wise, R. G., and Singh, K. D. (2012). Individual variability in the shape and amplitude of the BOLD-HRF correlates with endogenous GABAergic inhibition. *Hum. Brain Mapp.* 33, 455–465. doi:10.1002/hbm.21223

Naccarato, M., Calautti, C., Jones, P. S., Day, D. J., Carpenter, T. A., and Baron, J. C. (2006). Does healthy aging affect the hemispheric activation balance during paced index-to-thumb opposition task? An fMRI study. *Neuroimage* 32, 1250–1256. doi:10.1016/j.neuroimage.2006.05.003

Newton, J. M., Sunderland, A., and Gowland, P. A. (2005). fMRI signal decreases in ipsilateral primary motor cortex during unilateral hand movements are related to duration and side of movement. *Neuroimage* 24, 1080–1087. doi:10.1016/j.neuroimage.2004.10.003

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

Petitjean, M., and Ko, J. Y. (2012). An age-related change in the ipsilateral silent period of a small hand muscle. *Clin. Neurophysiol.* 124, 346–353. doi:10.1016/j.clinph.2012.07.006

Prakash, R. S., Voss, M. W., Erickson, K. I., Lewis, J. M., Chaddock, L., Malkowski, E., et al. (2011). Cardiorespiratory fitness and attentional control in the aging brain. *Front. Hum. Neurosci.* 4:229. doi:10.3389/fnhum.2010.00229

Rao, S. M., Binder, J. R., Bandettini, P. A., Hammeke, T. A., Yetkin, F. Z., Jesmanowicz, A., et al. (1993). Functional magnetic resonance imaging of complex human movements. *Neurology* 43, 2311–2318. doi:10.1212/WNL.43.11.2311

Riecker, A., Groschel, K., Ackermann, H., Steinbrink, C., Witte, O., and Kastrup, A. (2006). Functional significance of age-related differences in motor activation patterns. *Neuroimage* 32, 1345–1354. doi:10.1016/j.neuroimage.2006.05.021

Saad, Z. S., Glen, D. R., Chen, G., Beauchamp, M. S., Desai, R., and Cox, R. W. (2009). A new method for improving functional-to-structural MRI alignment using local Pearson correlation. *Neuroimage* 44, 839–848. doi:10.1016/j.neuroimage.2008.09.037

Sale, M. V., and Semmler, J. G. (2005). Age-related differences in corticospinal control during functional isometric contractions in left and right hands. *J. Appl. Physiol.* 99, 1483–1493. doi:10.1152/japplphysiol.00371.2005

Sarfeld, A. S., Diekhoff, S., Wang, L. E., Liuzzi, G., Uludag, K., Eickhoff, S. B., et al. (2012). Convergence of human brain mapping tools: neuronavigated TMS parameters and fMRI activity in the hand motor area. *Hum. Brain Mapp.* 33, 1107–1123. doi:10.1002/hbm.21272

Saucedo Marquez, C. M., Zhang, X., Swinnen, S. P., Meesen, R., and Wenderoth, N. (2013). Task-specific effect of transcranial direct current stimulation on motor learning. *Front. Hum. Neurosci.* 7:333. doi:10.3389/fnhum.2013.00333

Schulte, T., Sullivan, E. V., Muller-Oehring, E. M., Adalsteinsson, E., and Pfefferbaum, A. (2005). Corpus callosal microstructural integrity influences interhemispheric processing: a diffusion tensor imaging study. *Cereb. Cortex* 15, 1384–1392. doi:10.1093/cercor/bhi020

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

Spirduso, W. W. (1975). Reaction and movement time as a function of age and physical activity level. *J. Gerontol.* 30, 435–440. doi:10.1093/geronj/30.4.435

Spirduso, W. W. (1980). Physical fitness, aging, and psychomotor speed: a review. *J. Gerontol.* 35, 850–865. doi:10.1093/geronj/35.6.850

Spirduso, W. W., MacRae, H. H., MacRae, P. G., Prewitt, J., and Osborne, L. (1988). Exercise effects on aged motor function. *Ann. N. Y. Acad. Sci.* 515, 363–375. doi:10.1111/j.1749-6632.1988.tb33010.x

Stefanovic, B., Warnking, J. M., and Pike, G. B. (2004). Hemodynamic and metabolic responses to neuronal inhibition. *Neuroimage* 22, 771–778. doi:10.1016/j.neuroimage.2004.01.036

Stippich, C., Blatow, M., Durst, A., Dreyhaupt, J., and Sartor, K. (2007). Global activation of primary motor cortex during voluntary movements in man. *Neuroimage* 34, 1227–1237. doi:10.1016/j.neuroimage.2006.08.046

Szabo, A. N., Bangert, A. S., Reuter-Lorenz, P. A., and Seidler, R. D. (2012). Physical activity is related to timing performance in older adults. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn.* 20, 356–369. doi:10.1080/13825585.2012.715625

Talelli, P., Ewas, A., Waddingham, W., Rothwell, J. C., and Ward, N. S. (2008a). Neural correlates of age-related changes in cortical neurophysiology. *Neuroimage* 40, 1772–1781. doi:10.1016/j.neuroimage.2008.01.039

Talelli, P., Waddingham, W., Ewas, A., Rothwell, J. C., and Ward, N. S.

(2008b). The effect of age on task-related modulation of interhemispheric balance. *Exp. Brain Res.* 186, 59–66. doi:10.1007/s00221-007-1205-8

Van Impe, A., Coxon, J. P., Goble, D. J., Wenderoth, N., and Swinnen, S. P. (2009). Ipsilateral coordination at preferred rate: effects of age, body side and task complexity. *Neuroimage* 47, 1854–1862. doi:10.1016/j.neuroimage.2009.06.027

Verstynen, T., Diedrichsen, J., Albert, N., Aparicio, P., and Ivry, R. B. (2005). Ipsilateral motor cortex activity during unimanual hand movements relates to task complexity. *J. Neurophysiol.* 93, 1209–1222. doi:10.1152/jn.00720.2004

Verstynen, T., Spencer, R., Stinear, C. M., Konkle, T., Diedrichsen, J., Byblow, W. D., et al. (2007). Ipsilateral corticospinal projections do not predict congenital mirror movements: a case report. *Neuropsychologia* 45, 844–852. doi:10.1016/j.neuropsychologia.2006.08.019

Voelcker-Rehage, C., Godde, B., and Staudinger, U. M. (2010). Physical and motor fitness are both related to cognition in old age. *Eur. J. Neurosci.* 31, 167–176. doi:10.1111/j.1460-9568.2009.07014.x

Voelcker-Rehage, C., Godde, B., and Staudinger, U. M. (2011). Cardiovascular and coordination training differentially improve cognitive performance and neural processing in older adults. *Front. Hum. Neurosci.* 5:26. doi:10.3389/fnhum.2011.00026

Voss, M. W., Prakash, R. S., Erickson, K. I., Basak, C., Chaddock, L., Kim, J. S., et al. (2011). Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. *Front. Aging Neurosci.* 2:32. doi:10.3389/fnagi.2010.00032

Ward, B. D. (2002). Deconvolution analysis of fMRI time series data. Available at: http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dDeconvolve.html.

Ward, N. S., Swayne, O. B., and Newton, J. M. (2008). Age-dependent changes in the neural correlates of force modulation: an fMRI study. *Neurobiol. Aging* 29, 1434–1446. doi:10.1016/j.neurobiolaging.2007.04.017

Wu, T., and Hallett, M. (2005). The influence of normal human ageing on automatic movements. *J. Physiol.* 562, 605–615. doi:10.1113/jphysiol.2004.076042

Yuan, H., Perdoni, C., Yang, L., and He, B. (2011). Differential electrophysiological coupling for positive and negative BOLD responses during unilateral hand movements. *J. Neurosci.* 31, 9585–9593. doi:10.1523/JNEUROSCI.5312-10.2011

Zeharia, N., Hertz, U., Flash, T., and Amedi, A. (2012). Negative blood oxygenation level dependent homunculus and somatotopic information in primary motor cortex and supplementary motor area. *Proc. Natl. Acad. Sci. U.S.A.* 109, 18565–18570. doi:10.1073/pnas.1119125109

Zimerman, M., Heise, K. F., Gerloff, C., Cohen, L. G., and Hummel, F. C. (in press). Disrupting the ipsilateral motor cortex interferes with training of a complex motor task in older adults. *Cereb. Cortex.* doi:10.1093/cercor/bhs385

Zimerman, M., Nitsch, M., Giraux, P., Gerloff, C., Cohen, L. G., and Hummel, F. C. (2013). Neuroenhancement of the aging brain: restoring skill acquisition in old subjects. *Ann. Neurol.* 73, 10–15. doi:10.1002/ana.23761

Conflict of Interest Statement: The authors report no actual or potential conflicts of interest. The contents do not represent the views of the Department of Veterans Affairs or the United States Government. This work was supported by a Department of Veteran Affairs (VA) Rehabilitation R&D Center of Excellence #F2182C, Career Development Awards Level-1 (Keith M. McGregor; Joe R. Nocera), and Senior Research Career Scientist (Bruce Crosson: #B6364L) awards.

Received: 22 August 2013; accepted: 11 October 2013; published online: 30 October 2013.

*Citation: McGregor KM, Nocera JR, Sudhyadhom A, Patten C, Manini TM, Kleim JA, Crosson B and Butler AJ (2013) Effects of aerobic fitness on aging-related changes of interhemispheric inhibition and motor performance. Front. Aging Neurosci. **5**:66. doi: 10.3389/fnagi.2013.00066*

This article was submitted to the journal Frontiers in Aging Neuroscience.

frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 24 January 2014
doi: 10.3389/fnagi.2014.00005

Increased bilateral interactions in middle-aged subjects

***Jolien Heetkamp*[1,2]*, Tibor Hortobágyi*[2,3] *and Inge Zijdewind*[1]* ***

[1] *Department of Neuroscience, University Medical Center Groningen, University of Groningen, Groningen, Netherlands*
[2] *Center for Human Movement Sciences, University Medical Center Groningen, University of Groningen, Groningen, Netherlands*
[3] *Faculty of Health and Life Sciences, Northumbria University, Newcastle Upon Tyne, UK*

Edited by:
Brian C. Clark, Ohio University, USA

Reviewed by:
Julia B. Pitcher, The University of Adelaide, Australia
Minoru Shinohara, Georgia Institute of Technology, USA

****Correspondence:***
Inge Zijdewind, Department of Neuroscience, University Medical Center Groningen, University of Groningen, Hanzeplein 1, HPC FB43, Groningen 9700 AV, Netherlands
e-mail: c.a.t.zijdewind@umcg.nl

A hallmark of the age-related neural reorganization is that old versus young adults execute typical motor tasks by a more diffuse neural activation pattern including stronger ipsilateral activation during unilateral tasks. Whether such changes in neural activation are present already at middle age and affect bimanual interactions is unknown. We compared the amount of associated activity, i.e., muscle activity and force produced by the non-task hand and motor evoked potentials (MEPs) produced by magnetic brain stimulation between young (mean 24 years, $n = 10$) and middle-aged (mean 50 years, $n = 10$) subjects during brief unilateral (seven levels of % maximal voluntary contractions, MVCs) and bilateral contractions (4 × 7 levels of % MVC combinations), and during a 120-s-long MVC of sustained unilateral index finger abduction. During the force production, the excitability of the ipsilateral (iM1) or contralateral primary motor cortex (cM1) was assessed. The associated activity in the "resting" hand was ~2-fold higher in middle-aged (28% of MVC) versus young adults (11% of MVC) during brief unilateral MVCs. After controlling for the background muscle activity, MEPs in iM1 were similar in the two groups during brief unilateral contractions. Only at low (bilateral) forces, MEPs evoked in cM1 were 30% higher in the middle-aged versus young adults. At the start of the sustained contraction, the associated activity was higher in the middle-aged versus young subjects and increased progressively in both groups (30 versus 15% MVC at 120 s, respectively). MEPs were greater at the start of the sustained contraction in middle-aged subjects but increased further during the contraction only in young adults. Under these experimental conditions, the data provide evidence for the reorganization of neural control of unilateral force production as early as age 50. Future studies will determine if the altered neural control of such inter-manual interactions are of functional significance.

Keywords: fatigue, associated muscle activity, middle-aged, bimanual interactions, ipsilateral corticospinal excitability

INTRODUCTION

The contralateral primary motor cortex (M1) is the main controller of unimanual voluntary movements. However, evidence shows that especially when a task is more complex or requires a strong effort, the ipsilateral M1 (iM1) becomes increasingly active (Hess et al., 1986; Ugawa et al., 1993; Stedman et al., 1998; Tinazzi and Zanette, 1998; Hortobagyi et al., 2003; Zijdewind et al., 2006; van Duinen et al., 2007; Perez and Cohen, 2009; Post et al., 2009b). These excitatory ipsilateral effects can be so strong that contralateral, homologous muscles become active (Curschmann, 1906; Cernacek, 1961; Armatas et al., 1994; Zijdewind and Kernell, 2001; Cincotta and Ziemann, 2008; Post et al., 2009b). Compared with isolated strong muscle contractions, activation of ipsilateral cortical motor areas is even more pronounced during a sustained fatiguing contraction (Liu et al., 2003; Post et al., 2009b) and is accompanied by increased levels of associated contralateral muscle activity (Zijdewind and Kernell, 2001; Post et al., 2009a). This associated activity results in behavioral changes because subjects start to perform overt, associated movements with the hand contralateral to the target hand.

With advancing age, ipsilateral motor areas – including iM1 – become functionally more relevant (Talelli et al., 2008a; Fling et al., 2011; Boudrias et al., 2012; Fling and Seidler, 2012). One prediction could be that performing a unimanual sustained voluntary contraction would generate higher levels of excitability in the iM1 of old when compared with young adults, resulting in a greater contralateral associated activity. Because imaging studies across the lifespan suggest the appearance of anatomical changes in the motor brain already in late midlife (Haug and Eggers, 1991; Marner et al., 2003; Madden et al., 2004; Seidler et al., 2010; Taki et al., 2013; Zhou et al., 2013), it is reasonable to expect that neurophysiological changes in M1 and iM1 are also present. Therefore, the purpose of the present study was to determine if middle-aged compared with young adults execute unilateral motor tasks with higher iM1 excitability and with higher levels of associated contralateral activity. An additional question is whether a sustained contraction would further increase the already elevated ipsilateral activation and associated activity in middle-aged subjects. In other words, would middle-aged subjects who already demonstrate associated activity at the start of the contraction increase this associated activity even more during a fatiguing contraction or do they just start at higher levels and end up producing the same amount of associated activity as young subjects? Data in older adults (>65 years) provide evidence for this latter scenario (Shinohara et al., 2003). However, if increased cortical activation is required to maintain appropriate voluntary drive to the relevant muscles, as is suggested by data of McNeil et al. (2009, 2011a), one would expect that the increase would be similar in all participants, independent of the starting point. A decrease or a smaller increase in cortical activation would otherwise result in diminished activation of the target muscles. Thus, if ipsilateral activation in the middle-aged subjects reflects the amount of effort added upon increased ipsilateral activation (due to age-related changes), one would expect a progressive increase in associated activity during a sustained contraction.

MATERIALS AND METHODS

SUBJECTS

Twenty right-handed volunteers (10 females) were subdivided into two age groups, young adults ($n = 10$, age 24 years, 2 SD, range 21–27; 5 females) and middle-aged adults ($n = 10$, age 50 years, 3 SD, range 46–53, 5 females). Prior to the experiment, a checklist was issued to exclude subjects with migraine, neurologic or muscle diseases, or epileptic episodes. All subjects signed an informed consent, approved by the local ethics committee. Right handedness was confirmed with the Handedness Questionnaire (Brainmapping.org. adapted from Oldfield, 1971; mean laterality index: 89.8, range 65–100). All subjects performed the experiment twice, 1 week apart. In one experiment, transcranial magnetic brain stimulation (TMS) targeted the right hand and in the other experiment, the left hand. The order of the experiments was alternated between subjects. In the methods, we describe the set-up for the experiment in which TMS was given to the left motor cortex (see **Figure 1**).

EXPERIMENTAL SET-UP

Subjects sat in a height-adjustable chair with both arms resting on a table instrumented with force transducers. With the elbows flexed at 135°, both forearms were clamped in a vertical position halfway between pronation and supination. The wrists and hands were kept in a vertical position with pressure plates. The

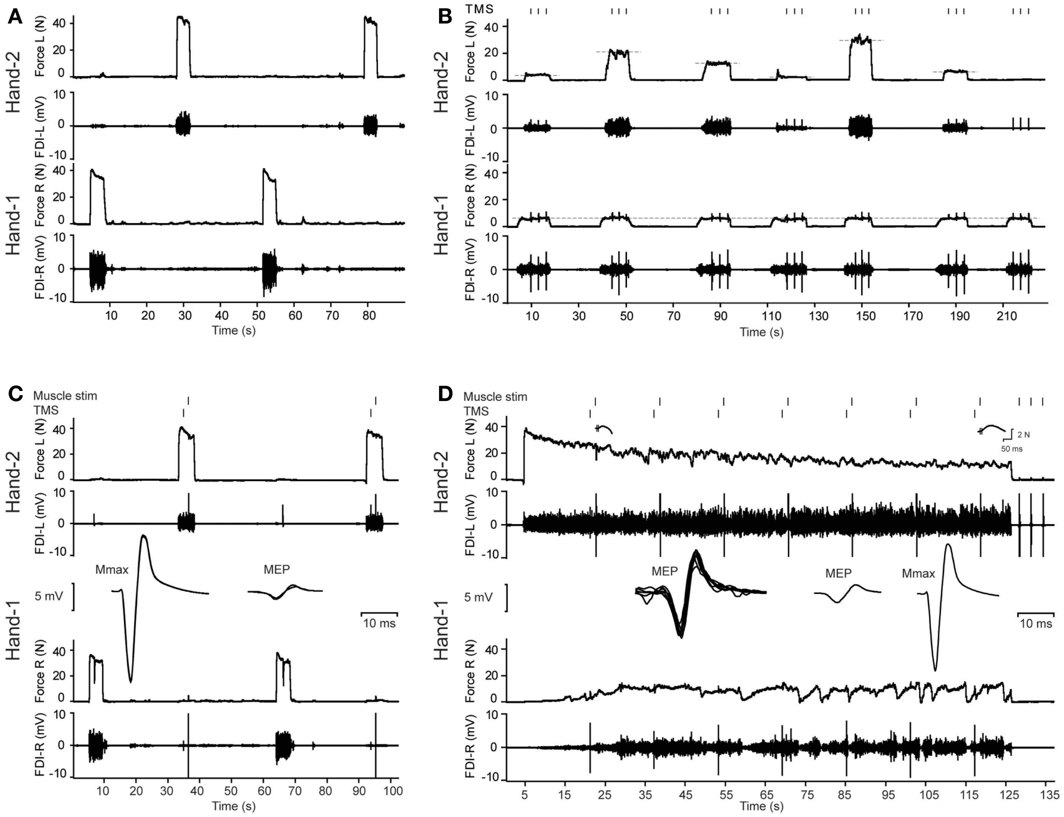


FIGURE 1 | Overview of the protocol and illustrative data from a middle-aged male subject. **(A)** Three maximal voluntary contractions (MVCs) of the first dorsal interosseus (FDI) intermittently with the left and right hand (only two MVCs are presented in this figure). **(B)** Example of the bilateral contractions. The subject started with Hand-1 (in this figure the right hand) followed by Hand-2 (in this figure the left hand). During the contractions, three transcranial magnetic stimuli (TMS) were given to the motor cortex contralateral to Hand-1. Feedback of the target and actual produced forces were presented to the subject on-line. **(C)** MVCs combined with muscle stimulation of Hand-2 and TMS of the motor cortex contralateral to Hand-1. Before the MVCs, the ulnar nerve of Hand-1 was stimulated to evoke maximal M-waves ($M_{\max}$). **(C)** Shows an overlay of five $M_{\max}$ responses, followed by an overlay of three MEPs (recorded in the right hand) obtained during MVCs of the left hand. **(D)** Two-minute contraction with Hand-2. During the contractions, MEPs were evoked in Hand-1; an overlay of all MEPs during the fatigue test is presented together with the MEP during a brief contraction of the left hand and $M_{\max}$ ($n = 5$) obtained after the fatiguing task. Note the increase in associated activity in Hand-1.

middle, ring, and little fingers were mechanically isolated from the index finger using a small plastic plate. The thumb was slightly stretched toward extension with a strap. Both index fingers were inserted into snugly fitting rings around the proximal interphalangeal joint, and connected to a force transducer (Zijdewind and Kernell, 1994), which was adjustable in height to keep the index fingers in a slightly abducted position.

EMG recordings

Surface electromyographic (EMG) activity was recorded from the first dorsal interosseus (FDI) muscle of both hands. For the right FDI, one electrode (Ag–AgCl, 4 mm, *in vivo* metrics, Gainesville, FL, USA) was placed over the muscle belly and a second electrode close to on the metacarpophalangeal joint of the index finger. For the left FDI, one adhesive electrode was placed on the proximal border of FDI muscle, in between the first and second metacarpal bones. The second electrode was placed on the distal border of the FDI (see Zijdewind et al., 1998). This set of electrodes was also used to electrically stimulate the left FDI muscle (see "Muscle stimulation"). Adhesive grounding electrodes were strapped around each wrist.

Force and EMG data were amplified and sampled at 2000, 5000, and 500 Hz for EMG, motor evoked potentials (MEPs), and force recordings, respectively (CED 1401 plus interface, Cambridge Electronic Design, UK). Data were stored on a personal computer for off-line analysis.

STIMULATION

Electrical nerve stimulation

Adhesive electrodes were placed on the skin at the wrist above the ulnar nerve. The ulnar nerve of the right side was stimulated with increasing current (5 mA steps, Digitimer DS7, UK) to obtain maximal M-waves ($M_{\max}$). During the experiment, the ulnar nerve was stimulated at 130% of the intensity to obtain $M_{\max}$.

Muscle stimulation

To estimate voluntary drive, we superimposed twitches on maximal voluntary contractions (MVCs) of the left FDI (twitch superimposition technique, Merton, 1954; Allen et al., 1995; Zijdewind et al., 1998). The stimulation consisted of two 200-μs-long pulses with an inter-pulse interval of 10 ms. We used the same electrodes for EMG recording and electrical stimulation of the left FDI (see "EMG Recordings"). The stimulating current was increased in steps of 5 mA until maximal force was evoked. Throughout the experiment, the current that produced the maximal twitch force was used for the muscle stimulation. The force evoked by the paired-pulse stimulation is referred to as doublet force.

Transcranial magnetic stimulation

A figure-of-eight branding iron coil (diameter 50 mm) connected to a TMS stimulator (Magstim 200 rapid, Dyfed, UK) was used to elicit MEPs in the contralateral FDI muscle. Subjects wore a tight fitting cap and the location on the head where the biggest response in the contralateral FDI could be evoked was marked. Because the rapid stimulator produces a biphasic pulse, both coil current directions were examined in a subject as suggested by the manufacturer. In all subjects and in both hemispheres, lower stimulation thresholds were found with the current in the coil in an anterio-posterior position. Resting motor threshold (RMT) was defined as the lowest stimulation intensity required for eliciting MEPs in the contralateral FDI muscle at rest of at least 50 μV in at least three out of five consecutive trials (Rossini et al., 1994). During the experiment, 110% of the RMT was used.

EXPERIMENTAL TASKS

The experiment was conducted twice in each subject with at least 1 week apart, preferably on the same day of the week but always at the same time. If during the first experiment MEPs and M-waves were evoked in the right FDI and superimposed twitches in the left FDI, then in the second experiment MEPs and M-waves were evoked in the left FDI and superimposed twitches in the right FDI. Half of the subjects started with TMS and M-waves in the right FDI, the other half with the left FDI.

The experiment consisted of four tasks. Continuous feedback of the index finger abduction force produced by the left and right FDI with the lines for the target forces being displayed in real-time on a computer screen in front of the subject (see **Figure 1**).

Maximal voluntary contractions

Subjects produced three MVCs with the left and right FDI with 1-min of rest between consecutive contractions, alternating between the two sides (**Figure 1A**). During the MVCs, maximal force and RMS-EMG (100 ms around the maximal peak force) was determined during each contraction, as well as the maximal force and RMS-EMG (100 ms around peak force) produced by the contralateral FDI.

Unilateral and bilateral sub-maximal contractions with MEPs

After the MVCs, subjects produced an abduction force with their right index finger (Hand-1) at four force levels (0, 5, 15, or 30% of MVC). When the subject reached the required force level, they were requested to produce a concurrent force with their left index finger abductor (Hand-2). Subjects received continuous feedback of the target and the produced forces.

During a set of contractions, the force level of Hand-1 was fixed at one of the four levels, whereas the force levels of Hand-2 was varied between 0, 5, 10, 15, 30, 50, and 70% of MVC (**Figure 1B**). Subjects were instructed to maintain the required force levels until the delivery of three TMS pulses was complete. A contraction lasted about 20 s and the subject received at least 30 s of rest between the contractions. One set of seven contractions lasted about 6 min.

In total, all subjects performed unilateral contractions with the FDI of Hand-1 (5, 15, or 30% of MVC) and Hand-2 (5, 10, 15, 30, 50, and 70% of MVC) and bilateral contractions consisting of 18 force combinations (Hand-1: 5, 15, or 30% of MVC and Hand-2: 5, 10, 15, 30, 50, and 70% of MVC). The MEPs were always evoked in the FDI of Hand-1, i.e., the hand that started the bilateral contraction.

Maximal voluntary contraction with twitch interpolation

After finishing the sub-maximal force task, we repeated the MVC measurements combined with different forms of stimulation (**Figure 1C**). During the MVCs of Hand-1 (right hand), the subject received a TMS stimulus over the (left) motor cortex contralateral to the contracting FDI. During MVCs with Hand-2 (left hand), a TMS stimulus was given over the (left) motor cortex ipsilateral to the contracting FDI, followed by an electrical stimulus to the contracting (left) FDI muscle (twitch superimposition; inter-stimulus interval between TMS pulse and electrical simulation, 1.5 s).

Sustained, fatiguing maximal contraction

Subjects produced a 2-min sustained contraction with the FDI of Hand-2 (left hand, i.e., the FDI muscle that received the muscle stimulation). The instruction to the subjects was to produce maximal abduction force with the left index finger for 2 min; no further instructions were given regarding their contralateral hand. Subjects were verbally encouraged to give maximum effort throughout the sustained contraction. During the 2 min, TMS was applied seven times to the (left) hemisphere ipsilateral to the fatiguing muscle (i.e., the Hand-2 FDI) followed by electrical muscle stimulation of the (left) fatiguing FDI (i.e., Hand-2 FDI). The interval between each pair of stimulating pulses (the TMS and electrical muscle stimulation) was 17 s and the interval between TMS and muscle stimulation was 1.5 s (**Figure 1D**). After 2 min, subjects relaxed the index finger abductor and muscle stimulation was applied three times within 5 s after the end of the fatiguing contraction, which was immediately followed by a brief MVC with the Hand-1 FDI (right non-fatigued FDI) during which TMS was applied and a brief MVC with Hand-2 FDI (left fatigued FDI) during which TMS and muscle stimulation was applied. To finish the protocol, ulnar nerve stimulation was applied five times in the Hand-1 FDI (right hand).

In the second experiment, the TMS and muscle stimulation were delivered to the contralateral side. The fatiguing task was also performed with the contralateral muscle.

DATA ANALYSIS

Maximal voluntary contractions

During the MVCs, the maximal force and RMS-EMG (100 ms time window around peak force) was determined. The maximal force value during the MVCs was considered as the "true" MVC and force values obtained during voluntary and associated contractions were expressed as a percentage of this MVC value. The maximal RMS-EMG value obtained during MVCs was used to normalize all EMG values (both voluntary contractions and associated activity). The RMS-EMG and force values during the associated contractions of the contralateral FDI during the MVCs were averaged over the three MVC-trials.

The MVC and associated activity was analyzed with repeated measures mixed design ANOVA with Hand (left and right) as within-subject factors, and Age-group (young and middle-aged) and sex (male and female) as between-subject factors.

Unilateral and bilateral sub-maximal contractions

When the subjects reached their force targets, the mean index finger abduction force was measured for a 1-s time window before the TMS stimulus. The three 1-s values obtained during one contraction were averaged. For the same time window, the mean RMS-EMG values were determined for both FDI muscles. Additionally, the mean RMS-EMG in the Hand-1 FDI was assessed 100 ms before the TMS stimulus. All force and EMG values were expressed as percentage of the MVC values. The amplitude and area of the MEPs were expressed as a percentage of the M-wave. To quantify performance on the bilateral task, we calculated the force difference with the following Eq. (1):

$$\text{Bilateral force difference} = \sqrt{\begin{aligned}&\left(\left(\text{target force}_{\text{Hand}-1} - \text{produced force}_{\text{Hand}-1}\right)^2\right.\\&\quad\left.+\left(\text{target force}_{\text{Hand}-2} - \text{produced force}_{\text{Hand}-2}\right)\right)^2\end{aligned}}$$

To investigate the effect of a contraction on the ipsilateral motor cortex excitability, we choose to analyze the force, MEP, and EMG values obtained during unilateral and bilateral contractions separately. During the unilateral contractions, changes in force, MEP amplitude and area, and background RMS-EMG were statistically analyzed with a repeated measures mixed design ANOVA. As within-subject factors were identified, force of Hand-1 (Force-H1: 5, 15, and 30% of MVC) or force of Hand-2 (Force-H2: 5, 10, 15, 30, 50, and 70% of MVC) and Hand (left and right); Age-group (young and middle-aged) was assigned as a between-subject factors.

During the bilateral contractions, we analyzed force difference, MEP, and EMG values. The mixed design repeated measures ANOVA that was used consisted of Force-H1 (5, 15, and 30% of MVC), Force-H2 (5, 10, 15, 30, 50, and 70% of MVC) and Hand (left and right) as within-subject factors, and Age-group (young and middle-aged) as a between-subject factors. For unilateral and bilateral contractions, *post hoc* analysis (least significant difference, LSD) in which we compared the data obtained at 5% of MVC versus data obtained at higher force levels (for Hand-1: 15 and 30% of MVC, and Hand-2: 10, 15, 30, 50, and 70% of MVC) were performed to break down significant effects where appropriate.

Fatigue task

Mean force and RMS-EMG values were obtained for 2-s time periods during the sustained contraction. Epochs in which TMS stimuli or muscle stimuli were given (7×4 s-periods) were excluded from the analysis. This resulted in 46 epochs of 2 s. The mean force and RMS-EMG data were expressed as a percentage of the prefatigue MVC values. The forces evoked by the muscle stimulation were measured and expressed as a percentage of the potentiated doublet-force obtained before the fatiguing contractions. The amplitude and area of the MEP was measured and expressed as a percentage of the M-wave.

Changes in force and EMG values (% MVC) during the sustained maximal contraction were analyzed with a repeated measures mixed design ANOVA ($2 \times 46 \times 2$) with Hand (left and right) and Time (1–46 periods of 2 s) as within-subjects factors; Age-group was included as a between-subject factor.

Some of the doublet-forces evoked during the sustained contraction could not be analyzed due to fast variations in voluntary background force. It was then impossible to decide which part of the force increase was due to voluntary activation and which part was due to the evoked twitch. Instead of using a fixed time interval to determine the evoked force, we excluded this data point and analyzed the twitch forces with a multilevel analysis. The multilevel analysis is less affected by missing data points (in contrast to the repeated measures ANOVA; Snijders and Bosker, 1999). We also used the multilevel analysis for the MEPs evoked during unilateral contractions of Hand-2. During these contractions (especially at higher forces), some subjects could not completely relax Hand-1 and EMG activity was visible before the TMS stimulus. These MEPs were excluded from the analysis. Because this resulted in missing data points in some subjects, we choose to perform multilevel statistical tests.

Associations between the relevant parameters (MVC, amount of associated activity, fatigability) obtained in the two sessions were determined with linear regression analysis. Similar statistics were used to explore associations between values of associated activity and bimanual interference.

Statistical significance was set at $\alpha = 0.05$; if violation of sphericity of the data occurred, degrees of freedom were corrected using Huynh–Feldt estimates of sphericity.

RESULTS

Table 1 shows the main characteristics of the subjects. There was no difference in the intensity used for muscle, nerve, and cortical stimulation between the two experiments and age-groups ($p > 0.1$). During the sustained contraction, the force recording in one subject and the EMG recording in another subject could not be used due to technical problems. There was some noise interference ($> 10\ \mu V$) in 20% of the EMG recordings. This noise could be due to having both the electrical stimulator and the EMG amplifier simultaneously connected to the electrodes. Although the noise was small, the noise occurred more often in the middle-aged subjects than in the younger subjects. Therefore, we analyzed in those cases, both the non-filtered and notch-filtered EMG signals (IRR 50 Hz filter). In the text, we present the notch-filtered EMG data, if the analysis shows differences between the non-filtered and notch-filtered data, we present both results.

MAXIMAL VOLUNTARY CONTRACTIONS ARE SIMILAR IN THE TWO AGE GROUPS

Males (45.2 *N*, 7.3 SD) had a higher maximal index finger abduction force than females [33.6 *N*, 6.8 SD; $F_{(1,16)} = 19.10, p < 0.001$]. The MVC force was not significantly different between the two age groups (young adults: 41.6 *N*, 8.7 SD; middle age adults: 37.2 *N*, 9.2 SD; $p = 0.12$), neither between the left (39.0 *N*, 9.0 SD) and right hand (39.7 *N*, 9.4 SD; $p = 0.67$), nor between the two experiments ($p = 0.67$). No interaction effects between Sex, Experiment, Age-group, or Hand were found ($p > 0.25$, for all interactions). For the MVC force in both the left and right hand, there was an association between the two experiments and there was an association between the MVC force of the left and right hand of the participants [$F_{(1,38)} = 123.20$, $R^2 = 0.76$ and $F_{(1,38)} = 39.10$, $R^2 = 0.51$, respectively; both $p < 0.001$].

AMOUNT OF ASSOCIATED ACTIVITY DIFFERS BETWEEN THE TWO AGE GROUPS

During the MVCs, most subjects showed some amount of contralateral activity. Statistical analysis demonstrated main effects of Experiment [force: $F_{(1,16)} = 5.04$, $p = 0.04$] and Age-group [force: $F_{(1,16)} = 4.43$, $p = 0.05$; EMG: $F_{(1,16)} = 5.23$, $p = 0.04$]. In addition, there was an Age-group by Experiment by Sex interaction for both the associated force [$F_{(1,16)} = 6.76$, $p = 0.02$] and associated EMG activity [$F_{(1,16)} = 4.58$, $p = 0.05$]. Associated activity was higher in middle-aged subjects (force: 28.9 and 11.5% MVC, for middle-aged and young subjects, respectively), and higher in females (force: 26.7 and 18.7% MVC, EMG: 22.4 and 15.7% MVC; for Experiments 1 and 2, respectively) compared with males (force: 14.4 and 12.8% MVC, EMG: 11.7 and 11.1% MVC; for Experiments 1 and 2, respectively) in Experiment 1. The amount of associated activity in Experiments 1 and 2, and also in left and right hands were positively associated [$F_{(1,38)} = 49.68$, $R^2 = 0.57$ and $F_{(1,38)} = 47.33$, $R^2 = 0.55$, for EMG and force between the two experiments, respectively; $F_{(1,38)} = 82.38$, $R^2 = 0.68$ and $F_{(1,38)} = 67.48$, $R^2 = 0.64$, for EMG and force of the left and right hand, respectively; $p < 0.001$ in all cases].

Table 1 | Subject characteristics displayed in mean ± SD.

	Young adults ($n = 10$)	Middle-aged adults ($n = 10$)	Total
Age (years)	23.6 (2.3)	49.8 (2.5)	36.7 (13.6)
Laterality index	86.5 (14.3)	93.0 (10.9)	89.8 (12.8)
RMT (% max stimulator output)	55.1 (6.6)	59.5 (8.5)	57.5 (7.9)
Muscle stimulation (mA)	36.2 (9.9)	38.7 (9.1)	37.6 (9.4)
Nerve stimulation (mA)	36.1 (9.8)	41.8 (8.7)	38.7 (9.1)
M-wave (mV)	24.5 (6.0)	24.6 (5.7)	24.5 (5.3)
Rest MEP[a] (mV)	0.6 (0.4)	0.7 (0.5)	0.7 (0.4)

Age in years, laterality index, RMT in percentage of maximum stimulator output, muscle and nerve stimulation in mA.

[a] *Rest MEP at 100% resting motor threshold.*

UNILATERAL CONTRACTIONS WITH TMS OF THE CONTRALATERAL M1

To investigate possible differences between the age groups in the effect of muscle activation on the MEPs, participants performed unilateral contractions with their FDI (Hand-1) at three different force levels (5, 15, and 30% MVC) and were instructed to keep their contralateral FDI (Hand-2) relaxed. During the contraction, the contralateral motor cortex was stimulated three times (inter-stimulus interval > 3 s).

All subjects performed the task as expected. The force data showed an Age-group by Hand by Force interaction for Force difference [$F_{(1.7,30.6)} = 3.60, p = 0.05$] because young subjects produced a marginally larger force with their left FDI at high force levels than middle-aged subjects (Force difference left FDI: young: +0.29% MVC and middle-aged: −1.3% MVC at 30% MVC target; $p = 0.05$). The evoked MEPs increased with increasing force and EMG levels [**Figures 2A,B**, right side; $F_{(2,36)} = 36.76$, $p < 0.001$; larger MEPs at 15% ($p = 0.001$) and 30% of MVC ($p < 0.001$)] without a difference between the two Age-groups ($p = 0.49$).

UNILATERAL CONTRACTIONS WITH TMS OF THE IPSILATERAL M1

The purpose of these runs was to determine: (a) the age-related differences in iM1 activation and (b) the magnitude of associated force and EMG activity in the resting hand. Participants performed unilateral contractions with their FDI of Hand-2 (ipsilateral to the cortex receiving TMS) at six different force levels (5, 10, 15, 30, 50,

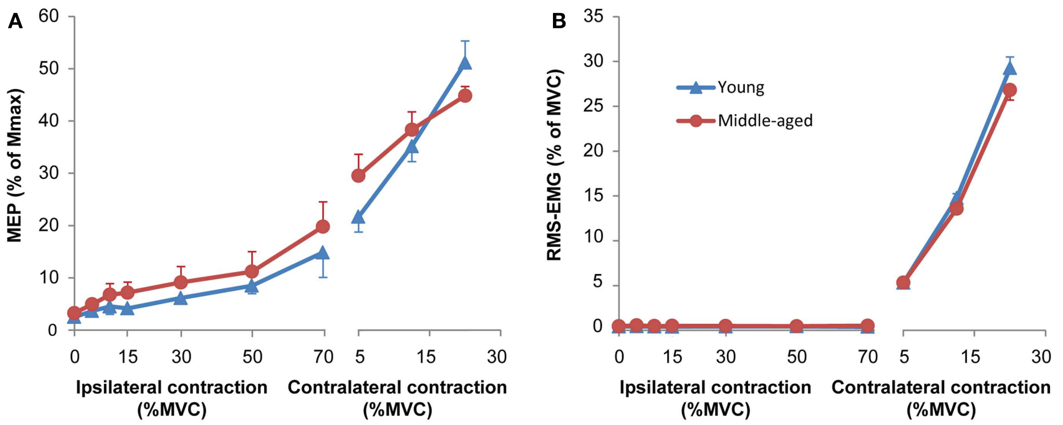


FIGURE 2 | (A) Mean and standard error of motor evoked potentials (MEPs) during unilateral force production for young (blue) and middle-aged subjects (red). The left side of the panel shows MEPs obtained during an ipsilateral contraction at increasing force levels. Only MEPs were included that were not preceded by any voluntary activity; all MEPs of 8 out of 40 experiments (seven subjects: five middle-aged, two young adults) were excluded because more than half of the MEPs at high force levels showed small signs of EMG activity. The right side of the panel the MEPs obtained during a contralateral contraction (only for the MEPs of the same subjects as included in the ipsilateral contraction). The MEPs increased with ipsilateral and contralateral force without significant difference between young and middle-aged subjects. **(B)** Mean and standard error of RMS-EMG (100 ms before MEP) upon which the MEPs were evoked at increasing force levels of the hand ipsilateral to the motor cortex receiving the TMS pulse (left panel) and the contralateral hand (right panel) for young (blue) and middle-aged subjects (red). The background RMS-EMG was close to zero during the ipsilateral contraction and increased proportional with the force during the contralateral contraction. No differences were observed between young and middle-aged subjects.

and 70% of MVC). They were instructed to keep their contralateral hand relaxed (i.e., the hand in which MEPs were evoked). However, if subjects forcefully contracted the FDI of Hand-2, the FDI of Hand-1 also became activated [force: $F_{(1.2,21.5)} = 4.37$, $p = 0.04$; RMS-EMG: $F_{(1.3,23.1)} = 5.20$, $p = 0.03$, **Figure 4A**; larger force in Hand-1 when ipsilateral hand contracted at 50% ($p = 0.02$) and a trend toward significance at 70% of MVC ($p = 0.06$); larger RMS-EMG in Hand-1 when the ipsilateral hand contracted at 70% of MVC ($p = 0.03$)].

As expected from the changes in force and EMG in Hand-1, the MEPs evoked in the FDI of Hand-1 increased together with the activation of the FDI in Hand-2 [$F_{(2.4,43.9)} = 34.73$, $p < 0.001$; from 4.4% of $M_{\max}$ (0.6 SD) at 5% MVC force to 6.4 of $M_{\max}$ at 30% ($p = 0.02$), 9.8% of $M_{\max}$ (1.2 SD) at 50% MVC ($p < 0.001$), and to 17.5% of $M_{\max}$ (2.2 SD) at 70% MVC ($p < 0.001$)]. To correct for the increase in background EMG, we excluded all MEPs from the statistical analysis that were preceded by EMG (100 ms before the TMS stimulus). In eight experiments (seven subjects, five middle-aged subjects), no MEPs at force levels above 30% of MVC remained after rejection of trials with background EMG. We therefore excluded all of the data for these subjects from the statistical analyses. To be able to perform the analysis despite missing data points, we analyzed the MEPs with multilevel analysis. The analysis showed a relationship between the RMS-EMG in Hand-2 FDI and the MEPs [$F_{(1,31.14)} = 31.14$, $p < 0.001$; **Figure 2A**, left side], no main or interaction effect of Age-group was found.

BILATERAL CONTRACTIONS

The purpose of these runs was to determine the effects of age on bilateral interaction. We parametrically increased the contraction intensity (5, 10, 15, 30, 50, and 70% of MVC) in one FDI (Hand-2) and measured the corticospinal excitability in the other FDI while contracting at three low intensities (5, 15, or 30% of MVC; Hand-1, **Figures 1** and **4**). During these contractions, three magnetic stimuli were given to evoke MEPs in the FDI of Hand-1.

To quantify the performance in the bilateral task, we used Eq. 1 to calculate the difference between the target force and the force subjects actually produced. The force difference showed significant main effects for the force levels of Hand-1 [$F_{(2,34)} = 26.68$, $p < 0.001$; 5 versus 15%, $p = 0.03$, versus 30% $p < 0.001$], Hand-2 [$F_{(1.8,29.8)} = 40.63$, $p < 0.01$; 5 versus 50 and 70%, both $p < 0.001$], and an interaction effect for Hand-1 by Hand-2 [$F_{(6.4,108.3)} = 4.14$, $p = 0.001$; see **Figure 3** for contrasts] with the force difference being larger at higher force levels of Hand-1 (**Figure 3**). There was an Age-group by Hand interaction in the force difference [$F_{(1,17)} = 7.4$, $p = 0.01$]; the force difference was smaller when the left hand started the contraction in the young subjects. Overall, the force difference was larger for middle-aged subjects than for young subjects [$F_{(1,17)} = 4.56$, $p = 0.05$].

The EMG values in Hand-1 (both the 1-s as well as the 100-ms before the TMS stimulus data) showed a main effect of the force in Hand-1 [$F_{(1.2,21.9)} = 312.18$ and 284.70 for 1-s and 100 ms epochs, both $p < 0.001$; 5 versus 15 and 30% $p < 0.001$] and the force in Hand-2 [$F_{(3.4,62.1)} = 7.51$ and 6.51, both $p < 0.001$; 5% versus all force levels $p < 0.05$ for 1-s, 5% versus force >15% $p < 0.05$ for 100 ms epoch]. In addition, there was an Age-group by Hand-1 interaction [$F_{(1.2,21.9)} = 5.19$ and 4.65, both $p < 0.03$ for 1-s and 100-ms epochs] because the middle-aged compared with young subjects had lower EMG activity at 30% MVC (26.9 and 33.4% RMS-MVC; **Figure 4D**; only significant effect for 100 ms epoch). The EMG in Hand-2 was modulated with the force level of Hand-2 [$F_{(2.5,45.7)} = 628.60$, $p < 0.001$]. No further main or interaction effects occurred.

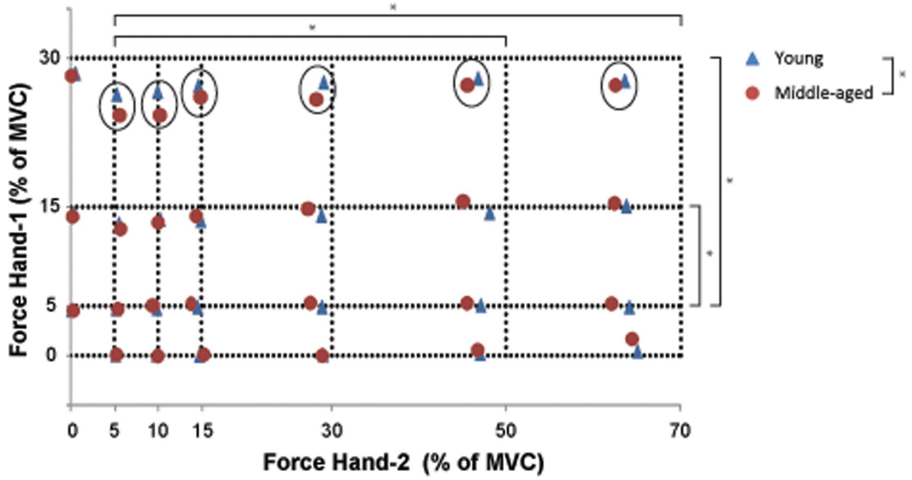


FIGURE 3 | The combination of bimanual forces produced by young (blue) and middle-aged subjects (red). The crossing of the interrupted lines represents the target force combination for Hand-1 (*y*-axis) and Hand-2 (*x*-axis). The measure of bilateral performance (force difference) is calculated as the Euclidean distance between the requested force combination and the produced force combination (see Eq. 1). Significant differences in force difference across bilateral force combinations are indicated by an asterisk (unilateral contractions were not included in the statistical analysis; main effect of Hand-1 and -2). The circles point to an Age-group effect on the amplitude of the force difference at high force levels in Hand-1. Overall, the force difference was larger for the middle-aged than for the young participants.

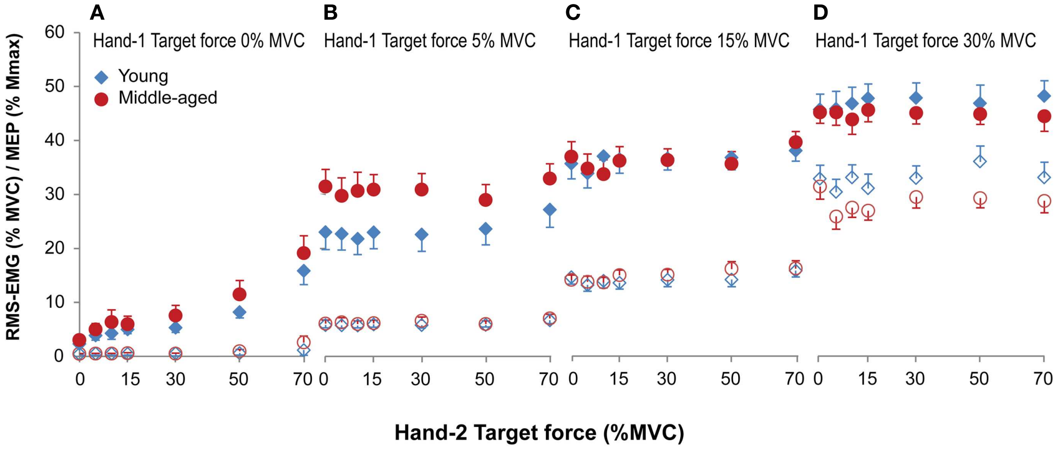


FIGURE 4 | Mean and standard error of RMS-EMG (100 ms, open symbols, bottom row) and MEPs (closed symbols, top row) during unilateral **(A)** and bilateral **(B–D)** forces at different force combinations for young (blue) and middle-aged (red) subjects. Hand-1 is the hand in which the MEPs in the FDI were evoked and the hand that started the contraction during the bilateral contractions. For the values presented in **(A)** and the unilateral contractions (force Hand-2 equals 0) in **(B–D)** all MEPs were included for calculating the mean values. **(A)** Shows a small but significant increase in RMS-EMG and an increase in MEP amplitude with increasing ipsilateral force. **(B–D)** Shows that the RMS-EMG and the MEPs in Hand-1 were affected by both the force production of Hand-1 and -2. At low force levels (5% MVC) MEPs were larger in middle-aged participants, whereas at high force levels (30% MVC) middle-aged participants had lower EMG values compared to young participants.

The MEPs were affected by both the force produced by Hand-1 [$F_{(1.7,30.6)} = 74.09$, $p < 0.001$] and the force produced by Hand-2 [$F_{(4.7,84.9)} = 4.18$, $p = 0.002$]. In addition, there was an Age-group by Hand-1 interaction [$F_{(1.7,30.64)} = 5.29$, $p = 0.014$]. In contrast to the RMS-EMG, the MEPs at 5% MVC were larger in the middle-aged subjects (30% of $M_{\max}$) than in young subjects (23% of $M_{\max}$; **Figure 4B**; 5 versus 15%, $p = 0.006$; 5 versus 30%, $p = 0.02$).

SUSTAINED CONTRACTION INDUCED MORE ASSOCIATED ACTIVITY IN MIDDLE-AGED SUBJECTS

Voluntary activity

During the sustained contraction, the index finger abduction force progressively decreased from 86% MVC (7.0 SD) to 36% MVC (11 SD). The statistical analysis showed a significant decline over time [$F_{(45,765)} = 196.27$, $p < 0.001$; **Figures 1D**, **5**, and **6A**] but no Hand nor Age-group effects. The RMS-EMG values showed a

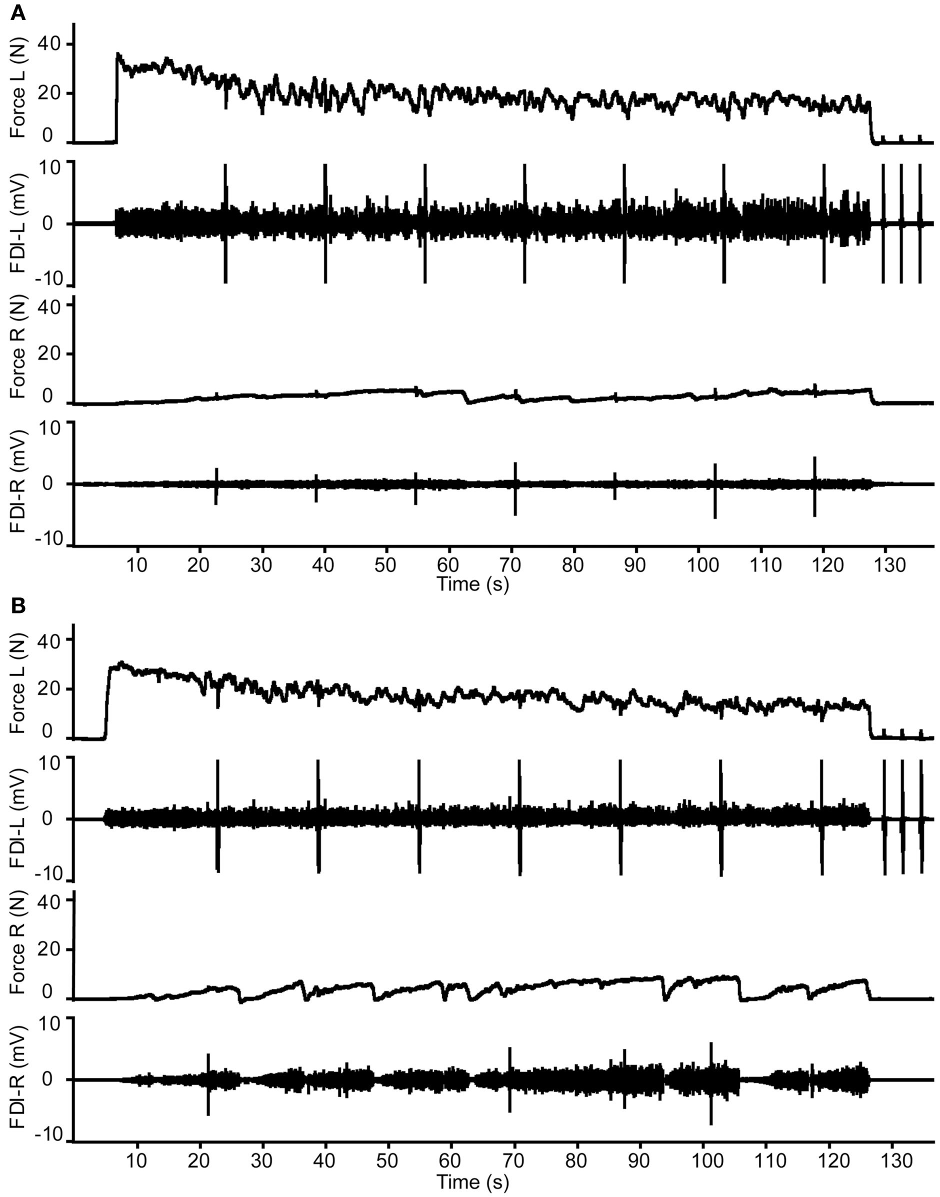


FIGURE 5 | Example of the changes in target and associated force and electromyography during the 2-min contraction with the FDI muscle of Hand-2 (left) in a young male (A) and middle-aged female participant (B). Please note the stronger activity in right hand (Hand-1) in the middle-aged participant.

more variable time course during the sustained task (**Figure 6B**), revealing a main effect of Time [$F_{(45,765)} = 2.49, p < 0.001$], and a Time by Hand interaction [$F_{(13.72,233.16)} = 2.12, p = 0.012$)]. The general trend was a decline in RMS-EMG in the left hand and a smaller change in the right hand.

During the sustained contraction, the FDI that performed the fatiguing task was stimulated seven times. The evoked force was used to estimate the voluntary drive during the sustained contraction. During the fatiguing task, the evoked doublet-force increased significantly (suggesting a decrease in voluntary drive) ($F = 3.22$, $p = 0.005$; **Figure 6E**); no main or interaction effects with Age-group were found.

Associated activity

During the sustained contraction, the amount of associated force and EMG increased significantly [force: $F_{(45,810)} = 9.58, p < 0.001$; RMS-EMG: $F_{(45,810)} = 10.97$, $p < 0.001$]. The amount of associated activity was significantly different between the Age-groups (**Figures 5** and **6A,B**). The associated force increased from 6.2 to 29.7% of MVC in the middle-aged subjects and from 2.7 to 15.2%MVC in the young subjects [Age-group: $F_{(1,18)} = 7.05$, $p = 0.016$]. The RMS-EMG showed a similar pattern; increase from 9.8 to 39.7% of MVC in the middle-aged subjects and from 3.8 to 18.4% of MVC for the young subjects [Age-group $F_{(1,18)} = 5.99, p = 0.025$].

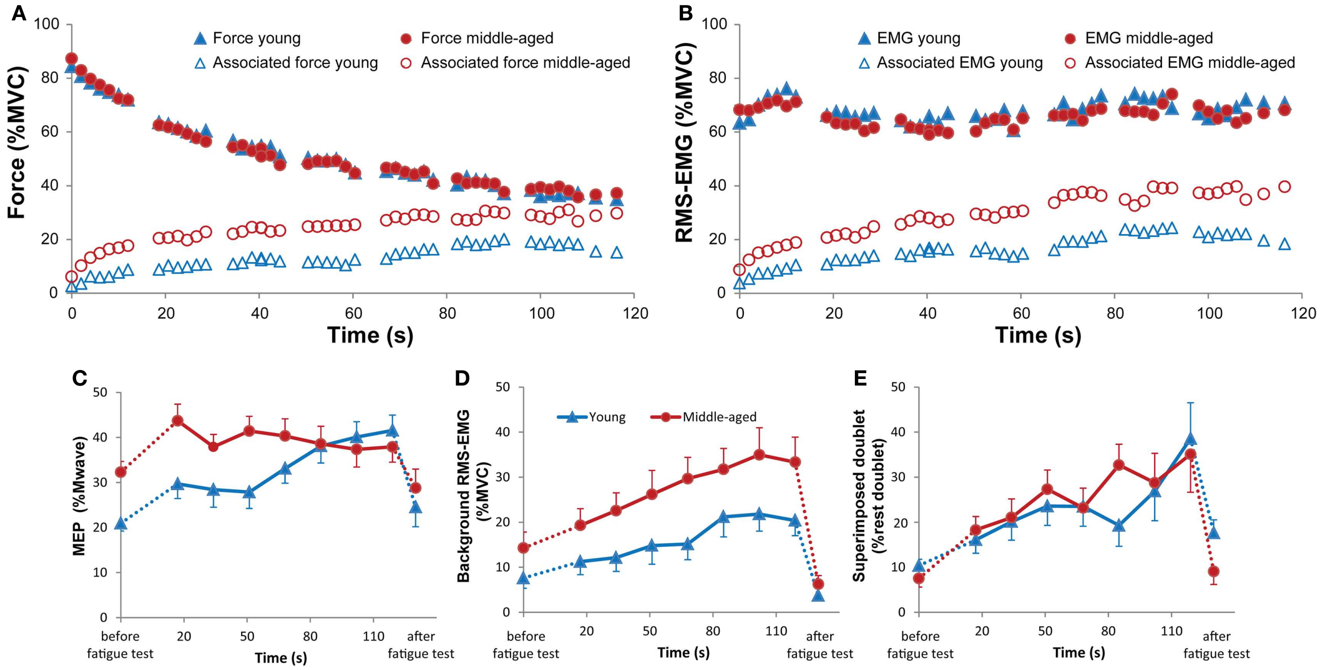


FIGURE 6 | Changes in mean force [(A), closed symbols] and RMS-EMG [2 s-values; (B), closed symbols] expressed as % MVC, and mean associated force [(A), open symbols] and RMS-EMG [2 s-values; (B), open symbols] expressed as % MVC (A,B) during the sustained 2 min contraction for young (blue) and middle-aged subjects (red). During the test, stimuli are given to the cortex ipsilateral to the target muscle, and to the target (fatiguing) muscle. During the stimuli, no average force or RMS-EMG is calculated. Therefore, short time periods are missing in the graphs. **(C)** Changes in mean MEP amplitude (and standard error) during the sustained contraction for young (blue) and middle-aged (red) subjects separately. The first value shows the mean MEP during the contralateral MVC before the sustained contraction. The last values show MEP during the contralateral MVC after the sustained contraction. The analysis demonstrated a Time by Age group interaction ($p = 0.006$), revealing a decrease in MEP difference between the two Age groups with time. **(D)** Changes in mean (and standard error) RMS-EMG 100 ms before the TMS pulse. First and last values are the values obtained during the contralateral MVC. Note that the background RMS-EMG is associated activity. In contrast to the MEPs, the amount of ipsilateral activity increased progressively during the sustained contraction of young and middle-aged subjects ($p < 0.001$). **(E)** Changes in the mean (and standard error) superimposed doublet-force evoked in the FDI muscle that produces the maximal force during the sustained contraction. The doublet twitch increased throughout the sustained contraction reflecting a progressive decline in voluntary drive ($p = 0.005$), without a difference between the two Age-groups.

Evoked potentials

During the sustained contraction, MEPs were evoked in the FDI showing the associated activity. **Figure 6C** shows the Time by Age-group interaction for the MEP amplitude [MEP peak: $F_{(5.2,94.4)} = 3.53$, $p = 0.006$; MEP area: $F_{(5.2,94.4)} = 3.19$, $p = 0.009$]. The first MEP during the sustained contraction increased in comparison with the control MVC before the sustained contraction (young: from 20.9 to 29.7% of $M_{\max}$, middle-aged: from 32.3 to 43.7% of $M_{\max}$). During the sustained contraction, the MEP in the middle-aged participants started at a higher value (44% of $M_{\max}$) than the MEP in the younger subjects and slowly decreased to 38% of $M_{\max}$, whereas in the young participants the MEP progressively increased (from 30 to 41% of $M_{\max}$) during the sustained contraction. As it was expected from the overall EMG measurement, the amount of background EMG upon which the MEP was evoked increased progressively during the fatiguing task [$F_{(8,144)} = 12.45, p < 0.001$; **Figure 6D**]. Overall, the EMG activity at the time of the TMS was higher in the middle-aged than younger subjects [$F_{(1,18)} = 4.50$, $p = 0.06$; **Figures 6B,D**]. Thus, the increase in MEP reflected the increase in background EMG in the young but not in the middle-aged subjects.

FATIGUE-RELATED CHANGES AFTER THE SUSTAINED CONTRACTIONS

The MVC of the fatigued FDI immediately after the fatiguing contraction decreased significantly to 67.2% of the pre-fatigue MVC [10.2 SD; $F_{(1,38)}$, 43.40, $p < 0.001$], without an Age-group effect. The MVC of the non-fatigued FDI also showed a small decline in force to 92.2% of MVC (SD 10.5); this decline was larger in the right (88.1% of MVC, 10.4 SD) than in the left FDI (95.1% of MVC, 10.3 SD, $p = 0.003$); no main or interaction effects were found for Age-group. The doublet-force evoked in the fatigued FDI declined to 47.3% compared to the control values in both age groups ($p = 0.22$).

The amplitude and area of the MEPs evoked during contralateral MVCs did not change after the fatiguing task (106.7%, 38.2 SD of pre-fatigue values), whereas the background (associated) EMG was smaller but similar in the two age groups after the fatiguing contraction [pre-fatigue: 10.9% of RMS-MVC and post-fatigue: 4.9% of RMS-MVC; $F_{(1,12)} = 12.41$, $p = 0.02$].

There was a main effect of Time [$F_{(1,33)} = 4.79$, $p = 0.05$] for the doublet-force superimposed on the MVC before and after the fatiguing contraction. The evoked force was larger after the fatiguing contraction (pre-fatigue: 7.8% versus post-fatigue:

12.2% doublet force at rest), suggesting a decline in voluntary activation after the fatiguing task. No interaction effect with Age-group was found.

WEAK ASSOCIATION BETWEEN BILATERAL PERFORMANCE AND ASSOCIATED ACTIVITY

The data demonstrated a weak but significant association between the measure of bilateral performance, i.e., force difference and the amount of associated activity during the MVCs for the left and right FDI (RMS-EMG: $R^2 = 0.17$, $p = 0.008$; force: $R^2 = 0.15$, $p = 0.015$; see **Figure 7**). Force difference was not significantly associated with the average amount of associated activity during the fatiguing sustained contraction ($p > 0.5$ for both average RMS-EMG and average force).

DISCUSSION

We compared the amount of associated activity and ipsilateral corticospinal excitability between young and middle-aged subjects during isometric contractions. We observed that the associated activity was ~2-fold higher in middle-aged (28% of MVC) when compared with young adults (11% of MVC) during brief as well as sustained MVCs (at 120 s: 15 versus 30% of MVC, for the young and middle-aged subjects). After carefully selecting MEPs that were not preceded by background EMG activity, no difference in ipsilateral corticospinal excitability was found between middle-aged versus young subjects during sub-maximal contractions. During the sustained contraction, MEPs were greater at the start of the contraction but there was no further increase *during* the contraction in middle-aged compared with young adults.

ASSOCIATED ACTIVITY DURING BRIEF MAXIMAL CONTRACTIONS IS HIGHER IN MIDDLE-AGED SUBJECTS

The increased levels of associated activity in middle-aged subjects during strong contractions confirm previous data obtained in elderly subjects [Bodwell et al., 2003 (65–85 years); Shinohara et al., 2003 (65–85 years); Baliz et al., 2005 (60–70 years); Addamo et al., 2009 (60–80 years); Fling and Seidler, 2012 (65–76 years)]. In a previous study, we demonstrated that the spinal motoneurons responsible for the associated contractions were activated via the contralateral corticospinal pathways; that is, the motor cortex ipsilateral to the target muscle (Zijdewind et al., 2006). Thus, our data demonstrate an additional increase in activity of these corticospinal pathways (ipsilateral to the target muscles) in middle-aged subjects during strong voluntary contractions. On basis of the present study, we cannot conclude whether these changes are present on cortical, spinal, or at both levels.

During a unilateral contraction, a MEP evoked in the ipsilateral motor cortex becomes facilitated (Hess et al., 1986; Ugawa et al., 1993; Stedman et al., 1998; Tinazzi and Zanette, 1998; Muellbacher et al., 2000; Liepert et al., 2001; Perez and Cohen, 2008, 2009). The larger MEPs during activation of the ipsilateral muscle are probably due to subliminal activation of the motor cortex contralateral to the target hemisphere. We did not find a significant difference in the ipsilateral MEPs between the two age groups during the sub-maximal contractions. It is possible that intra- and inter-cortical processes affect associated activity and ipsilateral excitability differently or we missed the increase in ipsilateral MEPs. The facilitation of the ipsilateral MEPs is more pronounced at high contralateral force levels (Hess et al., 1986; Ugawa et al., 1993; Stedman et al., 1998; Tinazzi and Zanette, 1998; Muellbacher et al., 2000; Liepert et al., 2001; Perez and Cohen, 2008, 2009) and since subjects were less able to prevent associated activation at higher force levels (see also Zijdewind and Kernell, 2001), hardly any MEPs at relatively high contralateral force levels remained.

Associated activity can be induced if the net excitation is above the spike-generating threshold for cortical neurons. Thus, the observation that middle-aged compared to young subjects more often show associated activity during strong contractions, suggests that the inhibition to the ipsilateral motor cortex is smaller or that the amount of excitation it receives is larger. It is often reported that intracortical inhibition (Peinemann et al., 2001; Hortobagyi et al., 2006; however, see Oliviero et al., 2006; Smith et al., 2009; McGinley et al., 2010), length of the silent period (Sale and Semmler, 2005) and interhemispheric inhibition (Talelli et al., 2008a,b; McGregor et al., 2011, 2013; Davidson and Tremblay, 2013) declines with age. However, one would expect to find an additional increase

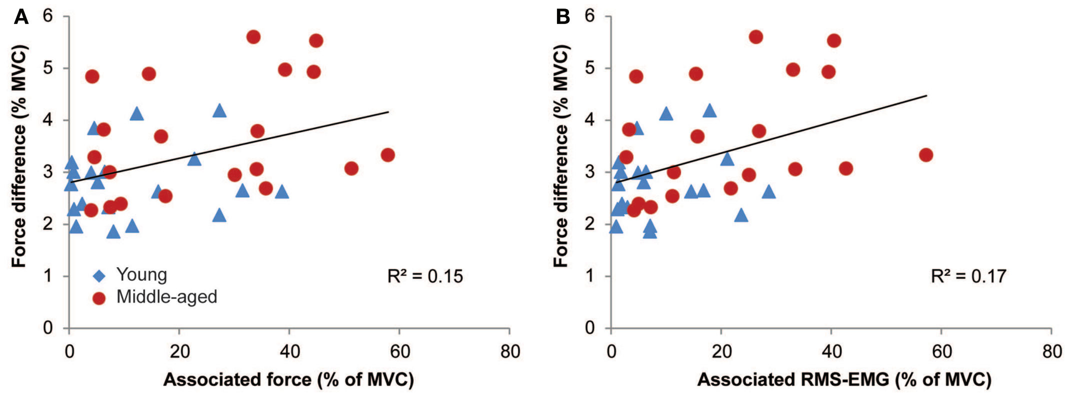


FIGURE 7 | Relationships between associated activity [EMG and force, in (A,B), respectively] and the measure of bilateral performance, i.e., force difference for young (blue triangle) and middle-aged subjects (red circles). Participants with high levels of associated activity tended to have an inferior bilateral performance.

in ipsilateral MEPs (see Perez and Cohen, 2008). On the other hand, Perez and Cohen (2008) showed that the ipsilateral MEPs did correlate with changes in short-latency intracortical inhibition but less with changes in interhemispheric inhibition. So, maybe the increased associated activity during strong contractions does reflect differences in interhemispheric inhibition between the two age groups (Talelli et al., 2008a,b; Fling and Seidler, 2012). One other possible explanation could be a reduction in synchronized I-waves in middle-aged subjects (see also *larger MEPs during low contralateral activation*). A TMS stimulus can evoke both direct (D) and a series of indirect (I) waves (Kernell and Chien-Ping, 1967; Amassian et al., 1987). At low stimulation intensities, the contribution of I-waves to the excitation of corticospinal pathways is more important than the contribution from D-waves. A decrease in synchronized I-waves would thus result in smaller MEPs (see also discussion of Pitcher et al., 2003). Small changes in synchronization will probably have less effect during voluntary (or associated) activation. Hence, this could explain the higher level of associated activity during strong contractions without an increase in ipsilateral MEP size at rest.

The increase in associated activity in middle-aged subjects during effortful contractions is consistent with fMRI data that showed higher blood oxygenation level dependent (BOLD) activation of ipsilateral motor areas during motor tasks in old compared with young adults [Hutchinson et al., 2002 (54–76 years); Ward and Frackowiak, 2003 (26–80 years); Heuninckx et al., 2005 (62–71 years); Wu and Hallett, 2005 (57–73 years); Naccarato et al., 2006 (18–79 years); Riecker et al., 2006 (58–82 years); Talelli et al., 2008a (19–78 years); McGregor et al., 2011 (60–85 years)]. Yet, in most of these studies the authors claim that no associated activity was present. Still, the BOLD response in fMRI is more sensitive to a change in input, and processing of this input in a certain area, than to the actual output of this area (Logothetis, 2002) and thus subliminal activation of the ipsilateral primary motor cortex would show up during fMRI even if no associated muscle activity is observed. Only if the ipsilateral activity results in an increase in the corticofugal output that is strong enough to activate motoneurons, associated activity is seen. Nevertheless, even before associated movement is seen small motor unit potentials can be seen in the EMG resulting in a small change in EMG activity (often smaller than 25 μV). We expected that this increase in (subliminal) ipsilateral activation would show up as an increase in MEP. However after carefully selecting the MEPs without background EMG activity, we found no difference in MEP size between young and middle-aged subjects.

The relevance of the ipsilateral activation and the probably related associated activity is still unclear but better motor performance seemed to be associated with higher ipsilateral activation (Mattay et al., 2002). However, not all studies confirm the functional importance of the age-related increase in cortical activity. For example, Riecker et al. (2006) showed increased activation in elderly subjects (58–82 years) during a tapping task but with no further age-related increase in activity with increasing frequency. Additionally, recent data obtained in middle-aged (McGregor et al., 2011) and older subjects (McGregor et al., 2011) showed that increased iM1 activation was related to shorter ipsilateral silent periods and decreased motor function. On the other hand, in a recent study, Zimerman et al. (2012) demonstrated reduced motor learning in older subjects after cathodal DC-stimulation of the ipsilateral motor cortex. Cathodal DC-stimulation induces a reduction in excitability of the stimulated cortex (for reviews, see Nitsche and Paulus, 2011; Jacobson et al., 2012). Hence, their data suggest that the ipsilateral cortex is more important for motor learning in older compared with younger subjects (Zimerman et al., 2012). Our data showed a weak but significant association between the amount of associated activity and bimanual interference (as measured by the difference between target force and actual produced force), suggesting that high levels of associated activity could be detrimental for bimanual control (cf. McGregor et al., 2013). Again, the mechanisms underlying associated activity and ipsilateral activation could be different and probably, the relationship between these two variables is task-dependent.

ASSOCIATED ACTIVITY DURING SUSTAINED CONTRACTIONS IS HIGHER IN MIDDLE-AGED SUBJECTS

The present study showed that, similarly to previous data in old adults [Shinohara et al., 2003 (66–80 years)], middle-aged compared with young subjects demonstrated higher associated activity already at the start of the voluntary muscle contraction. In the present experiment, this difference in associated activity was maintained throughout the sustained contraction and at the end of the 2-min contraction, the middle-aged compared with young subjects demonstrated a twofold larger level of associated activity. In the only other study that investigated associated activity during fatiguing contractions (Shinohara et al., 2003), the difference in associated activity between young and older subjects became progressively smaller as the contractions progressed. It is possible that this difference is due to age-differences; our middle-aged group was younger than the older subjects used by Shinohara et al. (2003) or to a difference in contraction type (anisometric contraction in Shinohara et al., 2003 versus isometric contractions in the present study).

During a sustained contraction, changes in excitability occur at different levels of the neuromuscular system. For instance, the excitability of the active motoneurons starts to decline as soon as 20 s after the start of the contraction (McNeil et al., 2009, 2011b). To maintain sufficient force production, the voluntary drive to motoneurons has to increase. This increase in drive is seen as an increase in activation of the contralateral primary motor cortex, as demonstrated by fMRI experiments (Dettmers et al., 1995; Liu et al., 2003; van Duinen et al., 2007; Post et al., 2009b). Furthermore, this increase in activity is accompanied by an increase in activity in the ipsilateral primary motor cortex (Dettmers et al., 1995; Liu et al., 2003; van Duinen et al., 2007; Post et al., 2009b), which could generate an increase in associated activity (see also Sehm et al., 2010). If the increase in voluntary drive is indeed reflected as an increase in associated activity, one would expect a progressive increase in associated activation during a sustained contraction. Since Shinohara et al. (2003) did not measure the voluntary drive, it is possible that during the sustained contraction the elderly subjects did not increase their drive similar to the young subjects and therefore did not increase their associated activity further as young subjects did. In the present experiment, both young and middle-aged subjects showed some decline in voluntary activation, as measured with the twitch superimposition technique, but we did not find a difference between the two age groups (see also Hunter et al., 2008).

AGE-RELATED DIFFERENCES IN IPSILATERAL CORTICOSPINAL EXCITABILITY DURING A SUSTAINED CONTRACTION

During a fatiguing task, the associated EMG progressively increases (Post et al., 2008). Despite the increase in background EMG in both groups, the MEPs remained unchanged in the middle-aged compared with young adults in whom the MEPs and the background EMG increased in parallel. The MEPs were comparable to the maximal MEPs obtained by Devanne et al., 1997; 45% $M_{\max}$) in the FDI muscle with different levels of background activity and stimulation intensity. The relationship between background EMG and MEP amplitude in the FDI muscle is not linear but the MEP peaks between 25 and 50% MVC (Devanne et al., 1997; Martin et al., 2006; Perez and Cohen, 2009). At higher background EMG levels, the MEP starts to decline. This reduction in MEP amplitude starts at relatively low force levels in the FDI muscle compared to for instance, the biceps brachii muscle (Martin et al., 2006). The main reason seems to be a change in the balance between two mechanisms of force control, recruitment gradation, and rate modulation. In the FDI muscle, only a few additional motor units become activated at force levels at or higher than 50% MVC, whereas in the biceps brachii muscle recruitment of new motor units continues up to 80% MVC (Milner-Brown et al., 1973; Kukulka and Clamann, 1981). Thus, at higher force levels, the FDI hand muscle completely relies on rate gradation.

After activation of a motoneuron, the motoneuron displays a refractory period followed by afterhyperpolarization (AHP). The time course of the AHP shows an exponential decline until the resting membrane potential (Matthews, 1996; Kernell, 2006). With increasing firing rates, the chance that a TMS pulse reaches a motoneuron during the refractory period or at the initial part of the AHP increases. During this period, the motoneuron is less likely to be activated by the TMS pulse. If smaller number of motoneurons are activated, this will result in a smaller TMS evoked muscle response. During the sustained contraction, the amount of associated activity increased from 20 to 35% of max RMS-EMG in the middle-aged subjects and 12–20% of max RMS-EMG. Thus, for the younger subjects the MEP still has more potential to grow during the sustained contraction, whereas in the middle-aged subjects the MEPs will be closer to their maximal value. Furthermore, there are indications that during a sustained (sub)maximal contraction the intrinsic properties of the motoneuron change to lower excitability levels (McNeil et al., 2011b). This would also result in smaller MEPs especially at higher firing rates. Thus, the lack of increase in MEPs in middle-aged subjects is probably due to fatigue-related changes on a spinal level, but these changes can be accompanied by time-related changes on cortical levels. In young subjects, the excitability changes at spinal levels are partly compensated by an increase in cortical activity, accompanied by increased ipsilateral activity (Post et al., 2008, 2009b). It is not known whether the increase in cortical activity is similar in young and middle-aged subjects but our data did not show any indication that the voluntary drive in the middle-aged subjects was smaller or the voluntary drive changed differently during the sustained contraction. Furthermore, the increase in the amount of associated activity suggests that also the ipsilateral motor cortex increases its activity with time.

NO DIFFERENCE IN FATIGUE BETWEEN YOUNG AND MIDDLE-AGED SUBJECTS

During the fatiguing maximal contraction, there were no age-related differences in the amount of fatigue as indexed by force loss, voluntary activation, and twitch force. Previous studies showed inconsistent data with respect to muscle fatigability of hand muscles in young and older subjects (see for review Allman and Rice, 2002). We are unaware of other studies reporting age-related differences in voluntary activation in the FDI but data in the upper arm muscles suggest that older subjects have a comparable but more variable voluntary activation [Hunter et al., 2008 (67–78 years)]. During their fatiguing task, the voluntary activation decreased as subjects repeated the 22-s-long MVCs. Both, their and our data showed a progressive but similar decline in voluntary activation in the two age groups (Hunter et al., 2008). The decline in voluntary activation was, however, larger than expected (Zijdewind et al., 1998). It is possible that the TMS-response in the ipsilateral motor cortex induced a short ipsilateral silent period resulting in a small decline in force 1.5 s before the muscle stimulation. We looked for ipsilateral silent periods but they were rarely visible (but cf. Fling and Seidler, 2012) and the duration of the reduced EMG was much shorter, but still the stimulation could have affected the attention of the subjects, resulting in a small extra decline in their voluntary activation. After the sustained contraction, the force decline in the fatigued and non-fatigued FDI (see also Post et al., 2008) was not different for the two groups.

GREATER MEPs AT LOW FORCES DURING BILATERAL CONTRACTIONS IN MIDDLE-AGED SUBJECTS

At rest, there is evidence that with age the relationship between stimulus intensity and MEP size (the stimulus-response curve) shifts to the right without a change in the RMT (Pitcher et al., 2003). This observation demonstrates that with age, higher stimulus intensities are needed to obtain maximal MEPs. The most likely explanation for this shift in stimulus–response curve is reduced synchronization of I-waves (indirect activation of corticospinal neurons via interneurons) or changes in recruitment spacing in the motoneuron pool (e.g., due to loss of cortico-motoneurons, see Pitcher et al., 2003). In the present experiment, we used relatively low stimulus intensities, i.e., 110% RMT. It is therefore possible that with the TMS pulse we activated different portions of the corticospinal pathway in young or middle-aged subjects. However, we would expect to activate a smaller portion in the middle-aged subjects, resulting in smaller MEPs. At low force levels, the MEPs were larger in the middle-aged compared with young subjects (with similar background EMG). Although we only found a significant differential effect of background force and MEP size with age in the bilateral condition, the trend in the unilateral condition ($p = 0.097$) suggests that the effect was probably not confined to the bilateral condition.

The maximal rate at which motor units discharge action potentials declines with age (Kamen et al., 1995; Connelly et al., 1999). In hand muscles, all motor units are recruited at low force levels (below 50% MVC; Milner-Brown et al., 1973; Kukulka and Clamann, 1981). Thus, in hand muscles, high forces are extremely susceptible to changes in maximal firing rate and furthermore, these changes will affect the balance between recruitment and rate gradation. The change in balance between the two mechanisms of force control could be responsible for the larger MEP amplitude at low compared to high forces in middle-aged subjects. However, this possibility will require further confirmation in more detailed experiments.

In summary, our data show changes in associated activity during effortful contralateral contractions already in middle-aged subjects. Future experiments will have to determine if such changes in motor control at middle age are functionally relevant. Considering the widespread and increasing use of electronic devices that require high levels of bimanual coordination at work, the observed changes in corticospinal activity and bimanual control at middle age may have implications for screening individuals for such tasks and for designing interventions studies that modulate the levels of associated activity and improve motor function.

REFERENCES

Addamo, P. K., Farrow, M., Hoy, K. E., Bradshaw, J. L., and Georgiou-Karistianis, N. (2009). The influence of task characteristics on younger and older adult motor overflow. *Q. J. Exp. Psychol. (Hove)* 62, 239–247. doi:10.1080/17470210802269217

Allen, G. M., Gandevia, S. C., and McKenzie, D. K. (1995). Reliability of measurements of muscle strength and voluntary activation using twitch interpolation. *Muscle Nerve* 18, 593–600. doi:10.1002/mus.880180605

Allman, B. L., and Rice, C. L. (2002). Neuromuscular fatigue and aging: central and peripheral factors. *Muscle Nerve* 25, 785–796. doi:10.1002/mus.10116

Amassian, V. E., Stewart, M., Quirk, G. J., and Rosenthal, J. L. (1987). Physiological basis of motor effects of a transient stimulus to cerebral cortex. *Neurosurgery* 20, 74–93. doi:10.1097/00006123-198701000-00022

Armatas, C. A., Summers, J. J., and Bradshaw, J. L. (1994). Mirror movements in normal adult subjects. *J. Clin. Exp. Neuropsychol.* 16, 405–413. doi:10.1080/01688639408402651

Baliz, Y., Armatas, C., Farrow, M., Hoy, K. E., Fitzgerald, P. B., Bradshaw, J. L., et al. (2005). The influence of attention and age on the occurrence of mirror movements. *J. Int. Neuropsychol. Soc.* 11, 855–862. doi:10.1017/S1355617705051003

Bodwell, J. A., Mahurin, R. K., Waddle, S., Price, R., and Cramer, S. C. (2003). Age and features of movement influence motor overflow. *J. Am. Geriatr. Soc.* 51, 1735–1739. doi:10.1046/j.1532-5415.2003.51557.x

Boudrias, M. H., Goncalves, C. S., Penny, W. D., Park, C. H., Rossiter, H. E., Talelli, P., et al. (2012). Age-related changes in causal interactions between cortical motor regions during hand grip. *Neuroimage* 59, 3398–3405. doi:10.1016/j.neuroimage.2011.11.025

Cernacek, J. (1961). Contralateral motor irradiation – cerebral dominance. Its changes in hemiparesis. *Arch. Neurol.* 4, 165–172. doi:10.1001/archneur.1961.00450080047005

Cincotta, M., and Ziemann, U. (2008). Neurophysiology of unimanual motor control and mirror movements. *Clin. Neurophysiol.* 119, 744–762. doi:10.1016/j.clinph.2007.11.047

Connelly, D. M., Rice, C. L., Roos, M. R., and Vandervoort, A. A. (1999). Motor unit firing rates and contractile properties in tibialis anterior of young and old men. *J. Appl. Physiol.* 87, 843–852.

Curshmann, H. (1906). Beitrage zur Psysiologie und Pathologie der kontralateralen mitbewegungen. *Dtsch. Z. Nervenheilkd.* 31, 1–52. doi:10.1007/BF01668345

Davidson, T., and Tremblay, F. (2013). Age and hemispheric differences in transcallosal inhibition between motor cortices: an ispsilateral silent period study. *BMC Neurosci.* 14:62. doi:10.1186/1471-2202-14-62

Dettmers, C., Fink, G. R., Lemon, R. N., Stephan, K. M., Passingham, R. E., Silbersweig, D., et al. (1995). Relation between cerebral activity and force in the motor areas of the human brain. *J. Neurophysiol.* 74, 802–815.

Devanne, H., Lavoie, B. A., and Capaday, C. (1997). Input-output properties and gain changes in the human corticospinal pathway. *Exp. Brain Res.* 114, 329–338. doi:10.1007/PL00005641

Fling, B. W., Peltier, S. J., Bo, J., Welsh, R. C., and Seidler, R. D. (2011). Age differences in interhemispheric interactions: callosal structure, physiological function, and behavior. *Front. Neurosci.* 5:38. doi:10.3389/fnins.2011.00038

Fling, B. W., and Seidler, R. D. (2012). Fundamental differences in callosal structure, neurophysiologic function, and bimanual control in young and older adults. *Cereb. Cortex* 22, 2643–2652. doi:10.1093/cercor/bhr349

Haug, H., and Eggers, R. (1991). Morphometry of the human cortex cerebri and corpus striatum during aging. *Neurobiol. Aging* 12, 336–338; discussion 352–355. doi:10.1016/0197-4580(91)90013-A

Hess, C. W., Mills, K. R., and Murray, N. M. (1986). Magnetic stimulation of the human brain: facilitation of motor responses by voluntary contraction of ipsilateral and contralateral muscles with additional observations on an amputee. *Neurosci. Lett.* 71, 235–240. doi:10.1016/0304-3940(86)90565-3

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

Hortobagyi, T., del Olmo, M. F., and Rothwell, J. C. (2006). Age reduces cortical reciprocal inhibition in humans. *Exp. Brain Res.* 171, 322–329. doi:10.1007/s00221-005-0274-9

Hortobagyi, T., Taylor, J. L., Petersen, N. T., Russell, G., and Gandevia, S. C. (2003). Changes in segmental and motor cortical output with contralateral muscle contractions and altered sensory inputs in humans. *J. Neurophysiol.* 90, 2451–2459. doi:10.1152/jn.01001.2002

Hunter, S. K., Todd, G., Butler, J. E., Gandevia, S. C., and Taylor, J. L. (2008). Recovery from supraspinal fatigue is slowed in old adults after fatiguing maximal isometric contractions. *J. Appl. Physiol.* 105, 1199–1209. doi:10.1152/japplphysiol.01246.2007

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

Jacobson, L., Koslowsky, M., and Lavidor, M. (2012). tDCS polarity effects in motor and cognitive domains: a meta-analytical review. *Exp. Brain Res.* 216, 1–10. doi:10.1007/s00221-011-2891-9

Kamen, G., Sison, S. V., Du, C. C., and Patten, C. (1995). Motor unit discharge behavior in older adults during maximal-effort contractions. *J. Appl. Physiol.* 79, 1908–1913.

Kernell, D. (2006). *The Motoneurone and Its Muscle Fibres.* Oxford: Oxford University Press.

Kernell, D., and Chien-Ping, W. U. (1967). Responses of the pyramidal tract to stimulation of the baboon's motor cortex. *J. Physiol.* 191, 653–672.

Kukulka, C. G., and Clamann, H. P. (1981). Comparison of the recruitment and discharge properties of motor units in human brachial biceps and adductor pollicis during isometric contractions. *Brain Res.* 219, 45–55. doi:10.1016/0006-8993(81)90266-3

Liepert, J., Dettmers, C., Terborg, C., and Weiller, C. (2001). Inhibition of ipsilateral motor cortex during phasic generation of low force. *Clin. Neurophysiol.* 112, 114–121. doi:10.1016/S1388-2457(00)00503-4

Liu, J. Z., Shan, Z. Y., Zhang, L. D., Sahgal, V., Brown, R. W., and Yue, G. H. (2003). Human brain activation during sustained and intermittent submaximal fatigue muscle contractions: an FMRI study. *J. Neurophysiol.* 90, 300–312. doi:10.1152/jn.00821.2002

Logothetis, N. K. (2002). The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 357, 1003–1037. doi:10.1098/rstb.2002.1114

Madden, D. J., Whiting, W. L., Huettel, S. A., White, L. E., MacFall, J. R., and Provenzale, J. M. (2004). Diffusion tensor imaging of adult age differences in cerebral white matter: relation to response time. *Neuroimage* 21, 1174–1181. doi:10.1016/j.neuroimage.2003.11.004

Marner, L., Nyengaard, J. R., Tang, Y., and Pakkenberg, B. (2003). Marked loss of myelinated nerve fibers in the human brain with age. *J. Comp. Neurol.* 462, 144–152. doi:10.1002/cne.10714

Martin, P. G., Gandevia, S. C., and Taylor, J. L. (2006). Output of human motoneuron pools to corticospinal inputs during voluntary contractions. *J. Neurophysiol.* 95, 3512–3518. doi:10.1152/jn.01230.2005

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

Matthews, P. B. (1996). Relationship of firing intervals of human motor units to the trajectory of post-spike after-hyperpolarization and synaptic noise. *J. Physiol.* 492, 597–628.

McGinley, M., Hoffman, R. L., Russ, D. W., Thomas, J. S., and Clark, B. C. (2010). Older adults exhibit more intracortical inhibition and less intracortical facilitation than young adults. *Exp. Gerontol.* 45, 671–678. doi:10.1016/j.exger.2010.04.005

McGregor, K. M., Nocera, J. R., Sudhyadhom, A., Patten, C., Manini, T. M., Kleim, J. A., et al. (2013). Effects of aerobic fitness on aging-related changes of interhemispheric inhibition and motor performance. *Front. Aging Neurosci.* 5:66. doi:10.3389/fnagi.2013.00066

McGregor, K. M., Zlatar, Z., Kleim, E., Sudhyadhom, A., Bauer, A., Phan, S., et al. (2011). Physical activity and neural correlates of aging: a combined TMS/fMRI study. *Behav. Brain Res.* 222, 158–168. doi:10.1016/j.bbr.2011.03.042

McNeil, C. J., Giesebrecht, S., Gandevia, S. C., and Taylor, J. L. (2011a). Behaviour of the motoneurone pool in a fatiguing submaximal contraction. *J. Physiol.* 589, 3533–3544. doi:10.1113/jphysiol.2011.207191

McNeil, C. J., Giesebrecht, S., Khan, S. I., Gandevia, S. C., and Taylor, J. L. (2011b). The reduction in human motoneurone responsiveness during muscle fatigue is not prevented by increased muscle spindle discharge. *J. Physiol.* 589, 3731–3738. doi:10.1113/jphysiol.2011.210252

McNeil, C. J., Martin, P. G., Gandevia, S. C., and Taylor, J. L. (2009). The response to paired motor cortical stimuli is abolished at a spinal level during human muscle fatigue. *J. Physiol.* 587, 5601–5612. doi:10.1113/jphysiol.2009.180968

Merton, P. A. (1954). Interaction between muscle fibres in a twitch. *J. Physiol.* 124, 311–324.

Milner-Brown, H. S., Stein, R. B., and Yemm, R. (1973). The orderly recruitment of human motor units during voluntary isometric contractions. *J. Physiol.* 230, 359–370.

Muellbacher, W., Facchini, S., Boroojerdi, B., and Hallett, M. (2000). Changes in motor cortex excitability during ipsilateral hand muscle activation in humans. *Clin. Neurophysiol.* 111, 344–349. doi:10.1016/S1388-2457(99)00243-6

Naccarato, M., Calautti, C., Jones, P. S., Day, D. J., Carpenter, T. A., and Baron, J. C. (2006). Does healthy aging affect the hemispheric activation balance during paced index-to-thumb opposition task? An fMRI study. *Neuroimage* 32, 1250–1256. doi:10.1016/j.neuroimage.2006.05.003

Nitsche, M. A., and Paulus, W. (2011). Transcranial direct current stimulation – update 2011. *Restor. Neurol. Neurosci.* 29, 463–492. doi:10.3233/RNN-2011-0618

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

Oliviero, A., Profice, P., Tonali, P. A., Pilato, F., Saturno, E., Dileone, M., et al. (2006). Effects of aging on motor cortex excitability. *Neurosci. Res.* 55, 74–77. doi:10.1016/j.neures.2006.02.002

Peinemann, A., Lehner, C., Conrad, B., and Siebner, H. R. (2001). Age-related decrease in paired-pulse intracortical inhibition in the human primary motor cortex. *Neurosci. Lett.* 313, 33–36. doi:10.1016/S0304-3940(01)02239-X

Perez, M. A., and Cohen, L. G. (2008). Mechanisms underlying functional changes in the primary motor cortex ipsilateral to an active hand. *J. Neurosci.* 28, 5631–5640. doi:10.1523/JNEUROSCI.0093-08.2008

Perez, M. A., and Cohen, L. G. (2009). Scaling of motor cortical excitability during unimanual force generation. *Cortex* 45, 1065–1071. doi:10.1016/j.cortex.2008.12.006

Pitcher, J. B., Ogston, K. M., and Miles, T. S. (2003). Age and sex differences in human motor cortex input-output characteristics. *J. Physiol.* 546, 605–613. doi:10.1113/jphysiol.2002.029454

Post, M., Bakels, R., and Zijdewind, I. (2009a). Inadvertent contralateral activity during a sustained unilateral contraction reflects the direction of target movement. *J. Neurosci.* 29, 6353–6357. doi:10.1523/JNEUROSCI.0631-09.2009

Post, M., Steens, A., Renken, R., Maurits, N. M., and Zijdewind, I. (2009b). Voluntary activation and cortical activity during a sustained maximal contraction: an fMRI study. *Hum. Brain Mapp.* 30, 1014–1027. doi:10.1002/hbm.20562

Post, M., Bayrak, S., Kernell, D., and Zijdewind, I. (2008). Contralateral muscle activity and fatigue in the human first dorsal interosseous muscle. *J. Appl. Physiol.* 105, 70–82. doi:10.1152/japplphysiol.01298.2007

Riecker, A., Groschel, K., Ackermann, H., Steinbrink, C., Witte, O., and Kastrup, A. (2006). Functional significance of age-related differences in motor activation patterns. *Neuroimage* 32, 1345–1354. doi:10.1016/j.neuroimage.2006.05.021

Rossini, P. M., Barker, A. T., Berardelli, A., Caramia, M. D., Caruso, G., Cracco, R. Q., et al. (1994). Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalogr. Clin. Neurophysiol.* 91, 79–92. doi:10.1016/0013-4694(94)90029-9

Sale, M. V., and Semmler, J. G. (2005). Age-related differences in corticospinal control during functional isometric contractions in left and right hands. *J. Appl. Physiol.* 99, 1483–1493. doi:10.1152/japplphysiol.00371.2005

Sehm, B., Perez, M. A., Xu, B., Hidler, J., and Cohen, L. G. (2010). Functional neuroanatomy of mirroring during a unimanual force generation task. *Cereb. Cortex* 20, 34–45. doi:10.1093/cercor/bhp075

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

Shinohara, M., Keenan, K. G., and Enoka, R. M. (2003). Contralateral activity in a homologous hand muscle during voluntary contractions is greater in old adults. *J. Appl. Physiol.* 94, 966–974. doi:10.1152/japplphysiol.00836.2002

Smith, A. E., Ridding, M. C., Higgins, R. D., Wittert, G. A., and Pitcher, J. B. (2009). Age-related changes in short-latency motor cortex inhibition. *Exp. Brain Res.* 198, 489–500. doi:10.1007/s00221-009-1945-8

Snijders, T., and Bosker, R. (1999). *Multilevel Analysis: An Introduction to Basic and Advanced Multilevel Modeling.* London: Sage Publications Inc.

Stedman, A., Davey, N. J., and Ellaway, P. H. (1998). Facilitation of human first dorsal interosseous muscle responses to transcranial magnetic stimulation during voluntary contraction of the contralateral homonymous muscle. *Muscle Nerve* 21, 1033–1039. doi:10.1002/(SICI)1097-4598(199808)21:8<1033::AID-MUS7>3.0.CO;2-9

Taki, Y., Thyreau, B., Kinomura, S., Sato, K., Goto, R., Wu, K., et al. (2013). A longitudinal study of age- and gender-related annual rate of volume changes in regional gray matter in healthy adults. *Hum. Brain Mapp.* 34, 2292–2301. doi:10.1002/hbm.22067

Talelli, P., Ewas, A., Waddingham, W., Rothwell, J. C., and Ward, N. S. (2008a). Neural correlates of age-related changes in cortical neurophysiology. *Neuroimage* 40, 1772–1781. doi:10.1016/j.neuroimage.2008.01.039

Talelli, P., Waddingham, W., Ewas, A., Rothwell, J. C., and Ward, N. S. (2008b). The effect of age on task-related modulation of interhemispheric balance. *Exp. Brain Res.* 186, 59–66. doi:10.1007/s00221-007-1205-8

Tinazzi, M., and Zanette, G. (1998). Modulation of ipsilateral motor cortex in man during unimanual finger movements of different complexities. *Neurosci. Lett.* 244, 121–124. doi:10.1016/S0304-3940(98)00150-5

Ugawa, Y., Hanajima, R., and Kanazawa, I. (1993). Interhemispheric facilitation of the hand area of the human motor cortex. *Neurosci. Lett.* 160, 153–155. doi:10.1016/0304-3940(93)90401-6

van Duinen, H., Renken, R., Maurits, N., and Zijdewind, I. (2007). Effects of motor fatigue on human brain activity, an fMRI study. *Neuroimage* 35, 1438–1449. doi:10.1016/j.neuroimage.2007.02.008

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

Wu, T., and Hallett, M. (2005). The influence of normal human ageing on automatic movements. *J. Physiol.* 562, 605–615. doi:10.1113/jphysiol.2004.076042

Zhou, D., Lebel, C., Evans, A., and Beaulieu, C. (2013). Cortical thickness asymmetry from childhood to older adulthood. *Neuroimage* 83, 66–74. doi:10.1016/j.neuroimage.2013.06.073

Zijdewind, I., Butler, J. E., Gandevia, S. C., and Taylor, J. L. (2006). The origin of activity in the biceps brachii muscle during voluntary contractions of the contralateral elbow flexor muscles. *Exp. Brain Res.* 175, 526–535. doi:10.1007/s00221-006-0570-z

Zijdewind, I., and Kernell, D. (1994). Index finger position and force of the human first dorsal interosseus and its ulnar nerve antagonist. *J. Appl. Physiol.* 77, 987–997.

Zijdewind, I., and Kernell, D. (2001). Bilateral interactions during contractions of intrinsic hand muscles. *J. Neurophysiol.* 85, 1907–1913.

Zijdewind, I., Zwarts, M. J., and Kernell, D. (1998). Influence of a voluntary fatigue test on the contralateral homologous muscle in humans? *Neurosci. Lett.* 253, 41–44. doi:10.1016/S0304-3940(98)00609-0

Zimerman, M., Heise, K. F., Gerloff, C., Cohen, L. G., and Hummel, F. C. (2012). Disrupting the ipsilateral motor cortex interferes with training of a complex motor task in older adults. *Cereb. Cortex*. doi:10.1093/cercor/bhs385

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

Received: 22 November 2013; accepted: 10 January 2014; published online: 24 January 2014.

Citation: Heetkamp J, Hortobágyi T and Zijdewind I (2014) Increased bilateral interactions in middle-aged subjects. Front. Aging Neurosci. ***6****:5. doi: 10.3389/fnagi.2014.00005*

This article was submitted to the journal Frontiers in Aging Neuroscience.

frontiers in
AGING NEUROSCIENCE

HYPOTHESIS AND THEORY ARTICLE
published: 27 June 2014
doi: 10.3389/fnagi.2014.00140

Aging induced loss of complexity and dedifferentiation: consequences for coordination dynamics within and between brain, muscular and behavioral levels

Rita Sleimen-Malkoun[1,2]*, Jean-Jacques Temprado[1] and S. Lee Hong[3]

[1] CNRS, Institut des Sciences du Mouvement UMR 7287, Aix-Marseille Université, Marseille, France
[2] Inserm, Institut de Neurosciences des Systèmes UMR_S 1106, Faculté de Médecine Timone, Aix-Marseille Université, Marseille, France
[3] Ohio Musculoskeletal and Neurological Institute, Ohio University, Athens, OH, USA

Edited by:
Sige Zou, National Institute on Aging, USA

Reviewed by:
Xiaopeng Zhao, University of Tennessee, USA
Thomas Arendt, Universität Leipzig, Germany

****Correspondence:***
Rita Sleimen-Malkoun, Inserm, Institut de Neurosciences des Systèmes UMR_S 1106, Faculté de Médecine Timone, Aix-Marseille Université, 27 BD Jean Moulin 13385, Marseille Cedex 05, France
e-mail: rita.sleimen-malkoun@univ-amu.fr

Growing evidence demonstrates that aging not only leads to structural and functional alterations of individual components of the neuro-musculo-skeletal system (NMSS) but also results in a systemic re-organization of interactions within and between the different levels and functional domains. Understanding the principles that drive the dynamics of these re-organizations is an important challenge for aging research. The present *Hypothesis and Theory* paper is a contribution in this direction. We propose that age-related declines in brain and behavior that have been characterized in the literature as *dedifferentiation* and the *loss of complexity* (LOC) are: (i) synonymous; and (ii) integrated. We argue that a causal link between the aforementioned phenomena exists, evident in the dynamic changes occurring in the aging NMSS. Through models and methods provided by a dynamical systems approach to coordination processes in complex living systems, we: (i) formalize operational hypotheses about the general principles of changes in cross-level and cross-domain interactions during aging; and (ii) develop a theory of the aging NMSS based on the combination of the frameworks of coordination dynamics (CD), dedifferentiation, and LOC. Finally, we provide operational predictions in the study of aging at neural, muscular, and behavioral levels, which lead to testable hypotheses and an experimental agenda to explore the link between CD, LOC and dedifferentiation within and between these different levels.

Keywords: aging, coordination dynamics, complexity, dedifferentiation, variability

INTRODUCTION

Understanding the mechanisms underlying age-related declines across multiple functional subsystems ranks highly on the agenda of science and society. To achieve this objective, the most commonly adopted approach in aging research has emphasized dividing the neuro-musculo-skeletal system (NMSS) into smaller and presumably, more tractable units. From this perspective, declines in neural, cognitive, sensori-motor and muscular functioning are generally considered as separate domains, each having its own evolution over time. During the last 30 years, this approach has considerably improved our understanding of how aging affects the different levels of observation and functional sub-systems of the organism. However, it has also made aging research a complicated intellectual puzzle, with pieces that do not necessarily fit together, hence limiting our understanding of the aging NMSS as a whole. Despite (or rather, because of) the proliferation of isolated theories and potential mechanisms operating at different levels (about 300 have been identified by Medvedev, 1990), aging research remains data rich and theoretically poor.

In contrast to classic research, a growing body of literature in both aging and biomedical research acknowledges the fact that the human NMSS is a complex system comprising many interacting (complex) component subsystems that are connected over a variety of different scales of space and time (Chauvet, 1995; Buchman, 1996; Yates, 2008). Accordingly, it is also becoming clear that aging is a "parallel distributed process". which not only affects the structures and functions of the individual subsystems but also the interactions between them. These changes alter the range of behaviors that the system can achieve, leading to impairments in behavioral adaptability (Lipsitz, 2002; Vaillancourt and Newell, 2002; Newell et al., 2006; Hong and Rebec, 2012). To better understand the coordination/coupling processes that occur during aging, both within and between the different subsystems and their consequences, an integrated framework—inspired by system biology and/or dynamical systems approach—is required (Haken, 1983; Kelso, 1995; Yates, 2008). The goal of the current paper is to develop a conceptual framework inspired by dynamical systems analysis to understand the general principles of age-related reorganization of the NMSS and its consequences on brain, behavioral and muscular dynamics. In the following, firstly, we review the literature on two phenomena that characterize the aging NMSS, namely, *dedifferentiation* and *loss of complexity* (LOC). We argue in this respect that these phenomena could actually be closely related. Indeed, although they seem to refer to different facets of aging, they both reflect both systemic and systematic reorganizations in the NMSS. Then, using the theory of coordination dynamics (CD; Kelso, 1995, 2009), we attempt to explain how dedifferentiation and LOC affect variability of system outputs and patterns dynamics at the levels of brain, muscles and behavior. Finally, we present hypotheses and empirical predictions that could be tested experimentally.

THE DEDIFFERENTIATION HYPOTHESIS

Dedifferentiation can be defined as "*a process by which structures, mechanisms of behavior that were specialized for a given function lose their specialization and become simplified, less distinct or common to different functions*" (modified from Baltes and Lindenberger, 1997). Historically, the concept of dedifferentiation was introduced by Baltes and colleagues (Baltes, 1980; Baltes et al., 1998) to account for age-related increases in the correlation between levels of performance on different cognitive tasks. Dedifferentiation suggests the existence of a common cause of cognitive declines in aging (e.g., a general slowing of information processing; Birren, 1965; Birren et al., 1980; Cerella, 1985, 1991, 1994; Bashore, 1994; Salthouse, 1996), arising from reduced distinctiveness of mental representations and/or increased neural noise (e.g., a deficit in catecholaminergic modulation; Li et al., 2001). Both cross-sectional and longitudinal studies show that performance on sensory, cognitive and motor tasks are more correlated in the elderly, supporting the existence of *cognitive-motor dedifferentiation* (Lindenberger and Baltes, 1994; Baltes and Lindenberger, 1997; Lindenberger and Ghisletta, 2009). The following sections review existing evidence on dedifferentiation in brain and muscles.

DEDIFFERENTIATION IN BRAIN FUNCTION

Numerous brain-imaging studies have shown that the aging brain accommodates anatomical and physiological changes by reorganizing activation patterns between neural ensembles (Cabeza, 2002; Reuter-Lorenz, 2002; Ward, 2006; Serrien et al., 2007; see Park and Reuter-Lorenz, 2009 for review and theoretical account; Seidler et al., 2010). Specifically, in addition to stronger activation in dedicated regions, older adults generally exhibit activation of additional areas of the brain not observed (or only marginally) in young participants. For instance, it has been shown that brain dedifferentiation manifests in a shift from unilateral to bilateral activation (Cabeza, 2002; Cabeza et al., 2002; Ward, 2006) and/or an increase in activation of prefrontal areas (Heuninckx et al., 2005, 2008; Serrien et al., 2007).

During motor tasks, dedifferentiation takes the form of an increase in activation of neural structures presumably dedicated to cognitive processes (Heuninckx et al., 2005, 2008; Serrien et al., 2007; Park and Reuter-Lorenz, 2009; Seidler et al., 2010). This expanded activation is generally more pronounced with increasing motor task complexity, presumably reflecting greater involvement of executive control processes (Mattay et al., 2002; Ward and Frackowiak, 2003; Heuninckx et al., 2005). This hypothesis is supported by dual-task studies that have shown cognitive permeation of the motor domain i.e., interdependencies between sensorimotor and cognitive processes, becomes accentuated during aging (Li and Lindenberger, 2002; Schäfer et al., 2006; Schaefer and Schumacher, 2010). Dedifferentiated activation is also not limited to performance-based contexts. Comparable effects of aging have also been described during learning (i.e., dedifferentiation between explicit and implicit learning; Dennis and Cabeza, 2011), visual processing (i.e., dedifferentiation between pathways involved in faces, places and objects recognition; Park et al., 2004) and memory functions (i.e., between episodic and working memory; Papenberg et al., 2011).

DEDIFFERENTIATION IN MUSCLE STRUCTURE AND FUNCTION

One of the primary effects of aging on human musculature is a change in muscle fiber composition. Specifically, as reviewed in Lexell (1995), and recently demonstrated by Nilwik et al. (2013), the loss of muscle mass in aging (i.e., sarcopenia) is dominated by declines in the size of the fast-twitch fibers. While young adults have a nearly even ratio of fast- (type II) and slow (type I)-twitch muscle fibers, the elderly exhibit a higher proportion of slow-twitch fibers (see Table 2 from Lexell, 1995, for a summary). In addition, apart from atrophy of the type II fibers, aging also results in "clustering" or "grouping" of muscle fibers. In the young, fast- and slow-twitch fibers are almost evenly distributed or scattered in a muscle cross-section. With aging, muscle fibers form clusters as type I fibers form visibly distinct groups from type II fibers (see Andersen, 2003 for a review).

While not often discussed, it is important to note that "hybrid" muscle fibers also exist (see Pette and Staron, 2000, for a review), leading to altered contractile properties that fall between exclusively type I and type II fibers (Hilber et al., 1999). Aging leads to an increase in the proportion of hybrid fibers within a muscle (Monemi et al., 1999; Pette and Staron, 2000). These morphological changes would lead to dedifferentiation in muscle function, as aged muscles will exhibit a high level of homogeneity in contractile rate and force generation capacity. Effectively, as muscle fiber structure and function is homogenized, their ability to contract at different speeds and generate different force levels is restricted, hence narrowing their functional range. The dedifferentiation in muscle structure and function would leave them in a state where they are limited to acting on narrower scales of space and time.

LOSS OF COMPLEXITY

The LOC hypothesis was introduced 30 years ago in biomedical research by the pioneering work of Lipsitz and Goldberger (1992) on heart rate variability (HRV). Using nonlinear time series analysis (i.e., approximate entropy, ApEn but see Costa et al., 2002; Peng et al., 2009; Bravi et al., 2011, for reviews of the different methods), these authors observed a tendency toward more regular fluctuations in HRV (i.e., "less complex patterns" of variability) during aging and disease, which remained undetected by variance-based measures (coefficient of variation, SD). These changes have been interpreted as a LOC, which is currently considered as a generic driving principle of aging in a wide range of functional systems. LOC has even been hypothesized to be an indicator of the transition from normal aging to frailty (Lipsitz, 2002, 2004; Lang et al., 2009). However, increased behavioral variability is widely viewed as a hallmark of aging (Hultsch et al., 2008). Greater magnitudes of intra-individual variability in cognitive and motor performance are commonly attributed to increased levels of Gaussian noise produced at anatomical, functional and neuro-modulatory levels of the central nervous system (CNS; see MacDonald et al., 2009b for a review). However, there is further evidence that the magnitude and structure of variability may change independently of one another during aging (Slifkin and Newell, 1999; Sosnoff et al., 2006). This suggests that "variability" (amplitude) and "complexity" (pattern) of fluctuations stem from different origins and might have different functional significance (Sosnoff et al., 2006; McIntosh et al., 2010; Balasubramaniam and Torre, 2012).

The LOC hypothesis has been supported in studies of physiological, cognitive, and motor systems (see Vaillancourt and Newell, 2002; Newell et al., 2006; Rey-Robert et al., 2011). Yet, the effects of aging on the complexity of behavioral output fluctuations have been shown to depend on the functional system under investigation and/or the task being performed (Vaillancourt and Newell, 2002). This raised the proposal that aging impairs behavioral adaptability by restricting the ability to alter levels of behavioral complexity (Vaillancourt and Newell, 2002). Thus, a critical property of the system seems to be its capability to reorganize the interactions between its components (i.e., its functional degrees of freedom) to adjust the degree of unpredictability of behavioral fluctuations to meet task demands (Vaillancourt and Newell, 2002), leading to a proposal of the *Change in Complexity Hypothesis* by some of the authors of this article (CICH; Rey-Robert et al., 2011).

Changes in complexity have also been investigated in brain aging research. In resting state EEG studies where the subject is not engaged in any type of cognitive or motor task (i.e., under the instruction to relax), the elderly exhibit higher levels of brain signal complexity (Anokhin et al., 1996; Pierce et al., 2000, 2003; Müller and Lindenberger, 2012). Similar findings were also reported using fMRI (Yang et al., 2013). Conversely, task-driven brain activation signals seem to express a smaller complexity reduction in older subjects in comparison to the young (Müller and Lindenberger, 2012). Additionally, age-related changes of brain signal complexity appear to be scale-dependent. Using Multiscale entropy (MSE), McIntosh et al. (2014) found that, the elderly possess less complex brain signals at coarse time-scales, and more complex signaling at fine time-scales in comparison to the young. fMRI studies show an age-related decrease in brain signal variance as measured by the standard deviation of BOLD activity, and this was reported in both resting and task-driven states (Garrett et al., 2011, 2013; however, see Yang et al., 2013 for a conflicting result).

Altogether these findings support the systemic nature of age-related changes in the complexity of behavioral and brain signals. However, the direction of these changes (increase versus decrease) and the in-between level mapping is not straightforward and deserves further investigation.

LINKING LOSS OF COMPLEXITY AND DEDIFFERENTIATION IN THE NEURO-MUSCULO-SKELETAL SYSTEM

Although LOC and dedifferentiation hypotheses have developed independently in the literature, there is evidence to indicate that they constitute two intertwined facets of the same underlying aging process. The systemic breakdown of the structure of fluctuations of behavioral outputs observed during aging are currently attributed to changes in coupling interactions (i.e., functional synergies) between the components of the different system over multiple temporal and spatial scales (Lipsitz, 2002; Vaillancourt and Newell, 2002; Newell et al., 2006). A plausible hypothesis is that LOC might arise, at least in part, from dedifferentiation occurring within and between the different subsystems.

At this juncture, an integrative theoretical framework that connects the LOCH and dedifferentiation hypotheses is needed. Four critical domains must be accounted for, namely: (1) *tasks*—classification of constraints and metrics of behavioral difficulty; (2) *structures*—anatomical and biochemical changes from organ to molecular level; (3) *function*—coordination of the individual structures and levels of organization; and (4) *behavior*—overt measures of systems outputs (i.e., pattern dynamics and behavioral output fluctuations). In this respect, we contend that principles of self-organization in complex systems identified by physics/dynamical systems theory (e.g., Glass and Mackey, 1988; Lipsitz, 2002, 2004; West, 2006) are essential. As a step in this direction, Vaillancourt and Newell (2002) proposed a standard approach to infer changes in the complexity of a system (independent of its nature) and its consequences on behavioral state and output fluctuations. They argued that a system's complexity depends on: (i) the number of independent variables that is needed to reproduce or predict the output of the system; (ii) the functional states of the different components; and (iii) noise present in the system. To our knowledge, no systematic exploration of the consequences of separate or concomitant changes in the different factors identified by Vaillancourt and Newell (2002) has been undertaken in the literature. To achieve this objective, the challenge is finding task protocols that are rich enough to capture the coupling mechanism and properties of the neuro-behavioral system, but not so complicated that it precludes modeling. We contend that it could be done through the use of the conceptual framework, task paradigms and the methods of analysis of *CD*.

COORDINATION DYNAMICS AS A CONCEPTUAL FRAMEWORK FOR THE STUDY OF THE NMSS

CD is a conceptual framework dedicated to the study of coordinative processes that occur within and between brain and behavioral levels in a wide range of tasks. It refers to set of principles developed to capture the formation and functional adaptation of synergies and coordination patterns to meet different demands (Kelso, 2009, 2012; Tognoli and Kelso, 2009). From this perspective, coupling and self-organization properties allow the adaptive assembly, stabilization and dismantling of synergies between functional components and subsystems. Coupling over multiple spatial and temporal scales also ensure efficient informational exchanges within the neurobehavioral system through feedback loops and regulation processes (Slifkin and Newell, 1999; West, 2006; West and Grigolini, 2010; McIntosh et al., 2014).

These coordinative processes are evident in the presence of multiple stable states in the neurobehavioral repertoire and the ability to switch between these stable states to adapt to task or environmental constraints. Whatever the level of observation or the system under consideration, pattern dynamics capture the time-evolution of collective variables characterizing the state of the system (order parameters) under the influence of a set of internal and external constraints of various origins (control parameters). These control parameters may trigger switching between the different spontaneous states of the system, without prescribing these states. At a more abstract level, CD can be conceived as an evolving landscape of "attractor" wells, which is best represented by a potential function (Haken, 1977, 1983): the deeper the wells of the landscape, the more stable the patterns and the more resistant these patterns will be to perturbations. Control parameters modulate the landscape of attractors, thereby leading to loss of stability of behavioral states and phase transitions between them.

BEHAVIORAL COORDINATION DYNAMICS

One of the most representative paradigms of CD in living systems is that using rhythmic bimanual movements (Kelso et al., 1981; Kelso, 1984; Haken et al., 1985; see Kelso, 1995, for an overview). In this task, the relative phase between the displacements of each limb is considered as the collective variable (order parameter), which captures the dynamics of coordination patterns (i.e., their evolution over time) under the effects of constraints of various origins. The neurobehavioral repertoire is characterized by the presence of two preferred stable patterns of coordination: in-phase and anti-phase (Kelso, 1984), which can be spontaneously produced when participants are instructed to move their arms rhythmically in synergy. The in-phase pattern involves symmetric motion of the hands in opposite directions, whereas the anti-phase pattern involves motion in the same direction (**Figure 1**).

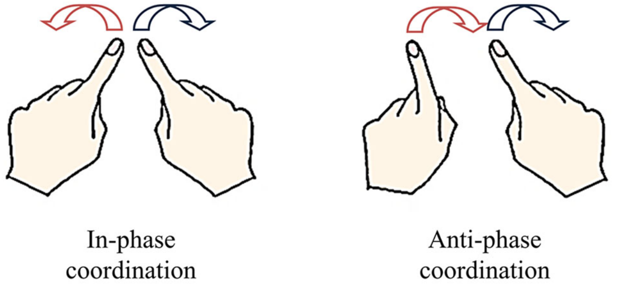


FIGURE 1 | Stable patterns of spontaneous bimanual coordination. The in-phase pattern consists in symmetric movements in opposite directions (0° of relative phase) involving the simultaneous activation of homologous muscles. The anti-phase pattern consists in parallel movements in the same directions (180° of relative phase) involving the simultaneous activation of antagonist muscles.

Stability and flexibility are salient features of CD that have been elucidated by driving the bimanual system toward a point of instability where a *phase transition* subsequently occurs (i.e., an abrupt switch in the order parameter). The anti-phase pattern is generally considered to be less stable than the in-phase pattern, as a spontaneous switch from the former to the latter occurs when oscillation frequency (control parameter) increased beyond a given critical value (Kelso, 1981, 1984). Phase transitions are preceded by a destabilization of the current pattern (anti-phase), resulting from decrease in coupling strength, assuming the presence of noise of constant magnitude (Schöner et al., 1986), evidenced by a dramatic increase in relative phase fluctuations. Such "critical fluctuations" decrease following the phase transition, once the in-phase pattern is adopted (Kelso et al., 1986). These spontaneous/intrinsic dynamics of bimanual coordination are formalized through a tripartite scheme (**Figure 2**) in which the dynamics of the relative phase arise from a low-energy (nonlinear) coupling function linking nonlinear oscillators that represent the limbs (Haken et al., 1985; see Kelso, 1995, 2009, for detailed developments).

The CD formalization of attractor landscape and pattern dynamics is not limited to spontaneous dynamics of bimanual coordination patterns. For one, it has been extended to the study of different movement tasks (e.g., Kelso et al., 1990; Bardy et al., 1999; Temprado and Laurent, 2004; Salesse and Temprado, 2005; Sleimen-Malkoun et al., 2012) and in different populations (e.g., Temprado et al., 2010; Sleimen-Malkoun et al., 2011, 2013). In addition, it has been applied to the study of how the spontaneous dynamics is shaped through cognitive factors as attention (Temprado et al., 1999; Monno et al., 2002), intention (Scholz and Kelso, 1990), and learning (Zanone and Kelso, 1992),

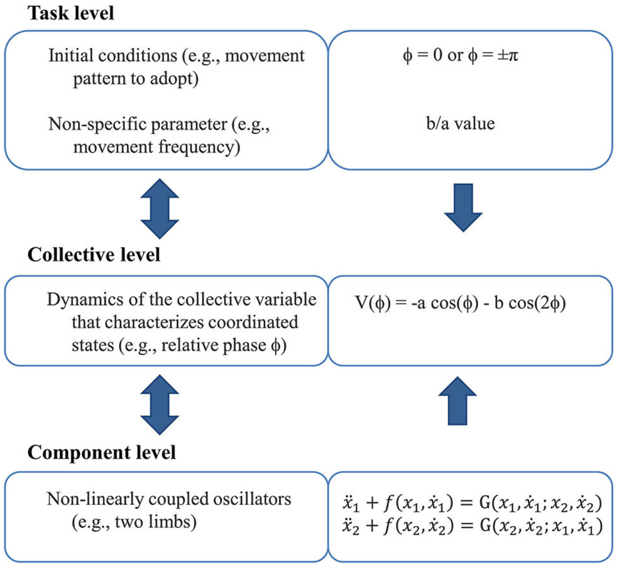


FIGURE 2 | The tripartite scheme (inspired from Kelso, 1995). It links the three phenomenological levels of description from the perspective of dynamic pattern theory.

sometimes termed "directed or goal-directed dynamics". Here, intention, attention and learning provide behavioral information that forms a continuous "force" to shape the dynamics of the collective variable. Intentionally switching from one pattern to another is an example in this regard (Scholz and Kelso, 1990). Selective attentional focus on an existing pattern (e.g., in-phase or anti-phase) generates behavioral information that does not compete with intrinsic tendencies, increases the stability of the coordination pattern (Lee et al., 1996; Temprado et al., 1999) and delays or even prevents the phase transition from occurring. In the case of learning, behavioral information may be perceptually specified by metronomes or memory, leading to greater stability of a previously unstable coordination pattern (Yamanishi et al., 1980; Zanone and Kelso, 1992). Although the information is different in both cases, visual feedback versus memorized information, similar modifications to the dynamics of bimanual coordination have been found (e.g., Schöner et al., 1992).

COORDINATION DYNAMICS IN BRAIN AND BEHAVIOR

The presence and the switching between multiple patterns of activity across neural ensembles have now been shown in the brain (Meyer-Lindenberg et al., 2002; Jantzen et al., 2009; see Fuchs and Jirsa, 2008, and Kelso, 2009, for reviews). Subsequently, a multi-level approach was developed to connect phenomenological findings at the behavioral level to underlying neural mechanisms (see Jirsa and Haken, 1996; Jirsa et al., 1998; Kelso et al., 1999, 2013). To that aim, functionally relevant (coupled) components were identified at the brain level as it was previously done for the behavioral level. Fuchs et al. (2000) proposed a model to capture the relationship between rhythmic finger movements and neuronal activation. The model accounts for the presence of two stable states at low movement frequencies and predicts the destabilization of the anti-phase at higher frequencies. Thus, CD allowed traversing the different scales of the neuro-behavioral system to connect neural and behavioral dynamics (see Kelso et al., 2013, for a recent overview), presented in **Figure 3**.

COORDINATION DYNAMICS AT MUSCULAR LEVEL

Whether and how neuro-muscular factors have a role in neuro-behavioral CD has led to considerable debate over the last decade (Carson et al., 2000; Mechsner et al., 2001; Temprado et al., 2003; Carson and Kelso, 2004; Mechsner, 2004). Initially (Kelso, 1981, 1984), phase transitions reflected a switch from simultaneous activation of non-homologous muscle groups (flexors-extensors) to activation of homologous muscles (flexor-flexor/extensor-extensor). These observations have been extended to wrist and upper limb oscillations, suggesting that the "default" output of brain CD was the activation of homologous muscles,

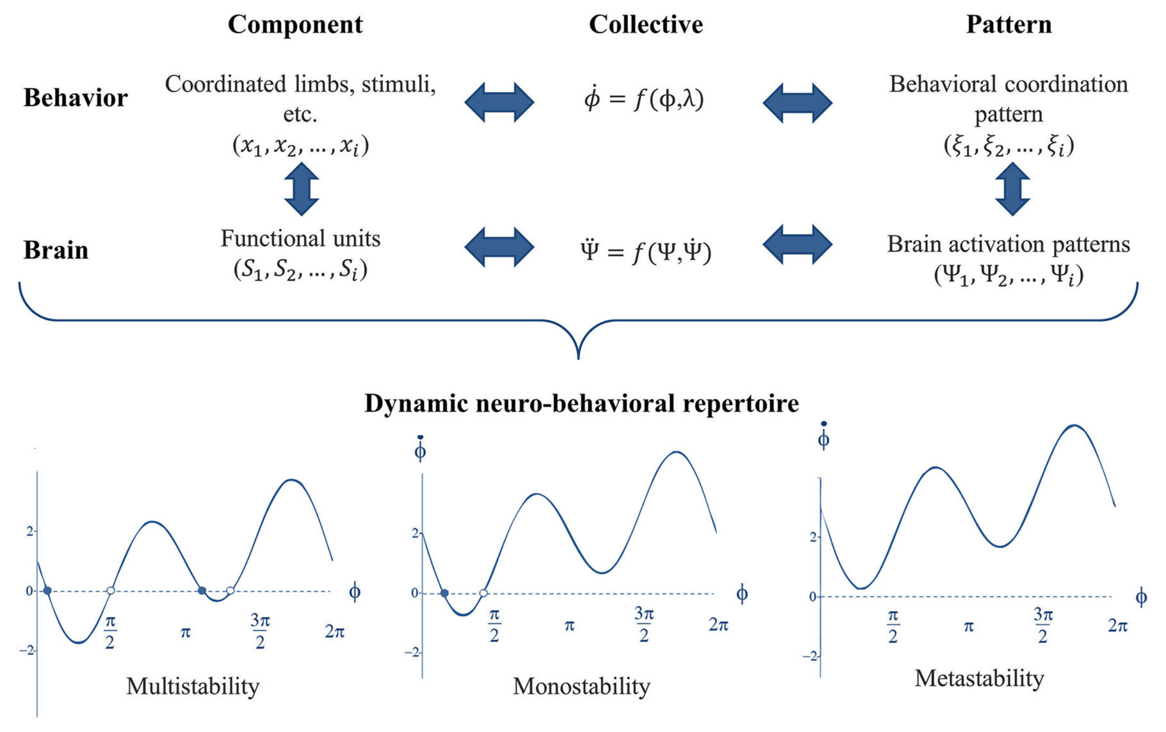


FIGURE 3 | Traversing scales of the neuro-behavioral system by virtue of shared dynamics. At each level of organization, e.g., brain and behavior, the complex dynamics is expressed through lower dimensional patterns that can be captured through the dynamics of the collective variable(s). Accordingly, the neurobehavioral system possesses a dynamic repertoire of attractor states, in which multiple stable attractors can coexist (multistability) or not (monostability). Attractors can also be virtually present as "ghost attractors" giving rise to both phase trapping and phase scattering dynamical flows (metastability).

forming the core of inter-limb CD in a wide range of different tasks.

However, a number of subsequent experiments have demonstrated that the intrinsic dynamics of behavioral patterns were relatively independent of neuro-muscular factors. For instance, in ipsilateral hand-foot coordination, Baldissera et al. (1982, 1991) showed that phase transition prominently depended on directional coupling, instead of muscular synergies. This hypothesis was confirmed in inter-personal coordination tasks: transitions from movements performed in opposite directions to patterns of iso-directional movements were systematically observed (e.g., Schmidt et al., 1990; Temprado and Laurent, 2004). These findings were interpreted as evidence supporting task-dependent informational coupling at the brain level. Mechsner et al. (2001) challenged the *neuro-muscular hypothesis* in bimanual finger coordination by showing that the bias of two-finger oscillations was towards perceptually-based spatial symmetry, irrespective of the muscles involved. Accordingly, they suggested that spontaneous bimanual coordination phenomena were perceptually driven (see also Mechsner, 2004). These debates about the role of intrinsic muscular synergies in inter-limb CD (e.g., Carson, 2004; Carson and Kelso, 2004), eventually converged on a consensus that behavioral CD result from a coalition of (task-dependent) constraints of various origins, including those arising from neuro-muscular factors (e.g., Temprado et al., 2003; Temprado and Salesse, 2004; Salesse and Temprado, 2005).

A COORDINATION DYNAMICS PERSPECTIVE ON NEURO-BEHAVIORAL AGING

The framework of CD has been scarcely applied in aging research (see Greene and Williams, 1996; Temprado et al., 2010; Sleimen-Malkoun et al., 2013, for noticeable exceptions). The above developments suggest however that it might constitute a conceptual framework to age-related adaptations of a complex neuro-behavioral system on fast and slow time-scales.

AGING[1] AS COMPLEX NEURO-BEHAVIORAL SYSTEM DYNAMICS

The description of the time-evolution of the whole neuro-behavioral system, which emerges from complex interactions, is a critical issue in aging research. Performance curves alone are not able to capture declines in behavioral adaptability as it demands the capacity to preserve two apparently contradictory properties, namely stability and flexibility. Stability is classically indexed by variability surrounding a behavioral pattern that is to be maintained and the ability to resist perturbations to this pattern. Flexibility is indexed by the number of intrinsic patterns in the repertoire (i.e., multi-stability) and the ability to switch between them (i.e., transitions). It should be noted that long-range correlations within a time-series are sometimes considered as an indirect marker of system flexibility (Lipsitz, 2002), although (to our knowledge) the empirical confirmation of this hypothesis through appropriate protocols (i.e., perturbation studies) is lacking in aging literature. Despite this lack of direct evidence, from a dynamical systems perspective, variability and pattern dynamics are markers of system's adaptability that should also be able to serve as indices of functional status in the aging NMSS.

THE DYNAMICS OF FUNCTIONAL STATUS DURING AGING

Although it is currently admitted that age-related LOC of the entire neuro-behavioral system may lead to nonlinear changes in functional status over time (Goldberger et al., 2002), a precise description of these states is lacking in the literature. This issue refers to whether and how many "biological ages" can be distinguished on the basis of specific markers, independent of chronological age. Frailty—a geriatric syndrome associated with increased vulnerability, higher rate of morbidity and loss of autonomy—might be heuristic in this respect. Indeed, frailty is viewed as the signature of the degradation of multiple subsystems that normally contribute, through their (weak) couplings, to flexible behavioral adaptations to stressors of various origins (see Clegg et al., 2013; Cesari et al., 2014, for overviews). Even if this general definition is widely accepted in the literature, true system views of frailty are scarce and there are few issues that remain a matter of debate, namely: (i) how frailty can be characterized systemically, if not as the sum of declines in individual parts; and (ii) how changes in levels of systemic (dys) function are detected during healthy aging, at the onset of frailty, and during its progression. Lipsitz (2002, 2004) hypothesized that frailty might be reflected in a global loss of physiological complexity (**Figure 4**). Unfortunately, there is no absolute measure of optimal complexity (i.e., only relative change is informative) and, consequently, precluding a definition of a critical threshold that determines the transition to frailty (e.g., Lipsitz, 2002, 2004; Vaillancourt and Newell, 2002; Newell et al., 2006).

The empirical focus on physiological or behavioral output complexity, however, did not provide concrete framework to describe the age-related changes in coordination processes operating within and between the different subsystems. Thus, at least, the general characterizations of functional status through variability/complexity analysis (i.e., long range correlated structures), at a system level, should be complemented by a precise description of the time-evolution of the behavioral repertoire during aging. In the ensuing sections we describe how pattern dynamics, as a marker of evolving stability and flexibility, evolve in aging.

THE DYNAMICS OF INTRINSIC PATTERNS OF THE BEHAVIORAL REPERTOIRE DURING AGING

At a general level, the aging NMSS can be addressed by studying: (i) the emergence of new patterns; (ii) the stabilization, destabilization and transitions between existing patterns; or even (iii) the loss of patterns of the behavioral repertoire. Landscapes of behavioral attractors can be used to represent these macroscopic dynamics (**Figure 5**). For instance, the epigenetic landscape initially introduced by Waddington (1942, 1957) has been subsequently popularized in development literature by Muchisky et al. (1996), and is now used in numerous domains (e.g., Aimetti, 2009; see Baedke (2013), for overview and discussion).

These landscapes allow one to envision the expression of aging in cognitive-motor skills (posture, locomotion, object manipulation, inter-limb coordination, etc.) as evolving behavioral

---

[1] Aging currently refers to changes that occur over life span. Here we use it to refer to the period from adulthood to old chronological age.

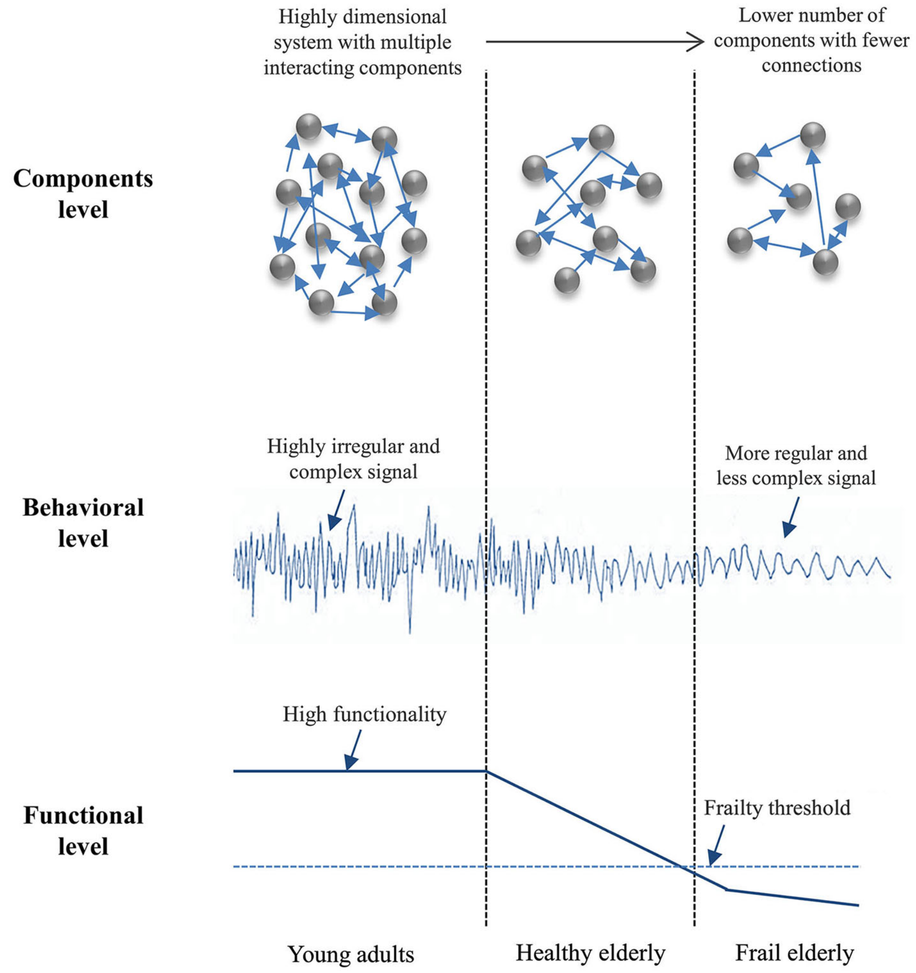


FIGURE 4 | Loss of complexity with age and frailty (inspired from Lipsitz, 2002). A representation of how the interacting sub-systems/components (system's inputs) produce highly complex dynamics (system's output) in young adults with high functionality, due to the richness of the underlying interactions; and as the number of components and the complexity of their interactions drop down, behavior becomes increasingly predictable and the organism loses its functionality (e.g., in elderly). The frailty threshold represents the critical level of function below which the organism can no longer adapt to stress.

(attractor) states. An increase in the number of wells represents the enrichment of the repertoire through a differentiation process, which can be formalized as pitchfork bifurcations. Smith and Thelen (2003) elegantly laid the ground for this idea by characterizing behavioral dynamics during development as a landscape with wells of different depths, i.e., varying stability (see also Newell et al., 2003, 2005). The framework of developmental epigenetic landscape can be extended to lifespan to account for emerging, modifying and dissolving behavioral patterns during aging as a result of the coalition of multiple (i.e., genetic, chemical, cellular, structural, environmental) underlying factors. A decrease in the number of wells can be considered a signature of dedifferentiation that could result from saddle-node bifurcations (old wells cease to exist by dead-ending) or from merging with another well.

Taking bimanual coordination as a representative illustration, we can envision age-related changes from the Haken-Kelso-Bunz model (HKB) potential function. We introduce the dimension of time (i.e., chronological age taken as a control parameter) to represent the deformation of the HKB potential landscape that mimics the changes in the spontaneous dynamics of bimanual patterns. At the most basic level of the HKB model: (i) only two terms are used, thus, only in-phase and anti-phase wells are present; and (ii) the attractor strengths are scaled in proportion to one another. What this means is that the healthy landscape comprises stronger and weaker attractors whose attractiveness is scaled in proportion to one another. Age can be hypothesized to drag the system to function in the middle where all wells tend to have lower and progressively more similar levels of attractiveness. The landscape would be dedifferentiated as all of the attractors would lose their scale-invariance, leading to greater similarity in strength as the highs and lows are no longer present. The result is a more evenly distributed landscape with attractors of equal or near-equal strength.

The complete dedifferentiation at the level of the collective variables (i.e., attractors on the landscape) would mean that the subcomponents are de-coupled from one another as any

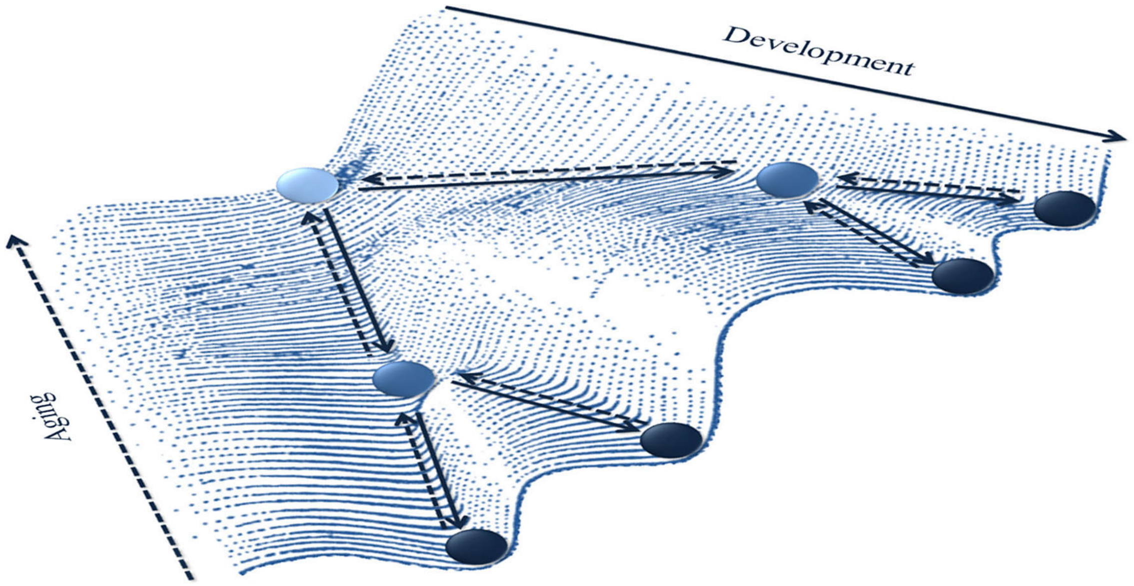


FIGURE 5 | Aging as a macro dynamic phenomenon on an epigenetic landscape (inspired by Waddington, 1942). A metaphoric representation of the life-span evolution of the landscape of behavioral attractors. During development, the number of attractor stable states (represented by wells in which a rolling ball can be trapped) increases through a differentiation process (filled lines arrows). Conversely, during aging (dashed lines arrows), the landscape goes through a dedifferentiation process leading to the disappearance or merging of some attractors.

dynamic relationship between any of them would be equally viable, leading to increased magnitude of variability. Correspondingly, the individual subcomponents would then return to their natural oscillations or intrinsic dynamics (Haken et al., 1985), or even cease to oscillate (Daido, 2008), leading to a LOC. At the most general level, such a deformation of the HKB model would represent a system in which the potential energy is not conserved, since the tradeoff between potential and the number of attractor wells is broken.[2] As Zanone and Kelso (1997) have demonstrated (in conjunction with the inherent properties of the HKB model), a solution for maintaining potential energy constant in the system is strengthening an existing attractor wells, at the expense of the other well. This perspective of aging-induced loss of multistability affords a different account from the dedifferentiation perspective, which was discussed above. Indeed, one could expect that during aging some attractors become deeper and stronger. Such changes would come at the expense of reduced strength at the other attractors or even their disappearance. This assumption is consistent with recent studies by some of us, in which we provided empirical evidence of age-related change in attractor landscape, namely, a decrease in pattern stability (Temprado et al., 2010) and a loss of existing patterns (Sleimen-Malkoun et al., 2013). From this perspective, one can envision the deformation of the HKB model as if the subject started with a higher level of *b/a* ratio and the decrease of lower, critical values. However, in the HKB model, *b/a* supposedly mimics the effect of frequency on coupling strength at task-related time scale. Consequently, the longer time dimension of aging should be rather added under the form of another extension that changes the initial stability of intrinsic patterns, decrease their stability over time or even leads to loss of attractor states (see Newell et al., 2008 for modeling the inverse tendency during development).

Age-related deformation of the HKB potential landscape that represents the dynamics of intrinsic patterns presumably influences the directed dynamics that is, how the behavioral repertoire is shaped, temporarily or durably, through cognitive factors as attention, intention and learning in older adults. This issue is of particular importance for aging research, according to the cognitive-motor dedifferentiation that occurs over time.

LINKING VARIABILITY AND COMPLEXITY OF NEURO-BEHAVIORAL OUTPUTS TO PATTERN DYNAMICS: AN ENTRY POINT FOR UNDERSTANDING AGE-RELATED REORGANIZATION IN THE NMSS

At this point in the paper, the question remains of how pattern dynamics give rise to the observed NMSS declines in aging. In addition, the role of noise must also be incorporated in the conceptualization which is frequently considered to be an explanation for increased variability in cognitive and motor tasks in aging (see MacDonald et al., 2009a). Empirically, attempts to describe changes in system's output variability (including structured fluctuations) and pattern dynamics using the same task have been scarce. In the following, we offer a dynamical system reading/interpretation of studies of relevance to this issue at behavioral, brain and mus-

---

[2] Indeed, the HKB model is founded on a Fourier series with a doubling process that increases the number of potential wells in the system. When the number of parameters is increased, the number of attractor wells increases, but their "attractiveness", is decreased.

cular levels, and that, in both young and aged NMSS. We also point out the directions that must be explored in future work.

VARIABILITY AND THE DYNAMICS OF BEHAVIORAL PATTERNS

Originally, fluctuations in rhythmic behavior were considered to be a product of random events (Wing and Kristofferson, 1973). Pioneering studies demonstrated long-range correlations structure of fluctuations of coordination patterns in finger tapping tasks (i.e., syncopation and synchronization, Chen et al., 1997; Ding et al., 2002) exhibiting that fluctuations in the tapping pattern were not random. In this type of task, participants must flex their index finger “on-” (synchronization) or “off-” a metronome beat (syncopation), at different frequencies. The synchronization (corresponding to in-phase pattern) and syncopation (i.e., anti-phase) patterns have been shown to follow the same dynamics as those described in bimanual coordination (see modeling efforts in Kelso et al., 1990; Kelso, 1995). In these experiments, the authors showed that correlated structures of fluctuations: (i) were different between syncopation and synchronization patterns; and (ii) depended on the cognitive strategy used to perform the task (e.g., finger extension on the beat instead of flexion off).

Torre and collaborators (Torre et al., 2007; Torre, 2010) extended these studies from one finger to bimanual coordination (see also Schmidt et al., 1991). They hypothesized that these fluctuations are indicative of the compromise between stability and flexibility of the neuro-behavioral system and thus, play a specific role in pattern dynamics. Their results provided evidence for $1/f$ noise in both in-phase and anti-phase patterns and showed a greater presence of long-range correlations in relative phase fluctuations were negatively correlated with the critical frequency of transition in young adults (Torre et al., 2007). From a LOC perspective, participants with more complex relative fluctuations were able to delay the phase transition to a higher critical frequency. In contrast, no relation was observed between the amplitude of variability (as measured by the signal variance) and critical frequency. This result suggests different and specific functional roles for structure and amplitude of variability.

Torre and Balasubramaniam (Torre and Balasubramaniam, 2011; Balasubramaniam and Torre, 2012) tested the potential relationship between magnitude and pattern of variability in bimanual coordination tasks. Their reasoning was that a positive correlation between magnitude and pattern of variability would create a “snowball effect”, pushing relative phase away from its current value. Conversely, a negative correlation would have a conservative effect, thereby maintaining the pattern within its current boundaries. Their results confirmed this hypothesis as a negative correlation between amplitude and structure of variability was observed for the anti-phase pattern at high frequencies. However, how these phenomena are related to mechanisms underlying pattern dynamics (coupling strength, time delays, component-pattern relationship…) remains to be determined. Moreover, aging consequences have never been investigated in this context. One would suspect that if aging reduces the complexity of coordinated fluctuations, it would also reduce the maximal frequency at which a given pattern can be sustained.

VARIABILITY AND THE DYNAMICS OF BRAIN ACTIVITY

As it was recently argued by some of us (Hong and Rebec, 2012), variability and noise in brain activity serve a functional role (Ghosh et al., 2008; Deco et al., 2009, 2011; Garrett et al., 2011), making the ability to “shift” and distribute noise around the brain essential. Effectively, the healthy brain is able to modulate noise and variability depending on task demands and desired behavioral output (Hong and Rebec, 2012).

Network model studies showed how the interplay between brain structural connectivity, noise level and interaction delays shapes the functional dynamics (Ghosh et al., 2008; Deco et al., 2011). Specifically, they showed that neuro-anatomical connectivity gives rise to a dynamic multistable attractor landscape that is functionally relevant. Indeed, even in the absence of any task and any external stimulation (i.e., the resting-state of the brain), brain activity shows structured spatio-temporal patterns characterized by a latent multistable dynamics. As a critical property, the healthy brain is continuously exploring its dynamic repertoire of attractor states without getting trapped in a single state. In the brain aging literature, the most investigated aspect of the dynamics is related to brain signal fluctuations, their magnitude, structure and distribution over cerebral areas. Despite a number of discrepancies in available literature (e.g., in terms of used methods, task conditions and reported results), some guiding principles can still be extracted.

One recurrent observation is an inverted relation between age-related changes in resting-state and in task-evoked activity. Specifically, whereas at rest EEG signals show more complex fluctuations in older than in younger adults (i.e., less deterministic and with higher dimensionality—Anokhin et al., 1996; Pierce et al., 2000, 2003; Müller and Lindenberger, 2012), during task-relevant activity the tendency seems to be reversed: MSE decreases for coarse scales, as well as distributed entropy (McIntosh et al., 2014), whereas dimensional complexity reduction during task has a tendency to attenuate (Müller and Lindenberger, 2012). However, McIntosh et al. (2014) revealed the presence of temporal-scale dependency, according to which complexity values were higher in elderly at fine time-scales. On slow-time scales (i.e., in fMRI studies), brain activity was found to be less variable in elderly, in both fixation (no task) and different cognitive tasks (Garrett et al., 2011, 2013), with a greater increase from fixation to task in younger adults (Garrett et al., 2013). Specifically, young participants exhibited higher variability in 84% of brain areas, whereas, in the remaining 16% (mainly cerebellum and subcortical structures) older subjects were the more variable (Garrett et al., 2011).

In a similar vein, McIntosh et al. (2014) found that multi-scale entropy at fine scales (taken as an indicator of the amount of information processed locally) increased with aging, whereas distributed entropy (i.e., mutual information shared by two sources and linked to functional connectivity) and complexity at coarse time-scales decreased. Aging, in this context, leads to the spatial clustering of information processing, instead of transmitting information across the brain like the young subjects. Pierce et al. (2000, 2003) found that older subjects displayed a higher complexity of spatial distribution of EEG activity suggesting a decrease in the degree of coordination among cortical areas in the aged-brain. Garrett et al. (2011) showed that the elderly exhibited nearly indistinguishable levels of variability across brain structures (i.e., spatial dedifferentiation) while young adults had a 78% difference between the less (mainly sub-cortical) and more variable (cortical) structures. Interestingly, young subjects appear to modulate the magnitude and the spatial representation of the variability of their brain activation to a greater extent and in a more expansive set in region than older subjects do (Garrett et al., 2013). These findings converge to indicate that aging leads to a reduction in coordinated activity. The elderly seem to rely on localized information processing in a manner that is similar to the clustering of different muscle fiber types.

VARIABILITY AND THE INTERACTION BETWEEN BRAIN AND BEHAVIORAL LEVELS

Age-related increases in behavioral variability are currently considered to reflect the amount of neural noise, that is, the age-related increase in random background of activity in the CNS (Li et al., 2000; Li and Sikström, 2002). The presence of continually fluctuating background activity, random or not, is pervasive at all levels of the CNS, even at the most molecular level (see Faisal et al., 2008). Based on widely accepted declines in dopaminergic neurotransmission with aging, neuro-computational models predict a greater variability in neural signaling, and as a consequence, greater behavioral variability and loss of distinctiveness of mental representations (Li et al., 2001). Still, there is debate regarding whether there is truly random (white) noise in the NMSS (Sosnoff and Newell, 2011). This debate, however, is only pertinent if one assumes that neural noise must be: (i) white (i.e., flat power spectrum); and (ii) truly random and uncorrelated. Actually, the activity of neurons *in-vitro* is correlated, following a power law distribution known as the avalanche dynamic (Beggs and Plenz, 2003). Moreover, the relationship between dopamine and neural dynamics takes on an inverted U-shape, where correlations within the signal (i.e., lowest noise or least randomness) are achieved at the mid-range of dopamine levels (Stewart and Plenz, 2006). Either too much or too little dopamine leads to a breakdown in the internal correlations and a flattening of the neural activity distribution, which has consequence of reduced precision and consistency of the produced behavior, based on Li et al. (2000) computational model.

Whether brain signal variability could be taken as a performance predictor is yet another unsettled debate. A strong evidence for a positive correlation was provided by Garrett et al. (2011) by measuring SD of BOLD activity in young and older subjects in three cognitive tasks. In this study, the authors found that brain variability was highly correlated with age and performance: younger, faster (i.e., shorter reaction times) and more consistent (i.e., lower intra-individual standard deviations) participants exhibited greater levels of brain signal variability. Using similar task conditions, McIntosh et al. (2014) reported scale-dependent differences in brain signal (recorded with EEG and MEG) complexity between young and older participants, who displayed comparable accuracy but slower reaction times. Nevertheless, no direct correlation analyses were performed between behavioral (performance) and entropy (brain complexity) measures. In other studies, also investigating brain variability in the context of perceptual and cognitive tasks, the relation between brain fluctuations and performance was even less clear. For instance, Müller and Lindenberger (2012) found associations between perceptual speed performance and brain dynamics for only a few EEG electrodes. Another example can be seen in the Pierce et al. (2000) study in which significant correlations were found between complexity in the spatial distribution over time of EEG activity and only one measure amongst the twelve measures provided by the Visual and Auditory Continuous Performance Test. In particular, higher algorithmic complexity was associated with higher scores on the Consistency-Visual measure. It should be noted, however, that in this specific context, older adults performed significantly better than younger adults.

Strikingly, in all of the reviewed studies, none investigated movement tasks, thereby raising a number of open questions, which should be addressed in future research. One issue of great interest is the systematic exploration of age-related changes in magnitude and structure of fluctuations in both brain and behavior, along with the respective correspondences. A preliminary step would be determining how amplitude and structure of fluctuations relate to meta-stability/self-organizing criticality of activation patterns in the brain (Kelso, 2012). This constitutes an exciting entry point to explore whether and how the aging modifies of the functional relationship between amplitude and structure of variability first within the brain then, between the different levels of organization such as brain and behavior, but also muscular activation.

VARIABILITY AND THE DYNAMICS OF MUSCULAR ACTIVITY

It is striking that in most studies on brain-behavior relationships, the dynamics of muscular activity is omitted. However, since aging leads to significant structural and functional changes in the nervous system (NS), at both central and peripheral levels, muscular function should be subsequently affected (Manini et al., 2013).

Most studies carried out to explore age-related changes in muscular activity focused on the consequences of peripheral modifications on the variability of force production.[3] In this respect, structural changes in muscle composition are consistent with the findings of a LOC in force output in the elderly (see Morrison and Newell, 2012 for a recent review). Supposedly, the loss of range in muscle fiber contractility leads to a decreased number of time-scales along which force output can be modulated, hence, a less complex force output. With a reduction in capacity to alter force output on different time-scales and force amplitudes, the motor behavior of the elderly consistent with the LOCH would be expected. The literature is replete with evidence of narrowed functional ranges in motor behavior, where the LOC is observed across a variety of different functions, including gait, posture, tremor, and muscle force output (see Morrison and Newell, 2012 for a recent review). These findings support the hypothesis that there are commonalities between LOC and dedifferentiation.

---

[3] The relationship between kinematic and kinetic fluctuations remains to be elucidated.

Despite this, there is far less empirical evidence on the LOC in the musculature beyond motor behavior, that is, in terms of motor unit activity. Thus, experiments should be conducted to explore systematically the links between dedifferentiation, LOC in the musculature and behavioral dynamics (i.e., force outputs). As we reviewed earlier, one of the consequences of aging is a change in muscle fiber proportions, where there is a transition toward a greater proportion of slower, hybrid fibers. The consequence of dedifferentiation at this level would be to reduce the number of different time-scales of muscle contraction. Consequently, a decline in the ability to generate high and low forces (and consequently, fast and slow movements) is to be expected. Smoothness at high speeds would become difficult to achieve, as the necessary bell-shaped velocity profiles (see Harris and Wolpert, 1998) require large muscle forces both to initiate and terminate the movement. At low speeds (e.g., tai chi), jerky movements would still occur as all of the muscle contractions are occurring at a single rate. Thus, instead of a single, continuous movement arising from a combination of fast and slow contractions, the aged muscle would be restricted to a sequence of smaller movements, resulting in a jerky action. This phenomenon is identical to finding that the elderly have a reduced ability to generate smooth sinusoidal isometric force traces and difficulty in generating rapid corrections while attempting to maintain a constant force output (Vaillancourt and Newell, 2002).

Age-related alterations of central processes may also affect how the CNS generates patterns of muscle synergies (Carson, 2006) that is, how the large number of degrees of freedom of the musculoskeletal system is mastered to achieve goal-directed tasks (Bernstein, 1967). In this respect, the coordination problem encountered by the aging CNS at neuro-muscular level is fundamentally a dimensional reduction problem, consisting of the mapping of an infinite number of different task goals onto an infinite set of muscle patterns. A current efficient solution envisaged in the literature is that pre-assembled muscular synergies would be represented in the CNS under the form of a small set of discrete, time-varying muscle synergies, which are combined to generate muscle patterns (d'Avella and Tresch, 2002; d'Avella et al., 2003; Tresch and Jarc, 2009; Dominici et al., 2011). As a general adaptation principle, these synergies would be scaled in amplitude and time to achieve flexible goals in a wide variety of motor tasks (see d'Avella et al., 2003, for details). If one accepts this hypothesis, the question arises of how age-related dedifferentiation and LOC in the CNS: (i) modifies the repertoire of pre-assembled muscular synergies; and (ii) affects the scaling process, thereby impairing movement adaptability.

HYPOTHESES AND EXPERIMENTAL AGENDA

As developed above, using CD affords an unique opportunity to connect, within an integrative approach, the LOC and dedifferentiation hypotheses by focusing on uncovering the effects of aging on complementary aspects of the NMSS (i.e., variability and pattern dynamics) and studying functional ranges rather than single dimensions of brain, muscles and behavior, leading to the following hypotheses:

A. Aging leads to a generalized intra-individual LOC and dedifferentiation in the different functional subsystems. The LOC hypothesis arises from separate studies carried out with different groups of participants. Thus, an intra-individual comparison of changes in complexity occurring across the different physiological, cognitive and motor systems is lacking in the literature. The hypothesis of intra-individual LOC could be tested by measuring intra-individual variability (including complexity indexes) of behavioral outputs of cognitive, sensori-motor, physiologic, neural, etc. systems in specific tasks (reaction time, force control, postural control, gait, etc.). One would expect to observe a convergence in behavior complexity in older participants across all of the subsystems being examined. Such general tendency would represent a dedifferentiation of the different subsystems, which leads to a less complex NMSS overall. An interesting avenue would be to explore conditions under which young and older adults differentially modulate their levels of behavioral and brain signal complexity in response to task constraints. Indeed, the modulation of the levels of complexity (depending on the task and the environment) presumably reflects the ability of the NMSS to manage its multiple of degrees of freedom in an optimal manner. Experimentally, it requires testing the subjects under: (i) spontaneous or minimally constrained conditions, in which the system can freely express its complex dynamics (e.g., resting state, postural tremor, oscillation at a natural frequency); and (ii) complex task constraints requiring the system to significantly reduce its fluctuations (e.g., cognitive-motor task-evoked activity, constrained trajectory, force production levels, or frequency).

B. Information transmission underlying the control of cognitive-motor tasks is altered as a result of age-related LOC of the neurobehavioral system. To explore this hypothesis, one could exploit the Complexity Matching Principle (West and Grigolini, 2010), which predicts that when several coupled sub-systems exchange information within a complex system to perform a task, the most efficient information transmission occurs when complexity is optimal. This hypothesis could be tested through the use of a dual-task situation associating a force control paradigm and a RT task. In this type of situation, in addition to the complexity of force fluctuations, one can assess the efficiency and cost of information processing by specific variables (i.e., signal to noise ratio and RT, respectively, Slifkin and Newell, 1999). At a preferred level of force production, one expects to observe the highest level of complexity, associated with optimal information processing, a high signal to noise ratio and a low RT.

Another hypothesis is that when initially independent systems with different levels of output complexity, are coupled, the system with a lower output complexity will move toward the one generating the higher level of complexity (Stepp and Turvey, 2010; Marmelat and Delignières, 2012). This hypothesis could be tested in an inter-personal coordination task (see Temprado and Laurent, 2004; Oullier and Kelso, 2009; Riley et al., 2011) by comparing: (i) young-young; (ii) old-old; and (iii) young-old pairs of participants. One predicts that limb components would modify their individual dynamics when assembled/coupled to produce a stable synergy. Specifically, when young and older participants are paired, informational coupling should allow for a transfer of complexity from higher (young adult) to lower (old). Thus, the motor output of the elderly will be more complex when performed in tandem with the young if compared against a solo performance of a similar motor task. If affirmative, it would have theoretical and practical implications for the use dyadic intergenerational associations in complex motor tasks as a mode of motor rehabilitation.

C. As a result of dimensional reduction (i.e., decrease in functional degrees of freedom), aging leads to a narrowing the neurobehavioral repertoire and reduced adaptability to task demands. At the very general level of epigenetic landscape, one should observe a decrease in the number of behavioral patterns in the repertoire. To limit the analysis to a single dimension, one could examine the deformation of behavioral landscape using a bimanual task protocol (i.e., the scanning paradigm; Zanone and Kelso, 1992, 1997). In case of an age-related loss of multistability, destabilization of one of the existing states is expected, hence deforming the behavioral landscape toward monostability. The state to-be lost will exhibit a flatter potential, i.e., lower stability. Empirically, these changes should be observable in elderly through an increase in behavioral variability (measured by relative phase variability) and attentional cost (measured by RT in a dual-task) associated with the anti-phase pattern, as well as more frequent transitions toward the in-phase pattern starting at rather low movement frequencies. Conversely, if aging modifies the landscape towards greater similarity between attractors, coordination patterns will exhibit similar levels of stability and behavior would be more easily locked into a single pattern. Changes in the structure of behavioral fluctuations would also be expected revealing a loss of criticality in the system, i.e., an inability to seamlessly transition between behavioral states.

As a result of the modification of intrinsic dynamics of the behavioral repertoire, one also predicts to observe increasing difficulties in learning new behavioral patterns. To test this hypothesis, one could explore whether phase transitions from anti-phase to in-phase can be delayed by extensive practice that is, by stabilization of an already existing pattern in the intrinsic repertoire. One could also explore whether phase transitions from anti-phase to in-phase can be delayed by extensive practice that is, by stabilizing an already existing pattern. This issue is important since it might show that older adults are able to preserve adaptability of their repertoire of cognitive-motor skills through appropriate training procedures. It would also be of interest to explore whether learning capacity depends on the route adopted to acquire and stabilize a new pattern (Kostrubiec et al., 2012).

The loss of adaptability that would be observed at the behavioral level should be mirrored in brain dynamics and in brain signal variability. Accordingly, several issues should be investigated using brain activity recordings (fMRI, EEG, MEG): (i) changes in complexity at different spatial and temporal scales; and (ii) loss of multistability in the aged-dynamic repertoire; (iii) changes in terms of coupling strength; (iv) expression of metastability; and (v) the relative contribution of local and global connectivity.

D. Aging reduces the ability to resist and recover from perturbations. An example of the reduced capacity to recovery from perturbations in the elderly is the cardiovascular response to the tilt-table (Lipsitz, 2002). Similar tests can be conducted using sensory or mechanical perturbations to test this hypothesis in motor behavior. Transcranial magnetic stimulation provides an opportunity to perturb the CNS, allowing the effects on neural communication to be measured using EEG, for example. Based on this hypothesis, it would be predicted that the elderly: (i) are more easily displaced from a given coordination pattern; and (ii) require more time to recover their original pattern following the perturbation.

E. Dedifferentiation is accompanied by LOC in individual cognitive and sensorimotor functions and assembling of specific cognitive-motor synergies. Here, the hypothesis is that age-related changes in cognitive-motor interplay (dedifferentiation) should modify the assembling of synergies associating cognitive and sensorimotor processes. In addition, cognitive-motor synergies should allow preserving the internal complexity of the whole cognitive-motor systems (and its adaptability), while the complexity of individual cognitive/sensorimotor outputs should decrease. This hypothesis could be tested using classic dual-task paradigms (see Temprado et al., 1999; Pellecchia et al., 2005). Such experiments would contribute to the current and still unsettled debate about the adaptive/non adaptive function of cognitive-motor dedifferentiation (e.g., Mattay et al., 2002; Heuninckx et al., 2008). Specifically, they will permit the determination of whether increased coupling between cognitive and motor processes allows preserving the complexity of the whole cognitive-motor system by association of functional structures (Chauvet, 1995). Experiments could also be carried out to study the effects of aging on intentional switching from in-phase to anti-phase and vice-versa. One can predict that switching time would be influenced by age due to the differential strength of coupling between limb components.

F. The repertoire of pre-assembled muscular synergies should be reduced, thereby impairing movement adaptability. To our knowledge, these issues have not been addressed in the literature until now. In this context, it can be predicted that: (i) in each muscle system, the repertoire of synergies should be reduced toward intrinsic synergies or even a subset of intrinsic synergies, thereby limiting flexible adaptation of movements (i.e., similar to dedifferentiation); and (ii) central and peripheral changes that are at origin of loss of muscular strength (i.e., dynapenia/sarcopenia) should strongly constrain the assembling of synergies within which the muscles are activated. How changes in variability (amplitude and structure) of behavioral outputs (kinetic and kinematic) reflect the modifications of these coordinative processes underlying the formation of muscle synergies remain to be further explored and modeled.

G. Aging affects the interactions between behavioral dynamics, variability and complexity, and underlying large-scale neural network mechanisms. CD in brain and behavior have been previously studied using MEG (e.g., Kelso et al., 1992; Fuchs et al., 2000) and EEG (Wallenstein et al., 1995; Mayville et al., 1999; Banerjee et al., 2012). However, to our knowledge, the effects of aging on the re-organization of cortical networks underlying stable behavioral patterns, the resulting instabilities, and phase transitions that occur under changes in control parameter have never been explored. In particular, the question arises as to: (i) whether maintaining bimanual coordination patterns is associated with more recruitment of additional networks to those that control unimanual movements instead of simply a temporal modulation of these unimanual networks; and (ii) what are the consequences of such recruitment on correlated evolutions of variability/complexity at brain and behavioral levels. Although in young participants, maintaining stable bimanual patterns seems to result from temporal modulation (Banerjee et al., 2012), the hypothesis of additional recruitment in the elderly is consistent with the dedifferentiation hypothesis. It would reflect more age-related cognitive involvement in maintaining coordination patterns (Heuninckx et al., 2005, 2008). In addition, evidence supporting a small amount of additional recruitment at the vicinity of the transition from anti-phase to in-phase has been provided by Banerjee et al. (2012). One can hypothesize that such amount of recruitment could be larger in older adults.

The issue of correlated changes in variability/complexity indexes at brain and behavioral levels also deserves to be addressed. Indeed, it has been suggested that amplitude and structure of variability might play specific roles in behavioral pattern dynamics (see above). Thus, it should be determined how these two types of variability are correlated with those observed for pattern of neural activity. To our knowledge, no strict correspondences have been established yet between the amplitude and structure of variability in brain and behavior. Additionally, existing literature on aging is largely biased towards the study of cognitive performance. Indeed, sensori-motor aging is largely under-investigated, although the use of continuous movement tasks offers the possibility of conducting nonlinear analyses on time series recorded for both brain and behavioral levels.

SUMMARY AND CONCLUSION

The present paper offers an integrative theoretical framework that provides a broader perspective on the consequences of aging on coordination processes that occur within the NMSS. It affords a global picture of the age-related dimensional reduction of the neuro-behavioral system leading to loss of behavioral flexibility. This systems view diverges from the conventional viewpoint that aging is the sum of decline(s) in function(s) away from a youthful state. Instead, driven by complexity changes and dedifferentiation within and between the different functional subsystems, aging is viewed as a systemic re-organization of the whole NMSS. From this perspective, our general hypothesis is that the emergence of order within and between the different levels during aging obeys to general principles (LOC) and underlying mechanisms (dedifferentiation) independent of the level of observation (i.e., neural, muscular, behavioral). At a methodological level, variability and pattern dynamics are two key markers to follow the functional status of the NMSS during aging and frailty. Employing a systems approach to study aging, i.e., a view that transcends different sub-systems and functional domains, significantly adds to the currently dominant approach comprising the study of separate sub-systems. By understanding how many different components and their interactions change with the course of aging yields important insight into compensatory and adaptive processes that occur as we age. Such a level of understanding could lead to novel approaches to promote healthy aging and reduce levels of disability in the elderly.

ACKNOWLEDGMENTS

The present *Hypothesis and Theory* paper concretizes the motivation behind the *CoordAge* project that is currently funded by *Aix-Marseille University* foundation *A*MIDEX*. We thank the *CoordAge* team, in particular Viktor Jirsa and Frédérique Retornaz for many helpful exchanges on how to link complexity, changes in brain dynamic repertoire, aging and frailty.

REFERENCES

Aimetti, G. (2009). "Modelling early language acquisition skills: towards a general statistical learning mechanism," in *Proceedings of the 12th Conference of the European Chapter of the Association for Computational Linguistics: Student Research Workshop* (Athens, Greece: Association for Computational Linguistics).

Andersen, J. L. (2003). Muscle fibre type adaptation in the elderly human muscle. *Scand. J. Med. Sci. Sports* 13, 40–47. doi: 10.1034/j.1600-0838.2003.00299.x

Anokhin, A. P., Birbaumer, N., Lutzenberger, W., Nikolaev, A., and Vogel, F. (1996). Age increases brain complexity. *Electroencephalogr. Clin. Neurophysiol.* 99, 63–68. doi: 10.1016/0921-884x(96)95573-3

Baedke, J. (2013). The epigenetic landscape in the course of time: conrad hal Waddington's methodological impact on the life sciences. *Stud. Hist. Philos. Biol. Biomed. Sci.* 44, 756–773. doi: 10.1016/j.shpsc.2013.06.001

Baldissera, F., Cacallari, P., and Civashi, P. (1982). Preference coupling between voluntary movements of ipsilateral limbs. *Neurosci. Lett.* 34, 95–100. doi: 10.1016/0304-3940(82)90098-2

Balasubramaniam, R., and Torre, K. (2012). Complexity in neurobiology: perspectives from the study of noise in human motor systems. *Crit. Rev. Biomed. Eng.* 40, 459–470. doi: 10.1615/critrevbiomedeng.2013006841

Baldissera, F., Cavallari, P., Marini, G., and Tassone, G. (1991). Differential control of in-phase and anti-phase coupling of rhythmic movements of ipsilateral hand and foot. *Exp. Brain Res.* 83, 375–380. doi: 10.1007/bf00231161

Baltes, B. P. (1980). Integration versus differentiation of fluid/crystallized intelligence in old age. *Dev. Psychol.* 16, 625–635. doi: 10.1037//0012-1649.16.6.625

Baltes, B. P., Lindenberger, U., and Staudinger, U. M. (1998). "Life-span theory in developmental psychology," in *Theoretical Models of Human Development*, ed R. M. Lerner 5th Edn. (New York: Wiley), 1029–1143.

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

Banerjee, A., Tognoli, E., Kelso, J. A., and Jirsa, V. K. (2012). Spatiotemporal reorganization of large-scale neural assemblies underlies bimanual coordination. *Neuroimage* 62, 1582–1592. doi: 10.1016/j.neuroimage.2012.05.046

Bardy, B. G., Marin, L., Stoffregen, T. A., and Bootsma, R. J. (1999). Postural coordination modes considered as emergent phenomena. *J. Exp. Psychol. Hum. Percept. Perform.* 25, 1284–1301. doi: 10.1037//0096-1523.25.5.1284

Bashore, T. R. (1994). Some thoughts on neurocognitive slowing. *Acta Psychol. (Amst)* 86, 295–325. doi: 10.1016/0001-6918(94)90006-x

Beggs, J. M., and Plenz, D. (2003). Neuronal avalanches in neocortical circuits. *J. Neurosci.* 23, 11167–11177.

Bernstein, N. A. (1967). *The Co-Ordination and Regulation of Movements.* Oxford: Pergamon Press.

Birren, J. E. (1965). "Age changes in speed of behavior: its central nature and physiological correlates," in *Behavior, Aging and the Nervous System*, eds A. T. Welford and J. E. Birren (Springfield, IL: Charles C. Thomas), 191–216.

Birren, J. E., Woods, A. M., and Williams, M. W. (1980). "Behavioral slowing with age: causes, organization and consequences," in *Aging in the 1980's*, ed L. W. Poon (Washington, DC: American Psychological Association), 293–308.

Bravi, A., Longtin, A., and Seely, A. (2011). Review and classification of variability analysis techniques with clinical applications. *Biomed. Eng. Online* 10:90. doi: 10.1186/1475-925X-10-90

Buchman, T. G. (1996). Physiologic stability and physiologic state. *J. Trauma* 41, 599–605. doi: 10.1097/00005373-199610000-00002

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., 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

Carson, R. G. (2004). "Governing coordination: why do muscles matter," in *Coordination Dynamics: Issues and Trends*, eds V. K. Jirsa and J. A. S. Kelso (Berlin: Springer-Verlag), 141–154.

Carson, R. G. (2006). Changes in muscle coordination with training. *J. Appl. Physiol. (1985)* 101, 1506–1513. doi: 10.1152/japplphysiol.00544.2006

Carson, R. G., and Kelso, J. A. S. (2004). Governing coordination: behavioural principles and neural correlates. *Exp. Brain Res.* 154, 267–274. doi: 10.1007/s00221-003-1726-8

Carson, R. G., Riek, S., Smethurst, C. J., Parraga, J. F., and Byblow, W. D. (2000). Neuromuscular-skeletal constraints upon the dynamics of unimanual and bimanual coordination. *Exp. Brain Res.* 131, 196–214. doi: 10.1007/s002219900272

Cerella, J. (1985). Information processing rates in the elderly. *Psychol. Bull.* 98, 67–83. doi: 10.1037//0033-2909.98.1.67

Cerella, J. (1991). Age effects may be global, not local: comment on Fisk and Rogers (1991). *J. Exp. Psychol. Gen.* 120, 215–223. doi: 10.1037/0096-3445.120.2.215

Cerella, J. (1994). Generalized slowing in Brinley plots. *J. Gerontol.* 49, P65–P71. doi: 10.1093/geronj/49.2.p65

Cesari, M., Gambassi, G., van Kan, G. A., and Vellas, B. (2014). The frailty phenotype and the frailty index: different instruments for different purposes. *Age Ageing* 43, 10–12. doi: 10.1093/ageing/aft160

Chauvet, G. (1995). *La Vie dans la Matière: Le Rôle de L'espace en Biologie (Life in Material: The Role of Space in Biology)*. Paris: Champs Flammarion.

Chen, Y. Q., Ding, M. Z., and Kelso, J. A. S. (1997). Long memory processes (1/f(alpha) type) in human coordination. *Phys. Rev. Lett.* 79, 4501–4504. doi: 10.1103/physrevlett.79.4501

Clegg, A., Young, J., Iliffe, S., Rikkert, M. O., and Rockwood, K. (2013). Frailty in elderly people. *Lancet* 381, 752–762. doi: 10.1016/S0140-6736(12)62167-9

Costa, M., Goldberger, A. L., and Peng, C. K. (2002). Multiscale entropy analysis of complex physiologic time series. *Phys. Rev. Lett.* 89:068102. doi: 10.1103/PhysRevLett.89.068102

Daido, H. (2008). Aging transition and disorder-induced coherence in locally coupled oscillators. *EPL* 84:10002. doi: 10.1209/0295-5075/84/10002

d'Avella, A., Saltiel, P., and Bizzi, E. (2003). Combinations of muscle synergies in the construction of a natural motor behavior. *Nat. Neurosci.* 6, 300–308. doi: 10.1038/nn1010

d'Avella, A., and Tresch, M. C. (2002). "Modularity in the motor system: decomposition of muscle patterns as combinations of time-varying synergies," in *Advances in Neural Information Processing Systems* 14, eds T. G. Dietterich, S. Becker and Z. Ghahramani (Cambridge, MA: MIT Press), 141–148.

Deco, G., Jirsa, V., Mcintosh, A. R., Sporns, O., and Kötter, R. (2009). Key role of coupling, delay and noise in resting brain fluctuations. *Proc. Natl. Acad. Sci. U S A* 106, 10302–10307. doi: 10.1073/pnas.0906701106

Deco, G., Jirsa, V. K., and McIntosh, A. R. (2011). Emerging concepts for the dynamical organization of resting-state activity in the brain. *Nat. Rev. Neurosci.* 12, 43–56. doi: 10.1038/nrn2961

Dennis, N. A., and Cabeza, R. (2011). Age-related dedifferentiation of learning systems: an fMRI study of implicit and explicit learning. *Neurobiol. Aging* 32, 2318.e17–2318.e30. doi: 10.1016/j.neurobiolaging.2010.04.004

Ding, M., Chen, Y., and Kelso, J. A. (2002). Statistical analysis of timing errors. *Brain Cogn.* 48, 98–106. doi: 10.1006/brcg.2001.1306

Dominici, N., Ivanenko, Y., Cappellini, G., d'avella, A., Mondı, V., Cicchese, M., et al. (2011). Locomotor primitives in newborn babies and their development. *Science* 334, 997–999. doi: 10.1126/science.1210617

Faisal, A. A., Selen, L. P. J., and Wolpert, D. M. (2008). Noise in the nervous system. *Nat. Rev. Neurosci.* 9, 292–303. doi: 10.1038/nrn2258

Fuchs, A., and Jirsa, V. K. (2008). *Coordination: Neural, Behavioral and Social Dynamics.* Heidelberg: Springer.

Fuchs, A., Jirsa, V. K., and Kelso, J. A. S. (2000). Theory of the relation between human brain activity (MEG) and hand movements. *Neuroimage* 11, 359–369. doi: 10.1006/nimg.1999.0532

Garrett, D. D., Kovacevic, N., Mcintosh, A. R., and Grady, C. L. (2011). The importance of being variable. *J. Neurosci.* 31, 4496–4503. doi: 10.1523/JNEUROSCI.5641-10.2011

Garrett, D. D., Kovacevic, N., Mcintosh, A. R., and Grady, C. L. (2013). The modulation of BOLD variability between cognitive states varies by age and processing speed. *Cereb. Cortex* 23, 684–693. doi: 10.1093/cercor/bhs055

Ghosh, A., Rho, Y., Mcintosh, A. R., Kötter, R., and Jirsa, V. K. (2008). Noise during rest enables the exploration of the brain's dynamic repertoire. *PLoS Comput. Biol.* 4:e1000196. doi: 10.1371/journal.pcbi.1000196

Glass, L., and Mackey, M. (1988). *From Clocks to Chaos: The Rythms of Life.* Princeton: Princeton University Press.

Goldberger, A. L., Amaral, L. A. N., Hausdorff, J. M., Ivanov, P. C., Peng, C.-K., and Stanley, H. E. (2002). Fractal dynamics in physiology: alterations with disease and aging. *Proc. Natl. Acad. Sci. U S A* 99(Suppl. 1), 2466–2472. doi: 10.1073/pnas.012579499

Greene, L. S., and Williams, H. G. (1996). "Aging and coordination from the dynamic pattern perspective," in *Advances in Psychology: Changes in Sensory Motor Behavior in Aging*, eds A.-M. Ferrandez and N. Teasdale (Amsterdam: Elsevier), 89–131.

Haken, H. (1977). *Synegetics.* Berlin: Springer.

Haken, H. (1983). *Synergetics: An Introduction.* Berlin: Springer-Verlag.

Haken, H., Kelso, J. A., and Bunz, H. (1985). A theoretical model of phase transitions in human hand movements. *Biol. Cybern.* 51, 347–356. doi: 10.1007/bf00336922

Harris, C. M., and Wolpert, D. M. (1998). Signal-dependent noise determines motor planning. *Nature* 394, 780–784. doi: 10.1038/29528

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

Hilber, K., Galler, S., Gohlsch, B., and Pette, D. (1999). Kinetic properties of myosin heavy chain isoforms in single fibers from human skeletal muscle. *FEBS Lett.* 455, 267–270. doi: 10.1016/s0014-5793(99)00903-5

Hong, S. L., and Rebec, G. V. (2012). Biological sources of inflexibility in brain and behavior with aging and neurodegenerative diseases. *Front. Syst. Neurosci.* 6:77. doi: 10.3389/fnsys.2012.00077

Hultsch, D. F., Strauss, E., Hunter, M. A., and Macdonald, S. W. (2008). "Intraindividual variability, cognition and aging," in *The Handbook of Aging and Cognition*, eds F. I. M. Craik and T. A. Salthouse 3rd Edn. (New York, NY: Psychology Press), 491–556.

Jantzen, K. J., Steinberg, F. L., and Kelso, J. A. S. (2009). Coordination dynamics of large-scale neural circuitry underlying rhythmic sensorimotor behavior. *J. Cogn. Neurosci.* 21, 2420–2433. doi: 10.1162/jocn.2008.21182

Jirsa, V. K., Fuchs, A., and Kelso, J. A. (1998). Connecting cortical and behavioral dynamics: bimanual coordination. *Neural Comput.* 10, 2019–2045. doi: 10.1162/089976698300016954

Jirsa, V. K., and Haken, H. (1996). Field theory of electromagnetic brain activity. *Phys. Rev. Lett.* 77, 960–963. doi: 10.1103/physrevlett.77.960

Kelso, J. A. (1984). Phase transitions and critical behavior in human bimanual coordination. *Am. J. Physiol.* 246, R1000–R1004.

Kelso, J. A., Dumas, G., and Tognoli, E. (2013). Outline of a general theory of behavior and brain coordination. *Neural Netw.* 37, 120–131. doi: 10.1016/j.neunet.2012.09.003

Kelso, J. A., Holt, K. G., Rubin, P., and Kugler, P. N. (1981). Patterns of human interlimb coordination emerge from the properties of non-linear, limit cycle oscillatory processes: theory and data. *J. Mot. Behav.* 13, 226–261. doi: 10.1080/00222895.1981.10735251

Kelso, J. A. S. (1981). On the oscillatory basis of movement. *Bull. Psychon. Soc.* 18, 63.

Kelso, J. A. S. (1995). *Dynamic Patterns: The Self-Organization of Brain and Behavior.* Cambridge: MIT Press.

Kelso, J. A. S. (2009). Synergies: atoms of brain and behavior. *Adv. Exp. Med. Biol.* 629, 83–91. doi: 10.1007/978-0-387-77064-2_5

Kelso, J. A. S. (2012). Multistability and metastability: understanding dynamic coordination in the brain. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 367, 906–918. doi: 10.1098/rstb.2011.0351

Kelso, J. A. S., Bressler, S. L., Buchanan, S., Deguzman, G. C., Ding, M., Fuchs, A., et al. (1992). A phase transition in human brain and behavior. *Phys. Lett. A* 169, 134–144. doi: 10.1016/0375-9601(92)90583-8

Kelso, J. A. S., Delcolle, J., and Schöner, G. (1990). "Action-Perception as a pattern formation process," in *Attention and Performance XIII*, ed M. Jeannerod (Hillsdale, NJ: Erlbaum), 139–169.

Kelso, J. A. S., Fuchs, A., and Jirsa, V. (1999). "Traversing scales of brain and behavioral organization I: concepts and experiments," in *Analysis of Neurophysiological Brain Functioning*, ed C. Uhl (Berlin Heidelberg: Springer), 73–89.

Kelso, J. A. S., Scholz, J. P., and Schöner, G. (1986). Nonequilibrium phase transitions in coordinated biological motion: critical fluctuations. *Phys. Lett. A* 118, 279–284. doi: 10.1016/0375-9601(86)90359-2

Kostrubiec, V., Zanone, P. G., Fuchs, A., and Kelso, J. A. (2012). Beyond the blank slate: routes to learning new coordination patterns depend on the intrinsic dynamics of the learner-experimental evidence and theoretical model. *Front. Hum. Neurosci.* 6:222. doi: 10.3389/fnhum.2012.00222

Lang, P.-O., Michel, J.-P., and Zekry, D. (2009). Frailty syndrome: a transitional state in a dynamic process. *Gerontology* 55, 539–549. doi: 10.1159/000211949

Lee, T. D., Blandin, Y., and Proteau, L. (1996). Effects of task instructions and oscillation frequency on bimanual coordination. *Psychol. Res.* 59, 100–106. doi: 10.1007/bf01792431

Lexell, J. (1995). Human aging, muscle mass and fiber type composition. *J. Gerontol. A Biol. Sci. Med. Sci.* 50, 11–16. doi: 10.1093/gerona/50a.special_issue.11

Li, K. Z. H., 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

Li, S., Lindenberger, U., and Sikström, S. (2001). Aging cognition: from neuromodulation to representation. *Trends Cogn. Sci.* 5, 479–486. doi: 10.1016/s1364-6613(00)01769-1

Li, S. C., Lindenberger, U., and Frensch, P. A. (2000). Unifying cognitive aging: from neuromodulation to representation to cognition. *Neurocomputing* 32–33, 879–890. doi: 10.1016/s0925-2312(00)00256-3

Li, S. C., and Sikström, S. (2002). Integrative neurocomputational perspectives on cognitive aging, neuromodulation and representation. *Neurosci. Biobehav. Rev.* 26, 795–808. doi: 10.1016/s0149-7634(02)00066-0

Lindenberger, U., and Baltes, P. B. (1994). Sensory functioning and intelligence in old age: a strong connection. *Psychol. Aging* 9, 339–355. doi: 10.1037/0882-7974.9.3.339

Lindenberger, U., and Ghisletta, P. (2009). Cognitive and sensory declines in old age: gauging the evidence for a common cause. *Psychol. Aging* 24, 1–16. doi: 10.1037/a0014986

Lipsitz, L. A. (2002). Dynamics of stability: the physiologic basis of functional health and frailty. *J. Gerontol. A Biol. Sci. Med. Sci.* 57, B115–B125. doi: 10.1093/gerona/57.3.b115

Lipsitz, L. A. (2004). Physiological complexity, aging and the path to frailty. *Sci. Aging Knowledge Environ.* 2004:pe16. doi: 10.1126/sageke.2004.16.pe16

Lipsitz, L. A., and Goldberger, A. L. (1992). Loss of complexity and aging. Potential applications of fractals and chaos theory to senescence. *JAMA* 267, 1806–1809. doi: 10.1001/jama.1992.03480130122036

MacDonald, S. W. S., Cervenka, S., Farde, L., Nyberg, L., and Bäckman, L. (2009a). Extrastriatal dopamine D2 receptor binding modulates intraindividual variability in episodic recognition and executive functioning. *Neuropsychologia* 47, 2299–2304. doi: 10.1016/j.neuropsychologia.2009.01.016

MacDonald, S. W. S., Li, S.-C., and Bäckman, L. (2009b). Neural underpinnings of within-person variability in cognitive functioning. *Psychol. Aging* 24, 792–808. doi: 10.1037/a0017798

Manini, T. M., Hong, S. L., and Clark, B. C. (2013). Aging and muscle: a neuron's perspective. *Curr. Opin. Clin. Nutr. Metab. Care* 16, 21–26. doi: 10.1097/MCO.0b013e32835b5880

Marmelat, V., and Delignières, D. (2012). Strong anticipation: complexity matching in interpersonal coordination. *Exp. Brain Res.* 222, 137–148. doi: 10.1007/s00221-012-3202-9

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

Mayville, J. M., Bressler, S. L., Fuchs, A., and Kelso, J. A. (1999). Spatiotemporal reorganization of electrical activity in the human brain associated with a timing transition in rhythmic auditory-motor coordination. *Exp. Brain Res.* 127, 371–381. doi: 10.1007/s002210050805

McIntosh, A. R., Kovacevic, N., Lippe, S., Garrett, D., Grady, C., and Jirsa, V. (2010). The development of a noisy brain. *Arch. Ital. Biol.* 148, 323–337.

McIntosh, A. R., Vakorin, V., Kovacevic, N., Wang, H., Diaconescu, A., and Protzner, A. B. (2014). Spatiotemporal dependency of age-related changes in brain signal variability. *Cereb. Cortex* 24, 1806–1817. doi: 10.1093/cercor/bht030

Mechsner, F. (2004). "A perceptual-cognitive approach to bimanual coordination," in *Coordination Dynamics: Issues and Trends*, eds V. K. Jirsa and J. A. S. Kelso (Berlin: Springer), 177–195.

Mechsner, F., Kerzel, D., Knoblich, G., and Prinz, W. (2001). Perceptual basis of bimanual coordination. *Nature* 414, 69–73. doi: 10.1038/35102060

Medvedev, Z. A. (1990). An attempt at a rational classification of theories of ageing. *Biol. Rev. Camb. Philos. Soc.* 65, 375–398. doi: 10.1111/j.1469-185x.1990.tb01428.x

Meyer-Lindenberg, A., Ziemann, U., Hajak, G., Cohen, L., and Berman, K. F. (2002). Transitions between dynamical states of differing stability in the human brain. *Proc. Natl. Acad. Sci. U S A* 99, 10948–10953. doi: 10.1073/pnas.162114799

Monemi, M., Eriksson, P. O., Kadi, F., Butler-Browne, G. S., and Thornell, L. E. (1999). Opposite changes in myosin heavy chain composition of human masseter and biceps brachii muscles during aging. *J. Muscle Res. Cell Motil.* 20, 351–361. doi: 10.1023/A:1005421604314

Monno, A., Temprado, J.-J., Zanone, P.-G., and Laurent, M. (2002). The interplay of attention and bimanual coordination dynamics. *Acta Psychol. (Amst)* 110, 187–211. doi: 10.1016/s0001-6918(02)00033-1

Morrison, S., and Newell, K. M. (2012). Aging, neuromuscular decline and the change in physiological and behavioral complexity of upper-limb movement dynamics. *J. Aging Res.* 2012:891218. doi: 10.1155/2012/891218

Muchisky, M., Gershkoff-Stowe, L., Cole, E., and Thelen, E. (1996). "The epigenetic landscape revisited: a dynamic interpretation," in *Advances in Infancy Research*, ed C. Rovee-Collier (Norwood, NJ: Ablex), 121–159.

Müller, V., and Lindenberger, U. (2012). Lifespan differences in nonlinear dynamics during rest and auditory oddball performance. *Dev. Sci.* 15, 540–556. doi: 10.1111/j.1467-7687.2012.01153.x

Newell, K. M., Liu, Y.-T., and Mayer-Kress, G. (2003). A dynamical systems interpretation of epigenetic landscapes for infant motor development. *Infant Behav. Dev.* 26, 449–472. doi: 10.1016/j.infbeh.2003.08.003

Newell, K. M., Liu, Y.-T., and Mayer-Kress, G. (2005). Learning in the brain-computer interface: insights about degrees of freedom and degeneracy in a landscape model of motor learning. *Cognit. Process.* 6, 37–47. doi: 10.1007/s10339-004-0047-6

Newell, K. M., Liu, Y.-T., and Mayer-Kress, G. (2008). "Landscapes beyond the HKB model," in *Coordination: Neural, Behavioral and Social Dynamics*, eds A. Fuchs and V. K. Jirsa (Berlin: Springer Verlag), 27–44.

Newell, K., Vaillancourt, D., and Sosnoff, J. (2006). "Aging, complexity and motor performance," in *Handbook of the Psychology of Aging*, eds J. E. Birren and K. W. Schaie (London, UK: Elsevier Academic Press), 163–178.

Nilwik, R., Snijders, T., Leenders, M., Groen, B. B., Van Kranenburg, J., Verdijk, L. B., et al. (2013). The decline in skeletal muscle mass with aging is mainly attributed to a reduction in type II muscle fiber size. *Exp. Gerontol.* 48, 492–498. doi: 10.1016/j.exger.2013.02.012

Oullier, O., and Kelso, J. A. S. (2009). "Coordination from the perspective of social coordination dynamics," in *The Encyclodedia of Complexity and Systems Science*, ed R. A. Meyer (Heideberg: Springer), 8198–8213.

Papenberg, G., Backman, L., Chicherio, C., Nagel, I. E., Heekeren, H. R., Lindenberger, U., et al. (2011). Higher intraindividual variability is associated with more forgetting and dedifferentiated memory functions in old age. *Neuropsychologia* 49, 1879–1888. doi: 10.1016/j.neuropsychologia.2011.03.013

Park, D. C., Polk, T. A., Park, R., Minear, M., Savage, A., and Smith, M. R. (2004). Aging reduces neural specialization in ventral visual cortex. *Proc. Natl. Acad. Sci. U S A* 101, 13091–13095. doi: 10.1073/pnas.0405148101

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

Pellecchia, G. L., Shockley, K., and Turvey, M. T. (2005). Concurrent cognitive task modulates coordination dynamics. *Cogn. Sci.* 29, 531–557. doi: 10.1207/s15516709cog0000_12

Peng, C.-K., Costa, M., and Goldberger, A. L. (2009). Adaptative data analysis of complex fluctuations in physiologic time series. *Adv. Adapt. Data Anal.* 1, 61–70. doi: 10.1142/s1793536909000035

Pette, D., and Staron, R. S. (2000). Myosin isoforms, muscle fiber types and transitions. *Microsc. Res. Tech.* 50, 500–509. doi: 10.1002/1097-0029(20000915)50:6<500::aid-jemt7>3.3.co;2-z

Pierce, T. W., Kelly, S. P., Watson, T. D., Replogle, D., King, J. S., and Pribram, K. H. (2000). Age differences in dynamic measures of EEG. *Brain Topogr.* 13, 127–134. doi: 10.1023/A:1026659102713

Pierce, T. W., Watson, T. D., King, J. S., Kelly, S. P., and Pribram, K. H. (2003). Age differences in factor analysis of EEG. *Brain Topogr.* 16, 19–27. doi: 10.1023/A:1025654331788

Reuter-Lorenz, P. A. (2002). New visions of the aging mind and brain. *Trends Cogn. Sci.* 6, 394–400. doi: 10.1016/s1364-6613(02)01957-5

Rey-Robert, B., Temprado, J.-J., and Berton, E. (2011). Aging and changes in complexity in the neurobehavioral system. *Medicina (Kaunas)* 47, 1–10.

Riley, M. A., Richardson, M. J., Shockley, K., and Ramenzoni, V. C. (2011). Interpersonal synergies. *Front. Psychol.* 2:38. doi: 10.3389/fpsyg.2011.00038

Salesse, R., and Temprado, J. J. (2005). The effect of visuo-motor transformations on hand-foot coordination: evidence in favor of the incongruency hypothesis. *Acta Psychol. (Amst)* 119, 143–157. doi: 10.1016/j.actpsy.2004.12.002

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

Schaefer, S., and Schumacher, V. (2010). 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

Schäfer, S., Huxhold, O., and Lindenberger, U. (2006). Healthy mind in healthy body? A review of sensorimotor–cognitive interdependencies in old age. *Eur. Rev. Aging Phys. Act.* 3, 45–54. doi: 10.1007/s11556-006-0007-5

Schmidt, R. C., Beek, P. J., Treffner, P. J., and Turvey, M. T. (1991). Dynamical substructure of coordinated rhythmic movements. *J. Exp. Psychol. Hum. Percept. Perform.* 17, 635–651. doi: 10.1037//0096-1523.17.3.635

Schmidt, R. C., Carello, C., and Turvey, M. T. (1990). Phase transitions and critical fluctuations in the visual coordination of rhythmic movements between people. *J. Exp. Psychol. Hum. Percept. Perform.* 16, 227–247. doi: 10.1037/0096-1523.16.2.227

Scholz, J. P., and Kelso, J. A. (1990). Intentional switching between patterns of bimanual coordination depends on the intrinsic dynamics of the patterns. *J. Mot. Behav.* 22, 98–124. doi: 10.1080/00222895.1990.10735504

Schöner, G., Haken, H., and Kelso, J. A. (1986). A stochastic theory of phase transitions in human hand movement. *Biol. Cybern.* 53, 247–257. doi: 10.1007/bf00336995

Schöner, G., Zanone, P. G., and Kelso, J. A. (1992). Learning as change of coordination dynamics: theory and experiment. *J. Mot. Behav.* 24, 29–48. doi: 10.1080/00222895.1992.9941599

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

Serrien, D. J., Ivry, R. B., and Swinnen, S. P. (2007). The missing link between action and cognition. *Prog. Neurobiol.* 82, 95–107. doi: 10.1016/j.pneurobio.2007.02.003

Sleimen-Malkoun, R., Temprado, J. J., and Berton, E. (2013). Age-related changes of movement patterns in discrete Fitts' task. *BMC Neurosci.* 14:145. doi: 10.1186/1471-2202-14-145

Sleimen-Malkoun, R., Temprado, J. J., Huys, R., Jirsa, V., and Berton, E. (2012). Is Fitts' law continuous in discrete aiming? *PLoS One* 7:e41190. doi: 10.1371/journal.pone.0041190

Sleimen-Malkoun, R., Temprado, J.-J., Thefenne, L., and Berton, E. (2011). Bimanual training in stroke: how do coupling and symmetry-breaking matter? *BMC Neurol.* 11:11. doi: 10.1186/1471-2377-11-11

Slifkin, A. B., and Newell, K. M. (1999). Noise, information transmission and force variability. *J. Exp. Psychol. Hum. Percept. Perform.* 25, 837–851. doi: 10.1037//0096-1523.25.3.837

Smith, L. B., and Thelen, E. (2003). Development as a dynamic system. *Trends Cogn. Sci.* 7, 343–348. doi: 10.1016/S1364-6613(03)00156-6

Sosnoff, J. J., and Newell, K. M. (2011). Aging and motor variability: a test of the neural noise hypothesis. *Exp. Aging Res.* 37, 377–397. doi: 10.1080/0361073x.2011.590754

Sosnoff, J. J., Valantine, A. D., and Newell, K. M. (2006). Independence between the amount and structure of variability at low force levels. *Neurosci. Lett.* 392, 165–169. doi: 10.1016/j.neulet.2005.09.010

Stepp, N., and Turvey, M. T. (2010). On strong anticipation. *Cogn. Syst. Res.* 11, 148–164. doi: 10.1016/j.cogsys.2009.03.003

Stewart, C. V., and Plenz, D. (2006). Inverted-U profile of dopamine-NMDA-mediated spontaneous avalanche recurrence in superficial layers of rat prefrontal cortex. *J. Neurosci.* 26, 8148–8159. doi: 10.1523/jneurosci.0723-06.2006

Temprado, J.-J., and Laurent, M. (2004). Attentional load associated with performing and stabilizing a between-persons coordination of rhythmic limb movements. *Acta Psychol. (Amst)* 115, 1–16. doi: 10.1016/j.actpsy.2003.09.002

Temprado, J. J., and Salesse, R. (2004). Interlimb coordination: real constraints and false dichotomies. *J. Mot. Behav.* 36, 398–400, 402–407; discussion 408–417.

Temprado, J. J., Swinnen, S. P., Carson, R. G., Tourment, A., and Laurent, M. (2003). Interaction of directional, neuromuscular and egocentric constraints on the stability of preferred bimanual coordination patterns. *Hum. Mov. Sci.* 22, 339–363. doi: 10.1016/s0167-9457(03)00049-6

Temprado, J. J., Vercruysse, S., Salesse, R., and Berton, E. (2010). A dynamic systems approach to the effects of aging on bimanual coordination. *Gerontology* 56, 335–344. doi: 10.1159/000262445

Temprado, J. J., Zanone, P. G., Monno, A., and Laurent, M. (1999). Attentional load associated with performing and stabilizing preferred bimanual patterns. *J. Exp. Psychol. Hum. Percept. Perform.* 25, 1579–1594. doi: 10.1037/0096-1523.25.6.1579

Tognoli, E., and Kelso, J. A. S. (2009). Brain coordination dynamics: true and false faces of phase synchrony and metastability. *Prog. Neurobiol.* 87, 31–40. doi: 10.1016/j.pneurobio.2008.09.014

Torre, K. (2010). The correlation structure of relative phase variability influences the occurrence of phase transition in coordination. *J. Mot. Behav.* 42, 99–105. doi: 10.1080/00222890903507891

Torre, K., and Balasubramaniam, R. (2011). Disentangling stability, variability and adaptability in human performance: focus on the interplay between local variance and serial correlation. *J. Exp. Psychol. Hum. Percept. Perform.* 37, 539–550. doi: 10.1037/a0020556

Torre, K., Delignieres, D., and Lemoine, L. (2007). 1/f (beta) fluctuations in bimanual coordination: an additional challenge for modeling. *Exp. Brain Res.* 183, 225–234. doi: 10.1007/s00221-007-1035-8

Tresch, M. C., and Jarc, A. (2009). The case for and against muscle synergies. *Curr. Opin. Neurobiol.* 19, 601–607. doi: 10.1016/j.conb.2009.09.002

Vaillancourt, D. E., and Newell, K. M. (2002). Changing complexity in human behavior and physiology through aging and disease. *Neurobiol. Aging* 23, 1–11. doi: 10.1016/s0197-4580(01)00247-0

Waddington, C. H. (1942). The epigenotype. *Endeavour* 1, 18–20.

Waddington, C. H. (1957). *The Strategy of the Genes; a Discussion of Some Aspects of Theoretical Biology.* London: Allen and Unwin.

Wallenstein, G. V., Kelso, J. A. S., and Bressler, S. L. (1995). Phase transitions in spatiotemporal patterns of brain activity and behavior. *Phys. D* 84, 626–634. doi: 10.1016/0167-2789(95)00056-a

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

West, B. J. (2006). *Where Medicine Went Wrong: Rediscovering the Path to Complexity, Studies of Nonlinear Phenomena in Life Science (Vol. 11).* Teaneck, NJ: World Scientific.

West, B. J., and Grigolini, P. (2010). The living matter way to exchange information. *Med. Hypotheses* 75, 475–478. doi: 10.1016/j.mehy.2010.04.028

Wing, A. M., and Kristofferson, A. B. (1973). Response delays in the timing of discrete motor responses. *Percept. Psychophys.* 14, 5–12. doi: 10.3758/bf03198607

Yamanishi, J., Kawato, M., and Suzuki, R. (1980). Two coupled oscillators as a model for the coordinated finger tapping by both hands. *Biol. Cybern.* 37, 219–225. doi: 10.1007/bf00337040

Yang, A. C., Huang, C. C., Yeh, H. L., Liu, M. E., Hong, C. J., Tu, P. C., et al. (2013). Complexity of spontaneous BOLD activity in default mode network is correlated with cognitive function in normal male elderly: a multiscale entropy analysis. *Neurobiol. Aging* 34, 428–438. doi: 10.1016/j.neurobiolaging.2012.05.004

Yates, F. E. (2008). Homeokinetics/Homeodynamics: a physical Heuristic for life and complexity. *Ecol. Psychol.* 20, 148–179. doi: 10.1080/10407410801977546

Zanone, P. G., and Kelso, J. A. (1992). Evolution of behavioral attractors with learning: nonequilibrium phase transitions. *J. Exp. Psychol. Hum. Percept. Perform.* 18, 403–421. doi: 10.1037//0096-1523.18.2.403

Zanone, P. G., and Kelso, J. A. S. (1997). Cooordination dynamics of learning and transfer: collective and component levels. *J. Exp. Psychol. Hum. Percept. Perform.* 23, 1454–1480. doi: 10.1037//0096-1523.23.5.1454

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

Received: 10 March 2014; accepted: 11 June 2014; published online: 27 June 2014.
Citation: Sleimen-Malkoun R, Temprado J-J and Hong SL (2014) Aging induced loss of complexity and dedifferentiation: consequences for coordination dynamics within and between brain, muscular and behavioral levels. Front. Aging Neurosci. ***6****:140.* ***doi: 10.3389/fnagi.2014.00140***
This article was submitted to the journal Frontiers in Aging Neuroscience.

frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 17 March 2014
doi: 10.3389/fnagi.2014.00048

Benefits of physical exercise on basic visuo-motor functions across age

Marika Berchicci [1], ***Giuliana Lucci*** [2], ***Rinaldo Livio Perri*** [1,3], ***Donatella Spinelli*** [1,2] **and *Francesco Di Russo*** [1,2]*

[1] *Department of Human Movement, Social and Health Sciences, University of Rome "Foro Italico", Rome, Italy*
[2] *Neuropsychological Unit, IRCCS Santa Lucia Foundation, Rome, Italy*
[3] *Department of Psychology, University of Rome "La Sapienza", Rome, Italy*

Edited by:
S. Lee Hong, Ohio University, USA

Reviewed by:
Rita Sleimen-Malkoun, Aix-Marseille Université, France
Ross Andel, University of South Florida, USA

Correspondence:
Francesco Di Russo, Dipartimento di Scienze Motorie, Umane e della Salute, Università Degli Studi di Roma "Foro Italico", Piazza Lauro De Bosis, Roma 15, Italy
e-mail: francesco.dirusso@uniroma4.it

Motor performance deficits of older adults are due to dysfunction at multiple levels. Age-related differences have been documented on executive functions; motor control becomes more reliant on cognitive control mechanisms, including the engagement of the pre-frontal cortex (PFC), possibly compensating for age-related sensorimotor declines. Since at functional level the PFC showed the largest age-related differences during discriminative response task, we wonder whether those effects are mainly due to the cognitive difficulty in stimulus discrimination or they could be also detected in a much easier task. In the present study, we measured the association of physical exercise with the PFC activation and response times (RTs) using a simple response task (SRT), in which the participants were asked to respond as quickly as possible by manual key-press to visual stimuli. Simultaneous behavioral (RTs) and electroencephalographic (EEG) recordings were performed on 84 healthy participants aged 19–86 years. The whole sample was divided into three cohorts (young, middle-aged, and older); each cohort was further divided into two equal sub-cohorts (exercise and not-exercise) based on a self-report questionnaire measuring physical exercise. The EEG signal was segmented in epochs starting 1100 prior to stimulus onset and lasting 2 s. Behavioral results showed age effects, indicating a slowing of RTs with increasing age. The EEG results showed a significant interaction between age and exercise on the activities recorded on the PFC. The results indicates that: (a) the brain of older adults needs the PFC engagement also to perform elementary task, such as the SRT, while this activity is not necessary in younger adults, (b) physical exercise could reduce this age-related reliance on extra cognitive control also during the performance of a SRT, and (c) the activity of the PFC is a sensitive index of the benefits of physical exercise on sensorimotor decline.

Keywords: simple response task, response time, event-related potential, prefrontal cortex, lifespan

INTRODUCTION

The proportion of adults over the age of 65 is expected to increase over the years. With advancing age, structural and functional deterioration occurs in most physiological systems, even in the absence of overt disease, including the central and peripheral nervous systems, as well as the neuromuscular system. A significant amount of new evidence has accumulated regarding the benefits of regular physical activity and exercise for older healthy adults (see Miller et al., 2012; Hayes et al., 2013, for reviews). Regular physical activity increases average life expectancy through its influence on sensorimotor control and functioning, and represents a low-cost, large-scale behavioral intervention that may slow the progression of physiological age-related cognitive and motor decline in healthy older adults.

In the last few years, neuroimaging studies have provided support for a positive correlation between cardiorespiratory fitness and cerebral structures and functions in humans (Colcombe et al., 2003; Gordon et al., 2008; Erickson et al., 2010; Bugg and Head, 2011; Weinstein et al., 2012), showing that brain structures, in particular the hippocampus and frontal and parietal areas mediate the positive association between fitness and cognition with particular emphasis on the executive functions of older adults. Intervention studies confirmed that aerobic exercise positively impacts the abovementioned brain structures (Colcombe et al., 2006; Erickson et al., 2011; Ruscheweyh et al., 2011; Voss et al., 2012). Other studies linked physical fitness to enhanced cognitive performance, which was mediated by the activity in most of the aforementioned areas in high-fit older adults (Colcombe et al., 2004; Godde and Voelcker-Rehage, 2010; Rosano et al., 2010; McGregor et al., 2011; Prakash et al., 2011; Smith et al., 2011; Voelcker-Rehage et al., 2011).

Despite the extensive neuroimaging literature on the effects of physical activity on brain health and cognitive functions, there is less electrophysiological evidence to date. It is well known that aging is associated with slowing of speed processing (Salthouse, 2000). The behavioral variable most frequently used to measure processing speed is the response time (RT) that is the interval between the onset of an external stimulus (e.g., visual, acoustic, etc.) and the manual response, such as key-press; when the RTs are recorded simultaneously to electroencephalographic (EEG) recordings, very rich information can be derived. The event-related potentials (ERPs) provide a description at high-temporal resolution of the various stages of motor preparation and information processing. ERPs represent a powerful tool to investigate the temporal dynamic of neural processing and, thus, provide clues to understand the neural basis of age-related slowing, and the cognitive strategy adopted by older adults. Differential slowing of separable ERP components can be linked to specific decline at sensory, motor, or cognitive level (see Daffner et al., 2013; Li et al., 2013; Stothart et al., 2013; Wiegand et al., 2013, for more details); this subtle discrimination is not possible using neuroimaging techniques. Some ERP studies focused on the brain activities preceding the stimulus onset during the motor preparation process. The results indicated that older adults were slower to react, because the pre-response processing were slowed and/or enhanced rather than perceptual processing (Yordanova et al., 2004; Roggeveen et al., 2007; Wild-Wall et al., 2007). However, fewer studies have investigated the relationship between physical fitness and electrophysiological activity in older adults. Hillman et al. (2004) recorded the ERPs during a visuo-motor discrimination task, and showed that physically active elderly have faster stimulus-related cognitive processing (as indicated by the latency of the parietal activity, measured by means of the well-known P3 component) and faster RTs than their sedentary peers. In our previous work, we reported that older adults engaged more prefrontal cortex (PFC) resources than middle-aged and young adults during response preparation in a visuo-motor discrimination task; this enable them to reach the same task accuracy as their younger counterparts, while their response speed was slower (Berchicci et al., 2012). We also showed that the participation at physical exercise programs could slow down the age-related cognitive decline from 35 to 40 years of age onward (Berchicci et al., 2013). In particular, we observed that physical activity was linked to enhanced executive performance during a go/no-go task mediated by decreased activity in prefrontal regions during movement preparation.

These findings indicate that increased age is associated with slower performance and enhanced recruitment of prefrontal areas in visuo-motor discrimination tasks; moreover, physical exercise could slow down this age-related cognitive decline. Since at functional level, the PFC, supporting executive control (Ridderinkhof et al., 2004), showed the largest age-related differences, we wonder whether the observed effects of physical activity were detectable only for difficult tasks, such as discriminative tasks, or they could also be detected in a much easier task not requiring discrimination. In the present study, we measured the relationship between physical exercise and both PFC activity and RTs using a simple response task (SRT). Based on previous findings, we expected to not observe exercise-related differences in cortical and behavioral measures of young adults; in contrast, the effects of physical exercise could be found in older adults. The investigation of middle-aged and older adults will tell us whether the PFC hyperactivity emerges also in a SRT; if this holds true, as reported by Berchicci et al. (2012), we could disconfirm the cognitive difficulty explanation reported in the literature (Yordanova et al., 2004) and consider the PFC hyperactivity as a generalized effect of aging. Further, if physical exercise could favor a decreased engagement of higher-order cortical structures also in a simple task, this could support the view that physical exercise is a non-pharmacological intervention able to reduce the age-related reliance on cognitive control. Finally, if the benefits of physical exercise in a SRT were confirmed at the PFC level but not at the level of pre-motor regions, then we can suggest that the PFC activity is a more sensitive electrophysiological index of motor decline with age.

MATERIALS AND METHODS

PARTICIPANTS

A total of 84 participants volunteered. They were distributed across the following three adult age classes: younger ($n = 30$, 10 females, mean age = 24 years, age range: 19–35), middle-aged ($n = 32$, 12 females, mean age = 49 years, age range: 40–63), and older ($n = 22$, 14 females, mean age = 73 years, age range: 65–86). Education levels were similar in the two older groups (16.2 ± 2.1 and 16.0 ± 2.9 years of study for middle-aged and older, respectively) and slightly lower for younger adults (14.9 ± 1.6 years). Based on the self-report questionnaire about physical exercise (see below), the whole sample was equally divided into sub-cohorts: young adults who exercise (mean age: 24 ± 2.9 years) and do not exercise (mean age: 24 ± 5.4 years); middle-aged adults who exercise (mean age: 48 ± 3.8 years) and do not exercise (mean age: 51 ± 5.5 years); older adults who exercise (mean age: 74 ± 3.4 years) and do not exercise (mean age: 72 ± 4.2 years). To control potential confounds regarding gender and education level, the six sub-cohorts were preliminarily statistically compared. Results yielded not significant differences, indicating that they are matched for those factors. Furthermore, to control potential confounds regarding physical and mental health, only healthy people were included in the sample.

The general cognitive state of older participants was assessed using the mini-mental state examination (MMSE; Folstein et al., 1975). Older participants were not cognitively impaired, with an average MMSE score of 29 out of 30 (range: 28–30). All of the participants were healthy and without history of neurological, psychiatric, or chronic somatic problems. They were not taking psychoactive or vasoactive medication and had normal or corrected-to-normal vision. All of the participants were fully right-handed (Edinburgh Handedness Inventory; Oldfield, 1971). The older groups were recruited among friends of the authors and through the *Vitattiva Association* in Rome, the middle-aged participants were recruited among friends of the authors and among the employers of the University of Rome "Foro Italico," and the younger participants were recruited from the local student population. The study received prior approval by the ethical committee of the IRCCS Santa Lucia Foundation. Written informed consent was obtained according to the Declaration of Helsinki from each participant.

PHYSICAL ACTIVITY ASSESSMENT

Participants were asked to fill in a self-report questionnaire about physical exercise daily performed defined by the level of intensity in accordance with the American college of sport medicine guidelines (Chodzko-Zajko et al., 2009): moderate activity between three and six metabolic equivalent of tasks (METs) and vigorous activity greater than six METs. One MET is defined as the energy expenditure for sitting quietly, which, for the average adult, approximates 3.5 ml of oxygen uptake per kilogram of body weight per minute. Six METs was the threshold used to split the sample into not-exercise and exercise cohorts. The participants who reported general physical activities greater than six METs were also involved in regular physical exercise programs and sports at least 3 days/week, 1 h/session (i.e., swimming, running, martial arts, fencing, low- and high-impact exercise). Although the questionnaire approach may lead to omissions, inaccuracies, and bias, evidence has been reported about correlation between the results of subjective measures of physical activity and objective maximal oxygen consumption values (Bowles et al., 2004). Furthermore, the effects of physical fitness on cognitive and neural measures in older adults are consistent across different assessment methods (McAuley et al., 2011).

APPARATUS AND PROCEDURE

The participants were tested after a 64-channel EEG active-cap was mounted on their scalp; they were seated in a darkened room in front of a screen placed 114 cm from their eyes. The visual stimuli were four squared configurations made by vertical and horizontal bars subtending 4° × 4° presented on a dark gray background; one of these stimuli was randomly displayed for 260 ms with equal probability ($p = 0.25$). The inter-stimulus interval varied randomly from 1 to 2 s in order to maintain uncertainty of the RT. The order of presentation was randomized within blocks. The duration of each run was 2.5 min with a pause interleaved; five runs allowed us to obtain 500 trials. A yellow circle (diameter 0.15° of visual angle) placed at the center of the screen and set at the participant's eye level was the fixation point. Participants were asked to respond as fast as possible to all of the stimuli by pressing a button with the right index finger avoiding anticipations. Stimulus presentation and behavioral data acquisition were performed by Presentation™ software.

BEHAVIORAL DATA ANALYSIS

Accuracy was measured by the percentage of anticipations (i.e., responses shorter than 100 ms or responses issued before the stimulus onset). The RTs' medians for correct trials were calculated for each participant; the medians were used because the RTs' means distributions are usually positively skewed, and the median is the appropriate measure under such conditions as long as RT differences are relevant (Baayen and Milin, 2010). The median RTs of each subject were then averaged using the mean for each sub-cohort. Factorial (3 × 2) ANOVAs were separately performed on the RTs and accuracy using the following factors: age (younger vs. middle-aged vs. older) and physical exercise (not-exercise vs. exercise). *Post hoc* comparisons were conducted using Tukey's HSD test. The overall alpha level was fixed at 0.05 after the Geisser–Greenhouse correction.

ELECTROPHYSIOLOGICAL RECORDING AND ANALYSIS

The continuous EEG was recorded using the BrainVision™ system with 64 active (ActiCap™) electrodes (BrainProducts GmbH, Munich, Germany) mounted according to the 10–10 International System, which were referenced to the left mastoid. The EEG was digitized at 250 Hz, amplified (bandpass of 0.01–80 Hz, including a 50 Hz notch filter), and stored for off-line averaging. Off-line analysis was performed utilizing the BrainVision™ analyzer 2.0.1 software (Brain Products GmbH, Munich, Germany). Raw EEG data were visually inspected to identify and discard epochs contaminated with artifacts prior to the signal averaging. The first trial of each block was discarded from further analysis. The trials with artifacts (e.g., blinks or gross movements) and amplitude exceeding threshold of ±120 μV were automatically excluded from the averaging, whereas eye movement artifacts were corrected using the Gratton et al. (1983) algorithm. Horizontal eye movements (electro-oculogram, EOG) were monitored with bipolar recordings from electrodes at the left and right outer canthi. The blinks and vertical eye movements were recorded with an electrode below the left eye, which was referenced to site Fp1. The participants were required to concentrate on the task performance and minimize distractions as much as possible. Possible sources of distraction and noise were minimized.

To comprehensively study the brain activity related to both response preparation and stimulus perception, EEG recordings were separately segmented and averaged into non-overlapping 2000-ms epochs that were measured from 1100 ms before to 900 ms after the stimulus onset. To further reduce high-frequency noise, the time EEG grand-averages were low-pass filtered at 25 Hz. The baseline was derived from the mean amplitude over the initial 200 ms of the averaged epochs. This approach allows investigating not only the post-stimulus ERP components [i.e., P1, prefrontal positivity (Pp), N1, P2, and P3], but also the pre-stimulus components related to the movement preparation [i.e., Bereitschaftspotential (BP) and prefrontal negativity (pN)], since the baseline was calculated from more than 1 s before the stimulus onset and not 100–200 ms right before the stimulus onset, as usually done. The mean amplitude in the −500/0 ms time window, reflecting activity during the pre-stimulus preparation stage, has been selected for further analysis on the following electrodes: Cz (roughly overlaying pre-motor and motor areas) for the BP component; Fp1 and Fp21 (over the PFC) for the pN component. After stimulus onset, peak amplitudes and latencies of the major ERP components were calculated for each subject in the following standard time windows: P1: 80–150 ms; pP: 80–120 ms; N1: 130–200 ms; P2: 180–300 ms; and P3: 250–700 ms. The electrodes selection was based on the scalp topography which allowed identifying the greatest activity for a given component at the group level (i.e., the P1 and P2 on PO7 or PO8, the pP on Fp1 or Fp2, the N1 on O1 or O2, the P3 on Pz) and on previous reports (e.g., Shibasaki and Hallett, 2006; Berchicci et al., 2012).

Factorial (3 × 2) ANOVAs were separately performed on the mean amplitude in the −500/0 ms time windows (pN and BP components) and on the peak latency and amplitude of the aforementioned post-stimulus components. Factors were: age (younger vs. middle-aged vs. older) and physical exercise (not-exercise vs. exercise). *Post hoc* comparisons were conducted using Tukey's HSD test. The overall alpha level was fixed at 0.05 after the Geisser–Greenhouse correction. The correlation coefficients (Pearson's r coefficients) were separately computed for exercise and not-exercise cohorts between the RTs and mean activity preceding the stimulus onset over central (BP component) and prefrontal (pN component) derivations. The significance was set at 0.05 (two-tailed) for all of the analyses.

To visualize the voltage topography of the ERP components, spline interpolated three-dimensional maps were constructed using the BESA 2000 software (MEGIS Software GmbH, Gräfelfing, Germany).

RESULTS

BEHAVIORAL RESULTS

The accuracy and mean response times for the sub-cohorts are presented in **Table 1**. Older adults responded significantly slower than middle-aged and younger adults did, while not committing a greater number of anticipations (anticipation rates were below 1% and not differed between cohorts; all $ps > 0.05$). The factorial ANOVA did not reveal a significant age × physical exercise effect interaction ($F_{2,78} = 0.03$, $p = 0.968$, $\eta^2 = 0.000$). There was a main effect of age on the RTs ($F_{2,78} = 17.18$, $p < 0.0001$, $\eta^2 = 0.305$). Younger participants were on average 22 ms faster than middle-aged ($p = 0.004$) and 47 ms faster ($p = 0.0001$) than older participants, who were on average 25 ms slower ($p = 0.002$) than middle-aged. The RTs during this SRT were not significantly affected by physical exercise habits ($F_{2,78} = 2.54$, $p = 0.114$, $\eta^2 = 0.031$); however, **Table 1** indicates that, on average, exercise cohorts were 10 ms faster than not-exercise cohorts.

ELECTROPHYSIOLOGICAL RESULTS

Figure 1 shows the grand-averaged ERP waveforms at the representative prefrontal (Fp2) and central (Cz) sites, where the pN and BP components were maximal. Waveforms of the three age groups were superimposed and separately displayed for not-exercise and exercise cohorts. The activity over prefrontal sites was modulated by both age and exercise. Vertical dotted lines represent the RTs in each cohort. Within the not-exercise cohorts, the waveform of the young adults was slightly positive before the stimulus onset, whereas those of the middle-aged and older adults showed a slow rising negativity (pN), which began very early in the older cohort. Within the exercise cohorts, the pN of the three age groups was absent (did not differ from baseline). After stimulus onset, another main component over the PFC was detectable: the pP. The peak latency was approximately 196 ms in all of the cohorts independently from physical exercise, whereas pP amplitude increased with age. The BP component was very similar in all of the cohorts over the central derivation (Cz). This component showed the typical slow rising negativity that reflects motor preparation. This negativity reached the peak at approximately 100 ms after the stimulus onset.

Statistical analysis of the pN amplitude showed a main effect of physical exercise ($F_{1,78} = 6.17$, $p = 0.015$, $\eta^2 = 0.073$). The ANOVA did reveal a significant age × physical exercise effect interaction ($F_{2,78} = 3.12$, $p = 0.045$, $\eta^2 = 0.074$). *Post hoc* analysis showed that the participants who exercise did not recruit the PFC to accomplish this SRT regardless of the age group, whereas the older ($-2.23 \pm 0.9\,\mu V$) and middle-aged adults ($-1.86 \pm 0.6\,\mu V$) with a more sedentary lifestyle needed the intervention of the PFC control also in this very easy task. ANOVA on the pP amplitude did not reveal a significant age × physical exercise effect interaction, but there was a main effect of age ($F_{2,78} = 6.59$, $p = 0.002$, $\eta^2 = 0.172$), with larger pP amplitude in older ($6.43 \pm 0.5\,\mu V$) than middle-aged ($4.32 \pm 0.4\,\mu V$) and younger ($4.04 \pm 0.4\,\mu V$) adults. Physical exercise did not significantly affect the pP amplitude ($F_{1,78} = 1.38$, $p > 0.05$, $\eta^2 = 0.016$), even thought the exercise cohorts showed lower amplitude ($4.81 \pm 0.3\,\mu V$) than not-exercise ($5.48 \pm 0.3\,\mu V$) cohorts. The pP latency was not different across cohorts. Statistical analysis of the BP amplitude did not yield significant results. Similarly, analysis on the P1, N2, and P2 peak latency and amplitude were not significant. ANOVA on the P3 latency showed a main effect of age ($F_{2,78} = 8.059$, $p = 0.006$, $\eta^2 = 0.120$), with later P3 in older (417 ± 75.80 ms) than middle-aged (363 ± 77.68 ms) and younger (356 ± 87.65 ms) adults. The physical exercise effect and the interaction were not significant. Not significant effects were found on the P3 amplitude.

Figure 2 shows the scatter plot of the correlations between the RTs and the pN component on Fp2, which was the most representative site, for both exercise and not-exercise cohorts. A significant negative correlation was found in the not-exercise cohort (continuous line in the figure; $R = -0.48$; $p = 0.001$), whereas no correlation was observed in the participants that exercise (dashed line in the figure; $R = -0.17$; $p = 0.277$). Removing the two outliers (filled squares RTs: 332 and 348 ms) from middle-aged and older adults that do not exercise, the correlation was even stronger ($R = -0.55$; $p = 0.001$). No correlation was found between RTs and the BP component parameters.

Table 1 | Mean and standard deviation (Mean ± SD) of the response times (RT) and anticipations (An) for each sub-cohort.

Cohorts	Not-exercise		Exercise	
	RT (ms)	An (%)	RT (ms)	An (%)
Young	211 ± 19	0.31 ± 0.07	200 ± 20	0.21 ± 0.06
Middle-aged	233 ± 38	0.15 ± 0.04	221 ± 32	0.18 ± 0.05
Older	256 ± 31	0.30 ± 0.04	248 ± 30	0.22 ± 0.09

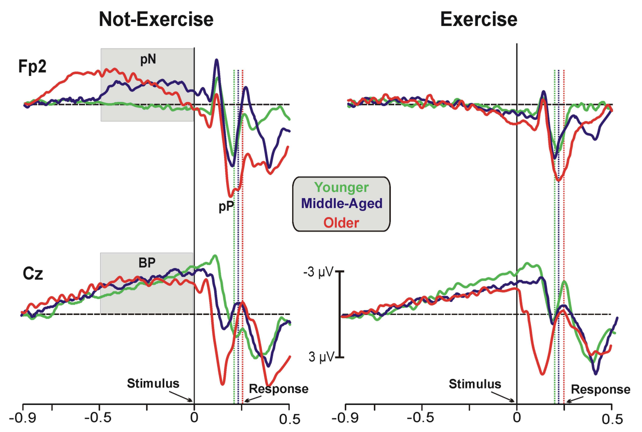


FIGURE 1 | Grand-average ERP waveforms at the prefrontal (Fp2) and central (Cz) electrodes. The age groups are superimposed with different colors (see the legend in the figure) and divided between not-exercise (left) and exercise (right) cohorts. The time zero represents the stimulus appearance; the vertical dotted lines represent the response emissions for each cohort, based on the color of the ERP waveforms.

TOPOGRAPHICAL MAPS

Three-dimensional topographical maps of the grand-averaged data for the pN and the pP components are displayed in **Figure 3**. The maps of younger, middle-aged, and older participants are displayed from the left to the right for not-exercise cohorts (a) and exercise cohorts (b). The top row maps show the negative activity over the PFC in the −500/0 ms time window, which was present only in the older not-exercise adults. The bottom row maps show the topography of the pP when it was maximal. The positivity was very large in older adults, but it was also visible in middle-aged and younger adults that do not exercise. The maps of the physical exercise cohorts show the smaller pP than not-exercise in all of the age groups.

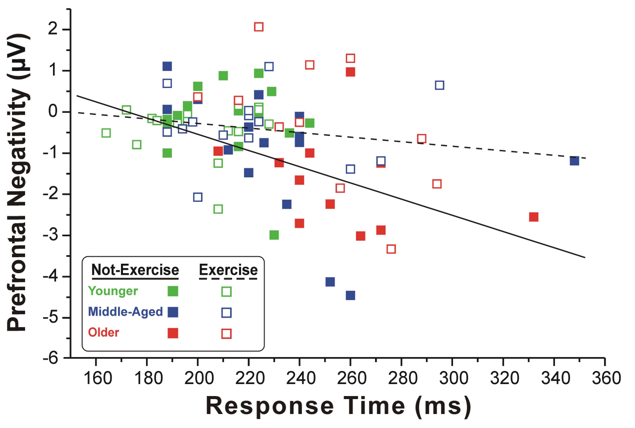


FIGURE 2 | Scatter plot of the correlation between the RTs and pN component in the two cohorts of exercise and not-exercise participants. The dashed line represents the linear fit of the exercise cohort, whereas the solid line refers to the not-exercise cohort. Only the former is significant, showing that larger is the PFC activity and slower is the RT.

DISCUSSION

This study examined the effects of active lifestyle on PFC activity and RTs across ages using a simple response task. The results indicate that: (a) the PFC control is needed also for a very simple task in older adults, while it is not necessary in younger adults, (b) physical exercise could reduce this age-related reliance on additional cognitive control, (c) age-related decline and physical exercise did not affect the activity of pre-motor and visual areas, and (d) as known, parietal areas were affected by age (delay of the P3 component), but not by physical exercise.

Task difficulty is a confounding factor in studies investigating sensorimotor changes with advancing age. Indeed, discrimination increases task difficulty, as indicated by errors increment and, remarkably, much longer RTs than in the SRT in all of the age groups (Berchicci et al., 2012). There is abundant evidence for a decreased efficiency of motor neuron recruitment in elderly that can be compensated by increased involvement of prefrontal cortical resources as a function of task difficulty, because the same task tend to be more demanding for older than younger adults (Stewart et al., 2013). Thus, older adults use compensatory mechanisms in order to maintain a performance level comparable to their younger counterparts (Reuter-Lorenz and Cappell, 2008) except for the slowing of RTs. However, present and past studies (Berchicci et al., 2012) showed a prefrontal hyperactivity also when the discrimination factor was excluded.

A study combining ERP and fMRI measures localized this preparatory prefrontal activity in the inferior frontal gyrus (iFg) of both hemispheres (Di Russo et al., 2013). Other fMRI studies using a SRT confirmed enhanced activity of prefrontal regions in elderly compared with younger participants (Sailer et al., 2000; Davis et al., 2008). Transcranial magnetic stimulation (TMS) studies

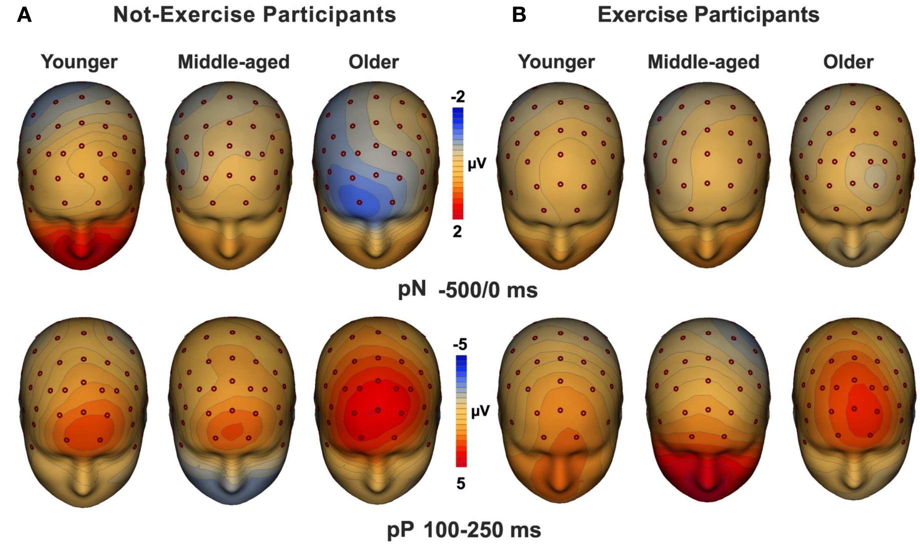


FIGURE 3 | Topographical maps of the pN (up) and pP (bottom) components. The maps for young, middle-aged, and older adults are displayed from the left to the right for not-exercise **(A)** and exercise **(B)** cohorts.

showed that the excitability of corticospinal pathways of older adults is tuned in advance to speed up response generation and enhance the response threshold of the ipsilateral cortex (Levin et al., 2011); this preparatory strategy could increase the readiness for fast and accurate response (Sinclair and Hammond, 2009). In the present study, although the task difficulty was minimal, older adults were slower than younger and middle-aged adults. Note also the remarkable difference in the RTs between young and middle-aged adults, confirming that the slowing of processing is detectable already in middle-aged, compromising activities of daily living (such as driving, crossing the street, grasping an object that is falling down, etc.), social interactions, decision making and learning (Birren and Fisher, 1995). Further, the RTs of the participants that have a more physically active life style tend to be shorter than their less active counterparts (see **Table 1**), although the difference did not reach significant level. Interestingly, in not-exercise cohort, we found a negative correlation between the RTs and pN amplitude, likely mediated by the iFg and reflecting the cognitive preparation of the response. The recruitment of the iFg increases with age, as well as the RTs: the larger the activity in prefrontal structures before the stimulus onset, the slower was the RT. On the other hand, the physical exercise reduced the age-related recruitment of the iFg and this was associated with faster RTs.

Another prefrontal activity characterized by positive polarity (the pP component) started about 100 ms after stimulus onset and reached the peak concomitantly to the key-press in young adults and few milliseconds before the response in older adults. The pP was localized in the anterior Insula and was considered as a process of sensory evidence accumulation up to reaching a threshold for motor response (Di Russo et al., 2013). The pP was larger in older than younger adults, but it was not modified in a significant way by physical exercise, although the topographical maps suggest this trend. Considering this activity as a process of sensory evidence accumulation for response execution, older people, and in part also middle-aged adults, need more time than younger adults to reach the response threshold, with a concomitant slowing in processing speed: this could make the person (i.e., elderly and sedentary) behaviorally slow, according to the literature on age-related slowing of nerve conduction (Macaluso and De Vito, 2004), and would explain the greater engagement of the brain structures involved. This conclusion is in line with other studies, showing a greater insular activation with increased task difficulty (Philiastides and Sajda, 2007) and aging (Williamson et al., 1999).

The activity in pre-motor and visual regions during this SRT was affected neither by age nor by physical exercise. As previously found (e.g., Berchicci et al., 2012), the age-related delay in response emission and categorization (indexed by the parietal P3) was confirmed, but no effects of physical exercise were found. This latter result is only partially in line with previous studies, because Hillman et al. (2004) showed that the P3 latency was modulated by physical exercise. However, they found differences in the P3 latency only between high physically active older adults and the other groups (moderate and low active participants); in the present study there are only two groups, and this methodological difference could explain the lack of differences between exercise and not-exercise cohorts. It is worth noting that one limitation of the present study is the size of the sample, which is relatively small especially for the older cohorts. Indeed, lack of significance on the P3 latency and at behavioural level could also be explained by the small size of the sub-cohorts analysed.

Meta-analyses of physical activity interventions confirmed that the effect of exercise on cognitive functions is both general and specific (Erickson et al., 2013). It is general because different cognitive domains are positively affected by exercise, regardless of the physical activity and fitness assessment used (Liu-Ambrose et al., 2012). It is specific because the executive functions are more improved by exercise interventions than other functions (Colcombe and Kramer, 2003; Hillman et al., 2008). This suggests that brain regions and networks supporting executive functions might be more sensitive to the effects of exercise than other brain areas. Changes in the frontal cortical areas cause the decline of cognitive processes associated with executive and attentional functioning, while other cognitive processes which do not rely on these brain areas, such as implicit memory, verbal ability, and word knowledge, remain relatively stable across lifespan (Ballesteros et al., 2013); these latter functions are also less affected by physical exercise. One possible explanation is that the PFC is more plastic than other brain regions (Van Praag et al., 2005; Kempermann et al., 2010). The ability to mitigate age-related motor and cognitive decline is critical for a successful aging (Seidler et al., 2010) and the physical exercise interventions hold great promise in this regard (Miller et al., 2012). Present findings expand previous studies, demonstrating that the beneficial effects of physical exercise are detectable at brain level also during an extremely simple response task, but were not indeed evident at behavioral level. This kind of task could be a handy tool suitable to investigate the effectiveness of training programs and to verify the outcomes of rehabilitation interventions, because it allows to assess both behavioral and cortical age-related changes with physical exercise. In particular, the behavioral variables are sensitive to sensorimotor age-related decline, but are not completely responsive to the exercise-related changes, which could be well disclosed using ERPs analysis. Furthermore, future studies using self-paced paradigms would also improve our knowledge about the exercise-induced modulation on spontaneous actions which are not activated by external events.

REFERENCES

Baayen, R. H., and Milin, P. (2010). Analyzing reaction times. *Int. J. Psychol. Res. (Medellin)* 3, 12–28.

Ballesteros, S., Mayas, J., and Reales, J. M. (2013). Does physically active lifestyle attenuate decline in all cognitive functions in old age? *Curr. Aging Sci.* 6, 189–198. doi:10.2174/18746098112059990001

Berchicci, M., Lucci, G., and Di Russo, F. (2013). The benefits of physical exercise on the aging brain: the role of the prefrontal cortex. *J. Gerontol. A Biol. Sci. Med. Sci.* 68, 1337–1341. doi:10.1093/gerona/glt094

Berchicci, M., Lucci, G., Pesce, C., Spinelli, D., and Di Russo, F. (2012). Prefrontal hyperactivity in older people during motor planning. *Neuroimage* 62, 1750–1760. doi:10.1016/j.neuroimage.2012.06.031

Birren, J. E., and Fisher, L. M. (1995). Aging and speed behavior: possible consequences for psychological functioning. *Annu. Rev. Psychol.* 46, 329–353. doi:10.1146/annurev.ps.46.020195.001553

Bowles, H. R., Fitzgerald, S. J., Morrow, J. R. Jr., Jackson, A. W., and Blair, S. N. (2004). Construct validity of self-reported historical physical activity. *Am. J. Epidemiol.* 160, 279–286. doi:10.1093/aje/kwh209

Bugg, J. M., and Head, D. (2011). Exercise moderates age-related atrophy of the medial temporal lobe. *Neurobiol. Aging* 32, 506–514. doi:10.1016/j.neurobiolaging.2009.03.008

Chodzko-Zajko, W. J., Proctor, D. N., Singh, M. A. F., Minson, C. T., Nigg, C. R., Salem, G. J., et al. (2009). Exercise and physical activity in older adults. *Med. Sci. Sports Sci.* 41, 1510–1530.

Colcombe, S. J., Erickson, K. I., Raz, N., Webb, A. G., Cohen, N. J., McAuley, E., et al. (2003). Aerobic fitness reduces brain tissue loss in aging humans. *J. Gerontol. A Biol. Sci. Med. Sci.* 58, 176–180. doi:10.1093/gerona/58.2.M176

Colcombe, S. J., Erickson, K. I., Scalf, P. E., Kim, J. S., Prakash, R., McAuley, E., et al. (2006). Aerobic exercise training increases brain volume in aging humans. *J. Gerontol. A Biol. Sci. Med. Sci.* 61, 1166–1170. doi:10.1093/gerona/61.11.1166

Colcombe, S. J., and Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol. Sci.* 13, 125–130. doi:10.1111/1467-9280.t01-1-01430

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

Daffner, K. R., Haring, A. E., Alperin, B. R., Zhuravleva, T. Y., Mott, K. K., and Holcomb, P. J. (2013). The impact of visual acuity on age-related differences in neural markers of early visual processing. *Neuroimage* 67, 127–136. doi:10.1016/j.neuroimage.2012.10.089

Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., and Cabeza, R. (2008). Qué PASA? The posterior-anterior shift in aging. *Cereb. Cortex* 18, 1201–1209. doi:10.1093/cercor/bhm155

Di Russo, F., Lucci, G., Sulpizio, V., Berchicci, M., Spinelli, D., Pitzalis, S., et al. (2013). Spatiotemporal mapping of response inhibition in the prefrontal cortex. *Neuropsychol. Trends* 79.

Erickson, K. I., Gildengers, A. G., and Butters, M. A. (2013). Physical activity and brain plasticity in late adulthood. *Dialogues Clin. Neurosci.* 15, 99–108.

Erickson, K. I., Raji, C. A., Lopez, O. L., Becker, J. T., Rosano, C., Newman, A. B., et al. (2010). Physical activity predicts gray matter volume in late adulthood: the Cardiovascular Health Study. *Neurology* 75, 1415–1422. doi:10.1212/WNL.0b013e3181f88359

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., et al. (2011). Exercise training increases size of hippocampus and improves memory. *Proc. Natl. Acad. Sci. U.S.A.* 108, 3017–3022. doi:10.1073/pnas.1015950108

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

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

Gordon, B. A., Rykhlevskaia, E. I., Brumback, C. R., Lee, Y., Elavsky, S., Konopack, J. F., et al. (2008). Neuroanatomical correlates of aging, cardiopulmonary fitness level, and education. *Psychophysiology* 45, 825–838. doi:10.1111/j.1469-8986.2008.00676.x

Gratton, G., Coles, M. G. H., and Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalogr. Clin. Neurophysiol.* 55, 468–484. doi:10.1016/0013-4694(83)90135-9

Hayes, S. M., Hayes, J. P., Cadden, M., and Verfaellie, M. (2013). A review of cardiorespiratory fitness-related neuroplasticity in the aging brain. *Front. Aging Neurosci.* 5:31. doi:10.3389/fnagi.2013.00031

Hillman, C. H., Belopolsky, A. V., Snook, E. M., Kramer, A. F., and McAuley, E. (2004). Physical activity and executive control: implications for increased cognitive health during older adulthood. *Res. Q. Exerc. Sport* 75, 176–185. doi:10.1080/02701367.2004.10609149

Hillman, C. H., Erickson, K. I., and Kramer, A. F. (2008). Be smart, exercise your heart: exercise effects on brain and cognition. *Nat. Rev. Neurosci.* 9, 58–65. doi:10.1038/nrn2298

Kempermann, G., Fabel, K., Ehninger, D., Babu, H., Leal-Galicia, P., Garthe, A., et al. (2010). Why and how physical activity promotes experience-induced brain plasticity. *Front. Neurosci.* 4:189. doi:10.3389/fnins.2010.00189

Levin, O., Cuypers, K., Netz, Y., Thijs, H., Nuttin, B., Helsen, W. F., et al. (2011). Age-related differences in human corticospinal excitability during simple reaction time. *Neurosci. Lett.* 487, 53–57. doi:10.1016/j.neulet.2010.09.072

Li, L., Gratton, C., Fabiani, M., and Knight, R. T. (2013). Age-related frontoparietal changes during the control of bottom-up and top-down attention: an ERP study. *Neurobiol. Aging* 34, 477–488. doi:10.1016/j.neurobiolaging.2012.02.025

Liu-Ambrose, T., Nagamatsu, L. S., Voss, M. W., Khan, K. M., and Handy, T. C. (2012). Resistance training and functional plasticity of the aging brain: a 12-month randomized controlled trial. *Neurobiol. Aging* 33, 1690–1698. doi:10.1016/j.neurobiolaging.2011.05.010

Macaluso, A., and De Vito, G. (2004). Muscle strength, power and adaptations to resistance training in older people. *Eur. J. Appl. Physiol.* 91, 450–472. doi:10.1007/s00421-003-0991-3

McAuley, E., Szabo, A. N., Mailey, E. L., Erickson, K. I., Voss, M., White, S. M., et al. (2011). Non-exercise estimated cardiorespiratory fitness: associations with brain structure, cognition, and memory complaints in older adults. *Ment. Health Phys. Act.* 4, 5–11. doi:10.1016/j.mhpa.2011.01.001

McGregor, K. M., Zlatar, Z., Kleim, E., Sudhyadhom, A., Bauer, A., Phan, S., et al. (2011). Physical activity and neural correlates of aging: a combined TMS/fMRI study. *Behav. Brain Res.* 222, 158–168. doi:10.1016/j.bbr.2011.03.042

Miller, D. I., Taler, V., Davidson, P. S. R., and Messier, C. (2012). Measuring the impact of exercise on cognitive aging: methodological issues. *Neurobiol. Aging* 33, .e29–.e622. doi:10.1016/j.neurobiolaging.2011.02.020

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 104, 199–206.

Philiastides, M. G., and Sajda, P. (2007). EEG-informed fMRI reveals spatiotemporal characteristics of perceptual decision making. *J. Neurosci.* 27, 13082–13091. doi:10.1523/JNEUROSCI.3540-07.2007

Prakash, R. S., Voss, M. W., Erickson, K. I., Lewis, J., Chaddock, L., Malkowski, E., et al. (2011). Cardiorespiratory fitness and attentional control in the aging brain. *Front. Hum. Neurosci.* **4**:229. doi:10.3389/fnhum.2010.00229

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

Ridderinkhof, K. R., van den Wildenberg, W. P. M., Segalowitz, S. J., and Carter, C. S. (2004). Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. *Brain Cogn.* 56, 129–140. doi:10.1016/j.bandc.2004.09.016

Roggeveen, A. B., Prime, D. J., and Ward, L. M. (2007). Lateralized readiness potentials reveal motor slowing in the aging brain. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 62, 78–84. doi:10.1093/geronb/62.2.P78

Rosano, C., Venkatraman, V. K., Guralnik, J., Newman, A. B., Glynn, N. W., Launer, L., et al. (2010). Psychomotor speed and functional brain MRI 2 years after completing a physical activity treatment. *J. Gerontol. A Biol. Sci. Med. Sci.* 65, 639–647. doi:10.1093/gerona/glq038

Ruscheweyh, R., Willemer, C., Kruger, K., Duning, T., Warnecke, T., Sommer, J., et al. (2011). Physical activity and memory functions: an interventional study. *Neurobiol. Aging* 32, 1304–1319. doi:10.1016/j.neurobiolaging.2009.08.001

Sailer, A., Dichgans, J., and Gerloff, C. (2000). The influence of normal aging on the cortical processing of a simple motor task. *Neurology* 55, 979–985. doi:10.1212/WNL.55.7.979

Salthouse, T. A. (2000). Aging and measures of processing speed. *Biol. Psychol.* 54, 35–54. doi:10.1016/S0301-0511(00)00052-1

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

Shibasaki, H., and Hallett, M. (2006). What is bereitschaftspotential? *Clin. Neurophysiol.* 117, 2341–2356. doi:10.1016/j.clinph.2006.04.025

Sinclair, C., and Hammond, G. R. (2009). Excitatory and inhibitory processes in primary motor cortex during the fore period of a warned reaction time task are unrelated to response expectancy. *Exp. Brain Res.* 194, 103–113. doi:10.1007/s00221-008-1684-2

Smith, J. C., Nielson, K. A., Woodard, J. L., Seidenberg, M., Verber, M. D., Durgerian, S., et al. (2011). Does physical activity influence semantic memory activation in amnestic mild cognitive impairment? *Psychiatry Res.* 193, 60–62. doi:10.1016/j.pscychresns.2011.04.001

Stewart, J. C., Tran, X., and Cramer, S. C. (2013). Age-related variability in performance of a motor action selection task is related to differences in brain function and structure among older adults. *Neuroimage* 14, 1635–1643. doi:10.2217/pgs.13.152

Stothart, G., Tales, A., and Kazanina, N. (2013). Evoked potentials reveal age-related compensatory mechanisms in early visual processing. *Neurobiol. Aging* 34, 1302–1308. doi:10.1016/j.neurobiolaging.2012.08.012

Van Praag, H., Shubert, T., Zhao, C., and Gage, F. H. (2005). Exercise enhances learning and hippocampal neurogenesis in aged mice. *J. Neurosci.* 25, 8680–8685. doi:10.1523/JNEUROSCI.1731-05.2005

Voelcker-Rehage, C., Godde, B., and Staudinger, U. M. (2011). Cardiovascular and coordination training differentially improve cognitive performance and neural processing in older adults. *Front. Hum. Neurosci.* 5:26. doi:10.3389/fnhum.2011.00026

Voss, M. W., Heo, S., Prakash, R. S., Erickson, K. I., Alves, H., Chaddock, L., et al. (2012). The influence of aerobic fitness on cerebral white matter integrity and cognitive function in older adults: results of a one-year exercise intervention. *Hum. Brain Mapp.* 34, 2972–2985. doi:10.1002/hbm.22119

Weinstein, A. M., Voss, M. W., Prakash, R. S., Chaddock, L., Szabo, A., White, S. M., et al. (2012). The association between aerobic fitness and executive function is mediated by prefrontal cortex volume. *Brain Behav. Immun.* 26, 811–819. doi:10.1016/j.bbi.2011.11.008

Wiegand, I., Finke, K., Muller, H. J., and Tollner, T. (2013). Event-related potentials dissociate perceptual from response-related age effects in visual search. *Neurobiol. Aging* 34, 973–985. doi:10.1016/j.neurobiolaging.2012.08.002

Wild-Wall, N., Hohnsbein, J., and Falkenstein, M. (2007). Effects of ageing on cognitive task preparation as reflected by event-related potentials. *Clin. Neurophysiol.* 118, 558–569. doi:10.1016/j.clinph.2006.09.005

Williamson, J. W., McColl, R., Matheus, D., Ginsburg, M., and Mitchell, J. H. (1999). Activation of the insular cortex is affected by the intensity of exercise. *J. Appl. Physiol.* 87, 1213–1219.

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

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

Received: 20 December 2013; accepted: 03 March 2014; published online: 17 March 2014.

Citation: Berchicci M, Lucci G, Perri RL, Spinelli D and Di Russo F (2014) Benefits of physical exercise on basic visuo-motor functions across age. Front. Aging Neurosci. ***6****:48. doi: 10.3389/fnagi.2014.00048*

This article was submitted to the journal Frontiers in Aging Neuroscience.

frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 09 May 2014
doi: 10.3389/fnagi.2014.00086

Aging interferes central control mechanism for eccentric muscle contraction

Wan X. Yao[1]*, Jinqi Li[2], Zhiguo Jiang[3,4], Jia-Hong Gao[5], Crystal G. Franklin[2], Yufei Huang[1], Jack L. Lancaster[2] and Guang H. Yue[3]*

[1] Department of Kinesiology, Health, and Nutrition, College of Education and Human Development, The University of Texas at San Antonio, San Antonio, TX, USA
[2] Research Imaging Institute, The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA
[3] Human Performance and Engineering Laboratory, Kessler Foundation Research Center, West Orange, NJ, USA
[4] Department of Biomedical Engineering, New Jersey Institute of Technology, Newark, NJ, USA
[5] IDG/McGovern Institute for Brain Research, Peking University, Beijing, China

Edited by:
Brian C. Clark, Ohio University, USA

Reviewed by:
Kentaro Oki, Ohio University, USA
Sheng Li, University Texas-Houston, USA

***Correspondence:**
Wan X. Yao, Department of Kinesiology, Health, and Nutrition, College of Education and Human Development, The University of Texas at San Antonio, San Antonio, TX 78249, USA
e-mail: wanxiang.yao@utsa.edu;
Guang H. Yue, Human Performance and Engineering Laboratory, Kessler Foundation Research Center, 1199 Pleasant Valley Way, West Orange, NJ 07052, USA
e-mail: gyue@kesslerfounation.org

Previous studies report greater activation in the cortical motor network in controlling eccentric contraction (EC) than concentric contraction (CC) despite lower muscle activation level associated with EC vs. CC in healthy, young individuals. It is unknown, however, whether elderly people exhibiting increased difficulties in performing EC than CC possess this unique cortical control mechanism for EC movements. To address this question, we examined functional magnetic resonance imaging (fMRI) data acquired during EC and CC of the first dorsal interosseous (FDI) muscle in 11 young (20–32 years) and 9 old (67–73 years) individuals. During the fMRI experiment, all subjects performed 20 CC and 20 EC of the right FDI with the same angular distance and velocity. The major findings from the behavioral and fMRI data analysis were that (1) movement stability was poorer in EC than CC in the old but not the young group; (2) similar to previous electrophysiological and fMRI reports, the EC resulted in significantly stronger activation in the motor control network consisting of primary, secondary and association motor cortices than CC in the young and old groups; (3) the biased stronger activation towards EC was significantly greater in the old than the young group especially in the secondary and association cortices such as supplementary and premotor motor areas and anterior cingulate cortex; and (4) in the primary motor and sensory cortices, the biased activation towards EC was significantly greater in the young than the old group. Greater activation in higher-order cortical fields for controlling EC movement by elderly adults may reflect activities in these regions to compensate for aging-related impairments in the ability to control complex EC movements. Our finding is useful for potentially guiding the development of targeted therapies to counteract age-related movement deficits and to prevent injury.

Keywords: brain activation, concentric contraction, eccentric contraction, fMRI, movement stability

INTRODUCTION

Our daily movements consist of shortening (concentric) and lengthening (eccentric) muscle contractions and it has well been documented that mechanical and neurophysiological characteristics of an eccentric contraction (EC) differ in many ways from those of a concentric contraction (CC) despite the fact that the two types of muscle activities are accomplished by the same muscle(s; See Duchateau and Enoka, 2008 for review). For example, after a period (30 min) of repetitive eccentric and concentric contractions at 50% maximal intensity, only those who performed eccentric exercise showed a significant reduction in mechanical stiffness and an increase in magnetic resonance imaging (MRI) T_2 relaxation time of the working muscle (Sesto et al., 2008). In addition, previous studies (Nardone et al., 1988; Howell et al., 1995) suggest that EC and CC may follow different motor-unit recruitment orders during non-fatigue muscle contractions [However, see Bawa and Jones (1999) and Kossev and Christova (1998) for contradictory findings]. Furthermore, compared to CC, EC had a smaller magnitude of electromyographic (EMG) signal against a given resistance, and depressed corticospinal neuron (Abbruzzese et al., 1994; Sekiguchi et al., 2001) and monosynaptic reflex (Moritani et al., 1988; Abbruzzese et al., 1994) excitability. Moritani et al. (1988) attributed the lower level of EMG for EC to fewer motor units being recruited and a lower discharge rate of the active motor units. Recent studies by Duclay and Martin (2005), Duclay et al. (2011) postulate that the differences in EMG activities between the two types of contractions are a result of differential modulations of motoneuron excitability at supraspinal and/or spinal levels and the modulation of the spinal motoneuron excitability by the supraspinal centers can be contraction-type specific (Duclay et al., 2009). T together, the aforementioned findings indicate a possible different neural control strategy for EC from the one for CC.

In an attempt to delineate potential differential central control mechanisms between voluntary EC and CC, Fang et al. (2001, 2004)conducted two studies to monitor electroencephalography (EEG) signals at submaxial and maximal intensity levels. They found that although the elbow flexor muscle activities (EMG) were lower during EC than CC, the magnitude of movement-related cortical potential (MRCP) derived from the EEG recordings was significantly greater for EC than CC at both intensity levels. They hypothesized that the greater cortical signal (MRCP) for EC might be due to greater effort in planning and programming the lengthening contractions that are more difficult to perform, prone to muscle tissue damage, and may possibly be involved with a different control strategy such as a reversed motor unit recruitment order. More recently, Kwon and Park (2011) examined brain activation patterns by quantifying functional MRI (fMRI) signals in the primary motor cortex, inferior parietal lobe, pre-supplementary area, anterior cingulate cortex, prefrontal cortex, and cerebellum in healthy young adults. They found that except in the right primary motor cortex, the EC resulted in greater fMRI signals than CC in all examined cortical areas. In summary, all three studies that directly monitored brain activities (Fang et al., 2001, 2004; Kwon and Park, 2011) reported a greater activation level in the cortical functional neural network in controlling eccentric than concentric muscle contractions despite a lower muscle activation level associated with EC than CC in healthy young individuals.

In the field of motor control research in aging, literature has consistently demonstrated that elderly individuals exhibit poorer movement stability or force steadiness during EC than CC (Laidlaw et al., 1999, 2002). Although movement stability during EC is also poorer than CC in young individuals, the magnitude of deficit is significantly larger in old than young age groups (Laidlaw et al., 1999, 2002), indicating force/movement control ability for EC is more affected in older adults and this poses greater risks for injury during EC activities. However, central control mechanisms between CC and EC in older adults have never been investigated. Given the expectation that poor control of EC by muscles such as quadriceps during walking downstairs may increase chances of falls, it is important to understand the central nervous systems (CNS) physiological factors contributing to a loss of EC control ability in later life. All findings from previous research seem to support the notion that differential central control mechanisms for EC and CC movements reflect activities of the CNS in dealing with unique strategies in recruiting motor units, altered means in producing force and power, and increased risks of tissue damage during EC. However, it is unknown whether old people exhibiting increased difficulties in performing EC than CC still possess the unique cortical control mechanism for EC like their younger counterparts. The purpose of the study was to address this question. It was hypothesized that the control mechanism (indicated by brain activation pattern) for EC and CC in an aging population would be different from the one adopted by young individuals based on the observation of different neuromuscular characteristics in aging including substantially worsened EC performance compared to young adults (Burnett et al., 2000; Hortobagyi et al., 2001; Laidlaw et al., 2002).

MATERIALS AND METHODS

SUBJECTS

Eleven young (4 males, 23.25 ± 4.09 years old, ranging from 20 to 32 years) and nine old (3 males, 68.72 ± 3.14 years old, ranging from 67 to 73) subjects participated in the study. All subjects were right-handed determined by the Edinburgh inventory (Oldfield, 1971) without neurological, neuromuscular, and musculoskeletal impairments. The study was approved by the Institutional Review Boards of the University of Texas at San Antonio and the University of Texas Health Science Center at San Antonio. Written informed consents were obtained from all the subjects prior to their participation.

TASKS AND EXPERIMENTAL SETUP

The subjects performed either concentric (muscle shortening, index finger moving towards the thumb) or eccentric (muscle lengthening, index finger passively moving away from the thumb) contractions of the first dorsal interosseous (FDI) muscle. Each type of contraction resulted in a 20-degree angular movement from the initial position against a constant load (30% of maximal isometric contraction of the FDI) with a constant speed (∼10 degree/s or ∼0.174 rad/s). After a practicing block of 20 concentric contractions (CC) and 20 eccentric contractions (EC), a total of 20 CC and 20 EC testing trials were performed while functional brain images were taken. During the practice and testing, CC and EC were performed alternately (e.g., CC → EC → CC. . .) while the subjects were lying supine in the MRI chamber with right arm and hand resting prone on a wooden board. The right arm was abducted 10° at shoulder joint with the elbow joint flexed to ∼10°. The wrist, thumb, and the other three (middle, ring, and little) fingers of the right hand were constrained. The right index finger was fastened to a movable lever attached to a load (30% maximal) through a non-elastic cable and a pulley fixed on the wooden board. The subjects performed CC of the right FDI muscle from the initial position (IP) by lifting the weight to the end position (EP) and EC from the EP by "lowering" the weight to the IP. A 10-s rest was provided after each contraction during which the weight was supported by an external mechanism.

MEASUREMENTS AND DATA PROCESSING

Maximum voluntary contraction

Isometric maximum voluntary contraction (MVC) force was measured by requesting the subjects maximally abduct their right index figure against an unmovable force transducer (Sensotec, Columbus, OH, USA). Each subject performed two MVC trials and the trial with the higher peak force was chosen for further analysis. There was a 1-min rest between the two MVC trials.

Movement distance, speed and stability

A custom-built, MRI-compatible goniometer for measuring the angular/movement distance and speed of the finger was attached to the movable lever. The movement data for both CC and EC were trigger-averaged across the 20 trials for each subject with a trigger signal, which was generated when the finger moved 2° from the IP (10% of the movement distance) for CC and 2° from the EP (Fang et al., 2001, 2004). The movement speed was then derived from the trigger-averaged movement data. Standard deviation of the speed was taken to indicate stability of each movement.

Image acquisition

The fMRI procedures (Gao et al., 1996; Yue et al., 2000) are based on detecting changes in brain blood oxygenation – the so-called blood oxygenation level dependent (BOLD) signal changes. Functional images were acquired by a 3-T Magnetom Trio scanner (Siemens, Erlangen, Germany) with a 8-channel RF head coil using a single shot gradient echo EPI pulse sequence (TR = 2 s, TE = 30 ms, flip angle = 90°). The subjects were positioned supine on the sliding board of the scanner with his/her head positioned in the head coil. The head was stabilized by padded restraints. Subjects were told to remain as still as possible during the experiments. Both T1-weighted anatomical images and functional images were collected in the same transverse plane (aligned with a line connecting the anterior and posterior commissures). Each brain volume consisted of 21 slices (5 mm slice thickness and 1 mm inter slice gap) that covered the brain and cerebellum. (The collection of 1 brain volume was referred to as 1 scan hereafter.) The image field of view and matrix for the anatomical images were 256 × 256 mm and 256 × 256, respectively; and those for the function images were 256 × 256 mm and 128 × 128, yielding an in-plane spatial resolution of 1 × 1 mm for anatomical images and 2 × 2 mm for functional images. Pulse sequence for the anatomic image acquisition was TR/TE/flip angle = 2200 ms/2.83 ms/13°, non-selective inversion pulse, TI = 785 ms. All anatomical images were acquired after fMRI scans.

DATA ANALYSIS

The fMRI data were processed using FMRIB Software Library (FSL; Woolrich et al., 2009) and codes written in MATLAB (Math Works, Natick, MA). Image pre-processing procedures included skull stripping, motion correction, temporal filtering, and spatial smoothing with a Gaussian filter of 5 mm at FWHM. A non-linear Gaussian temporal filter was applied using a high-pass threshold of 100 s. Activation maps were generated using the general linear modeling (GLM) in the FEAT toolbox in FSL on a voxel-by-voxel basis and a threshold of $Z = 3.0$ ($p < 0.01$). All echo-planar images were co-registered first to each subject's corresponding anatomical images and then to the Collin brain, a high-resolution template (0.2 mm isotropic resolution) from a population-based, pseudo-Talairach space, before the activated volume and the subsequent group fMRI data were analyzed. A 2-way ANOVA (group × task) was employed to analyze movement parameters (speed and stability) and fMRI (volume passing activation threshold) results in each brain region showing CC- or EC-related activation. To better understand the relative activation level in each cortical area displaying strong activities during CC and EC, we calculated an EC-to-CC activation ratio in each area in each group. Independent t-test was employed to analyze the ratio data between the groups. Statistic significance level was set at $P = 0.05$ for all the analyses.

RESULTS

MVC

The mean MVC forces for the young and old groups were 48.9 ± 3.67 N and 40.3 ± 3.89 N, respectively. The independent t-test revealed a non-significant difference in MVC force between the two groups, $t(18) = 1.597$, $p = 0.128$.

MOVEMENT SPEED AND STABILITY

The mean speeds of EC and CC for the young group were 0.167 ± 0.015 rad/s and 0.174 ± 0.011 rad/s, respectively. For the old group, the speeds of EC and CC were 0.171 ± 0.020 rad/s and 0.170 ± 0.014 rad/s, respectively. The main effects for the age group and movement type analyzed by the 2-way ANOVA were not significant, $F(1,18) = 0.003$, $P = 0.96$, and $F(1,18) = 0.252$, $P = 0.622$, respectively; nor was the interaction between the two factors, $F(1,18) = 0.51$, $P = 0.484$. The standard deviations of the speed, representing movement stability, revealed a significant main effect for movement type but not group, $F(1,18) = 15.65$, $P = 0.001$, and $F(1,18) = 2.572$, $P = 0.126$, respectively. The interaction between the two factors on the movement stability was also significant, $F(1,18) = 5.896$, $P = 0.026$. The *post hoc* paired t-test on the movement stability was not significant between EC and CC for the young group, $t(10) = 1.299$, $P = 0.22$. In contrast; it was significant between the two movement types for the old group, $t(8) = 3.789$, $P < 0.01$ (**Figure 1**).

fMRI

The fMRI results revealed activation of a number of motor control-related cortical fields associated with the CC and EC in the left hemisphere contralateral to the performing (right) hand (see **Table 1** and **Figure 2**). For the young group, the activation was almost exclusively in the left hemisphere with the common threshold ($Z = 3.0$) set for activation detection in both groups. For the old group, the ipsilateral (right hemisphere) activation was stronger than young group but was still at a low level compared to the contralateral side (**Figures 2** and **3**). Since our primary interest was to learn potential brain activation difference between controlling CC and EC and the effect of aging on the differences and since the young group had almost no ipsilateral activation, our analysis was mainly focused on activation of the contralateral hemisphere

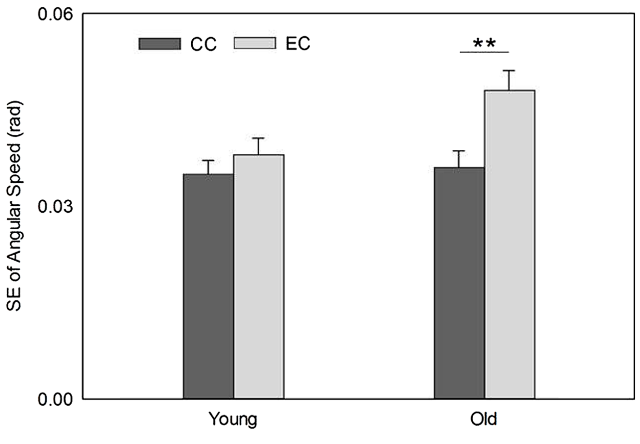


FIGURE 1 | Movement stability was poorer during EC (indicated by greater standard error [SE]) than CC in the old group but no such difference in the young group. $^{**}P < 0.01$.

Table 1 | The volume of brain areas activated during CC and EC.

		CC				EC				Volume (mm^3)	
		x	*y*	*z*	*Z*	*x*	*y*	*z*	*Z*	CC (M/SE)	EC (M/SE)
SMA	Young	3	−12	54	3.34	1	−12	54	4.13	533/86	1229/105
	Old	1	−13	52	3.23	2	−11	55	3.72	422/77	1635/167
ACC	Young	4	−6	44	3.41	−2	−10	43	3.27	301/35	457/64
	Old	−5	−10	42	3.26	4	−8	41	3.54	99/22	438/93
Lt. S1	Young	−40	−24	56	3.81	−28	−28	57	3.69	285/52	711/102
	Old	−41	−22	56	3.91	−27	−28	58	3.65	160/20	175/22
Rt. S1	Young	–	–	–	–	–	–	–	–	–	–
	Old	–	–	–	–	38	−28	56	3.05	–	136/22
Lt. PMC	Young	−24	−17	58	3.16	−21	−18	58	3.39	128/26	182/35
	Old	−23	−15	55	3.12	−22	−14	54	3.34	92/17	228/45
Lt. IPL	Young	−46	−33	52	3.45	−32	−38	52	3.21	249/29	278/31
	Old	−47	−32	52	3.56	−32	−37	53	3.61	196/23	265/62
Rt. IPL	Young	–	–	–	–	–	–	–	–	–	–
	Old	–	–	–	–	40	−43	44	3.41	186/23	192/48
Lt. M1	Young	−38	−23	57	3.46	−35	−22	57	3.42	129/35	748/114
	Old	−38	−21	55	3.12	−37	−26	56	3.70	98/18	443/76
Rt. M1	Young	–	–	–	–	–	–	–	–	–	–
	Old	–	–	–	–	20	−26	56	3.29	–	192/26
Rt. CBM	Young	28	−54	−26	3.06	30	−56	−20	3.32	108/7.6	178/14
	Old	33	−67	−21	3.27	32	−60	−20	3.20	188/36	172/23
Med. CBM	Young	–	–	–	–	–	–	–	–	–	–
	Old	8	−58	−28	3.12	16	−68	−24	3.02	90/12	330/27
Lt. Insula	Young	−47	−22	18	3.24	−40	−28	18	3.30	128/22	776/98
	Old	–	–	–	–	–	–	–	–	–	–
Lt. Sup Tem Gyri	Young	–	–	–	–	−46	−36	−14	3.07	–	784/116
	Old	–	–	–	–	–	–	–	–	–	–
Rt. Sup Tem Gyri	Young	–	–	–	–	−48	−45	−16	3.07	–	224/28
	Old	–	–	–	–	–	–	–	–	–	–
Lt. Putamen	Young	–	–	–	–	–	–	–	–	–	–
	Old	−22	3	−6	3.52	−22	−5	9	3.52	264/30	264/20
Rt. Putamen	Young	–	–	–	–	–	–	–	–	–	–
	Old	23	3	−6	3.17	21	−4	7	3.52	128/30	168/20

although ipsilateral activation results were also briefly reported and discussed.

ANOVA RESULTS

Medial BA6 (SMA)

Activation in the supplementary motor area (SMA) showed a significant main effect for movement type, $F(1,18) = 98.71$, $P < 0.0001$ but not for group, $F(1,18) = 2.07$, $P = 0.17$. There was a significant interaction between the two factors on the fMRI measure, $F(1,18) = 6.10$, $P = 0.024$. *Post hoc* independent *t*-test revealed a significantly greater activation for the elderly than young during EC but not during CC, $t(18) = 2.139$, $P = 0.046$, and $t(18) = 0.241$, $P = 0.81$, respectively (both **Figures 2** and **3** show SMA activation).

BA24 (anterior cingulate cortex)

Activation in the anterior cingulate cortex (ACC) showed a significant main effect for movement type, $F(1,18) = 24.95$, $P < 0.0001$ and a boarder-line significant main effect for group, $F(1,18) = 3.02$, $P = 0.099$. There was a significant interaction between the two factors on the fMRI signal, $F(1,18) = 4.46$, $P = 0.049$. *Post hoc* independent *t*-test demonstrated a significantly

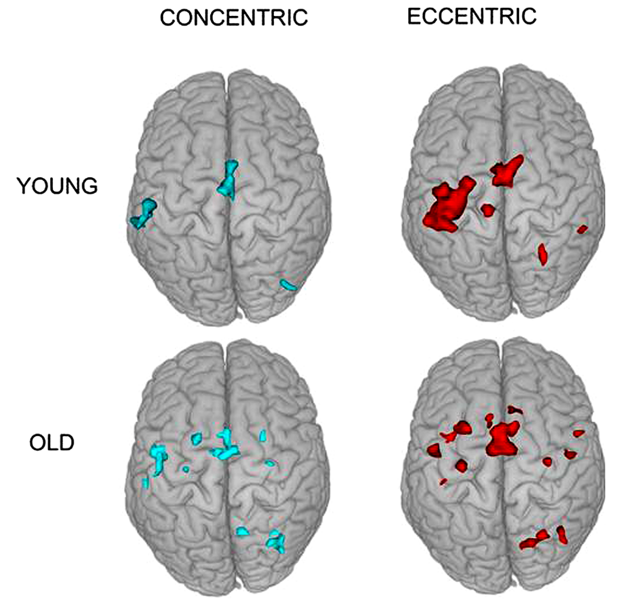


FIGURE 2 | Superior view of group activation during the two types of contractions in the two groups. It is clear that brain activation in young individuals are more localized in the contralateral (left) hemisphere but that in older adults are more distributed in the two hemispheres.

greater activation for the young than elderly during CC but not during EC, $t(18) = 4.94$, $P = 0.0001$, and $t(18) = 0.175$, $P = 0.86$, respectively (**Figure 3** shows ACC activation in both groups).

BA3,1,2 (primary sensory cortex)

Activation in the primary sensory cortex (S1) showed a significant main effect for both group and movement type, $F(1,18) = 22.07$, $P < 0.0001$ and $F(1,18) = 10.49$, $P < 0.005$, respectively. The interaction between the two factors was also significant, $F(1,18) = 11.01$, $P < 0.005$. *Post hoc* paired *t*-tests showed a significantly greater activation during EC than CC in the young group but not in the old group, $t(10) = 3.70$, $P = 0.004$, and $t(8) = 0.196$, $P = 0.849$, respectively.

BA4 (primary motor cortex)

Activation in the primary motor cortex (M1) showed a significant main effect for movement type, $F(1,18) = 53.10$, $P < 0.0001$ but not for group, $F(1,18) = 1.86$, $P = 0.19$; nor the interaction effect, $F(1,18) = 1.71$, $P = 0.21$.

Lateral BA6 (premotor cortex)

The premotor cortex (PMC) activation exhibited a significant main effect for movement type, $F(1,18) = 18.83$, $P < 0.0001$ but not for group, $F(1,18) = 2.05$, $P = 0.17$; nor the effect oFinteraction, $F(1,18) = 0.002$, $P = 0.97$.

BA40 (inferior parietal lobule)

Activation in the inferior parietal lobule (IPL) displayed a significant main effect for movement type, $F(1,18) = 4.74$, $P < 0.05$ but not for group, $F(1,18) = 0.70$, $P = 0.42$; nor the effect oFinteraction, $F(1,18) = 1.59$, $P = 0.22$.

Cerebellum

Activation in the cerebellum (CBM) showed a significant main effect for both movement type, $F(1,18) = 10.57$, $P < 0.01$ and group, $F(1,18) = 58.55$, $P < 0.001$. There was no significant interaction between the two factors on the fMRI signal, $F(1,18) = 2.90$, $P = 0.11$ (detailed activation results in all analyzed brain regions are listed in **Table 1**).

IPSILATERAL ACTIVATION AND ACTIVATION IN YOUNG OR OLD GROUP ONLY

Table 1 shows that ipsilateral (right) hemisphere activation during EC was only observed in S1, IPL and M1 in the elderly group. Only the old group had activation in both the left and right putamen during both CC and EC. Interestingly, only the young group demonstrated activation during EC in the left and right superior temporal gyri (Sup Tem Gyri) and during both CC and EC in the left insular cortex (**Table 1**).

EC-TO-CC RATIO RESULTS

The EC-to-CC activation ratio is a measure of relative cortical activation between the two types of contractions in a given brain region in a given subject or subject group. It is striking to see that all the seven regions in which activation occurred during both CC and EC in both groups showed a higher-than-1 ratio (greater activation during EC). In addition, three out of four higher-order cortical fields (SMA, ACC and PMC [except IPL]) exhibited a significantly higher EC-to-CC ratio in the old than the young group, $t(18) = 4.75$, $P < 0.001$; $t(18) = 4.36$, $P = 0.0001$; $t(18) = 3.96$, $P < 0.001$, respectively. The IPL and CBM although exhibited a higher EC-to-CC ratio in the old than the young group, the differences did not reach statistical significance, $t(18) = 1.15$, $P = 0.263$; $t(18) = 0.41$, $P = 0.687$, respectively. In contrast, the two primary motor and sensory cortices (M1 and S1) showed a reversed pattern: the EC-to-CC activation ratio was higher in the young than the old group, $t(18) = -3.86$, $P < 0.001$, and $t(18) = -5.01$, $P < 0.001$, respectively (**Table 2**).

DISCUSSION

The purpose of this study was to determine if older adults use different central nervous system (CNS) strategies to control concentric (CC, shortening) and eccentric (EC, lengthening) muscle contractions compared with young individuals. Gaining this knowledge is important as CC and EC comprise all of our daily movements. In addition, EC movements are more complex and difficult to control than CC especially for older adults, which poses increased chances of injuries such as falls during walking downstairs (EC of quadriceps) in elders. Knowing the mechanism could potentially help design more targeted therapeutic programs to prevent or reduce chances of such injuries. In general, the activation level (activation volume measured by fMRI) was higher during EC than CC in all cortical regions and cerebellum in both young and old groups, indicating that EC requires greater cortical resources to accomplish the movement. The finding of higher EC-to-CC activation ratio in a number of high-order cortical fields in the old than the young group suggests that the EC is even more difficult to perform in later life compared to early adulthood and this is supported by the poorer

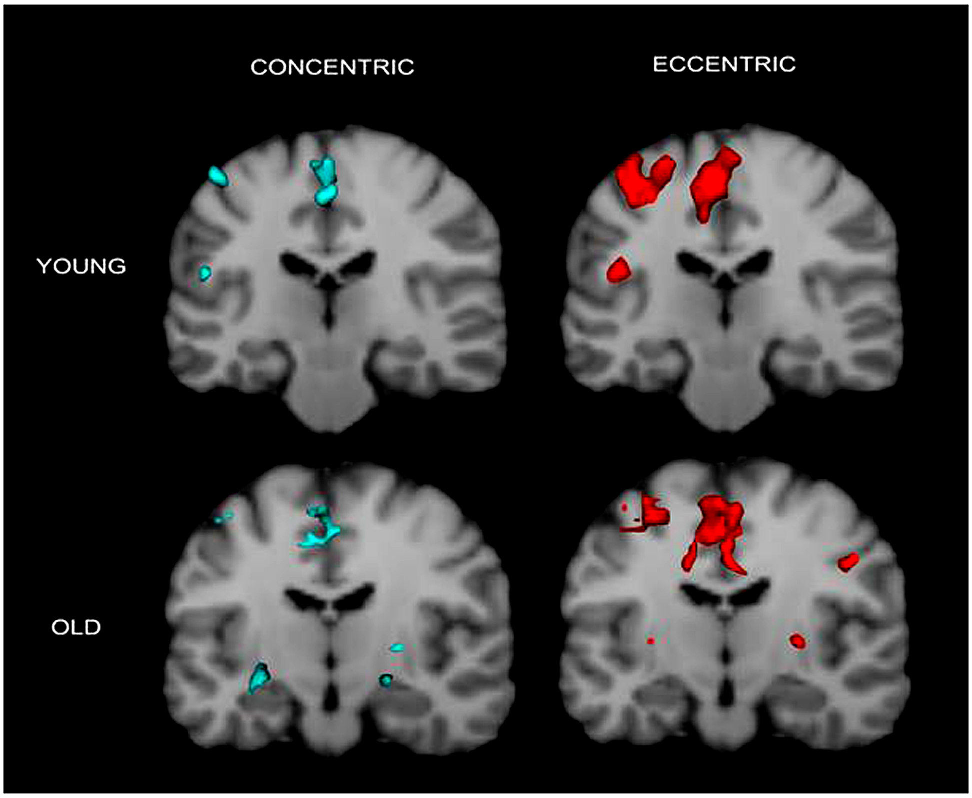


FIGURE 3 | Cronal view of group activation during the two types of contractions in the two groups. Again the figure shows that brain activation in young individuals are more localized in the contralateral (left) hemisphere but that in older adults are more distributed in the two hemispheres. Colored spots in the near-top central regions represent activated voxels in SMA and ACC.

Table 2 | EC-to-CC ratio in the cortical areas and cerebellum in young and old groups.

	SMA* (M/SE)	ACC* (M/SE)	S1* (M/SE)	PMC* (M/SE)	IPL (M/SE)	M1* (M/SE)	CBM (M/SE)
Young	2.31/0.21	1.52/0.23	2.49/0.29	1.42/0.10	1.12/0.04	5.80/0.24	1.65/0.12
Old	3.87/0.25	4.42/0.67	1.09/0.12	2.48/0.25	1.35/0.23	4.52/0.23	1.81/0.27

**t-test showing a significant difference in the ratio between young and old groups.*

movement stability during EC than CC in the old group (Laidlaw et al., 1999).

The general finding of greater cortical activation during EC than CC is consistent with all three previous studies that examined brain signals during the two types of muscle activities (Fang et al., 2001, 2004; Kwon and Park, 2011). The current study provides new evidence supporting the notion that a higher level of complexity of the EC movement poses greater difficulties for one to perform, which demands additional planning, programming, sensorimotor integration and movement execution by the entire central control network. Compared to a CC, an EC is associated with greater movement variability (Laidlaw et al., 1999, 2002), causes more muscle damage especially at a high contraction intensity (Shellock et al., 1991), is possibly accomplished by a different motor unit recruitment strategy (Nardone et al., 1988; Howell et al., 1995), and produces greater force with a given neural signal (EMG; Fang et al., 2001, 2004). These characteristics of EC likely make EC movements more complex and difficult to control compared with CC movements.

Although in principal our fMRI findings are similar to fMRI results of Kwon and Park (2011), there is a substantial contradiction regarding activation in the primary motor cortex (M1). While we observed a larger activation volume in M1 during EC than CC in both groups (see **Tables 1** and **2**), they found that CC was associated with greater M1 activities than EC in young individuals. Kwon and Park (2011) argued that because M1 was traditionally considered to be responsible for movement execution rather than for planning/programming, it was reasonable to see more M1 activity during CC than EC as CC is involved with a higher level of EMG or greater motor unit activities (Fang et al., 2001, 2004). However, recent studies (Lemon, 2008; Kalaska, 2009) report that M1 is not only involved in executing a movement via its direct pathway to motor neuron pool in the spinal cord but also plays an important role in planning the movement. Possible explanations for the different observations regarding M1 activation during EC and CC between the two studies may be attributed to distinct muscles employed for the movements [FDI in our study and wrist extensors in Kwon and Park (2011)] and the load applied to the contractions (we applied 30% maximal load but the other study did not apply an external load). In addition, stronger brain activities found in M1 during EC in our study could be due to M1's engagement in planning the EC movements to deal with its high degree of movement difficulty. Further research is warranted to better delineate the role of M1 in controlling EC and CC contractions. The following discussion focuses on old and young comparisons especially in the secondary and association cortical areas linked to the EC and CC tasks.

Activation during EC vs. CC in secondary and association cortices

A major finding of the current study is that although both young and old groups exhibited greater cortical activation during EC than CC, this biased brain activation towards EC was more prominent in the old than the young group especially in the secondary and association cortices. For example, the old group showed a significantly higher EC-to-CC ratio in SMA, PMC and ACC than the young group (the EC-to-CC activation ratio in the IPL was also higher in the old than the young group but did not reach the significance level; **Table 2**). The ANOVA results revealed significantly stronger EC-than-CC activation in the old than the young groups in the SMA and ACC. The role of these higher-order cortical fields in motor control is well described in a standard neuroscience textbook (Part VI / Movement, Kandel et al., 2013). Among these higher-order control centers, the SMA and ACC demonstrated a significantly higher activation level by old than young adults during EC vs. CC shown by both the ANOVA and EC-to-CC ratio analyses, indicating that the two areas play an exceptionally important role in modulating EC movement in later life. It is well known that the SMA is a secondary motor area (consisted of SMA proper and pre-SMA) and is involved in controlling complex and coordinated motor acts (Rizzolatti and Strick, 2013). Given the complex nature of the EC (compared to CC) and its increased level of difficulty (poorer EC movement stability) in late adulthood, it is not surprising to see augmented activity in the SMA during EC in older adults. It has been known that the cingulate association cortex is a part of limbic system that controls emotion, motivation and other cognitive functions. Within the cingulate cortex, however, there exist distinct motor areas in ACC adjacent to the SMA with connections to the M1 and parietal association cortex, and they (SMA and ACC) are considered as an integrated motor control center (termed as medial premotor area) and shared similar functions in motor control (Rizzolatti and Strick, 2013).

In the sole study that compared brain activation patterns between CC and EC in healthy young individuals using fMRI, activation level in the SMA and ACC was seen to be significantly higher during EC than CC (Kwon and Park, 2011). Our study not only confirms this finding in young adulthood but also demonstrates that the biased activation in the SMA and ACC towards EC was even significantly more prominent in older adults than their younger counterparts. We postulate that the SMA and ACC play a special role in modulating EC performance in aging, perhaps by compensating for age-related degenerative adaptations in the motor control network that might have specially deteriorated the network's ability to control more complex EC movements. The PMC (lateral BA6 consisted of dorsal and ventral PMC, a secondary motor area) showed a significantly higher EC-to-CC activation ratio and the IPL (part of parietal association cortex) also exhibited a clearly higher EC-to-CC ratio (**Table 2**). The motor function of PMC (Rizzolatti and Kalaska, 2013; Rizzolatti and Strick, 2013) and IPL (Fogassi and Luppino, 2005) has been well described and the role of their prominent activation during EC during late life may be similar to that played by the SMA and ACC.

Cerebellum activation during EC vs. CC

The 2-way ANOVA analysis revealed significant main effects for both movement type and group and no significant effect for interaction which means that the cerebellar activation was greater during EC than CC for both groups and the old group exhibited a higher level of cerebellar activation than the young group. Kwon and Park (2011) reported similar results in young adults. They attributed it (greater cerebellar activity during EC) to the performance of EC movement as early stage learning of the motor skill by their subjects. Although we cannot exclude this possibility (i.e., early learning effect on cerebellar activation), the practice provided before the fMRI scan in our study diminished this likelihood. Thus, we attribute the stronger cerebellar activities observed in EC than CC to its role in dealing with a higher degree of difficulties associated with performing EC than CC movements. The higher activation level in the cerebellum in the old than the young group during both EC and CC movements reflects an increased functional load in the cerebellum for controlling the two types of movements. Previous studies have indicated that the cerebellum is involved in cognitive processes for problem solving (Kim et al., 1994), preparation of motor actions (Coffman et al., 2011), and balance control and movement error correction (Lisberger and Thach, 2013).

Activation in M1 and S1 during CC and EC

Unlike the secondary and association motor cortices that showed a higher EC-to-CC activation ratio in late adulthood, the primary motor and sensory cortices (M1, S1), however, exhibited a significantly higher such ratio in young than old individuals. It should be noted that the MVC force, movement speed, and movement stability between the young and the old groups did not differ significantly and thus, cannot explain the biased EC-to-CC activation in the M1 and S1in the young group. Instead, while older individuals may need to rely more on the secondary and association cortices to deal with more complex EC movements, the young adults are apt to use the primary motor and sensory areas to handle the more difficult EC. However, the validity of this age-specific brain site for motor planning needs to be further tested by future studies.

Ipsilateral activation and activation in young or old group only

The above discussion was focused on brain activation in the contralateral (to the performing hand) hemisphere. Besides the major findings in the contralateral side, the fMRI data have shown that ipsilateral (right) hemisphere activation was observed only during

EC in M1, S1 and IPL in the elderly group. In addition, only the elderly group had activation in both the left and right putamen in the basal ganglia during both CC and EC. These observations have never been made before and we do not yet know the appropriate explanations. A simple guess would be that these regions played a role in compensating for the worsened ability in the aging control network to manipulate EC movements as these ipsilateral activities were not seen in the young group. Many studies reported increased ipsilateral motor cortex and other region activation and reduced activation laterality during motor performance in healthy aging (e.g., Naccarato et al., 2006). Regarding the observation of bilateral activation in putamen during both CC and EC in the old group, we believe it might be a reflection of heavier use of basal ganglia-cerebellum-cerebral cortex motor control loop during voluntary motor action by older adults. Another interesting finding was that only the young group showed activation during EC in the left and right superior temporal gyri and during both CC and EC in the left insular cortex (**Table 1**). Little is known about the exact role of the temporal and insular cortices in control of CC and EC. In general, the superior temporal cortex is related to perceiving motion (Saygin, 2007) and visuomotor integration (Tanaka et al., 1986). Considering that our subjects performed the motor tasks with visual feedback, it is reasonable to expect activation in the superior temporal cortex. It is unclear though why only the young group showed the activity during the EC action. For activation in the insular cortex, it has been reported that the posterior part of the anterior insular cortex is dedicated for motor control of both upper and lower extremity movements (Mutschler et al., 2009). Again, it is yet to be determined the reason(s) underlying the lack of activation in the insular cortex in late life. Perhaps aging-related structural degeneration such as grey and white matter atrophy in these cortical regions prevented adequate activities in these specific areas.

SUMMARY

Both young and old individuals demonstrated stronger fMRI-measured activation during EC than CC in almost all cortical areas examined and this biased activation towards EC was more prominent in the old than young groups. Furthermore, all the secondary and association cortices and cerebellum engaged in the two types of muscle contractions exhibited higher EC- than-CC activation in old than young individuals especially in the supplementary motor area and anterior cingulate cortex. On the contrary, the two primary cortices (M1 and S1) showed stronger biased EC activation in young than old age groups. Greater activation in higher-order cortical fields for controlling EC movement in late life may reflect activities in these regions to compensate for impaired ability (perhaps in the primary sensorimotor cortices) to control complex EC movements. All these results associated with aging-related control of EC and CC movements are new and the special roles of the identified cortical fields in modulating EC in late life, especially those at higher levels of the control network justify further delineation by future studies.

ACKNOWLEDGMENT

The current study was partially supported by a grant from San Antonio Life Science Institutes. The authors are grateful to the reviewers' insightful suggestions and comments on this paper. We would also like to thank Dr. Michelle Stevenson and Ms. Deborah Silliman Wolfe for their useful comments and assistance in the preparation of the manuscript. This study was supported in part by San Antonio Life Science Institutes.

REFERENCES

Abbruzzese, G., Morena, M., Spadavecchia, L., and Schieppati, M. (1994). Response of arm flexor muscles to magnetic and electrical brain stimulation during shortening and lengthening tasks in man. *J. Physiol.* 481, 499–507.

Bawa, P., and Jones, K. E. (1999). Do lengthening contractions represent a case of reversal in recruitment order? *Prog. Brain Res.* 123, 215–220. doi: 10.1016/S0079-6123(08)62858-7

Burnett, R. A., Laidlaw, D. H., and Enoka, R. M. (2000). Coactivation of the antagonist muscle does not covary with steadiness in old adults. *J. Appl. Physiol.* 89, 61–71.

Coffman, K. A., Dum, R. P., and Strick, P. L. (2011). Cerebellar vermis is a target of projections from the motor areas in the cerebral cortex. *Proc. Natl. Acad. Sci. U.S.A.* 108, 16068–16073. doi: 10.1073/pnas.1107904108

Duchateau, J., and Enoka, R. M. (2008). Neural control of shortening and lengthening contractions: influence of task constraints. *J. Physiol.* 586, 5853–5864. doi: 10.1113/jphysiol.2008.160747

Duclay, J., and Martin, A. (2005). Evoked H-reflex and V-wave responses during maximal isometric, concentric, and eccentric muscle contraction. *J. Neurophysiol.* 94, 3555–3562. doi: 10.1152/jn.00348.2005

Duclay, J., Pasquet, B., Martin, A., and Duchateau, J. (2011). Specific modulation of corticospinal and spinal excitabilities during maximal voluntary isometric, shortening and lengthening contractions in synergist muscles. *J. Physiol.* 589, 2901–2916. doi: 10.1113/jphysiol.2011.207472

Duclay, J., Robbe, A., Pousson, M., and Martin, A. (2009). Effect of angular velocity on soleus and medial gastrocnemius H-reflex during maximal concentric and eccentric muscle contraction. *J. Electromyogr. Kinesiol.* 19, 948–956. doi: 10.1016/j.jelekin.2008.04.011

Fang, Y., Siemionow, V., Sahgal, V., Xiong, F., and Yue, G. H. (2001). Greater movement-related cortical potential during human eccentric versus concentric muscle contractions. *J. Neurophysiol.* 86, 1764–1772.

Fang, Y., Siemionow, V., Sahgal, V., Xiong, F., and Yue, G. H. (2004). Distinct brain activation patterns for human maximal voluntary eccentric and concentric muscle actions. *Brain Res.* 1023, 200–212. doi: 10.1016/j.brainres.2004.07.035

Fogassi, L., and Luppino, G. (2005). Motor functions of the parietal lobe. *Curr. Opin. Neurobiol.* 15, 626–631. doi: 10.1016/j.conb.2005.10.015

Gao, J. H., Parsons, L., Bower, J., Xiong, J., Li, J., and Fox, P. (1996). Cerebellum implicated in sensory acquisition and discrimination rather than motor control. *Science* 272, 545–547. doi: 10.1126/science.272.5261.545

Hortobagyi, T., Tunnel, D., Moody, J., Beam, S., and Devita, P. (2001). Low- or high-intensity strength training partially restores impaired quadriceps force accuracy and steadiness in aged adults. *J. Gerontol. A Biol. Sci. Med. Sci.* 56, B38–B47. doi: 10.1093/gerona/56.1.B38

Howell, J. N., Fuglevand, A. J., Walsh, M. L., and Bigland-Richie, B. (1995). Motor unit activity during isometric and concentric-eccentric contractions of the human first dorsal interosseus muscle. *J. Neurophysiol.* 74, 901–904.

Kalaska, J. F. (2009). From intention to action: motor cortex and the control of reaching movements. *Adv. Exp. Med. Biol.* 629, 139–178. doi: 10.1007/978-0-387-77064-2_8

Kandel, E. R., Schwartz, J. H., Jessell, T. M., Siegelbaum, S. A., and Hudspeth, A. J. (2013). *Principles of Neural Science*, 5th Edn. New York: McGraw-Hill.

Kim, S., Ugurbil, K., and Strick, P. (1994). Activation of a cerebellar output nucleus during cognitive processing. *Science* 265, 949–951. doi: 10.1126/science.8052851

Kossev, A., and Christova, P. (1998). Discharge pattern of human motor units during dynamic concentric and eccentric contractions. *Electroencephalogr. Clin. Neurophysiol.* 109, 245–255. doi: 10.1016/S0924-980X(98)00012-5

Kwon, Y. H., and Park, J. W. (2011). Different cortical activation patterns during voluntary eccentric and concentric muscle contractions: an fMRI study. *Neurorehabilitation* 29, 253–259. doi: 10.3233/NRE-2011-0701

Laidlaw, D. H., Hunter, S. K., and Enoka, R. M. (2002). Nonuniform activation of the agonist muscle does not covary with index finger acceleration in old adults. *J. Appl. Physiol.* 93, 1400–1410. doi: 10.1152/japplphysiol.00391.2002

Laidlaw, D. H., Kornatz, K. W., Keen, D. A., Suzuki, S., and Enoka, R. M. (1999). Strength training improves the steadiness of slow lengthening contractions performed by old adults. *J. Appl. Physiol.* 87, 1786–1795.

Lemon, R. N. (2008). Descending pathways in motor control. *Annu. Rev. Neurosci.* 31, 195–218. doi: 10.1146/annurev.neuro.31.060407.125547

Lisberger, S. G., and Thach, W. T. (2013). "The cerebellum," in *Principles of Neural Science*, 5th Edn, eds E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum and A. J. Hudspeth (New York: McGraw-Hill).

Moritani, T., Muramatsu, S., and Muro, M. (1988). Activity of motor units during concentric and eccentric contractions. *Am. J. Phys. Med.* 66, 338–350. doi: 10.1097/00002060-198812000-00003

Mutschler, I., Wieckhorst, B., Kowalevski, S., Derix, J., Wentlandt, J., Schulze-Bonhage, A., et al. (2009). Functional organization of the human anterior insular cortex. *Neurosci. Lett.* 457, 66–70. doi: 10.1016/j.neulet.2009.03.101

Naccarato, M., Calautti, C., Jones, P. S., Day, D. J., Carpenter, T. A., and Baron, J. C. (2006). Does healthy aging affect the hemispheric activation balance during paced index-to-thumb opposition task? An fMRI study. *Neuroimage* 32, 1250–1256. doi: 10.1016/j.neuroimage.2006.05.003

Nardone, A., Romano, C., and Schieppati, M. (1988). Selective recruitment of high-threshold human motor units during voluntary isotonic lengthening of active muscles. *J. Physiol. (Lond.)* 409, 451–471.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 335–365. doi: 10.1016/0028-3932(71)90067-4

Rizzolatti, G., and Kalaska, J. F. (2013). "Voluntary movement: the parietal and premotor cortex," in *Principles of Neural Science*, 5th Edn, eds E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum, and A. J. Hudspeth (New York: McGraw-Hill).

Rizzolatti, G., and Strick, P. L. (2013). "Cognitive function of the premotor systems," in *Principles of Neural Science,* 5th Edn, eds E. R. Kandel, J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum, and A. J. Hudspeth (New York: McGraw-Hill).

Saygin, A. P. (2007). Superior temporal and premotor brain areas necessary for biological motion perception. *Brain* 130, 2452–2461. doi: 10.1093/brain/awm162

Sekiguchi, H., Kimura, T., Yamanaka, K., and Nakazawa, K. (2001). Lower excitability of the corticospinal tract to transcranial magnetic stimulation during lengthening contractions in human elbow flexors. *Neurosci. Lett.* 312, 83–86. doi: 10.1016/S0304-3940(01)02197-8

Sesto, M. E., Chourasia, A. O., Block, W. F., and Radwin, R. G. (2008). Mechanical and magnetic resonance imaging changes following eccentric or concentric exertions. *Clin. Biomech.* 23, 961–968. doi: 10.1016/j.clinbiomech.2008.03.068

Shellock, F. G., Fukunaga, T., Mink, J. H., and Edgerton, V. R. (1991). Exertional muscle injury: evaluation of concentric versus eccentric actions with serial MR imaging. *Radiology* 179, 659–664.

Tanaka, K., Hikosaka, K., Saito, H., Yukie, M., Fukada, Y., and Iwai, E. (1986). Analysis of local and wide-field movements in the superior temporal visual areas of the macaque monkey. *J. Neurosci.* 6, 134–144.

Woolrich, M. W., Beckmann, C. F., Nichols, T. E., and Smith, S. M. (2009). *Statistical Analysis of fMRI Data, Neuromethods.* New York: Humana Press.

Yue, G. H., Liu, J. Z., Siemionow, V., Ranganathan, V. K., Ng, T. C., and Sahgal, V. (2000). Brain activation during human finger extension and flexion movements. *Brain Res.* 856, 291–300. doi: 10.1016/S0006-8993(99)02385-9

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

Received: 15 March 2014; accepted: 23 April 2014; published online: 09 May 2014.
Citation: Yao WX, Li J, Jiang Z, Gao J-H, Franklin CG, Huang Y, Lancaster JL and Yue GH (2014) Aging interferes central control mechanism for eccentric muscle contraction. Front. Aging Neurosci. ***6****:86. doi: 10.3389/fnagi.2014.00086*
This article was submitted to the journal Frontiers in Aging Neuroscience.

frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 22 May 2014
doi: 10.3389/fnagi.2014.00097

Motor variability during sustained contractions increases with cognitive demand in older adults

Marnie L. Vanden Noven*[1], *Hugo M. Pereira*[1], *Tejin Yoon*[1], *Alyssa A. Stevens*[1], *Kristy A. Nielson*[2] and *Sandra K. Hunter*[1]

[1] *Exercise Science Program, Department of Physical Therapy, Marquette University, Milwaukee, WI, USA*
[2] *Department of Psychology, Marquette University, Milwaukee, WI, USA*

Edited by:
Brian C. Clark, Ohio University, USA

Reviewed by:
S. Lee Hong, Ohio University, USA
Shinichi Amano, Ohio University, USA

****Correspondence:***
Sandra K. Hunter, Exercise Science Program, Department of Physical Therapy, Marquette University, PO Box 1881, Milwaukee, WI, USA
e-mail: Sandra.Hunter@marquette.edu

To expose cortical involvement in age-related changes in motor performance, we compared steadiness (force fluctuations) and fatigability of submaximal isometric contractions with the ankle dorsiflexor muscles in older and young adults and with varying levels of cognitive demand imposed. Sixteen young (20.4 ± 2.1 year: 8 men, 9 women) and 17 older adults (68.8 ± 4.4 years: 9 men, 8 women) attended three sessions and performed a 40 s isometric contraction at 5% maximal voluntary contraction (MVC) force followed by an isometric contraction at 30% MVC until task failure. The cognitive demand required during the submaximal contractions in each session differed as follows: (1) *high-cognitive demand* session where difficult mental math was imposed (counting backward by 13 from a 4-digit number); (2) *low-cognitive demand* session which involved simple mental math (counting backward by 1); and (3) *control session* with no mental math. Anxiety was elevated during the high-cognitive demand session compared with other sessions for both age groups but more so for the older adults than young adults ($p < 0.05$). Older adults had larger force fluctuations than young adults during: (1) the 5% MVC task as cognitive demand increased ($p = 0.007$), and (2) the fatiguing contraction for all sessions ($p = 0.002$). Time to task failure did not differ between sessions or age groups ($p > 0.05$), but the variability between sessions (standard deviation of three sessions) was greater for older adults than young (2.02 ± 1.05 vs. 1.25 ± 0.51 min, $p < 0.05$). Thus, variability in lower limb motor performance for low- and moderate-force isometric tasks increased with age and was exacerbated when cognitive demand was imposed, and may be related to modulation of synergist and antagonist muscles and an altered neural strategy with age originating from central sources. These data have significant implications for cognitively demanding low-force motor tasks that are relevant to functional and ergonomic in an aging workforce.

Keywords: arousal, ankle dorsiflexor muscles, muscle fatigue, age, motor variability, steadiness, aging, stress

INTRODUCTION

Aging results in marked declines in both motor performance and cognitive function. For example, older adults are weaker and less steady (i.e., they exhibit greater fluctuations in force around a target force) than young adults (Enoka et al., 2003; Hunter et al., 2008). Decreased steadiness with age is greatest during low-intensity isometric contractions in lower and upper extremity muscles (Enoka et al., 2003; Tracy, 2007; Marmon et al., 2011) probably due to age-related changes in inputs to the motoneurone pool (Barry et al., 2007). Cognitive impairment can also be marked but subtle and often subclinical in early stages of cognitive dysfunction (Chen et al., 2001; Morris et al., 2001; Aine et al., 2011); it is often observed as degradation in short-term memory and executive function resulting in a decreased ability to perform daily tasks that are dependent upon memory-related abilities (Artero et al., 2001; Morris et al., 2001; Farias et al., 2012), including planning and decision-making in lower limb activities such as gait (Yogev-Seligmann et al., 2008). Age-related declines in motor and cognitive function are usually studied separately but are often performed simultaneously in daily tasks. The current study assessed motor function with a focus on steadiness and muscle fatigability in young and older adults while they were presented with low and high levels of cognitive demand.

In young adults, cognitive performance declines and force fluctuations increase when a cognitive task is imposed (reaction time) during sustained isometric tasks with hand muscles (Lorist et al., 2002; Zijdewind et al., 2006); however, force fluctuations were affected more during the isometric fatiguing contractions than during a 5% maximal voluntary contraction (MVC) non-fatiguing contraction (Lorist et al., 2002). We also previously found that steadiness of the elbow flexor muscles declined (increased force fluctuations) and time to failure of a sustained 20% MVC submaximal task was reduced (increased fatigability) in young adults when simultaneously performing a demanding cognitive task (‘high-cognitive demand’) that increased anxiety (counting backwards by 13). Accordingly, heart rate and blood pressure, which are indices of increased sympathetic activity with arousal (Kajantie and Phillips, 2006), were elevated during the “high-cognitive demand" session compared with control (Yoon et al., 2009; Keller-Ross et al., 2014a). Individuals who were weaker (primarily the women) showed the largest decrement in time to task failure when the stressful cognitive task was imposed during the fatiguing contraction (Yoon et al., 2009; Keller-Ross et al., 2014a). Older adults are typically weaker than young adults, and older women weaker than older men for upper and lower limb muscles (Galganski et al., 1993; Laidlaw et al., 2000; Tracy and Enoka, 2002), possibly increasing susceptibility to increased fatigability when a cognitive task is imposed. However, it is not known whether fatigability with increased cognitive demand is exacerbated with advanced age. Furthermore, the effects of increased cognitive demand on lower limb fatigability and steadiness in young or older adults are not known.

Initial evidence would suggest that age-related decrements in motor function of the upper limb (e.g., reduced steadiness) become larger with greater cortical involvement of non-motor centers (Voelcker-Rehage et al., 2006; Voelcker-Rehage and Alberts, 2007; Fraser et al., 2010) and may increase between- and within-participant variability particularly in older adults (Enoka et al., 2003; Sosnoff and Newell, 2006). Older adults display greater between- and within-participant variability than young in activation of supraspinal centers during maximal contractions with the upper limb (Hunter et al., 2008) indicating that variability within cortical motor areas is larger with advanced age. Increased cognitive involvement, particularly with tasks that tax attentional resources and that require the use of short-term memory or executive function, may contribute further to age-related variability in motor performance for older adults during functional tasks (Voelcker-Rehage et al., 2006; Yogev-Seligmann et al., 2008; Sommervoll et al., 2011).

Increased cognitive involvement however, can increase anxiety and stress levels (e.g., Noteboom et al., 2001), which may further decrease steadiness of upper limb muscles in older adults compared with young. Force fluctuations, for example, increased for older adults more than young when exposed to a noxious stressor (unpredictable electrical stimulation to the hand) prior to performing the pinch grip task (Christou et al., 2004). The increased force fluctuations therefore, could be due to age-related changes in monoaminergic drive modulating inputs to the motoneurone pool (Barry et al., 2007). A novel aspect of this current study is that we varied the level of cognitive demand administered simultaneously during motor task of the lower limbs to determine its influence on lower limb fatigability and steadiness and any accompanying changes in anxiety and stress.

The purpose of this study was to compare both the amplitude of force fluctuations (steadiness) and time to task failure (fatigability) for low-to-moderate-force isometric contractions in the presence and absence of varying levels of cognitive demand in young and older adults. Participants were exposed to two different levels of cognitive load, low- and high-cognitive demand while performing a motor task with the ankle dorsiflexor muscles, which are muscles that play a functional role controlling the position of the foot during walking and while maintaining balance. We *hypothesized* that older adults would show greater reductions in time to task failure and greater force fluctuations than young as cognitive demand increased. We also compared variability of fatigability between and within young and older adults with increased cognitive demand. We *hypothesized* that as cognitive demand increased, older adults would exhibit both greater between- and within-participant variability in fatigability. To understand the perceived and physiological arousal responses with the varying levels of cognitive demand in young and older adults, during each session we quantified perceived levels of exertion, stress and anxiety as well as heart rate and blood pressure.

MATERIALS AND METHODS

Sixteen young adults (8 men, 8 women; 18–24 years) and 17 older adults (9 men, 8 women; 62–79 years) participated in the study (see **Table 1** for physical characteristics). All participants were healthy with no known neurological or cardiovascular diseases, had controlled blood pressure and were naïve to the protocol. Six of the older adults were on medication to control blood pressure. Both young and older adults had low-to-moderate levels of anxiety (trait) according to the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970) and reported no history of current mental or psychological pathology, including anxiety or depressive disorders. Participants were right-leg dominant (0.81 ± 0.40 vs. 0.80 ± 0.54 for young and older adults, respectively, with a ratio of 1 indicating complete dominance of the right leg) (Oldfield, 1971). The physical activity level for each participant was assessed with a questionnaire that estimated the relative kilocalorie expenditure of energy per week (Kriska and Bennett, 1992). Prior to participation, each participant provided informed consent, and the protocol was approved by the Institutional Review Board at Marquette University.

Each participant reported to the laboratory on four occasions to perform a protocol that involved a fatiguing contraction with the left ankle dorsiflexor muscles: once for a familiarization session and three experimental sessions (*control*, *low-cognitive demand*, and *high-cognitive demand*), with each experimental session being at least 5 days apart. During the low-cognitive demand and high-cognitive demand sessions, each participant performed either a simple mental math task (low-cognitive demand session) or difficult mental math task (high-cognitive demand session) at rest, and also while performing isometric contractions at 5% maximum voluntary contraction (MVC) force (40 s duration) and a 30% MVC for as long as possible until task failure (**Figure 1**). During the control session, each participant performed the motor tasks without performing any mental math. Session order was counterbalanced among participants within each age group.

MECHANICAL RECORDING OF FORCE

Each participant was seated upright in an adjustable chair (Biodex Medical Systems, NY, USA) with the hips and knees at 90° of flexion. The setup is similar to that described elsewhere (Griffith et al., 2010). In brief, the left foot rested on a footplate in a custom made dynamometer to measure forces of the lower leg, with the ankle in a neutral position (0° dorsiflexion). The foot was secured to the footplate via a strap placed over the anterior aspect of the ankle and another strap placed 1–2 cm proximal to the metatarsophalangeal joint. Isometric force of the dorsiflexor muscles was recorded using a force transducer (Transducer Techniques, Temecula, CA, USA) and recorded online at 500 Hz using a Power 1401 analog-to-digital (A/D) converter and Spike2 software

Table 1 | Demographic and physical characteristics and age group means (±SD) for control, low-cognitive demand (low-CD), and high-cognitive demand (high-CD) sessions.

Variable	Session	Young	Older
Number of participants		16	17
Age (years)		20.4 ± 2.1	68.8 ± 4.4[a]
Height (cm)		168.9 ± 23.6	167.5 ± 11.3
Women age (years)		19.3 ± 1.5	68.4 ± 3.6[a]
Men age (years)		21.5 ± 2.0	69.2 ± 4.9[a]
Weight (kg)		74.4 ± 27.9	77.8 ± 15.2
Physical activity (METS hours per week)		59.5 ± 38.3	22.0 ± 21.8[a]
Baseline trait STAI scores		36.4 ± 7	34.8 ± 7.3
Baseline state STAI scores		26.0 ± 6.7	26.2 ± 5.3
MVC torque (Nm)	Control	22.4 ± 6.9	19.1 ± 6.6
	Low-CD	22.2 ± 6.6	18.3 ± 5.8
	High-CD	22.8 ± 7.7	18.7 ± 6.3
	Total	22.5 ± 7.0	18.7 ± 6.1[a]
MVC torque recovery (% of initial)	Control	96.3 ± 7.4	97.9 ± 6.8
	Low-CD	95.4 ± 3.7	93.2 ± 8.5
	High-CD	94.8 ± 3.9	94.7 ± 5.5
	Total	96.2 ± 7.4	97.6 ± 6.5
Time to task failure (min)	Control	6.1 ± 2.2	8.0 ± 3.2
	Low-CD	6.1 ± 2.0	7.6 ± 3.1
	High-CD	7.1 ± 2.5	8.7 ± 3.8
	Total	6.4 ± 2.2	8.1 ± 3.4
30% MVC CV of torque (%)	Control	4.5 ± 1.2	6.0 ± 3.0
	Low-CD	4.5 ± 0.8	7.2 ± 4.1
	High-CD	4.6 ± 2.7	6.8 ± 2.3
	Total	4.5 ± 1.0	6.7 ± 3.2[a]
TA EMG[a] (% MVC)	Control	23.5 ± 5.6	29.1 ± 6.0
	Low-CD	23.5 ± 6.2	27.2 ± 4.7
	High-CD	24.1 ± 4.8	28.7 ± 8.4
	Total	23.7 ± 4.3	28.3 ± 5.9[a]
TA EMG bursting activity (bursts per min)	Control	10.3 ± 9.7	5.7 ± 5.7
	Low-CD	11.5 ± 10.6	9.0 ± 9.2
	High-CD	9.4 ± 9.6	7.7 ± 7.6
	Total	10.4 ± 9.8	7.4 ± 7.6
Soleus EMG (% MVC)	Control	20.3 ± 9.6	28.4 ± 14.2
	Low-CD	19.2 ± 5.3	28.8 ± 12.2
	High-CD	17.4 ± 6.1	30.0 ± 13.9
	Total	18.9 ± 7.2	29.1 ± 13.2[a]
Gastrocnemius EMG (% MVC)	Control	26.7 ± 15.8	32.9 ± 13.8
	Low-CD	26.3 ± 9.9	30.6 ± 11.8
	High-CD	21.1 ± 6.1	29.9 ± 13.8
	Total	24.2 ± 11.3	31.1 ± 12.9[a]
Rectus femoris EMG (% MVC)	Control	5.4 ± 3.8	17.3 ± 22.0
	Low-CD	5.3 ± 4.2	18.5 ± 22.9
	High-CD	5.0 ± 3.0	15.8 ± 20.8
	Total	5.8 ± 3.8	17.2 ± 21.5[a]

(Continued)

[a] *Variables reaching statistical significance for main effect of age ($p < 0.05$). STAI, State-Trait Anxiety Index; MVC, maximal voluntary contraction; TA, tibialis anterior; EMG, electromyography; METS hours per week = metabolic equivalents hours per week.*

[Cambridge Electronics Design (CED), Cambridge, UK]. Force displayed on a 19-inch monitor was located at eye level 1.5 m in front of the participant. Each participant was asked to trace a horizontal cursor placed in the middle of the screen with the force signal as it appeared on the screen from the right side of the monitor.

ELECTRICAL RECORDINGS

Whole muscle electromyographic (EMG) signals of the tibialis anterior, medial head of the gastrocnemius, soleus, and rectus femoris were recorded using bipolar surface electrodes (sintered pellet Ag-AgCl, 8 mm diameter, 20 mm between electrodes) taped to the skin over the belly of each muscle. Reference electrodes were placed on the patella. The recording electrodes on each muscle were placed in line with the muscle fibers and in accordance with locations recommended by the European Recommendations for Surface Electromyography (Hermens et al., 2000). The EMG signals were amplified (1,000 ×) and band-pass filtered (13–1,000 Hz) with Coulbourn bioamplifiers (Coulbourn Instruments, Allentown, PA, USA) prior to being recorded directly to a computer using the Power 1401 and Spike2 software (CED). The EMG signals were digitized at 2,000 samples/s and analyzed offline using Spike2 software (CED).

CARDIOVASCULAR MEASUREMENTS

Heart rate and blood pressure were monitored during submaximal and fatiguing contractions and periods of rest or mental math with an automated beat-by-beat blood pressure monitor (Finapress 2300, Datex-Ohmeda, Louisville, CO, USA). The blood pressure cuff was placed around the middle finger of the left hand, and the arm was placed on a platform to maintain the hand at heart level. Blood pressure was sampled at 500 samples/s and collected online to PC using Spike2 software (CED).

COGNITIVE ASSESSMENT OF ANXIETY AND STRESS

Cognitive levels of anxiety and stress were assessed throughout the protocol using a visual analog scale (VAS) (Yoon et al., 2009) and the *state* portion of the STAI questionnaire (Spielberger et al., 1970). Each VAS (one for anxiety and another for stress) had a 10-cm line anchored at the far left by "none" and at the far right by "as bad as it could be." The right anchor corresponded to the most stressful or most anxious moment in the life of the

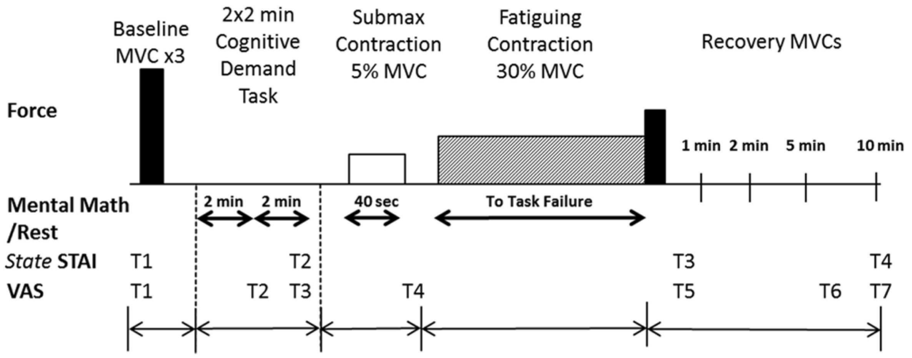


FIGURE 1 | Experimental protocol. The top panel illustrates in order the tasks performed by each participant with the ankle dorsiflexor muscles. Maximal voluntary contractions (MVC) (solid bars) were performed at the beginning of the experimental session and during recovery (immediately after the fatiguing contraction and at 1, 2, 5, and 10 min of recovery). The fatiguing contraction (30% MVC), symbolized by the hatched rectangle, was performed until task failure by each participant. The bottom panels indicate when the State-Trait Anxiety Inventory (STAI; four times) was performed and the Visual Analog Scale (VAS) for anxiety and stress were recorded (at seven time points, T1–T7). The schematic is not to scale for time or force.

participant. Anxiety was defined as the participant's negative feelings regarding the immediate future, whereas stress represented the physical changes (e.g., increase in heart rate and perspiration) occurring during the test perceived by the participant that were above and beyond the expectation for their level of exertion (Christou et al., 2004). VAS for anxiety and stress were recorded at seven time points (T1–T7) during the protocol: one baseline assessment before intended arousal (T1); during the rest period after each 2 × 2-min bout of mental math (low-cognitive demand or high-cognitive demand session) or quiet rest (control session) (T2, T3); immediately after the 5% MVC submaximal contraction (T4); immediately after the fatiguing contraction/MVC (T5); and 5 and 10 min after the fatiguing contraction (T6, T7) (**Figure 1**).

The *state* portion of the STAI-questionnaire consisted of 20 statements that required a response on a four-point Likert-type scale. Baseline *trait* and *state* assessments were conducted during the familiarization session. There was no significant difference between young and older adults in baseline *trait* STAI scores ($p = 0.54$) or baseline *state* STAI scores taken during the familiarization session ($p = 0.66$) (**Table 1**). *State* STAI assessments were also conducted at four different time points during the experimental protocol: baseline assessment before arousal; after 2 × 2-min bouts of quiet sitting (control session) or mental math (low-cognitive demand and high-cognitive demand sessions); immediately after the fatiguing contraction/MVC; and 10 min after completion of the fatiguing contraction (**Figure 1**).

COGNITIVE DEMAND CONDITIONS

Difficult mental math is an established psychosocial technique used to induce cognitive demand and increase levels of anxiety (Kajantie and Phillips, 2006) and was used for the *high-cognitive demand task* (Noteboom et al., 2001). Each participant performed serial subtraction from a four-digit number by 13 with one response required every 3 s (Noteboom et al., 2001). If the participant made an error in serial subtraction or was unable to provide the correct answer within 3 s, they were asked to restart the mental math from the first number in the series. After three errors, the investigator asked the participant to begin with a new four-digit number. The *simple mental math task*, performed during the *low-cognitive demand session*, was designed to increase cognitive demand above control without elevating arousal. Participants serially counted backward by 1's from 50 to 0 at a slow, even pace. If the participant made an error in counting, they were asked to restart counting from 50. During the *control session*, participants were instructed to rest quietly during the 2 × 2-min bouts, 5% MVC submaximal contraction (40 s) and 30% MVC fatiguing contraction. During the low-cognitive demand and high-cognitive demand sessions, participants performed the mental math task while at rest (2 × 2-min bouts), and then continuously during the 5% MVC submaximal contraction and 30% MVC fatiguing contraction until task failure.

EXPERIMENTAL PROTOCOL

The protocol for each experimental session (control, low-cognitive demand, and high-cognitive demand sessions) involved procedures in the following order: (1) MVCs of the ankle dorsiflexor, ankle plantarflexor, and knee extensor muscles; (2) assessment of cognitive and physiological arousal before and after 2 × 2-min bout of either quiet sitting (control session), simple mental math (low-cognitive demand session), or difficult mental math (high-cognitive demand session); (3) performance of one submaximal isometric contraction at 5% MVC force sustained for 40 s with assessment of cognitive and physiological arousal immediately following the contraction; (4) a submaximal fatiguing isometric contraction at 30% MVC force sustained until task failure; and (5) recovery MVCs immediately following the fatiguing contraction, and at 1, 2, 5, and 10 min recovery with assessment of anxiety and stress levels (**Figure 1**).

Participants performed two MVCs of the knee extensor and plantar flexor muscles each at the beginning of each experimental session in order to obtain peak EMG for the gastrocnemius, soleus, and rectus femoris muscles. Participants rested for 60 s between each trial. For both muscle groups, MVCs were performed with the participant seated in the same position as used for testing the ankle dorsiflexors muscles (described above). The aim was to obtain peak EMG values for each muscle group; forces were not recorded during knee extension and plantar flexion. Each participant was asked to push as hard as possible against an immovable restraint for 3–4 s to activate either the knee extensor or ankle plantar flexor muscles. For the knee extensor muscles, manual resistance was applied to the distal leg (just above the lateral malleolus) so that the lower leg was restrained at 90° of flexion while the participant performed maximal knee extension. For the ankle plantar flexor muscles, the foot of each participant was placed on the footplate, and vertical movement was minimized during each MVC by a block that eliminated movement of the footplate. The MVC trial with the greatest amount of EMG activity was used to normalize the EMG recordings of the rectus femoris, medial head of the gastrocnemius, and soleus muscles during the submaximal contractions.

Participants performed three to four MVC trials with the ankle dorsiflexors while their foot was attached to the footplate. Each participant was asked to dorsiflex as hard as possible for 3–4 s. Participants were given visual feedback on a display monitor and strong verbal encouragement to achieve and maintain maximal force. Participants rested for 60 s between each trial. If the peak force achieved for two of the first three trials was not within 5% of each other, additional trials were performed until this criterion was met. The greatest MVC force achieved with the ankle dorsiflexor muscles was used as the reference to calculate the target level for both the submaximal contractions at 5% MVC and the fatiguing contraction at 30% MVC. The MVC with the greatest amount of EMG activity was used to normalize the EMG recordings during the fatiguing contractions of the tibialis anterior muscle. MVCs of the ankle dorsiflexor muscles were also performed during recovery (**Figure 1**).

A fatiguing contraction was performed with the ankle dorsiflexor muscles at 30% MVC during each experimental session. Each participant was asked to trace a horizontal cursor with the force signal as it appeared from the right side of the monitor in order to match the vertical target force as displayed on the screen. Participants were encouraged to sustain the force for as long as possible. The fatiguing contraction was terminated when the force declined by 10% of the target force. To minimize the influence of transient fluctuations in motor output on the criteria for task failure, the task was terminated only after force fell below the predetermined threshold for 2.5 s of a 5 s interval. Participants were not informed of their time to task failure.

Rating of perceived exertion (RPE) was assessed using the modified Borg 10-point scale (Borg, 1982). Each participant was instructed to focus their assessment of exertion on the ankle muscles performing the fatiguing task. The scale was anchored so that 0 represented the resting state and 10 corresponded to the strongest contraction that the ankle muscles could perform. The RPE was recorded at the beginning of the fatiguing contraction and every minute thereafter until task failure. In order to obtain RPE while the participant was performing mental math during the low-cognitive demand and high-cognitive demand sessions, the participant was interrupted and asked to report their RPE. After reporting their RPE, participants resumed the mental math task of serial counting from 50 to 0 during the low-cognitive demand session or serial subtraction using a new four-digit number during the high-cognitive demand session.

DATA ANALYSIS

All data collected during the experiments were recorded online using a Power 1401 A/D converter and analyzed using Spike2 (CED). The MVC torque was quantified as the average value over a 0.5-s interval that was centered about the peak. The torque for the MVCs, submaximal and fatiguing contractions was calculated as the product of force and the distance between the ankle joint and the point at which the ankle was attached to the force transducer. The maximal EMG for each muscle was determined as the root mean square (RMS) value over a 0.5-s interval about the same peak interval of the MVC torque measurement. The maximal EMG value of the involved muscles was then used to normalize the RMS EMG values recorded during the 5% MVC task and the fatiguing contraction at 30% MVC. The RMS value of the 5% MVC task was averaged for each muscle over the middle 30 s of the 40 s contraction for the tibialis anterior, medial gastrocnemius, soleus, and rectus femoris. During the fatiguing contraction, the RMS EMG signal for each muscle was quantified at the following time intervals: the first 30 s; 15 s on both sides of 25, 50, and 75% of time to task failure; and the last 30 s of the task duration. The EMG activity of each muscle was normalized to the RMS EMG value obtained during the MVC for each respective muscle.

To quantify the bursts of EMG activity of the tibialis anterior during the fatiguing contraction at 30% MVC, the EMG signal was first rectified, smoothed (averages of 1 s duration, 500 data points), and then differentiated over 0.25 s averages. The differentiated signal represents the rate of change and was used to identify rapid changes in the rectified and smoothed EMG signal. The threshold for establishing if a burst of EMG had occurred was determined by first finding the minimum standard deviation (SD) of the differentiated EMG during the fatiguing contraction using a 30 s moving window; the threshold was then defined as the mean + 3 SD of the minimum differentiated signal. The minimal burst duration was 0.1 s. The EMG bursting activity (bursts/min) was quantified for five continuous intervals of 20% of the time to task failure.

The amplitude of the force fluctuations was quantified as the coefficient of variation (CV) ($CV = SD/mean \times 100$) for the 5% MVC task and 30% MVC fatiguing contraction. The fluctuations in torque during the 5% MVC task were quantified over the middle 30 s of the 40 s contraction. For the fatiguing contraction at 30% MVC, the fluctuations in torque were quantified for five continuous intervals of 20% of the time to task failure (between 0 and 100%).

Mean arterial pressure (MAP) and heart rate were evaluated only on participants not currently taking blood pressure medications with normal blood pressure. MAP and heart rate recorded during the fatiguing contraction at 30% MVC were analyzed by comparing ~15 s averages at 25% intervals throughout the fatiguing contraction; during the 5% MVC submaximal contraction they were quantified over the middle 30 s of the 40 s contraction. For each interval, the blood pressure signal was analyzed for the mean peaks [systolic blood pressure (SBP)], mean troughs [diastolic blood pressure (DBP)], and number of pulses per second (multiplied by 60 to determine heart rate). MAP was calculated for each epoch with the following equation: $MAP = DBP + 1/3\ (SBP - DBP)$. Rate-pressure product (RPP) was calculated as the product of heart rate and MAP for the equivalent time periods as stated above.

STATISTICAL ANALYSIS

Data were reported as means ± SD within the text, and displayed as means ± SE in the figures. Analyses of variances (ANOVA) models were used to compare the various dependent variables. Specifically, separate ANOVAs with repeated measures on session (control, low-cognitive demand, and high-cognitive demand), and with age (young and old) and sex (men and women) as fixed factors, were used to compare MVC torque and STAI (state) and VAS for anxiety and stress at baseline, MAP, heart rate, CV of torque, and EMG activity during the 5% MVC task, error rates (only low- and high-cognitive demand sessions included for error rate analysis) during the fatiguing contraction and the time to task failure of the fatiguing contraction. This ANOVA model was also used to compare the SD of the time to failure from the three sessions, and the SD of the mean CV of torque during the fatiguing contraction obtained from the three sessions. ANOVAs with repeated measures on session and time, and with age and sex as fixed factors, were used to compare VAS for stress and anxiety, STAI (state) and MVC torques throughout the sessions, i.e., before and after the fatiguing contraction (see **Figure 1** for time points). ANOVAs with repeated measures on session and time (five time points for each: see Data Analysis), and with age and sex as fixed factors, were used to compare the following variables during the fatiguing contraction: CV of torque, RMS EMG, EMG bursting activity, heart rate, MAP, RPP, and RPE. *Post hoc* analyses (Tukey) were used to test for differences among pairs when appropriate. Univariate ANOVAs were used to compare young and old men and women for the following variables: physical characteristics (age, height, and weight), physical activity level, handedness, and STAI (trait). The strength of an association is reported as the Pearson product–moment correlation coefficient (r). The statistical significance adopted was 5% ($p < 0.05$) and all analysis were performed in IBM Statistical Package for Social Sciences (SPSS) version 19.

RESULTS

Young and older adults were of similar height and weight ($p > 0.05$) but the older adults were less active than the young ($p < 0.05$). See **Table 1** for subject characteristics.

MVC TORQUE

At baseline, young adults were stronger than the older adults (22.5 ± 7 vs. 18.7 ± 6.1 Nm, respectively: age effect, $p = 0.005$) and men were stronger than women (sex effect, $p = 0.0001$) on all 3 days of testing, with no interaction between sex and age (age × sex, $p = 0.69$) (**Table 1**). The relative reduction (%) in MVC torque after the fatiguing contraction was similar across sessions (session effect, $p = 0.98$), and similar for young and older adults (session × age, $p = 0.26$). During recovery, MVC torque increased to near baseline levels within 10 min of completing the fatiguing contraction similarly for young and older adults across all sessions (session × age, $p = 0.57$) (**Table 1**). Furthermore, at the end of the recovery period, the MVC (% of baseline) was similar for young and older men and women ($p > 0.05$).

ANXIETY AND STRESS LEVELS

State STAI scores

Baseline *state* STAI scores taken at the beginning of each experimental session were similar for young and older men and women (age effect, $p = 0.88$; sex effect, $p = 0.57$) (**Table 1**). *State* STAI scores taken after exposure to the 2 × 2 min of difficult mental math were higher during the high-cognitive demand session compared with the control and low-cognitive demand sessions (control, 25.1 ± 6.6; low-cognitive demand, 30.4 ± 10.0; high-cognitive demand, 42.8 ± 13.1; and session effect, $p = 0.0001$) and immediately after the fatiguing contraction (control, 36.2 ± 9.2; low-cognitive demand, 38 ± 9; high-cognitive demand, 50.4 ± 13.8; and session effect, $p = 0.0001$). There was no difference between young and older adults across all three session after completing the fatiguing contraction (age effect, $p = 0.72$). Older adults however, demonstrated higher *state* STAI scores than young adults after the fatiguing contraction when exposed to the high-cognitive demand (session × time × age, $p = 0.02$).

VAS for stress and anxiety

Visual analog scale scores for stress and anxiety were similar at baseline for young and older adults, and men and women ($p > 0.05$, **Figure 2**). *Anxiety VAS* was significantly higher during the high-cognitive demand session compared to the control and low-cognitive demand sessions (session × time, $p = 0.0001$), and increased more for older adults than young over time (time × age, $p = 0.01$) (**Figure 2A**). There were no other interactions. *Stress VAS* scores were significantly higher for older adults than young during the high-cognitive demand session compared with the control and low-cognitive demand sessions (session × age, $p = 0.02$, **Figure 2B**) and for older adults than young over time (time × age, $p = 0.001$). There were no main effects of sex and no other interactions.

LOW-INTENSITY SUSTAINED CONTRACTION (5% MVC)

Fluctuations in torque

Older adults had greater fluctuations in torque (CV of torque) compared with young across all three sessions (age effect, $p = 0.007$) (**Figure 3**) and women had higher fluctuations in torque than men (sex effect, $p = 0.001$). On average, the older adults had a linear increase in fluctuations in torque as cognitive demand increased while young adults showed no change (linear interaction for session × age, $p = 0.04$, **Figure 3A**). Women demonstrated higher force fluctuations than men ($p = 0.001$), but there were no other interactions ($p > 0.05$).

MAP and heart rate

Cardiovascular measures were analyzed for only those older participants who were *not* currently taking blood pressure medications at the time of the experiment (young, $n = 16$; older, $n = 11$). During the 5% MVC task, MAP was higher during the high-cognitive demand session (105.1 ± 18.8 mmHg) than the low-cognitive demand session (87.2 ± 28.3 mmHg) and the control session (88.8 ± 23 mmHg; session effect, $p = 0.001$). There was no influence of age or sex on MAP ($p > 0.05$). Similarly, heart rate was greater during the high-cognitive demand session

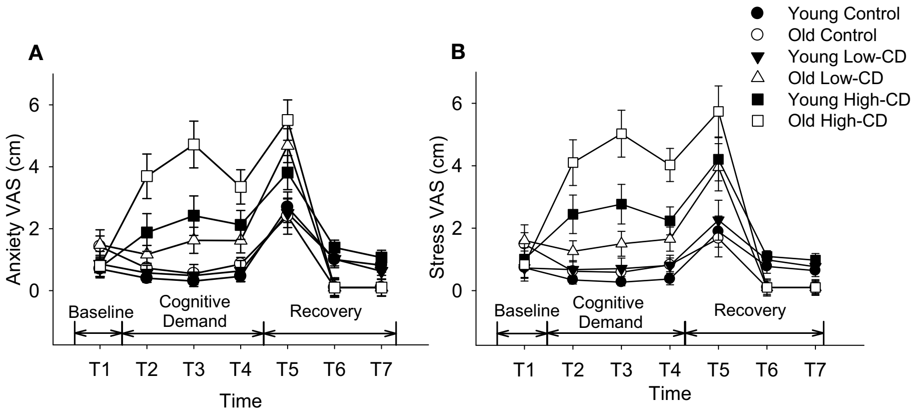


FIGURE 2 | Visual Analog Scale (VAS) scores for anxiety (A) and stress (B). Mean (±SE) VAS scores for young adults (closed symbols) and older adults (open symbols) are shown for anxiety **(A)** and stress **(B)** throughout the experimental protocol during the control session (circles), low-cognitive demand session (Low-CD, triangles), and high-cognitive demand session (High-CD, squares). Time intervals were as follows: baseline (T1), after the first bout of 2 min of quiet rest/mental math (T2), after the second bout of 2 min of quiet rest/mental math (T3), after the 5% submaximal contraction (T4), during recovery immediately after task failure (T5), and then at 5 min (T6) and 10 min of recovery (T7).

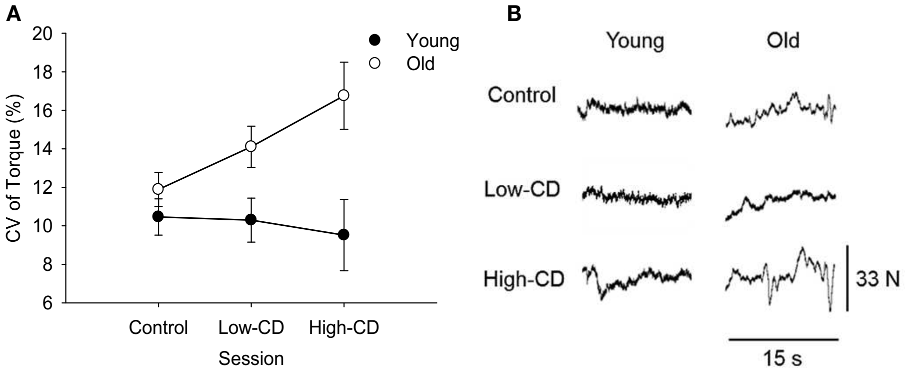


FIGURE 3 | Coefficient of Variation (CV) of torque during the 5% MVC task for young (closed symbols) and older (open symbols) adults during the control, low-cognitive demand (Low-CD), and high-cognitive demand (High-CD) sessions (A), and representative force tracings of a young and older adult (B). Shown are the mean (±SE) in **(A)**. Older adults had significantly higher CV of torque than young adults (age effect, $p = 0.007$).

(79.6 ± 15 beats/min) compared with the low-cognitive demand (71.6 ± 28 beats/min) and control sessions (68.2 ± 19.4 beats/min, session effect, $p = 0.04$) regardless of age of sex ($p > 0.05$, i.e., no interactions). Consequently, the *RPP* was higher during the high-cognitive demand session than the control and low-cognitive demand sessions (session effect, $p = 0.0001$), but there was no difference between young and older adults (age effect, $p = 0.52$) or men and women (sex effect, $p = 0.70$).

EMG activity

During the 5% MVC task, older adults had higher soleus RMS EMG (% MVC) (antagonist muscle) than young adults during the high-cognitive demand session (session × age, $p = 0.04$), but there were no other interactions, or main effects of age, sex or session for soleus or any other muscles (tibialis anterior, gastrocnemius, and rectus femoris).

FATIGUING CONTRACTION (30% MVC)

Time to task failure

There was no difference in time to task failure across sessions or with age ($p > 0.05$) (**Table 1**; **Figure 4**). There was no difference in time to task failure between men and women (sex effect, $p = 0.96$) and no interactions for age, sex, and session ($p > 0.05$). Variability between the three sessions in the time to task failure (comparison of SD generated from the three sessions for each participant) however, was greater for older adults than young adults (2.02 ± 1.05 vs. 1.25 ± 0.51 min, respectively, $p = 0.02$), but similar for men and women (sex effect, $p = 0.53$; sex × age, $p = 0.57$) (**Figure 4**). Furthermore, we compared the SD for time to task failure between sessions (SD for control and low-cognitive demand session vs. SD for control and high-cognitive demand session) to determine if variability increased with difficulty of the mental math. While the age effect remained (age effect, $p = 0.03$), there were no effects

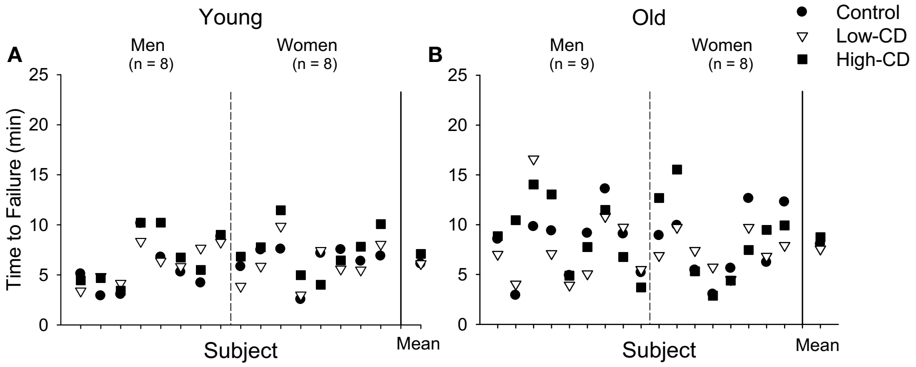


FIGURE 4 | Time to task failure during the fatiguing contraction for individual young (A) and older adults (B) during the control (circle), low-cognitive demand (Low-CD, triangle), and high-cognitive demand (High-CD, square) sessions. Time to task failure is shown for each young **(A)** and older **(B)** man and woman for each session (separated by dashed line). The aggregate mean (±SE) is shown for each session after the solid vertical line. The range and variability of time to task failure among the older adults was greater than for the young adults for each session. Older adults were more variable than young between the three sessions due to addition of a cognitive task (age effect, $p = 0.03$), but variability did not increase with task difficulty (session effect, $p = 0.38$).

of session (session effect, $p = 0.38$) or sex (sex effect, $p = 0.69$), and no interactions. Thus, although the older adults were more variable than young between the three sessions due to addition of a cognitive task, the variability between the older adults did not increase with to the difficulty of the cognitive task.

Fluctuations in torque

Fluctuations in torque (CV) increased over time during the sustained contraction (time, $p < 0.001$) similarly across sessions for both age groups (session × time, $p = 0.56$, **Figure 5C**). Older adults however, had larger fluctuations in torque than young adults (age effect, $p = 0.002$) and this difference was similar across sessions (session × age, $p = 0.11$). Women also had larger fluctuations in torque than men (sex effect, $p = 0.005$) and this sex difference was similar across sessions (session × sex, $p = 0.69$). There were no other interactions ($p > 0.05$). Because older and young adults can demonstrate more variability in motor performance than young adults, we evaluated variability of the fluctuations in torque (CV of torque) during the 30% MVC task (comparison of SD generated from the three sessions for each participant) between young and older adults. Variability was greater for older adults than young adults ($p = 0.01$), and greater for women than men (sex effect, $p = 0.02$), but there were no interactions (sex × age, $p = 0.94$) (**Figures 5A,B**).

EMG ACTIVITY OF AGONIST MUSCLES

The amplitude of the RMS EMG (% MVC) for the tibialis anterior (ankle dorsiflexors), increased during the fatiguing contraction (time effect, $p < 0.001$) and similarly across sessions (session × time, $p = 0.38$). Furthermore, tibialis anterior EMG activity was greater for the older adults than young during all three sessions (age effect, $p = 0.002$) (**Table 1**), but there was no difference between men and women (sex effect, $p = 0.80$), and no interactions.

Electromyographic bursting activity (bursts per minute) increased over time during the fatiguing contraction (30% MVC) for all three sessions (time effect, $p = 0.002$); however, there was no difference across the sessions (session effect, $p = 0.50$). Neither age nor sex influenced the bursting activity during the fatiguing contraction ($p > 0.05$, **Table 1**).

EMG ACTIVITY OF ANTAGONIST AND ACCESSORY MUSCLES

The RMS EMG amplitude (% MVC) for the soleus, gastrocnemius, and rectus femoris increased over time during the fatiguing contractions (time effect, $p < 0.001$ for all muscles) but was similar across sessions (session effect, $p > 0.05$ for all muscles). Older adults however, had higher RMS EMG for the soleus (age effect, $p = 0.04$), gastrocnemius ($p = 0.01$), and rectus femoris ($p = 0.03$) than young adults (see **Table 1**). There was no effect of sex for gastrocnemius and soleus (sex effect, $p > 0.05$) and there were no interactions ($p > 0.05$). For the rectus femoris, however, women had higher RMS EMG amplitudes than men (sex effect, $p = 0.04$), but there were no interactions ($p > 0.05$). There was a correlation between rectus femoris RMS EMG and CV of torque for the high-cognitive demand session only, indicating that participants who had greater torque fluctuations during the high-cognitive demand session also had greater rectus femoris EMG ($r_{33} = 0.31$, $p = 0.04$).

MAP AND HEART RATE

Cardiovascular measures were included only for older participants who were not currently taking blood pressure medications at the time of the experiment (young, $n = 16$; older, $n = 11$). MAP, heart rate, and RPP increased over time (time, $p < 0.05$) (**Figure 6**). MAP, heart rate, and RPP were higher during the high-cognitive demand session than the control or low-cognitive demand sessions (session effect, $p < 0.05$). MAP was higher for older adults during the fatiguing contraction in the high-cognitive demand session over time than other sessions (session × time × age, $p = 0.02$). Heart rate and RPP, however, were similar for older adults over time across sessions (session × time × age, $p > 0.05$), with no main effects of age or sex ($p > 0.05$).

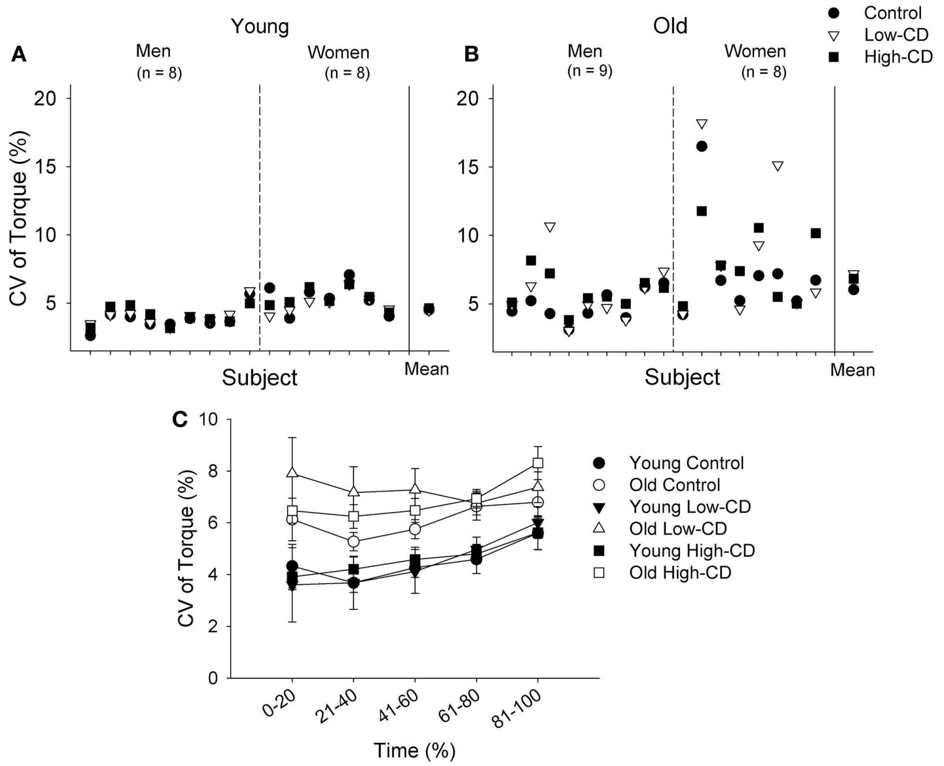


FIGURE 5 | Coefficient of variation of torque during the fatiguing contraction (30% MVC) for individual young (A) and older adults (B), and across time for young and older adults (C) during the control session (circle), low-cognitive demand session (Low-CD, triangle), and high-cognitive demand session (High-CD, square). CV of torque is shown for each young **(A)** and older **(B)** man and woman for each session. The aggregate mean (± SE) is shown for each session after the solid vertical line. The older adults and women exhibited greater variability in steadiness across sessions than the young and men respectively ($p < 0.05$). In **(C)**, the CV of torque (mean ± SE) is shown for the control (circle), low-CD demand (triangle), and high-CD (square) sessions for young (closed symbols) and older (open symbols) adults during five continuous intervals of 20% during the fatiguing contraction between 0 and 100% of the time to failure. Thus, the x axis intervals for **(C)** indicate the interval of data points averaged in each 20% interval. Older adults had significantly higher CV of torque than young adults (age effect, $p = 0.002$).

Rating of perceived exertion (RPE)

Perceived exertion increased during the fatiguing contraction (time effect, $p = 0.0001$) similarly across sessions (session effect, $p = 0.59$). RPE was similar for young and older adults (age effect, $p = 0.82$) and men and women (sex effect, $p = 0.62$), with no interactions ($p > 0.05$). Mean RPE across all three sessions was 4.2 ± 1.5 and 4.2 ± 1.8 at the beginning of the fatiguing contraction for young and older adults respectively and increased to 8.7 ± 2.3 vs. 9.1 ± 1.4 by the end of the fatiguing contraction.

Error rate

The mental math error rate during the fatiguing contraction (errors/min) was significantly higher during the high-cognitive demand session (2.9 ± 1.3 errors/min) compared with the low-cognitive demand session (0.4 ± 0.4 errors/min, session effect, $p < 0.001$). There was no main effect of age or sex ($p > 0.05$). There was also no correlation between error rate and CV of torque during the fatiguing contraction for the low-cognitive demand ($r_{33} = -0.17$, $p = 0.35$) or high-cognitive demand ($r_{33} = -0.26$, $p = 0.14$) sessions; nor were there significant associations between error rate during the fatiguing contraction and the time to task failure for the low-cognitive demand ($r_{33} = -0.12$, $p = 0.52$) or high-cognitive demand ($r_{33} = -0.06$, $p = 0.74$) sessions.

DISCUSSION

This study imposed several levels of cognitive demand during sustained low- and moderate-force isometric contractions with the ankle dorsiflexor muscles to determine the influence of increased cortical involvement on motor function and fatigability in young and older adults. The novel findings of this study were that as cognitive demand increased, steadiness decreased (i.e., CV of torque increased) during the very low-force contraction (5% MVC) for older adults but did not change for the young adults. While fatigability (time to failure) of a moderate intensity contraction (30% MVC) was not essentially different with imposed cognitive demand for young or older adults, variability in the time to failure and in the torque fluctuations across sessions was greater for the older adults than the young adults. These results provide evidence that increased cortical involvement of motor and non-motor cortical areas can disrupt motor performance of low-to-moderate intensity isometric contractions of the lower limb more so in older adults than young adults.

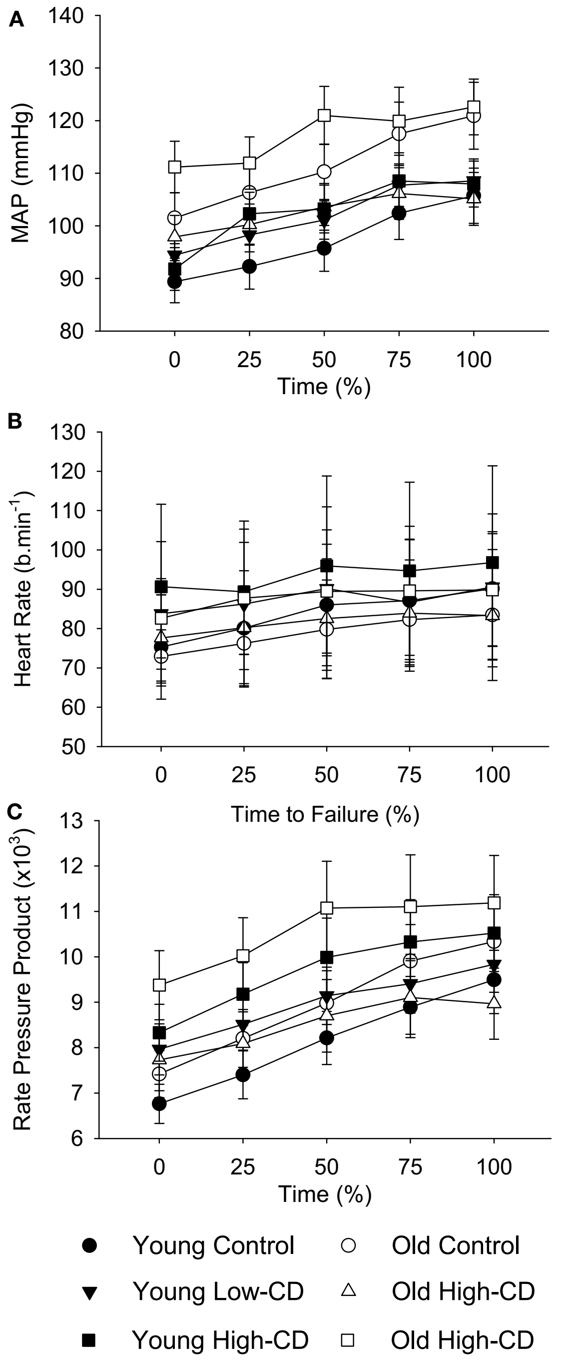


FIGURE 6 | Mean arterial pressure, heart rate, and rate-pressure product during the fatiguing contraction for young and older adults across sessions. The values are mean ± SE at 25% increments of time to task failure for young (closed symbols) and older (open symbols) adults during the control (circles), low-cognitive demand (Low-CD, triangles), and high-cognitive demand (High-CD, squares) sessions for mean arterial pressure **(A)**, heart rate **(B)**, and rate-pressure product **(C)** during the fatiguing contraction. Averages of 15-s intervals were used for the MAP and heart rate. Rate-pressure product was the product of heart rate and MAP for the equivalent time periods in **(A,B)**.

STEADINESS WAS REDUCED WITH AGE IN THE LOWER LIMB

Torque fluctuations (CV) were greater (steadiness reduced) during the low-intensity contraction (5% MVC) than at the start of the 30% MVC task (prior to fatigue), and also greater for older adults than young across all sessions. Larger torque fluctuations with advanced age have also been observed under control conditions across various muscle groups and particularly at the lower intensity contractions for both young and older men and women (Enoka et al., 2003; Tracy et al., 2005, 2007). Typically, the CV (%) will decrease as contraction intensity increases (Enoka et al., 2003; Taylor et al., 2003; Moritz et al., 2005; Tracy, 2007) and as we observed. Because we showed increased torque fluctuations during ankle dorsiflexion for the older adults during both 5% MVC and 30% MVC tasks compared with young, the age-related mechanism for reduced steadiness under control conditions influences both the low- and moderate-force tasks in the ankle dorsiflexor muscles. CV of torque across a range of low-to-high forces appear to be primarily modulated by low-frequency oscillations (<2–3 Hz) in neural drive found in motor unit action potentials trains (Negro et al., 2009; Dideriksen et al., 2012) with some contribution from increased motor unit variability at very low forces (Dideriksen et al., 2012; Jesunathadas et al., 2012). This low-frequency oscillating neural drive likely reflects an integration of both descending and afferent inputs onto the motoneurone pool (Negro et al., 2009; Dideriksen et al., 2012; Farina et al., 2012). With advanced age, the motoneurone pool undergoes remodeling that results in decreased motor units numbers and altered relations between discharge rates and recruitment thresholds (Barry et al., 2007); the age difference in torque fluctuations, therefore, appears to be due to age-related changes in the inputs to the motoneurone pool (Barry et al., 2007) with possibly some influence of greater motor unit discharge rate variability in older adults (Laidlaw et al., 2000; Kornatz et al., 2005; Tracy et al., 2005; Barry et al., 2007). Age-related changes in visual-motor processing may also contribute to altered motoneuronal inputs causing increased torque fluctuations during static contractions with age (Henningsen et al., 1997; Seidler-Dobrin and Stelmach, 1998; Tracy et al., 2007; Fox et al., 2013).

CARDIOVASCULAR RESPONSES AND ANXIETY WERE ELEVATED WITH HIGH-COGNITIVE DEMAND

While mental math was used to manipulate different levels of cognitive demand in this study, it can also increase anxiety and stress (Kajantie and Phillips, 2006) as it did for the young but more so in the older adults during the high-cognitive demand task (see **Figure 2**). Accordingly, MAP and heart rate were elevated when the difficult mental math was performed during both the 5% MVC and 30% MVC tasks, although similarly for the young and older adults. Older adults have reduced maximal heart rates compared with young, explaining the similar age-related increase in heart rate despite older adults reporting they felt more anxious and stressed. Because both MAP and heart rate were elevated, rate-pressure product was elevated for both young and older adults indicating increased cardiac work and myocardial oxygen consumption (Gobel et al., 1978; Wasmund et al., 2002) during the 5% MVC task and 30% MVC fatiguing contraction when cognitive demand was high. Chronicity of high blood pressure has been associated with an increased risk of stroke, cognitive decline, and dementia, especially in older adults with untreated high blood pressure (Tzourio et al., 1999; Tzourio, 2007). In the short term, increased stress and anxiety can increase monoaminergic drive; neuromodulatory inputs alter excitability of the motoneurone pool (Heckman et al., 2009) and potentially alter motor neuron output especially at low forces.

STEADINESS DECREASED WITH COGNITIVE DEMAND IN OLDER ADULTS

A novel finding was that the age difference in CV of torque grew linearly (i.e., steadiness decreased) with the increased levels of cognitive demand during a low-intensity contraction (5% MVC) of the lower limb. Although steadiness during the 30% MVC task was similar across sessions, older adults had greater variability in the CV of torque between sessions than the young. Increased torque fluctuations during the 5% MVC task between the low- and high-cognitive demand sessions indicate that the decline in steadiness was not solely due to the added distraction or challenge of talking because the low-cognitive demand task controlled for those factors. Because motor unit discharge rate variability can contribute to the force fluctuations at very low forces (Tracy et al., 2005; Jesunathadas et al., 2012), increased variability of the motor unit pool in the older adults may have been altered when high-cognitive demand was imposed.

Our findings indicate that increased antagonist muscle activation may also have contributed to the larger force fluctuations in the older adults when cognitive demand was high during the 5% MVC task. The older adults had greater soleus muscle activation during the high-cognitive demand session relative to the other sessions and compared with the young adults: this suggests less inhibition of the antagonist muscle from descending cortical sources. Increased antagonist muscle activity is a strategy adopted by older adults to stiffen joints and reduce movement variability with age (Hortobagyi and DeVita, 2006). For the higher force task (30% MVC) the torque fluctuations were larger with age, but there was no increase in the CV of torque with cognitive demand for young or older adults. Agonist (tibialis anterior), antagonist (gastrocnemius and soleus), and synergist (rectus femoris) activations were greater in the older adults than the young across all sessions, possibly contributing to the larger torque fluctuations with age. Because both the agonist (tibialis anterior) and antagonist activation were greater in the older adults compared with the young, activation differences had minimal effect on the greater CV of torque in the older adults.

There are numerous age-related changes along the neuroaxis that can alter inputs to the motoneurone pool and perhaps make it more susceptible to altering motor output when cognitive demand is imposed. Cortical size (Raz et al., 2007) and processing are diminished with age, along with reduced corticospinal fibers numbers (Eisen et al., 1996), and changes in spinal reflex pathways (Kido et al., 2004), which result in decreased cortical inhibition of both cognitive and motor processes with age (Peinemann et al., 2001; Sale and Semmler, 2005; Hunter et al., 2008). Age-related changes along the neuroaxis can also result in increased activation of antagonist muscles (Macaluso et al., 2002; Hortobagyi and DeVita, 2006) and as discussed may have been responsible for the greater activation of antagonist muscles with age in the current study.

Several theories of motor control assert that the division of attentional resources during a dual-task paradigm has limits and these limitations increase with advanced aging due to diminished cortical processing (Woollacott and Shumway-Cook, 2002). Consequently, some studies show older adults have less ability to simultaneously perform a cognitive task and motor task as well as they can be performed individually (Voelcker-Rehage and Alberts, 2007; Fraser et al., 2010; Johnson and Shinohara, 2012). Changes in performance for older adults in dual-tasks appear to be especially sensitive to cognitive tasks that require executive function (Yogev-Seligmann et al., 2008). Executive function (which included working memory, which was varied in this study), anxiety, and stress are modulated in prefrontal cortical regions and the anterior cingulate cortex (Miller, 2000; Owen et al., 2005; Banich et al., 2009; Schweizer et al., 2013). Prefrontal connections to motor areas (Takahara et al., 2012) along with input to neural connections between these and other cortical centers associated with cognition, anxiety, and motor function could directly alter motor output, as was observed in this study.

Capacity theories of attention that assume attentional resource limitations on the ability to perform multiple tasks simultaneously (Kahneman, 1973; McDowd, 2007; Hiraga et al., 2009) would predict even greater decrements in steadiness for older adults when descending drive from the motor cortex increased during the 30% MVC task and as the fatiguing contraction progressed. Interestingly, error rates in mental math (executive function task) during the fatiguing contraction did not differ across the age groups for the low-cognitive demand sessions and high-cognitive demand, indicating that mental math performance was not diminished in the older adults compared with the young. Although the variability in the CV of torque across the sessions was greater for the older adults than the young, the mean values in CV of torque were similar across the three sessions during the 30% MVC task and increased at similar rates to the young adults during the fatiguing contraction. Time to failure was also similar across sessions for each age group, and the increase in EMG activity, EMG bursting activity, and perceived effort during the fatiguing contraction progressed at similar rates across sessions. Increases in EMG and RPE during a fatiguing contraction are the result of increased descending drive to recruit more motor units in an effort to maintain the required force as the working muscle becomes progressively fatigued (Riley et al., 2008). Thus, while some older adults are clearly more affected than others by the increased cognitive demand during the sustained contractions (**Figure 5B**), capacity limitations in cortical regions of older adults cannot alone explain the loss of steadiness, especially at the very low forces when descending drive was not large.

Another explanation for the reduced steadiness in older adults as cognitive demand increased is that descending and afferent inputs to the motoneurone pool differed for the older and young adults. One input that likely differed between the young and older adults was monoaminergic drive (Christou et al., 2004). Increased monoaminergic drive to the spinal cord from the brainstem enables motoneurone activation and is essential for exercise

(Heckman, 2003), but monoaminergic drive is attenuated in older adults (Meltzer et al., 1998; Reynolds and Meltzer, 1999; Seals and Esler, 2000), potentially leading to decreased motor output and altered responses to increased anxiety and stress compared with young.

SEX DIFFERENCES IN STEADINESS

Both young and old women demonstrated heightened levels of stress and anxiety, and greater torque fluctuations during the very low-intensity and fatiguing contractions for all three sessions compared with men, regardless of the magnitude of cognitive demand. Similar sex differences in stress and anxiety (Christou et al., 2004) and in torque fluctuations have been shown previously in the upper limb (Yoon et al., 2009; Brown et al., 2010; Keller-Ross et al., 2014a); however, this is the first study to demonstrate increased torque fluctuations in women when performing submaximal contractions of the lower limb with varying levels of cognitive demand. Greater torque fluctuations in women when performing upper extremity tasks have been attributed to strength difference between men and women (Brown et al., 2010), although the mechanism is not known. When exposed to a stressful noxious stimulus prior to task performance, increased torque fluctuations have been attributed to greater activation of central neural mechanisms in response to increased stress and anxiety (Christou et al., 2004); however, in the current study, women demonstrated greater torque fluctuations and reported higher stress and anxiety than men regardless of the magnitude of cognitive demand (i.e., in both low- and high-cognitive demand tasks compared with control). Because both aging and decreased levels of estrogen in postmenopausal women possibly contribute to changes in monoaminergic drive (Meltzer et al., 1998), women may be even more vulnerable than men to diminished motor output with aging (see **Figure 5B**); however, it remains unclear if greater torque fluctuations in women are related to activation of alternate neural pathways, or a strength-related mechanism.

INCREASED VARIABILITY IN FATIGABILITY WITH COGNITIVE DEMAND AND AGING

Fatigability (time to task failure) of the ankle dorsiflexor muscles was similar across age groups and sessions. Hence, there was no systematic decrease in fatigability when cognitive demand was imposed during the sustained contraction with the ankle dorsiflexor muscles. In contrast, the elbow flexor muscles were more fatigable when high-cognitive demand was imposed in young men and women (Yoon et al., 2009; Keller-Ross et al., 2014a). Similarly, handgrip muscles were more fatigable in both young men and women when high-cognitive demand was imposed for high intensity contractions (Bray et al., 2008, 2012) but not for relatively strong men during a low-intensity sustained contraction (Keller-Ross et al., 2014b). The largest increases in fatigability were related to the initial muscle strength such that weaker participants experienced the greatest increases in fatigability (Yoon et al., 2009; Keller-Ross et al., 2014a). Perfusion associated changes within the muscle in response to a mental-math task (which was used to induce high-cognitive demand) was implicated but only partially explains these findings (Yoon et al., 2009; Keller-Ross et al., 2014a). In contrast to the elbow flexor muscles (Hunter et al., 2004), the ankle dorsiflexor muscles exhibit lesser differences between sub-populations including men and women (Avin et al., 2010), and young and older adults (Kent-Braun et al., 2002; Griffith et al., 2010) and we show here the fatigability of this muscle group is also less responsive to cognitive demand. Christie and Kamen (2009) attribute the lack of difference in fatigability of the dorsiflexor muscles between young and older adults to a lack of difference in motor unit discharge rates, suggesting young and older adults adopted similar neural adaptations during the fatiguing contractions. We found that the increase in EMG activity of the tibialis anterior muscle during the fatiguing contraction was similar across sessions for young and older adults, although older adults had greater EMG relative to the young. Another possible explanation for the different responses in fatigability with and without cognitive demand is a decreased number of corticospinal connections and larger motor unit ratio (motoneurone to fibers) in large lower limb muscles compared with the upper limb (Feinstein et al., 1955). A reduced number of corticomotor inputs to the dorsiflexor muscles relative to the upper limb muscles may minimize the modulating inputs from higher centers imposed with high-cognitive demand and lessen the responsiveness during the sustained fatiguing contractions at the moderate intensity.

While there was no systematic reduction in time to failure of the ankle dorsiflexor muscles as we have observed with the upper limb, older adults, particularly older women, demonstrated significantly more variability in their time to task failure between sessions than young adults (**Figure 4**). Variability between trials of a motor task can be exacerbated with increased cognitive demand in young people (Lorist et al., 2002) but is often greater with age as shown here. The greater variability in performance with advanced age can be due greater variability in cortical and motor nerve activation during motor tasks (Hunter et al., 2008; Yoon et al., 2008). This greater age-related variability in a motor task when a cognitive task was imposed further demonstrates the important role of cognitive control in determining reliability of performance of motor tasks especially during work-related tasks performed by an aging workforce.

CONCLUSION

This study demonstrated that older adults exhibit more variability than young adults in fatigability and less steadiness while performing low-force and moderate isometric with the ankle dorsiflexor muscles. For very low-force contractions, steadiness decreased further as greater cognitive demand increased. The reduced steadiness in older adults compared with the young, may be related to modulation of synergist and antagonist muscles and an altered neural strategy with age. Older adults also exhibited greater variability in steadiness between sessions and in fatigability as cognitive demand was imposed. Increased variability in lower extremity tasks may negatively impact activities of daily living and work tasks that require high-cognitive demand in an aging population. These data also expose differences within an older adult but also between older adults. Our results provide evidence that increased involvement of non-motor cortical areas can disrupt motor performance of low-to-moderate intensity isometric contractions of the lower limb more so in older adults than young adults. These findings have significant implications related to successful aging and performance of activities of daily living with advanced age especially those activities that require simultaneous execution of a cognitive task that involves working memory and maintenance of a static motor task.

REFERENCES

Aine, C. J., Sanfratello, L., Adair, J. C., Knoefel, J. E., Caprihan, A., and Stephen, J. M. (2011). Development and decline of memory functions in normal, pathological and healthy successful aging. *Brain Topogr.* 24, 323–339. doi:10.1007/s10548-011-0178-x

Artero, S., Touchon, J., and Ritchie, K. (2001). Disability and mild cognitive impairment: a longitudinal population-based study. *Int. J. Geriatr. Psychiatry* 16, 1092–1097. doi:10.1002/gps.477

Avin, K. G., Naughton, M. R., Ford, B. W., Moore, H. E., Monitto-Webber, M. N., Stark, A. M., et al. (2010). Sex differences in fatigue resistance are muscle group dependent. *Med. Sci. Sports Exerc.* 42, 1943–1950. doi:10.1249/MSS.0b013e3181d8f8fa

Banich, M. T., Mackiewicz, K. L., Depue, B. E., Whitmer, A. J., Miller, G. A., and Heller, W. (2009). Cognitive control mechanisms, emotion and memory: a neural perspective with implications for psychopathology. *Neurosci. Biobehav. Rev* 33, 613–630. doi:10.1016/j.neubiorev.2008.09.010

Barry, B. K., Pascoe, M. A., Jesunathadas, M., and Enoka, R. M. (2007). Rate coding is compressed but variability is unaltered for motor units in a hand muscle of old adults. *J. Neurophysiol.* 97, 3206–3218. doi:10.1152/jn.01280.2006

Borg, G. A. (1982). Psychophysical bases of perceived exertion. *Med. Sci. Sports Exerc.* 14, 377–381. doi:10.1249/00005768-198205000-00012

Bray, S. R., Graham, J. D., Martin Ginis, K. A., and Hicks, A. L. (2012). Cognitive task performance causes impaired maximum force production in human hand flexor muscles. *Biol. Psychol.* 89, 195–200. doi:10.1016/j.biopsycho.2011.10.008

Bray, S. R., Martin Ginis, K. A., Hicks, A. L., and Woodgate, J. (2008). Effects of self-regulatory strength depletion on muscular performance and EMG activation. *Psychophysiology* 45, 337–343. doi:10.1111/j.1469-8986.2007.00625.x

Brown, R. E., Edwards, D. L., and Jakobi, J. M. (2010). Sex differences in force steadiness in three positions of the forearm. *Eur. J. Appl. Physiol.* 110, 1251–1257. doi:10.1007/s00421-010-1600-x

Chen, P., Ratcliff, G., Belle, S. H., Cauley, J. A., Dekosky, S. T., and Ganguli, M. (2001). Patterns of cognitive decline in presymptomatic Alzheimer disease: a prospective community study. *Arch. Gen. Psychiatry* 58, 853–858. doi:10.1001/archpsyc.58.9.853

Christie, A., and Kamen, G. (2009). Motor unit firing behavior during prolonged 50% MVC dorsiflexion contractions in young and older adults. *J. Electromyogr. Kinesiol.* 19, 543–552. doi:10.1016/j.jelekin.2008.03.005

Christou, E. A., Jakobi, J. M., Critchlow, A., Fleshner, M., and Enoka, R. M. (2004). The 1- to 2-Hz oscillations in muscle force are exacerbated by stress, especially in older adults. *J. Appl. Physiol.* 97, 225–235. doi:10.1152/japplphysiol.00066.2004

Dideriksen, J. L., Negro, F., Enoka, R. M., and Farina, D. (2012). Motor unit recruitment strategies and muscle properties determine the influence of synaptic noise on force steadiness. *J. Neurophysiol.* 107, 3357–3369. doi:10.1152/jn.00938.2011

Eisen, A., Entezari-Taher, M., and Stewart, H. (1996). Cortical projections to spinal motoneurons: changes with aging and amyotrophic lateral sclerosis. *Neurology* 46, 1396–1404. doi:10.1212/WNL.46.5.1396

Enoka, R. M., Christou, E. A., Hunter, S. K., Kornatz, K. W., Semmler, J. G., Taylor, A. M., et al. (2003). Mechanisms that contribute to differences in motor performance between young and old adults. *J. Electromyogr. Kinesiol.* 13, 1–12. doi:10.1016/s1050-3411(02)00084-6

Farias, S. T., Mungas, D., Reed, B. R., Harvey, D., Cahn-Weiner, D., and Decarli, C. (2012). MCI is associated with deficits in everyday functioning: Alzheimer disease & associated disorders. *Alzheimer Dis. Assoc. Disord.* 20, 217–223. doi:10.1097/01.wad.0000213849.51495.d9

Farina, D., Negro, F., Gizzi, L., and Falla, D. (2012). Low-frequency oscillations of the neural drive to the muscle are increased with experimental muscle pain. *J. Neurophysiol.* 107, 958–965. doi:10.1152/jn.00304.2011

Feinstein, B., Lindegard, B., Nyman, E., and Wohlfart, G. (1955). Morphologic studies of motor units in normal human muscles. *Acta Anat. (Basel)* 23, 127–142. doi:10.1159/000140989

Fox, E. J., Baweja, H. S., Kim, C., Kennedy, D. M., Vaillancourt, D. E., and Christou, E. A. (2013). Modulation of force below 1 Hz: age-associated differences and the effect of magnified visual feedback. *PLoS ONE* 8:e55970. doi:10.1371/journal.pone.0055970

Fraser, S. A., Li, K. Z., and Penhune, V. B. (2010). Dual-task performance reveals increased involvement of executive control in fine motor sequencing in healthy aging. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 65, 526–535. doi:10.1093/geronb/gbq036

Galganski, M. E., Fuglevand, A. J., and Enoka, R. M. (1993). Reduced control of motor output in a human hand muscle of elderly subjects during submaximal contractions. *J. Neurophysiol.* 69, 2108–2115.

Gobel, F. L., Norstrom, L. A., Nelson, R. R., Jorgensen, C. R., and Wang, Y. (1978). The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. *Circulation* 57, 549–556. doi:10.1161/01.CIR.57.3.549

Griffith, E. E., Yoon, T., and Hunter, S. K. (2010). Age and load compliance alter time to task failure for a submaximal fatiguing contraction with the lower leg. *J. Appl. Physiol.* 108, 1510–1519. doi:10.1152/japplphysiol.01396.2009

Heckman, C. J. (2003). Active conductances in motoneuron dendrites enhance movement capabilities [article]. *Exerc. Sport Sci. Rev.* 31, 96–101. doi:10.1097/00003677-200304000-00008

Heckman, C. J., Mottram, C. J., Quinlan, K., Theiss, R., and Schuster, J. (2009). Motoneuron excitability: the importance of neuromodulatory inputs. *Clin. Neurophysiol.* 120, 2040–2054. doi:10.1016/j.clinph.2009.08.009

Henningsen, H., Knecht, S., and Ende-Henningsen, B. (1997). Influence of afferent feedback on isometric fine force resolution in humans. *Exp. Brain Res.* 113, 207–213. doi:10.1007/BF02450319

Hermens, H. J., Freriks, B., Disselhorst-Klug, C., and Rau, G. (2000). Development of recommendations for SEMG sensors and sensor placement procedures. *J. Electromyogr. Kinesiol.* 10, 361–374. doi:10.1016/S1050-6411(00)00027-4

Hiraga, C. Y., Garry, M. I., Carson, R. G., and Summers, J. J. (2009). Dual-task interference: attentional and neurophysiological influences. *Behav. Brain Res.* 205, 10–18. doi:10.1016/j.bbr.2009.07.019

Hortobagyi, T., and DeVita, P. (2006). Mechanisms responsible for the age-associated increase in coactivation of antagonist muscles. [article]. *Exerc. Sport Sci. Rev.* 34, 29–35. doi:10.1097/00003677-200601000-00007

Hunter, S. K., Critchlow, A., and Enoka, R. M. (2004). Influence of aging on sex differences in muscle fatigability. *J. Appl. Physiol.* 97, 1723–1732. doi:10.1152/japplphysiol.00460.2004

Hunter, S. K., Todd, G., Butler, J. E., Gandevia, S. C., and Taylor, J. L. (2008). Recovery from supraspinal fatigue is slowed in old adults after fatiguing maximal isometric contractions. *J. Appl. Physiol.* 105, 1199–1209. doi:10.1152/japplphysiol.01246.2007

Jesunathadas, M., Klass, M., Duchateau, J., and Enoka, R. M. (2012). Discharge properties of motor units during steady isometric contractions performed with the dorsiflexor muscles. *J. Appl. Physiol.* 112, 1897–1905. doi:10.1152/japplphysiol.01372.2011

Johnson, A. N., and Shinohara, M. (2012). Corticomuscular coherence with and without additional task in the elderly. *J. Appl. Physiol.* 112, 970–981. doi:10.1152/japplphysiol.01079.2011

Kahneman, D. (1973). *Attention and Effort*. Englewood Cliffs, NJ: Prentice Hall.

Kajantie, E., and Phillips, D. I. (2006). The effects of sex and hormonal status on the physiological response to acute psychosocial stress. *Psychoneuroendocrinology* 31, 151–178. doi:10.1016/j.psyneuen.2005.07.002

Keller-Ross, M., Pruse, J., Yoon, T., Harkins, A., and Hunter, S. (2014a). Stressor-induced increase muscle fatigability of young men and women is predicted by strength, but not voluntary activation. *J. Appl. Physiol.* 116, 767–778. doi:10.1152/japplphysiol.01129.2013

Keller-Ross, M. L., De-Lap, B. S., Doyel, R., Larson, G., and Hunter, S. K. (2014b). Muscle fatigability and control of force in men with posttraumatic stress disorder. *Med. Sci. Sports Exerc* doi:10.1249/MSS.0000000000000244

Kent-Braun, J. A., Ng, A. V., Doyle, J. W., and Towse, T. F. (2002). Human skeletal muscle responses vary with age and gender during fatigue due to incremental isometric exercise. *J. Appl. Physiol.* 93, 1813–1823. doi:10.1152/japplphysiol.00091.2002

Kido, A., Tanaka, N., and Stein, R. B. (2004). Spinal excitation and inhibition decrease as humans age. *Can. J. Physiol. Pharmacol.* 82, 238–248. doi:10.1139/y04-017

Kornatz, K. W., Christou, E. A., and Enoka, R. M. (2005). Practice reduces motor unit discharge variability in a hand muscle and improves manual dexterity in old adults. *J. Appl. Physiol.* 98, 2072–2080. doi:10.1152/japplphysiol.01149.2004

Kriska, A., and Bennett, P. (1992). An epidemiological perspective of the relationship between physical activity and NIDDM: from activity assessment to intervention. *Diabetes Metab. Rev.* 8, 355–372. doi:10.1002/dmr.5610080404

Laidlaw, D. H., Bilodeau, M., and Enoka, R. M. (2000). Steadiness is reduced and motor unit discharge is more variable in old adults. *Muscle Nerve* 23, 600–612. doi:10.1002/(SICI)1097-4598(200004)23:43.3.CO;2-4

Lorist, M. M., Kernell, D., Meijman, T. F., and Zijdewind, I. (2002). Motor fatigue and cognitive task performance in humans. *J. Physiol.* 545, 313–319. doi:10.1113/jphysiol.2002.027938

Macaluso, A., Nimmo, M. A., Foster, J. E., Cockburn, M., Mcmillan, N. C., and De Vito, G. (2002). Contractile muscle volume and agonist-antagonist coactivation account for differences in torque between young and older women. *Muscle Nerve* 25, 858–863. doi:10.1002/mus.10113

Marmon, A. R., Pascoe, M. A., Schwartz, R. S., and Enoka, R. M. (2011). Associations among strength, steadiness, and hand function across the adult life span. *Med. Sci. Sports Exerc.* 43, 560–567. doi:10.1249/MSS.0b013e3181f3f3ab

McDowd, J. M. (2007). An overview of attention: behavior and brain. *J. Neurol. Phys. Ther.* 31, 98–103. doi:10.1097/NPT.0b013e31814d7874

Meltzer, C. C., Smith, G., Dekosky, S. T., Pollock, B. G., Mathis, C. A., Moore, R. Y., et al. (1998). Serotonin in aging, late-life depression, and Alzheimer's disease: the emerging role of functional imaging. *Neuropsychopharmacology* 18, 407–430. doi:10.1016/S0893-133X(97)00194-2

Miller, E. K. (2000). The prefrontal cortex and cognitive control. *Nat. Rev. Neurosci.* 1, 59–65. doi:10.1038/35044578

Moritz, C. T., Barry, B. K., Pascoe, M. A., and Enoka, R. M. (2005). Discharge rate variability influences the variation in force fluctuations across the working range of a hand muscle. *J. Neurophysiol.* 93, 2449–2459. doi:10.1152/jn.01122.2004

Morris, J. C., Storandt, M., Miller, J. P., Mckeel, D. W., Price, J. L., Rubin, E. H., et al. (2001). Mild cognitive impairment represents early-stage Alzheimer disease. *Arch. Neurol* 58, 397–405. doi:10.1001/archneur.58.3.397

Negro, F., Holobar, A., and Farina, D. (2009). Fluctuations in isometric muscle force can be described by one linear projection of low-frequency components of motor unit discharge rates. *J. Physiol.* 587, 5925–5938. doi:10.1113/jphysiol.2009.178509

Noteboom, J. T., Fleshner, M., and Enoka, R. M. (2001). Activation of the arousal response can impair performance on a simple motor task. *J. Appl. Physiol.* 91, 821–831.

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

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

Peinemann, A., Lehner, C., Conrad, B., and Siebner, H. R. (2001). Age-related decrease in paired-pulse intracortical inhibition in the human primary motor cortex. *Neurosci. Lett.* 313, 33–36. doi:10.1016/S0304-3940(01)02239-X

Raz, N., Rodrigue, K. M., and Haacke, E. M. (2007). Brain aging and its modifiers: insights from in vivo neuromorphometry and susceptibility weighted imaging. *Ann. N. Y. Acad. Sci.* 1097, 84–93. doi:10.1196/annals.1379.018

Reynolds, C. C., and Meltzer, C. F. (1999). In vivo assessment of aging changes in serotonin function. *Neuropsychopharmacology* 21, 323–324. doi:10.1016/S0893-133X(99)00058-5

Riley, Z. A., Maerz, A. H., Litsey, J. C., and Enoka, R. M. (2008). Motor unit recruitment in human biceps brachii during sustained voluntary contractions. *J. Physiol.* 586, 2183–2193. doi:10.1113/jphysiol.2008.150698

Sale, M. V., and Semmler, J. G. (2005). Age-related differences in corticospinal control during functional isometric contractions in left and right hands. *J. Appl. Physiol.* 99, 1483–1493. doi:10.1152/japplphysiol.00371.2005

Schweizer, S., Grahn, J., Hampshire, A., Mobbs, D., and Dalgleish, T. (2013). Training the emotional brain: improving affective control through emotional working memory training. *J. Neurosci.* 33, 5301–5311. doi:10.1523/JNEUROSCI.2593-12.2013

Seals, D. R., and Esler, M. D. (2000). Human ageing and the sympathoadrenal system. *J. Physiol.* 528, 407–417. doi:10.1111/j.1469-7793.2000.00407.x

Seidler-Dobrin, R. D., and Stelmach, G. E. (1998). Persistence in visual feedback control by the elderly. *Exp. Brain Res.* 119, 467–474. doi:10.1007/s002210050362

Sommervoll, Y., Ettema, G., and Vereijken, B. (2011). Effects of age, task, and frequency on variability of finger tapping. *Percept. Mot. Skills* 113, 647–661. doi:10.2466/10.25.PMS.113.5.647-661

Sosnoff, J. J., and Newell, K. M. (2006). The generalization of perceptual-motor intra-individual variability in young and old adults. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 61, 304–310. doi:10.1093/geronb/61.5.P304

Spielberger, C. D., Gorsuch, R. L., and Lushene, R. D. (1970). *STAI: Manual for the State-Trait Anxiety Inventory.* Palo Alto, CA: Consulting Psychologists Press.

Takahara, D., Inoue, K., Hirata, Y., Miyachi, S., Nambu, A., Takada, M., et al. (2012). Multisynaptic projections from the ventrolateral prefrontal cortex to the dorsal premotor cortex in macaques – anatomical substrate for conditional visuomotor behavior. *Eur. J. Neurosci.* 36, 3365–3375. doi:10.1111/j.1460-9568.2012.08251.x

Taylor, A. M., Christou, E. A., and Enoka, R. M. (2003). Multiple features of motor-unit activity influence force fluctuations during isometric contractions. *J. Neurophysiol.* 90, 1350–1361. doi:10.1152/jn.00056.2003

Tracy, B. L. (2007). Force control is impaired in the ankle plantarflexors of elderly adults. *Eur. J. Appl. Physiol.* 101, 629–636. doi:10.1007/s00421-007-0538-0

Tracy, B. L., Dinenno, D. V., Jorgensen, B., and Welsh, S. J. (2007). Aging, visuomotor correction, and force fluctuations in large muscles. *Med. Sci. Sports Exerc* 39, 469–479. doi:10.1249/mss.0b013e31802d3ad300005768-200703000-00010

Tracy, B. L., and Enoka, R. M. (2002). Older adults are less steady during submaximal isometric contractions with the knee extensor muscles. *J. Appl. Physiol.* 92, 1004–1012. doi:10.1152/japplphysiol.00954.2001

Tracy, B. L., Maluf, K. S., Stephenson, J. L., Hunter, S. K., and Enoka, R. M. (2005). Variability of motor unit discharge and force fluctuations across a range of muscle forces in older adults. *Muscle Nerve* 32, 533–540. doi:10.1002/mus.20392

Tzourio, C. (2007). Hypertension, cognitive decline, and dementia: an epidemiological perspective. *Dialogues Clin. Neurosci.* 9, 61–70.

Tzourio, C., Dufouil, C., Ducimetiere, P., and Alperovitch, A. (1999). Cognitive decline in individuals with high blood pressure: a longitudinal study in the elderly. *Neurology* 53, 1948–1952. doi:10.1212/WNL.53.9.1948

Voelcker-Rehage, C., and Alberts, J. L. (2007). Effect of motor practice on dual-task performance in older adults. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 62, 141–148. doi:10.1093/geronb/62.3.P141

Voelcker-Rehage, C., Stronge, A. J., and Alberts, J. L. (2006). Age-related differences in working memory and force control under dual-task conditions. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn.* 13, 366–384. doi:10.1080/138255890969339

Wasmund, W. L., Westerholm, E. C., Watenpaugh, D. E., Wasmund, S. L., and Smith, M. L. (2002). Interactive effects of mental and physical stress on cardiovascular control. *J. Appl. Physiol.* 92, 1828–1834. doi:10.1152/japplphysiol.00019.2001

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

Yogev-Seligmann, G., Hausdorff, J. M., and Giladi, N. (2008). The role of executive function and attention in gait. *Mov. Disord.* 23, 329–342; quiz 472. doi:10.1002/mds.21720

Yoon, T., Keller, M. L., De-Lap, B. S., Harkins, A., Lepers, R., and Hunter, S. K. (2009). Sex differences in response to cognitive stress during a fatiguing contraction. *J. Appl. Physiol.* 107, 1486–1496. doi:10.1152/japplphysiol.00238.2009

Yoon, T., De-Lap, B. S., Griffith, E. E., and Hunter, S. K. (2008). Age-related muscle fatigue after a low-force fatiguing contraction is explained by central fatigue. *Muscle Nerve* 37, 457–466. doi:10.1002/mus.20969

Zijdewind, I., Van Duinen, H., Zielman, R., and Lorist, M. M. (2006). Interaction between force production and cognitive performance in humans. *Clin. Neurophysiol.* 117, 660–667. doi:10.1016/j.clinph.2005.11.016

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

Received: 03 March 2014; accepted: 05 May 2014; published online: 22 May 2014.
Citation: Vanden Noven ML, Pereira HM, Yoon T, Stevens AA, Nielson KA and Hunter SK (2014) Motor variability during sustained contractions increases with cognitive demand in older adults. Front. Aging Neurosci. ***6****:97. doi: 10.3389/fnagi.2014.00097*
This article was submitted to the journal Frontiers in Aging Neuroscience.

frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 14 July 2014
doi: 10.3389/fnagi.2014.00158

Safety margins in older adults increase with improved control of a dynamic object

Christopher J. Hasson[1]* and Dagmar Sternad[2]

[1] Neuromotor Systems Laboratory, Department of Physical Therapy, Movement and Rehabilitation Sciences, Northeastern University, Boston, MA, USA
[2] The Action Lab, Departments of Biology, Electrical and Computer Engineering, and Physics, Northeastern University, Boston, MA, USA

Edited by:
S. Lee Hong, Ohio University, USA

Reviewed by:
Matjaž Perc, University of Maribor, Slovenia
Hannah Justine Block, Indiana University, USA

***Correspondence:**
Christopher J. Hasson, Neuromotor Systems Laboratory, Department of Physical Therapy, Movement and Rehabilitation Sciences, Bouvé College of Health Sciences, Northeastern University, 360 Huntington Ave., 301 Robinson Hall, Boston, MA 02115-5005, USA
e-mail: c.hasson@neu.edu

Older adults face decreasing motor capabilities due to pervasive neuromuscular degradations. As a consequence, errors in movement control increase. Thus, older individuals should maintain larger safety margins than younger adults. While this has been shown for object manipulation tasks, several reports on whole-body activities, such as posture and locomotion, demonstrate age-related reductions in safety margins. This is despite increased costs for control errors, such as a fall. We posit that this paradox could be explained by the dynamic challenge presented by the body or also an external object, and that age-related reductions in safety margins are in part due to a decreased ability to control dynamics. To test this conjecture we used a virtual ball-in-cup task that had challenging dynamics, yet afforded an explicit rendering of the physics and safety margin. The hypotheses were: (1) When manipulating an object with challenging dynamics, older adults have smaller safety margins than younger adults. (2) Older adults increase their safety margins with practice. Nine young and 10 healthy older adults practiced moving the virtual ball-in-cup to a target location in exactly 2 s. The accuracy and precision of the timing error quantified skill, and the ball energy relative to an escape threshold quantified the safety margin. Compared to the young adults, older adults had increased timing errors, greater variability, and decreased safety margins. With practice, both young and older adults improved their ability to control the object with decreased timing errors and variability, and increased their safety margins. These results suggest that safety margins are related to the ability to control dynamics, and may explain why in tasks with simple dynamics older adults use adequate safety margins, but in more complex tasks, safety margins may be inadequate. Further, the results indicate that task-specific training may improve safety margins in older adults.

Keywords: aging, safety margin, human, dynamics, object manipulation, motor control, motor learning

INTRODUCTION

With aging comes an array of neuromuscular changes, such as weaker muscles, increased neural delays, and greater neuromuscular noise (Salthouse, 1996; Goodpaster et al., 2006), which together contribute to declines in motor function (Aoyagi and Shephard, 1992). Not only are the performance capabilities of older adults more limited than those of younger adults, the consequences of control errors are also more severe. This is particularly the case for locomotor activities, where a fall can cause life-threatening injuries (Berg et al., 1997). This combination of age-related neuromuscular degradations and greater costs of failure makes the maintenance of adequate safety margins a critical concern for older adults.

A common paradigm for studying safety margins is manipulation tasks, which often involve transporting a hand-held object. Here, the safety margin is typically defined as the difference between the grip force and the force required to prevent object slippage. Young adults are able to precisely regulate their grip force in response to varying object masses, staying just above the slip threshold (Johansson and Westling, 1984; Johansson and Cole, 1992). Young adults also modulate their grip force in response to load fluctuations during object acceleration (Flanagan and Wing, 1990, 1993). While older adults show similar patterns of adaptation, they generally produce higher grip forces compared to young adults (Cole, 1991; Cole and Beck, 1994; Gilles and Wing, 2003). This increases the safety margin against object slippage, which may be needed due to impaired control related to decrements in afferent function (Cole et al., 1999).

Although an age-related elevation in safety margins for object manipulation tasks is consistent with expectations, the opposite has been observed in whole-body activities, particularly locomotion and postural control. In locomotor tasks foot-obstacle clearance is critical. A small clearance implies a low safety margin against tripping. During level walking young and older adults maintain similar clearances (Winter et al., 1990). However, when the locomotor challenge is increased by adding different terrain features, older adults show reduced clearances. This includes when stepping over obstacles (McFadyen and Prince, 2002), stepping onto a raised platform (Begg and Sparrow, 2000), or descending stairs (Hamel et al., 2005). Older adults also show reduced safety margins in postural control. During upright standing older adults have reduced spatiotemporal margins of stability, which increases the risk of a fall (Slobounov et al., 1998; Van Wegen et al., 2002). Considering these observations, it appears paradoxical that in situations that warrant a larger safety margin due to more serious consequences of failure, e.g., falling, older adults use smaller, and not larger safety margins compared to young adults.

We posit that this paradox can be explained by the dynamic challenge presented by an activity or task. In grip force studies on age-related differences in object manipulation, the objects are usually rigid blocks with no further dynamics (Cole, 1991; Cole and Beck, 1994; Gilles and Wing, 2003). Changes in the load presented by the object are a linear function of the object's acceleration. On the other hand, in postural control and locomotion, the trajectory of the legs and center-of-mass are a complex function of inertial, ground reaction, and interaction forces between numerous body segments (Onyshko and Winter, 1980). In this case, older adults might be unable to control the dynamics of the body well enough to maintain adequate safety margins. In addition, in unpracticed tasks or novel dynamical experiences, individuals may be unable to utilize appropriate safety margins until sufficient skill is obtained. This is consistent with a report that in young adults improvements in performance on a virtual ball-in-a-cup transportation task are accompanied by increased safety margins (Hasson et al., 2012b).

We hypothesize that if safety margins depend on the ability to control object dynamics, then in a dynamically challenging task, older adults should have smaller safety margins than young adults (Hypothesis 1), but should increase their safety margins as their task performance improves with practice (Hypothesis 2). To test these hypotheses we used the task of moving a virtual ball-in-a-cup, representing a cup of coffee, to a target location (Hasson et al., 2012a,b; Sternad et al., 2014; Ye et al., 2014). This object has non-trivial dynamics and affords an explicit understanding of the object dynamics and a quantitative definition of the safety margin. The latter was defined as the ball energy relative to the energy needed to escape the cup. Young and older adults were asked to practice transporting the ball-and-cup to the target location in a time of exactly 2-s without letting the ball escape. This timing constraint prevented subjects from using a slowing strategy to increase safety margins but was still not fast enough to permit a range of movement strategies to achieve the task goal. Performance was assessed by the accuracy and precision of the timing error relative to the 2-s target time.

METHODS

PARTICIPANTS

Nine young subjects (21–35 years) and 10 healthy older adults (65–80 years) practiced moving a virtual cup and ball to a target point in 2 s. Data on the young subjects was previously reported in Hasson et al. (2012b). The older subjects were all community dwelling, ambulatory, independent, and had no major musculoskeletal problems affecting upper body control, and no major neurological problems. Prior to participating, subjects were given a mini-mental state exam to assess cognitive function (Folstein et al., 1975); all participants scored above 23 and were therefore eligible to participate (Tombaugh and McIntyre, 1992). Before participating, subjects were informed of all experimental procedures and read and signed an informed consent document approved by the Institutional Review Board at Northeastern University.

BALL AND CUP SIMULATION

The dynamics of the ball and cup object were based on that of a cart and pendulum system (**Figure 1A**). The cart and pendulum were haptically rendered with a robotic manipulandum (Haptic Master, Moog, Netherlands; Van der Linde and Lammertse, 2003). Details of the instrumentation are in Hasson et al. (2012b). A visual display on a rear-projection screen 2.4 m away showed the pendulum bob and a shallow "cup" drawn as an arc; the cart and the pendulum rod were not shown on the screen (**Figure 1B**). For subjects it appeared as if they were controlling a cup with a ball rolling inside, where the cup imposed an angular constraint on the ball. If the angle of the ball θ exceeded the maximum angle subtended by the cup, termed the escape angle $\theta_{ESC}(\theta_{ESC} = 35°)$, the ball escaped and visually "fell" out of the cup.

Subjects could manipulate the ball and cup object by applying horizontal forces to the manipulandum, which in turn accelerated the cart (cup) and the pendulum bob (ball). Forces could only be applied to the cup, and the moving ball exerted forces on the cup that subjects could feel through the manipulandum. The motion of the cup was confined to a horizontal line, and the ball could pivot about the pendulum axis of rotation, thus the system had two mechanical degrees of freedom. The cart and pendulum

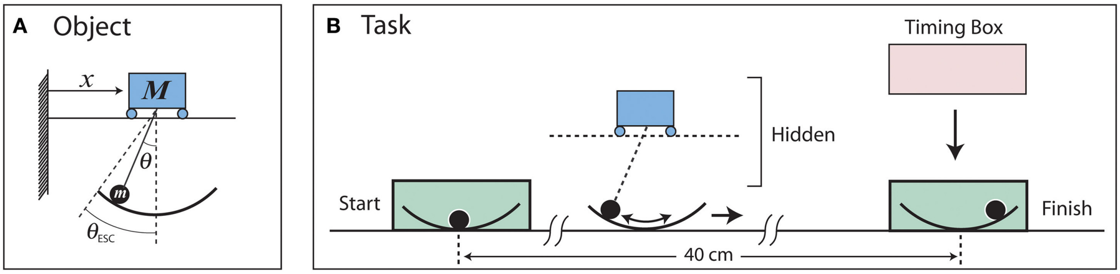


FIGURE 1 | (A) Model of the cart and pendulum system with variables and parameters. **(B)** Task implementation. The visual display showed the pendulum bob and an arc drawn for the cup; the cart and pendulum were not shown. The cart and pendulum were haptically rendered with a robotic manipulandum. Subjects applied forces to the manipulandum, which in turn accelerated the cart (cup) and pendulum bob (ball).

system behavior was governed by two equations of motion:

$$(m + M)\,\ddot{x} = F_A + F_B \tag{1}$$

and

$$\ddot{\theta} = \frac{\ddot{x}}{\ell}\cos\theta - \frac{g}{\ell}\sin\theta \tag{2}$$

where M is the cup mass ($M = 3.5\,\text{kg}$), m is the ball mass ($m = 0.3\,\text{kg}$), $\theta, \dot{\theta}$, and $\ddot{\theta}$ are the ball angle, angular velocity, and angular acceleration, respectively; $\ddot{x}$ is the cup's horizontal acceleration, ℓ is the pendulum length ($\ell = 0.35$ m), g is gravitational acceleration ($9.81\,\text{m/s}^2$), F_A is an external horizontal force applied to the cup by a human actor, and F_B is the horizontal reaction force of the ball on the cup, given by

$$F_B = m\ell\ddot{\theta}\cos\theta - m\ell\dot{\theta}^2\sin\theta. \tag{3}$$

Details of the derivation of the equations of motion are in Hasson et al. (2012b).

TASK

Subjects were asked to transport the ball-and-cup to a spatial target located 0.4 m away in a target time of 2.0 s without letting the ball escape from the cup (**Figure 1B**). The 2.0 s movement time was a "comfortable" time for healthy young subjects. Because the task goal was not a limit performance, i.e., as fast as possible, a number of movement strategies could be used to complete the task in the target time; some strategies would be riskier than others, i.e., some would carry a greater risk of losing the ball. To prevent participants from spending a disproportional amount of time trying to keep the cup still in the goal region, the goal box was made "sticky" by applying a damping force $F_\text{D} = -26\dot{x}$ to the cup when both edges of the cup were inside the goal.

VISUAL FEEDBACK

Two filled green rectangles were displayed, one serving as the start box and one as the goal box. The timing error was signaled with a "timing box" that descended onto the spatial target with a constant velocity so that it passed through the target at a time of 2.0 s. The timing box stopped moving when the cup was brought to a stop ($\dot{x} < 0.02\,\text{m/s}$). If the cup stopped too early (<2.0 s), the timing box was above the spatial target, if too late (>2.0 s), the timing box stopped below the spatial target. At the end of the trial, subjects were shown their temporal error in numeric form.

PROTOCOL

Data were collected while the participants practiced the transportation task in four blocks of 60 trials (240 total), with brief breaks between blocks.

ENERGY MARGIN

The "safety" or "riskiness" of a movement strategy was determined by computing the energy margin EM as

$$EM = \left(E_{ESC} - TE_{BALL}\right)/E_{ESC} \tag{4}$$

where

$$E_{ESC} = mg\ell\left(1 - \cos\theta_{ESC}\right) - m\left|\ddot{x}\right|\ell\sin\theta_{ESC} + m\left|\ddot{x}\right|\ell \tag{5}$$

and

$$TE_{BALL} = \frac{1}{2}m\left(\ell\dot{\theta}\right)^2 + mg\ell\left(1 - \cos\theta\right) + PSE_{BALL} \tag{6}$$

where

$$PSE_{BALL} = \begin{cases} \ddot{x} \geq 0 & -m\ddot{x}\ell\sin\theta + m\ddot{x}\ell \\ \ddot{x} < 0 & -m\ddot{x}\ell\sin\theta - m\ddot{x}\ell \end{cases}. \tag{7}$$

The escape energy E_{ESC} defined the instantaneous energy threshold for ball escape. If the ball's total energy TE_{BALL} was below E_{ESC}, then the ball just oscillated within the cup and did not escape (assuming constant $\ddot{x}$). Otherwise, the ball would escape in the future (unless $\ddot{x}$ was changed). Note that E_{ESC} depended on $\ddot{x}$ and therefore changed during cup transportation.

The energy margin EM represented how close the current ball energy was to exceeding E_{ESC}. If EM was between 0 and 1, the ball did not escape. However, it would escape if EM was negative, assuming $\ddot{x}$ was not changed. It should be emphasized that EM extrapolated, i.e., it took the instantaneous energy of the ball and predicted whether the ball would escape in the future with constant $\ddot{x}$. Accordingly, E_{ESC} was not a "hard" constraint and could be exceeded for brief periods, provided an appropriate and timely correction was made before the ball reached the cup rim.

DEPENDENT VARIABLES

Manipulation ability was quantified with measures related to the goal of the task: the average and standard deviation of the absolute movement timing error across trials (MTE_{AVG} and MTE_{STD}, respectively). The timing error was the absolute value of the difference between subjects' movement time and the 2.0 s target time. A subject with high manipulation ability should be able to reach the goal accurately (small MTE_{AVG}) and reliability (small MTE_{STD}). The safety margin was quantified via the average energy margin EM_{AVG} and standard deviation of EM across multiple trials EM_{STD}. All measures (MTE_{AVG}, MTE_{STD}, EM_{AVG}, and EM_{STD}) were computed across the first 30 trials (excluding the first two trials) of Block 1 and the last 30 trials of Blocks 2–4.

DATA ANALYSIS

All data analysis was performed with MATLAB (R2012b, MathWorks, Natick, MA, USA). The raw data included time histories for $x, \dot{x}, \ddot{x}, \theta, \dot{\theta}, \theta, \ddot{\theta}$ and F_A, which were filtered with a dual-pass fourth-order low-pass Butterworth digital filter, and used to calculate the dependent variables (MTE_{AVG}, MTE_{STD}, EM_{AVG}, and EM_{STD}). Only trials in which the target location was reached and the ball was not dropped were analyzed. To facilitate averaging movement patterns across subjects for graphical presentation, time histories were normalized to a unitary movement time (0–100%) using linear interpolation.

STATISTICS

All statistical tests were performed with SPSS (Version 21, IBM Corporation, Armonk, NY, USA). A repeated-measures ANOVA was performed for each dependent variable with age as a between-subjects factor and practice block as a within-subjects factor. For all statistical tests, two subjects in the young group were identified as outliers and excluded. In contrast to the other seven subjects in the group, these subjects increased the variability of their movement patterns and used a different high-acceleration movement strategy (see Hasson et al., 2012b for more details). One subject in the older group was excluded due to excessively poor performance on the task. When appropriate, *post-hoc* comparisons were performed using Tukey's honestly significant difference test. Significance was set at $p < 0.05$ for all tests.

RESULTS

GENERAL TASK CHARACTERISTICS

The averaged ball and cup kinematics and kinetics for the young and older subjects in early and late practice are shown in **Figure 2A**. The ball and cup transit was divided into three phases. (1) Subjects applied a positive force to the cup, which accelerated the cup toward the spatial target and caused the ball to move backwards toward the rim of the cup (**Figure 2B**). These events caused the energy margin *EM* to rapidly decrease. If the force that accelerated the cup was too high, the *EM* could become negative and the ball may exceed the escape angle. (2) Subjects reduced their applied force as the cup reached the center of the workspace and the ball descended toward the center of the cup. (3) Subjects applied forces counter to the cup motion, which brought the cup to a stop at the spatial target; this was by far the riskiest part of the movement, highlighted by the rapid *EM* decrease. In early practice, the older adults applied more force to the ball at the start of each trial, causing the cup velocity to increase faster, the ball to move more, and consequently, the *EM* to decrease faster. In

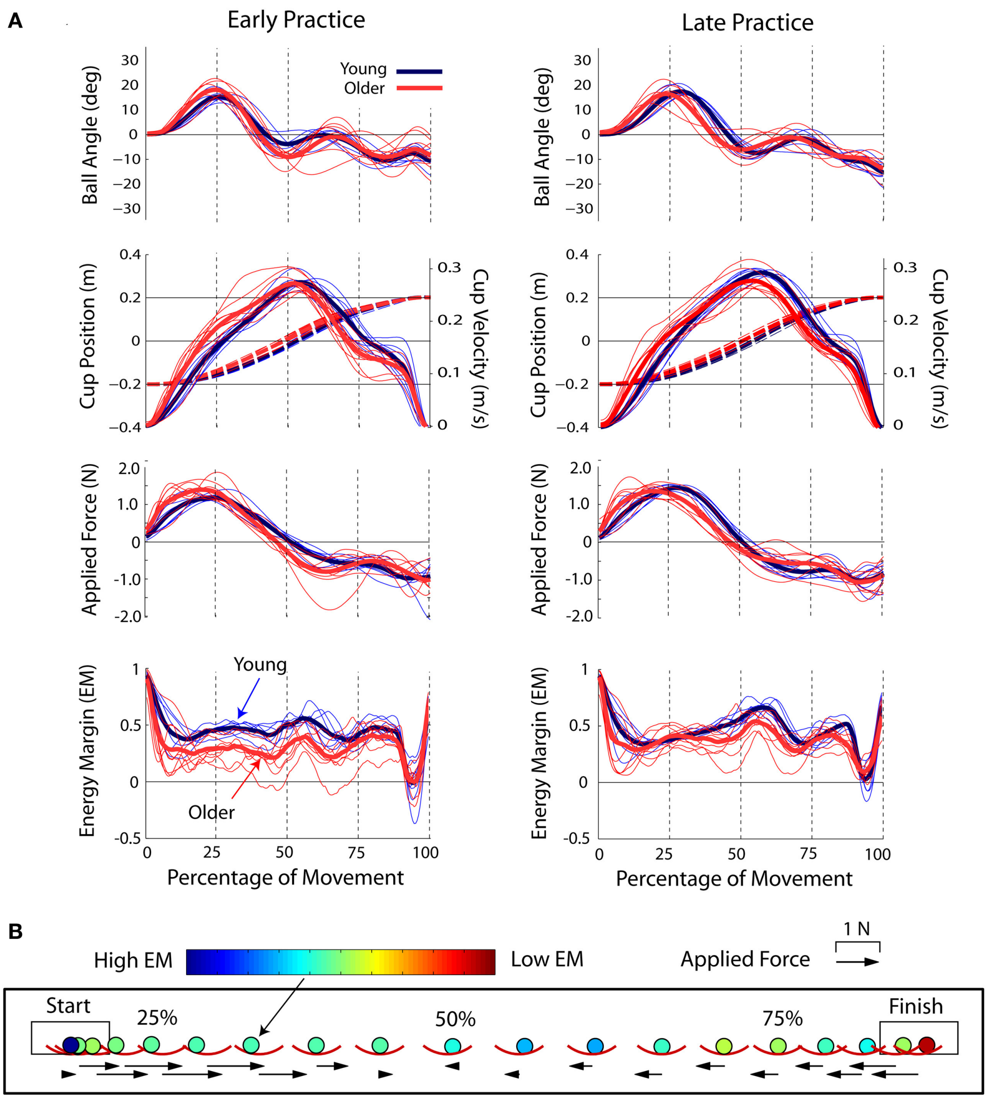


FIGURE 2 | (A) Ball angle, cup position (dashed lines), and velocity, applied force, and energy margin for the young (blue) and older (red) subjects. Individual subjects are shown as thin lines, group averages are the thick lines. **(B)** Example of a representative ball and cup transit of an older subject in late practice [shown in **(A)**]. Images are at 5% increments of the total movement time. The color of the ball represents the energy margin; dark blue represents a high energy margin ("safe") and dark red represents a low energy margin ("unsafe"). The arrows scale with the force applied to the cup. The size of the ball was enlarged for clarity.

early practice, the ball oscillation amplitudes remained larger in the older adults until the last quarter of the movement. In contrast, in late practice, the older adults reduced these amplitudes to be similar to the young adults, and therefore the *EM* was raised.

FAILURES

Overall the older adults had a higher failure rate, i.e., lost the ball more frequently, compared to young adults [main effect $F_{(1,\ 15)} = 6.8$; $p < 0.021$; **Figure 3A**]. Both groups decreased their failure rate with practice [main effect $F_{(3,\ 45)} = 5.7$; $p < 0.007$], but this decrease did not differ between the groups (i.e., no interaction; $p = 0.392$). For both young and old subjects, the point at which the ball was most likely to escape from the cup was when arriving at the goal (**Figure 3B**).

TASK PERFORMANCE

Performance was quantified with measures of timing accuracy and precision. Both young and older subjects decreased their average timing error MTE_{AVG} with practice [main effect $F_{(3,\ 45)} = 20.2$; $p < 0.001$; **Figure 4A**]. MTE_{AVG} in block 1 was higher than in blocks 2–4 ($p = 0.001$), errors in block 2 were higher than block 3 ($p = 0.034$), but not different from block 4 ($p = 0.546$). Blocks 3 and 4 were not different ($p = 0.195$). The young subjects had smaller MTE_{AVG} compared to older subjects [main effect $F_{(1,\ 15)} = 29.9$; $p < 0.001$]. There was no MTE_{AVG} interaction between the two factors practice and age ($p = 0.662$). The trial-to-trial variability of the timing error MTE_{STD} decreased with practice [main effect $F_{(3,\ 45)} = 15.7$; $p < 0.001$; **Figure 4B**]. MTE_{STD} in block 1 was higher than in blocks 2–4 ($p < 0.001$), but blocks 2–4 were not different from each other ($p > 0.759$ for all comparisons). The young subjects had smaller MTE_{STD} compared to older subjects [main effect $F_{(1,\ 15)} = 37.5$; $p < 0.001$]. There was no MTE_{STD} interaction between the factors practice and age ($p = 0.558$).

ENERGY MARGIN

The safety margin was quantified in terms of an energy margin *EM*. An illustration of the *EM* and an exemplar early-practice *EM* time-history is shown for one older participant (**Figure 5**). The *EM* depends on the ball angle and angular velocity and cup acceleration, and therefore varied as these variables changed during a cup transit. When $EM > 0$ (light blue shading; **Figure 5A**), the ball will never escape from the cup, given the current cup acceleration. At the next instant in time the cup acceleration could change, which would update *EM*. An $EM \leq 0$ (light red shading; **Figure 5A**) signals that the ball will escape from the cup given the current cup acceleration. Therefore a corrective action is needed to keep the ball in the cup. For the latter case, the time-to-escape is shown (dashed red lines; **Figure 5A**). For $EM > 0$ the time-to-escape is infinite (the ball will just oscillate within the cup).

The critical energy threshold at $EM = 0$ is the escape energy E_{ESC}. This threshold can be visualized as a two-dimensional manifold in the three-dimensional task execution space (blue mesh; **Figure 5B**). Each cup transit forms a trajectory in this space; as long as the trajectory stays inside E_{ESC} manifold, the ball is not in danger of escaping from the cup. As shown in **Figure 6**, early in practice subjects typically had high trial-to-trial variability and frequently exceeded E_{ESC}. However, with practice the trajectories conformed to stay largely within the E_{ESC} manifold, except for the period of high deceleration at the end of the cup transit.

EM_{AVG} was higher in young subjects compared to older subjects [main effect $F_{(1,\ 15)} = 17.6$; $p < 0.001$; **Figure 7A**]. There was a significant effect of practice [main effect $F_{(3,\ 45)} = 7.0$; $p = 0.001$], but no interaction between age and practice ($p = 0.078$). For both the young and older subject groups, EM_{AVG} in blocks 2–4 was greater than in block 1 ($p < 0.018$), but blocks 2–4 were not different from each other ($p > 0.7$ for all comparisons). EM_{STD} was lower in young subjects compared to older subjects [main effect $F_{(1,\ 15)} = 18.3$; $p < 0.001$; **Figure 7B**], there was a significant effect of practice [main effect $F_{(1,\ 15)} = 18.5$; $p \leq 0.001$], but no interaction between age and practice ($p = 0.146$).

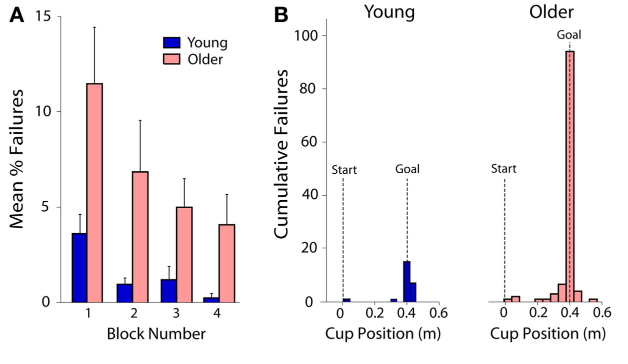


FIGURE 3 | (A) Both young and older subjects decreased their failure rate with practice, but older adults failed more often overall. Failure was defined when the ball exceeded the escape angle. The bars show the mean percentage of failures for young (blue bars) and older (red bars) across the four blocks of practice. Error bars show standard error. Each block includes 60 trials. **(B)** Failure rate as a function of cup position for young and old subjects separately. By far the riskiest part of the ball and cup transit was stopping in the goal (at 0.4 m). Shown is the number of failed trials across all subjects as a function of the cup position at the time of failure.

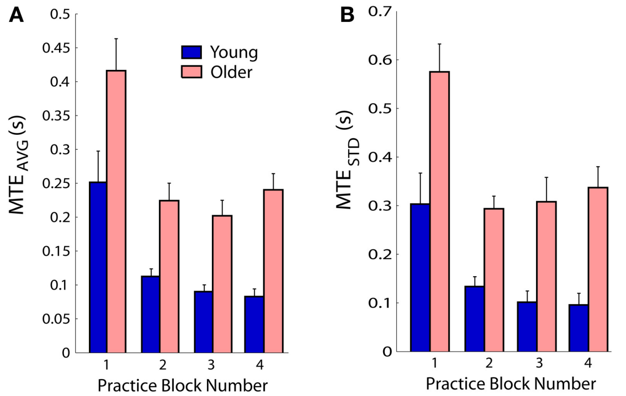


FIGURE 4 | (A) Average movement time error MTE_{AVG} improved with practice in both young and older subjects. **(B)** Trial-to-trial variability of movement time error MTE_{STD} decreased. Age-related differences in manipulation ability were reflected by main effects of age for MTE_{AVG} and MTE_{STD}. Error bars show standard errors; each block included 60 trials.

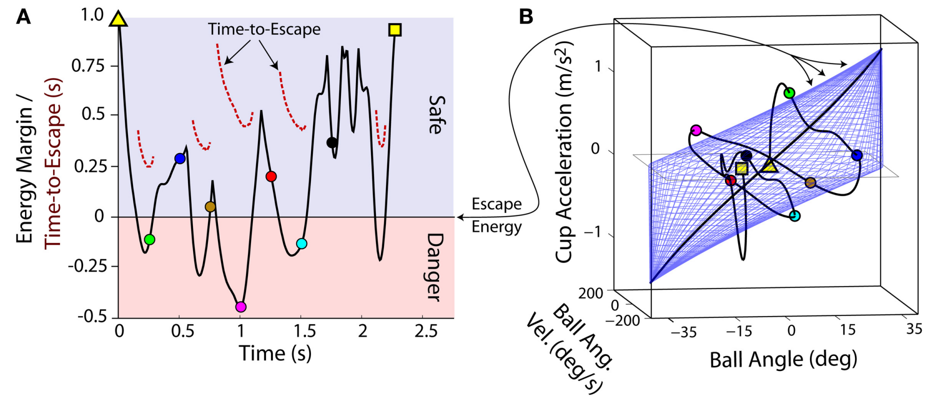


FIGURE 5 | (A) The energy margin *EM* as a function of time (black line) in one early practice trial for one older subject. If $EM > 0$, the ball will never escape from the cup, if the current cup acceleration is maintained. However, if $EM \leq 0$ the ball will escape from the cup, unless the cup acceleration is changed. For the latter case, the time-to-escape is shown (dashed red lines); for $EM > 0$ the time-to-escape is infinite (the ball will oscillate within the cup). **(B)** For the same trial, the three variables that determine *EM*, ball angle and angular velocity and cup acceleration, are shown in a three dimensional task execution space. The trial starts in the center (yellow triangle) and moves through the execution space as the trial progresses until the cup is stopped at the spatial target (yellow square). The blue mesh represents the critical *EM* level, i.e., where $EM = 0$. The colored circles provide timing landmarks every 0.25 s.

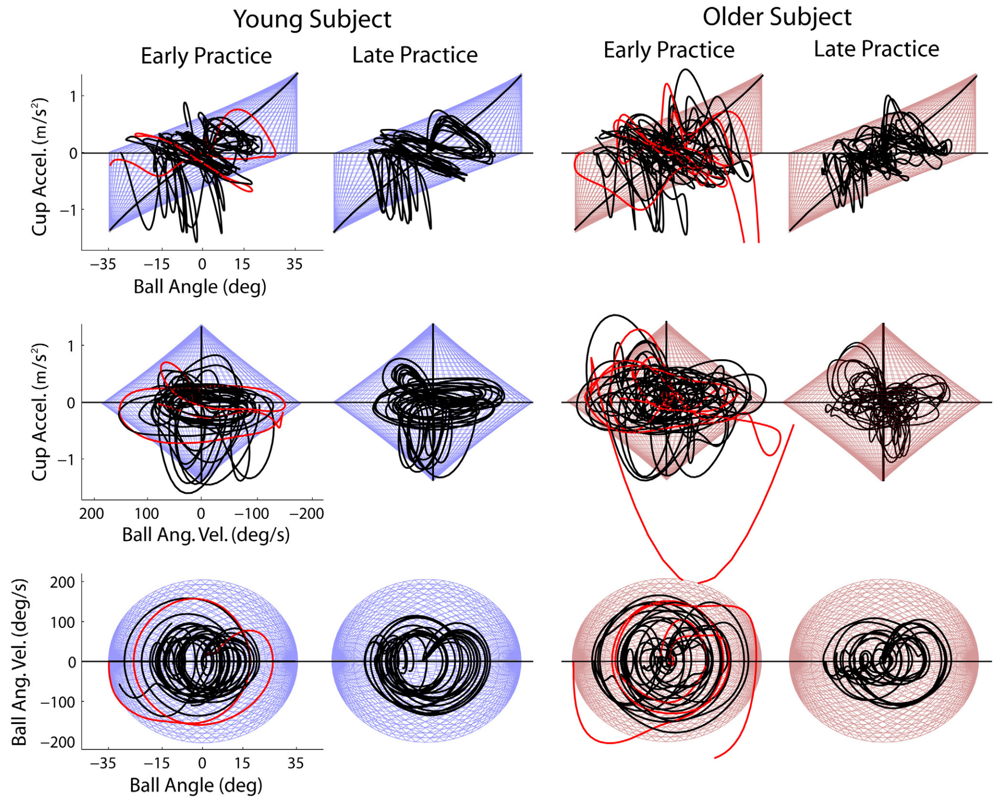


FIGURE 6 | Examples of early and late practice trials for a young and older subject. Trajectories are plotted in the execution space, defined by ball angle and velocity and cup acceleration. Three different views of the three-dimensional execution space are shown (three rows). Trials in which the ball escaped are shown in red.

DISCUSSION

Throughout practice of the virtual ball-and-cup transportation task the older adults employed a smaller safety margin, quantified in terms of an energy margin, than the younger adults, supporting hypothesis 1. Both the young and older adults increased their safety margins with practice, supporting hypothesis 2. This suggests that safety margins are learning-dependent, i.e., they were small when performance was low in

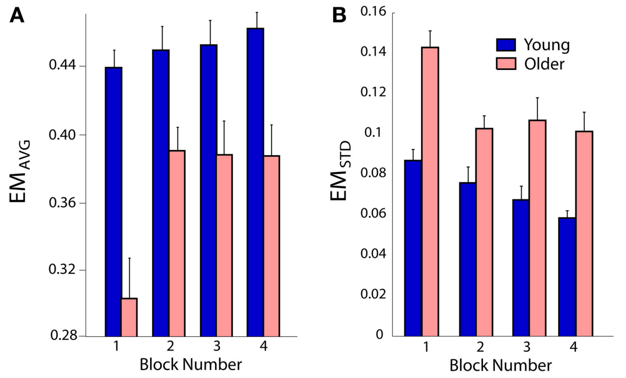


FIGURE 7 | (A) Both young and old subjects increased their mean energy margin EM_{AVG}. **(B)** Variability of EM_{STD} decreased from trial to trial. Overall the older subjects had smaller and more variable energy margins. Error bars show standard error; each block included 60 trials.

early skill acquisition, but increased in parallel to other performance measures.

SAFETY MARGINS AND AGE

The older adults used a movement strategy that was less safe than the young adults, placing them at a greater risk of failure, as shown by the greater number of ball escapes. This age-related reduction in safety margins is at odds with grip force studies that showed increased safety margins in older adults (Cole, 1991; Cole and Beck, 1994; Gilles and Wing, 2003). This could be explained by the dynamic challenges presented by the tasks. In the grip force studies (using older adults) the objects had rigid-body dynamics, i.e., the load was a linear function of the object's acceleration; the safety margins depended on only the ratio between the grip and load forces (Flanagan and Wing, 1990). In this case, the older adults may have been better able to predict the consequences of their manipulative actions, and therefore were able to maintain large safety margins. However, the increased dynamic challenge presented by the ball-and-cup object may have made it more difficult for the older adults to predict how the object would behave, reducing their ability to control the object and consequently maintain a sufficient safety margin. Note that the safety margin in the ball-and-cup task is a dynamic quantity that is a nonlinear function of three variables: the ball angle, the ball angular velocity, and the cup acceleration (Hasson et al., 2012b). The relatively smaller safety margins in the older adults is consistent with observations from whole-body tasks, such as posture and locomotion, in which older adults show reduced safety margins compared to younger adults (Slobounov et al., 1998; Begg and Sparrow, 2000; McFadyen and Prince, 2002; Van Wegen et al., 2002; Hamel et al., 2005). Together, the results of these studies suggest a link between the ability to control the dynamics of an object and the use of safety margins.

SAFETY MARGINS AND TASK PERFORMANCE

The connection between manipulation ability and safety margins is strengthened by the changes observed throughout practice. Despite having overall lower safety margins and performance (accuracy and precision), the older adults increased their safety margins by about 30% and improved performance by about 50%. These changes occurred almost entirely within the first half of task practice. In contrast, the young subjects showed much smaller increases (approximately 7%), and continued to improve their performance and increased safety margins throughout practice. The smaller relative increase in the younger adults could be due to a ceiling effect. Increases in the safety margin were paralleled by a decrease in the task failure rate, which over practice decreased by more than half in the older subjects. In young adults, it was reduced to almost zero. While changes in older subject task performance and safety margins leveled off with practice, the failure rate continued to decrease. This could be related to the binary nature of the failure rate, a large decrease in the failure rate could arise from a very small change in the safety margin if close to the safety margin threshold. Indeed, as shown in **Figure 2**, both young and older subjects came very close to the threshold as they brought the cup to the goal. This remained a "dangerous" point even after the practice period. Note that the safety margin does not necessarily increase with improvements in task performance, i.e., the safety margin could vary independently from the goal (accuracy and precision of the timing error) due to task redundancy afforded by the specification of a 2-s target time.

The reduced performance and lower safety margins of the older adults may be due to a combination of physiological limitations, such as less reliable sensory information (Light, 1990), slower sensory integration and cognitive processing (Myerson et al., 1990; Bashore et al., 1997), and increased neural noise and delays (Laidlaw et al., 2000; Pannese, 2011). Together, these changes may limit the ability of older subjects to make fast compensatory actions to keep the ball from escaping the cup, especially at the end of the movement, where the older adults had the lowest safety margin and lost the ball most frequently. Although the data are consistent with the hypothesis that safety margins are related to the ability of the older adults to control dynamics, a more nuanced view would suggest that additional factors might play a role in regulating safety margins. Maintaining large safety margins may incur an energy cost, i.e., lifting the foot high over an obstacle would require more effort than just clearing the obstacle (Chou et al., 1997). Large safety margins may also limit maneuverability, e.g., in posture keeping a large stability margin reduces the ability to make quick postural changes (Huang and Ahmed, 2011).

IMPLICATIONS AND APPLICATIONS

The task constraints imposed in the experiment raise the question of how these results may relate to the real world. The results show that, given a shallow cup and constrained movement time, older adults are less safe than younger adults. Instead of increasing their safety margins by improving their ability to control the dynamics of the ball and cup object, in real life older adults could take other steps to increase their safety margins. They could choose a very deep cup, place a lid on the cup, or move more slowly. The latter could reduce the cup accelerations, leading to less ball movement and therefore a greater safety margin. Along the same lines, older adults can increase the safety margins in activities like posture and locomotion by either walking more slowly and/or increasing the size of their base of support.

Experimentally, increasing the dynamic challenge presented to the subjects by adding movement time constraints had two key benefits. First, by stressing the neuromuscular system, limitations become clearer (Guadagnoli and Lee, 2004). If we had allowed subjects to slow down, it would have been unlikely that the age differences in safety margins would have been as large. In locomotor studies, if subjects walk on a level ground with no obstacles or cognitive challenges, there are no age differences in the safety margin (Winter et al., 1990). Second, there may be some instances in daily life, which preclude options, such as "slowing down." For example, while crossing the road one might need to quickly step up onto a curb due to errors in judging the speed of traffic. In this case, an inadequate safety margin may cause a fall leading to a serious injury or death.

LIMITATIONS

One of the challenges associated with the analysis of dynamically complex systems is the definition of the safety margin. For the ball-and-cup task we chose to define the safety margin in terms of the ball energy relative to escape. Clearly, there are other ways that the safety margin could be defined. For example, simpler versions could be just the angular distance of the ball from the cup rim, and/or the angular velocity of the ball as it approaches the rim. Our measure considers the ball angle, angular velocity, and cup acceleration, as all three variables determine the ball energy and thereby the risk of escape. More details about our rationale are provided in Hasson et al. (2012b).

CONCLUSIONS

This study demonstrated that in a constrained virtual ball-and-cup transportation task, older adults had less manipulation skill and utilized smaller safety margins compared to younger adults. However, with practice the older adults were able to improve their skill and increase their safety margins. These findings suggest that safety margins are related to the ability to control dynamics, and may explain why in tasks with simple dynamics older adults use adequate safety margins, but in more complex whole-body tasks safety margins are inadequate. Further, the results indicate that task-specific training may improve safety margins in older adults.

ACKNOWLEDGMENTS

This research was supported by a National Institutes of Health (NIH) Ruth L. Kirschstein National Research Service Award for Individual Postdoctoral Fellows (1F32AR061238) awarded to Christopher J. Hasson. Support was also provided by a National Institutes of Health grant (R01HD045639) and a National Science Foundation (NSF) grant (DMS-0928587) awarded to Dagmar Sternad. The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official views of the NIH or NSF.

REFERENCES

Aoyagi, Y., and Shephard, R. J. (1992). Aging and muscle function. *Sports Med.* 14, 376–396. doi: 10.2165/00007256-199214060-00005

Bashore, T. R., Ridderinkhof, K. R., and Van Der Molen, M. W. (1997). The decline of cognitive processing speed in old age. *Curr. Dir. Psychol.* 6, 163–169. doi: 10.1111/1467-8721.ep10772944

Begg, R. K., and Sparrow, W. A. (2000). Gait characteristics of young and older individuals negotiating a raised surface: implications for the prevention of falls. *J. Gerontol A Biol. Sci. Med.* 55, M147–M154. doi: 10.1093/gerona/55.3.M147

Berg, W. P., Alessio, H. M., Mills, E. M., and Tong, C. (1997). Circumstances and consequences of falls in independent community-dwelling older adults. *Age Ageing* 26, 261–268. doi: 10.1093/ageing/26.4.261

Chou, L.-S., Draganich, L. F., and Song, S.-M. (1997). Minimum energy trajectories of the swing ankle when stepping over obstacles of different heights. *J. Biomech.* 30, 115–120. doi: 10.1016/S0021-9290(96)00111-X

Cole, K. J. (1991). Grasp force control in older adults. *J. Mot. Behav.* 23, 251–258. doi: 10.1080/00222895.1991.9942036

Cole, K. J., and Beck, C. L. (1994). The stability of precision grip force in older adults. *J. Mot. Behav.* 26, 171–177. doi: 10.1080/00222895.1994.9941671

Cole, K. J., Rotella, D. L., and Harper, J. G. (1999). Mechanisms for age-related changes of fingertip forces during precision gripping and lifting in adults. *J. Neurosci.* 19, 3238–3247.

Flanagan, J. R., and Wing, A. M. (1990). The stability of precision grip forces during cyclic arm movements with a hand-held load. *Exp. Brain Res.* 105, 455–464. doi: 10.1007/BF00233045

Flanagan, J. R., and Wing, A. M. (1993). Modulation of grip force with load force during point-to-point arm movements. *Exp. Brain Res.* 95, 131–143. doi: 10.1007/BF00229662

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

Gilles, M. A., and Wing, A. M. (2003). Age-related changes in grip force and dynamics of hand movement. *J. Mot. Behav.* 35, 79–85. doi: 10.1080/00222890309602123

Goodpaster, B. H., Park, S. W., Harris, T. B., Kritchevsky, S. B., Nevitt, M., Schwartz, A. V., et al. (2006). The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. *J. Gerontol A Biol. Sci. Med.* 61, 1059–1064. doi: 10.1093/gerona/61.10.1059

Guadagnoli, M. A., and Lee, T. D. (2004). Challenge point: a framework for conceptualizing the effects of various practice conditions in motor learning. *J. Mot. Behav.* 36, 212–224. doi: 10.3200/JMBR.36.2.212-224

Hamel, K. A., Okita, N., Higginson, J. S., and Cavanagh, P. R. (2005). Foot clearance during stair descent: effects of age and illumination. *Gait Posture* 21, 135–140. doi: 10.1016/j.gaitpost.2004.01.006

Hasson, C. J., Hogan, N., and Sternad, D. (2012a). "Human control of dynamically complex objects," in *4th International IEEE RAS & EMBS Conference on Biomedical Robotics and Biomechatronics* (Rome: BioRob), 1235–1240.

Hasson, C. J., Shen, T., and Sternad, D. (2012b). Energy margins in dynamic object manipulation. *J. Neurophysiol.* 108, 1349–1365. doi: 10.1152/jn.00019.2012

Huang, H. J., and Ahmed, A. A. (2011). Tradeoff between stability and maneuverability during whole-body movements. *PLoS ONE* 6:e21815. doi: 10.1371/journal.pone.0021815

Johansson, R. S., and Cole, K. J. (1992). Sensory-motor coordination during grasping and manipulative actions. *Cur. Opin. Neurobiol.* 2, 815–823. doi: 10.1007/BF00237997

Johansson, R., and Westling, G. (1984). Roles of glabrous skin receptors and sensorimotor memory in automatic control of precision grip when lifting rougher or more slippery objects. *Exp. Brain Res.* 56, 550–564. doi: 10.1016/0959-4388(92)90139-C

Laidlaw, D. H., Bilodeau, M., and Enoka, R. M. (2000). Steadiness is reduced and motor unit discharge is more variable in old adults. *Muscle Nerve* 23, 600–612. doi: 10.1002/(SICI)1097-4598(200004)23:4%3C600::AID-MUS20%3E3.0.CO;2-D

Light, K. E. (1990). Information processing for motor performance in aging adults. *Phys. Ther.* 70, 820–826.

McFadyen, B. J., and Prince, F. (2002). Avoidance and accommodation of surface height changes by healthy, community-dwelling, young, and elderly men. *J. Gerontol A Biol. Sci. Med.* 57, B166–B174. doi: 10.1093/gerona/57.4.B166

Myerson, J., Hale, S., Wagstaff, D., Poon, L. W., and Smith, G. A. (1990). The information-loss model: a mathematical theory of age-related cognitive slowing. *Psychol. Rev.* 97:475. doi: 10.1037/0033-295X.97.4.475

Onyshko, S., and Winter, D. (1980). A mathematical model for the dynamics of human locomotion. *J. Biomech.* 13, 361–368. doi: 10.1016/0021-9290(80)90016-0

Pannese, E. (2011). Morphological changes in nerve cells during normal aging. *Brain Struct. Func.* 216, 85–89. doi: 10.1007/s00429-011-0308-y

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychol. Rev.* 103:403. doi: 10.1037/0033-295X.103.3.403

Slobounov, S. M., Moss, S. A., Slobounova, E. S., and Newell, K. M. (1998). Aging and time to instability in posture. *J. Gerontol. A Biol. Sci. Med.* 53, B71–B80. doi: 10.1093/gerona/53A.1.B71

Sternad, D., Huber, M. E., and Kuznetsov, N. (2014). "Acquisition of novel and complex motor skills: stable solutions where intrinsic noise matters less," in *Progress in Motor Control: Skill Learning, Performance, Health, and Injury, Chapter 8*, ed M. F. Levin (New York, NY: Springer).

Tombaugh, T. N., and McIntyre, N. J. (1992). The mini-mental state examination: a comprehensive review. *J. Am. Geriatr. Soc.* 40, 922–935.

Van der Linde, R., and Lammertse, P. (2003). HapticMaster–a generic force controlled robot for human interaction. *Ind. Robot.* 30, 515–524. doi: 10.1108/01439910310506783

Van Wegen, E., Van Emmerik, R., and Riccio, G. (2002). Postural orientation: age-related changes in variability and time-to-boundary. *Hum. Mov. Sci.* 21, 61–84. doi: 10.1016/S0167-9457(02)00077-5

Winter, D. A., Patla, A. E., Frank, J. S., and Walt, S. E. (1990). Biomechanical walking pattern changes in the fit and healthy elderly. *Phys. Ther.* 70, 340–347.

Ye, F., Nasseroleslami, B., and Sternad, D. (2014). "Predictability in human manipulation on nonlinear dynamic objects," in *IEEE Proceedings of the 40th Northeast Bioengineering Conference* (Boston, MA).

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

Received: 30 May 2014; paper pending published: 16 June 2014; accepted: 19 June 2014; published online: 14 July 2014.

Citation: Hasson CJ and Sternad D (2014) Safety margins in older adults increase with improved control of a dynamic object. Front. Aging Neurosci. ***6****:158. doi: 10.3389/fnagi.2014.00158*

This article was submitted to the journal Frontiers in Aging Neuroscience.

frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 11 April 2014
doi: 10.3389/fnagi.2014.00068

Site-specific differences in the association between plantar tactile perception and mobility function in older adults

Yenisel Cruz-Almeida[1], Mieniecia L. Black[2], Evangelos A. Christou[3] and David J. Clark[2,4]*

[1] Pain Research and Intervention Center of Excellence, University of Florida, Gainesville, FL, USA
[2] Department of Aging and Geriatric Research, University of Florida, Gainesville, FL, USA
[3] Department of Applied Physiology and Kinesiology, University of Florida, Gainesville, FL, USA
[4] Brain Rehabilitation Research Center, Malcom Randall VA Medical Center, Gainesville, FL, USA

Edited by:
Brian C. Clark, Ohio University, USA

Reviewed by:
Matthieu Pascal Boisgontier, KU Leuven, Belgium
Guang H. Yue, Kessler Foundation Research Center, USA

***Correspondence:**
David J. Clark, Brain Rehabilitation Research Center (151A), Malcom Randall VA Medical Center, 1601 SW Archer Road, Gainesville, FL 32608, USA
e-mail: davidclark@ufl.edu

Introduction: Impaired somatosensation is common in older adults and contributes to age-related loss of mobility function. However, little is known about whether somatosensation at different sites on the plantar surface of the foot are differentially related to mobility function. Such a finding may have important implications for clinical care of older adults and other at-risk populations, such as for optimizing interventions (e.g., footwear for augmenting somatosensory feedback) and for improving the efficiency of clinical assessment.

Materials and Methods: Tactile perception was evaluated with a 10 g monofilament at four sites on the plantar surface of each foot: great toe (GT), first metatarsal head (MT1), heel (H) and fifth metatarsal head (MT5). Mobility function was assessed with the Berg Balance Scale and walking speed.

Results: Sixty-one older adults participated. Tactile perception was significantly positively associated with Berg Balance Score (adjusted $r = 0.30 - 0.75$; $p = 0.03 - < 0.001$), with the strongest association found at the site of the MT1. Only at this site was tactile perception found to be significantly associated with usual walking speed (adjusted $r = 0.51$; $p < 0.001$) and maximal walking speed (adjusted $r = 0.38$, $p = 0.004$). Clinically mild somatosensory impairment at MT1, but not at other sites, was found to yield substantial deficits in both Berg Balance Score and walking speed.

Discussion: The present findings indicate that tactile perception at MT1 is more closely linked to mobility function than is tactile perception at GT, MT5 or H. These findings warrant further research to examine whether interventions (e.g., textured insoles) and assessments that preferentially or exclusively focus on the site of MT1 may be more effective for optimizing clinical care.

Keywords: somatosensation, aging, mobility, walking, balance

INTRODUCTION

Impaired somatosensation is common in older adults (Mold et al., 2004; Shaffer and Harrison, 2007). A large study of peripheral nerve function in older adults found bilateral somatosensory deficits in approximately 26% of individuals 65–74 years of age, 36% of individuals 75–84 and 54% of individuals ≥85 (Mold et al., 2004). This age-related impairment of somatosensation has important functional implications for older adults, as it has been linked to deficits in balance and walking ability (Resnick et al., 2000; Mold et al., 2004; Deshpande et al., 2008; Buchman et al., 2009). A particular concern with somatosensory impairment is increased risk of injurious falls (Sorock and Labiner, 1992; Richardson and Hurvitz, 1995), which are a major contributor to disability and death in older adults (Soriano et al., 2007). The issue is compounded by the fact that many older adults are unaware that they have peripheral neurological impairment (Mold et al., 2004), and are therefore unlikely to seek preemptive intervention.

Given the importance of somatosensory function to mobility in older adults, there is a clear need for research that can contribute to enhanced clinical assessment and intervention of somatosensory deficits. A potentially important question is whether mobility outcomes are differentially affected by the site of somatosensory deficits. For example, the presence of site-specific differences in the relationship with balance or walking function could have important implications for intervening with sensory augmentation footwear. Sensory augmentation footwear involves placing specialized insoles in the shoes (i.e., textured or vibrating insoles), and has shown promise for enhancing mobility function in older adults (Priplata et al., 2003; Palluel et al., 2008, 2009; Qiu et al., 2012; Stephen et al., 2012; Hatton et al., 2013). However, there are also studies which report no benefit or possibly even deleterious effects of somatosensory augmentation (Hatton et al., 2009, 2012; Hartmann et al., 2010). Knowledge of site-specific associations with mobility function may be helpful for explaining such discrepancies and for guiding future development of footwear. This knowledge may also be valuable for refining clinical assessment protocols so that somatosensory screening can be conducted in a time and cost-effective manner. Accordingly, the objective of the present study is to investigate the extent to which tactile perception at four different sites on the plantar surface of the foot may be differentially associated with mobility function, including tests of balance and walking speed.

MATERIALS AND METHODS

PARTICIPANTS

Older adult volunteers were recruited by newspaper advertisement and mass mailing to a research recruitment database. The database consisted of a heterogeneous mix of older adults who had previously indicated willingness to volunteer for research studies. Screening of inclusion/exclusion criteria was conducted by telephone. Inclusion criteria for this study were: (1) age between 65 and 85 years and (2) agreement with the statement "You find it physically tiring to walk a quarter mile, or climb two flights of stairs, or perform household chores (at least one of these should be true)". Exclusion criteria included use of an assistive device for walking (cane, crutch, walker, brace, etc.); lower extremity pain while walking; involuntary weight gain or loss exceeding 10 pounds within the past 6 months; myocardial infarction or symptomatic cardiovascular disease in the past year; bone fracture in the past year; injury or illness to the central nervous system; uncontrolled hypertension exceeding 160 systolic and/or 95 diastolic; or terminal illness. Volunteers who met these criteria were invited to our research center to participate in the assessments described below. During this visit, we also acquired demographic and health-related information (e.g., medication use, weight and height) and administered the Mini Mental State Examination to assess cognitive status. In order to determine if volunteers were aware of the presence of a clinically significant neuropathy, they were asked to reply "Yes" or "No" to the question: "Do you regularly experience either numbness or tingling in your feet (when sitting or walking)?" All study procedures were approved by the University of Florida Institutional Review Board. All individuals participating in on-site assessments provided their written informed consent.

ASSESSMENT OF CUTANEOUS TACTILE PERCEPTION

Cutaneous tactile perception was assessed at four sites on the plantar surface of each foot using a Semmes–Weinstein 5.07 (10 g) monofilament. The sites tested were the great toe (GT), first metatarsal head (MT1), fifth metatarsal head (MT5) and heel (H). Participants laid flat on their back on an examination table. They were provided with an illustration of a set of "footprints" (**Figure 1**), with each testing site labeled with a code that specified side and testing site. When prompted by the examiner, the participants were instructed to indicate whether they felt a touch and, if so, at what site. The examiner performed 24 trials (three trials at each of the four sites for both feet) in random order. At each site, one of the three trials was a "sham" in which the examiner did not actually touch the participant but still asked for a response. One point was awarded for each correct response (including a "no" response for a sham trial) for a total cutaneous tactile score of up to 24 points (12 points per foot). For ease of interpretation, the number of correct responses was converted to a percent value.

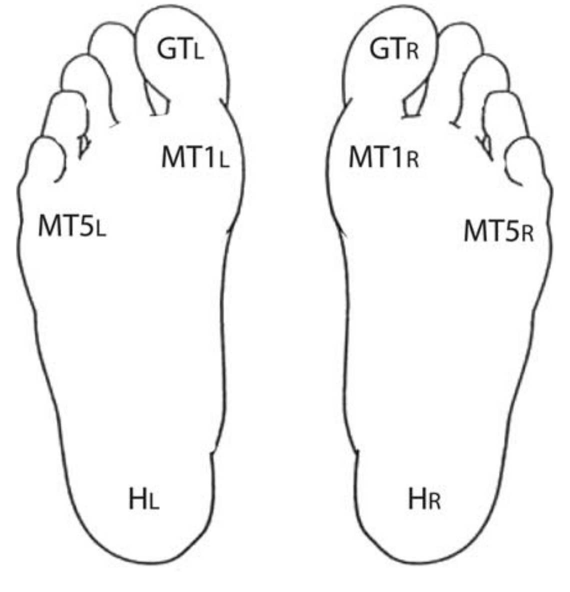


FIGURE 1 | Testing sites for tactile perception. Using the figure shown, participants were instructed to report which site was touched by the monofilament. A total of 24 trials were conducted, including 16 with a tactile stimulus and 8 sham trials with no stimulus.

FUNCTIONAL MEASURES

Balance was assessed with the Berg Balance Scale (Berg et al., 1989), which is a 14-item performance assessment of balance related tasks. Each task is scored on an ordinal scale from 0 (unable) to 4 (independent). The sum of all scores is used as the final outcome. Both walking tests (usual and maximal speed) were timed with a stopwatch. In order to ensure that we recorded steady state walking speed during the 10 m fast walk, the beginning and end of the course included 5 m acceleration/deceleration zones such that the total distance walked was 20 m. The watch was started and stopped when the individual's torso passed over the lines marking the start and end, respectively, of the 10 m course. Three fast walking trials were conducted, and the average was used for subsequent analysis. Only one trial was conducted for 400 m usual walking speed.

STATISTICS

Values are reported as mean ± standard deviation unless otherwise stated. The data were checked for normality and homoscedasticity. Consistency of results for left and right sides (i.e., inter-item reliability) was assessed by examining Cronbach's α coefficients. For the primary analysis, associations between continuous variables were quantified by Pearson's moment correlations, and partial correlations accounted for age, sex, body mass index, MMSE score and number of medications. Regression models were used to compare the strength of associations between different somatosensory sites and mobility tests, after adjusting for confounding variables. Statistical analysis was conducted using SPSS 21, and significance level was set to $\alpha < 0.05$. For the secondary analysis, two tailed t-tests were used to compare subgroups of participants. The False Discovery Rate Procedure was used to correct for multiple comparisons (Curran-Everett, 2000).

RESULTS

PARTICIPANT CHARACTERISTICS

A total of 198 individuals underwent screening by telephone. Of these, 72 passed the phone screen and were invited to our research center for on-site screening and assessment. Ultimately, 61 (38 females and 23 males) were found to meet all criteria and were able to complete all necessary assessments. The mean age was 74.5 ± 6.6 years. The mean body mass index was 28.0 ± 3.6 (range 16.2–34.5) and the mean score on the Mini-Mental State Exam was 27.5 ± 1.7 (range 24–30). Participants used on average 3 prescription medications (range 0–13 medications).

SOMATOSENSORY FUNCTION

Tactile perception data were examined for the statistical assumptions of normality, independence and homoscedasticity. The data were found to be significantly non-normally distributed (skewness statistic = -1.961 ± 0.31, $p < 0.01$), and were transformed with a square root transformation prior to conducting regression analysis. Tactile perception for the left and right sides (including data from all four testing sites) were significantly correlated ($r = 0.73$, $p < 0.001$), with high inter-item reliability (Cronbach's $\alpha = 0.85$). Therefore, the left and right sides were averaged by testing site to yield four tactile perception scores, which were used for subsequent analysis. The group mean scores for each testing site were: GT: 86.1 ± 22.2%, MT1: 89.0 ± 21.1%, H: 87.1 ± 21.0% and MT5: 90.6 ± 19.9%. Scores from the four sites were significantly positively associated with one another, with correlations ranging from 0.48 to 0.62 ($p < 0.001$). Seventeen participants (out of 61) had at least one false positive response to the sham trials, with the overall proportion of false positive responses being about 6%.

Approximately 37% of participants self-reported regularly experiencing tingling and/or numbness in their feet (i.e., abnormal somatosensation). Tactile perception at MT1 was significantly worse in those reporting abnormal somatosensation compared to those who did not report this deficit (81.8% vs. 95.2%, $p = 0.005$). Similar non-significant trends were also observed at MT5 ($p = 0.05$) and GT ($p = 0.11$).

RELATIONSHIP BETWEEN SOMATOSENSATION AND MOBILITY FUNCTION

Tactile perception at each site was significantly associated with performance on the Berg Balance Scale. These findings were maintained after adjusting for age, sex, body mass index, MMSE score and medication use (**Table 1**). Tactile perception at MT1 was the only site found to be significantly associated with usual and maximal walking speed. The strength of the association between Berg Balance score and tactile perception at MT1 was significantly stronger than the associations between Berg Balance score and tactile perception at each other site (adjusted $p < 0.05$). The results also show that the strength of the association between MT1 and Berg Balance score was stronger than the association between MT1 and maximal speed (adjusted $p < 0.05$). The same trend was evident for the relationship between MT1 and Berg Balance score relative to that of MT1 and usual walking speed (adjusted $p = 0.07$).

A secondary analysis was conducted to examine the extent to which the occurrence of clinically mild somatosensory impairment at each plantar testing site may affect mobility function. For each testing site, we compared subgroups of older adults with no clinically detectable impairment (i.e., no incorrect responses at the plantar site) to those with clinically mild impairment (i.e., only one incorrect response at the plantar site). Results of this analysis are shown in **Table 2**. Compared to participants with no impairment at MT1, those with mild impairment at MT1 had lower scores for the Berg Balance Scale (53.0 ± 3.1 vs. 50.3 ± 3.0, $p = 0.006$), usual walking speed (1.12 ± 0.12 vs. 0.97 ± 0.12 m/s, $p = 0.007$), and a trend for lower maximal walking speed (1.61 ± 0.23 vs. 1.45 ± 0.37 m/s, $p = 0.073$). For each other site (GT, H, MT5) there were no statistically significant differences for any mobility test between the subgroup with no impairment vs. the subgroup with mild impairment (all $p > 0.17$).

DISCUSSION

The primary objective of this study was to investigate the extent to which tactile perception at four different sites on the plantar surface of the foot may be differentially related to mobility function in older adults. The results indicate that tactile perception at MT1 is more closely linked to mobility function than is tactile perception at GT, H or MT5. The strength of the association

Table 1 | Associations between somatosensory scores and mobility function.

	GT	MT1	H	MT5
Adjusted r*				
Berg Balance Score	0.41, $p < 0.002$	0.75, $p < 0.001$	0.39, $p = 0.003$	0.30, $p = 0.03$
400m Usual (m/s)	0.17, $p = 0.22$	0.51, $p < 0.001$	0.17, $p = 0.21$	0.07, $p = 0.59$
10m Maximal (m/s)	0.11, $p = 0.44$	0.38, $p = 0.004$	0.00, $p = 0.98$	−0.15, $p = 0.25$

** adjusted for age, sex, body mass index, MMSE score and number of medications.*

Abbreviations: GT (great toe); MTI (first metatarsal head); H (heel); MT5 (fifth metatarsal head).

Table 2 | Mobility function for subgroups without somatosensory impairment vs. with mild somatosensory impairment.

	GT		MT1		H		MT5	
	Not Impaired (*n* = 40)	**Mildly Impaired (*n* = 10)**	**Not Impaired (*n* = 41)**	**Mildly Impaired (*n* = 11)**	**Not Impaired (*n* = 37)**	**Mildly Impaired (*n* = 14)**	**Not Impaired (*n* = 44)**	**Mildly mpaired (*n* = 10)**
Berg Balance Score	52.0 ± 3.6	52.3 ± 3.5	***53.0 ± 3.1***	***50.3 ± 3.0****	52.8 ± 3.4	50.1 ± 5.5	52.1 ± 3.5	50.9 ± 6.0
Usual Speed (m/s)	1.09 ± 0.13	1.04 ± 0.14	***1.12 ± 0.12***	***0.97 ± 0.12****	1.07 ± 0.13	1.05 ± 0.19	1.07 ± 0.12	1.09 ± 0.20
Maximal Speed (m/s)	1.59 ± 0.29	1.5 ± 0.16	1.61 ± 0.23	1.45 ± 0.37	1.55 ± 0.26	1.58 ± 0.37	1.53 ± 0.22	1.62 ± 0.44

** indicates adjusted $p < 0.05$.*

Abbreviations: GT (great toe); MTI (first metatarsal head); H (heel); MT5 (fifth metatarsal head).

between Berg Balance score and tactile perception at MT1 was significantly stronger than the associations between Berg Balance score and tactile perception at each other site. Furthermore, MT1 was the only site that was significantly associated with usual and maximal walking speed. What accounts for the finding that tactile perception at MT1 is especially highly linked to mobility function? It might be explained in part by the prior finding that somatosensory thresholds are lower (i.e., more sensitive) in the ball of the foot, which includes MT1, compared to the heel and toe regions (Inglis et al., 2002). This could be due to the relatively high density of slow and fast adapting cutaneous receptors at MT1 (Kennedy and Inglis, 2002; Fallon et al., 2005). These anatomical characteristics may be an evolutionary adaptation in response to the important role of the forefoot in control of walking. The forefoot, including MT1, is highly involved in the crucial biomechanical task of forward propulsion during gait (Melai et al., 2013). In this role, the forefoot bears high levels of pressure that likely provides important neural input that is relevant to controlling speed and directional steering during walking.

Even clinically mild somatosensory impairment at MT1 appears to have a marked influence on mobility function. This was evidenced by our subgroup analyses of individuals with clinically mild somatosensory impairment vs. those with no clinically detectable somatosensory impairment. For tactile perception at MT1, Berg Balance Scale score was 2.7 points lower for the subgroup with mild impairment vs. the subgroup with no impairment (50.3 vs. 53.0 points). This difference approaches the value of 3.3 points that has been reported as a meaningful change for independently ambulating older adults (Donoghue and Stokes, 2009). Furthermore, the score of 53 in the subgroup with no impairment remains above the threshold of 51 that is indicative of a higher fall risk in elders who have a prior history of falling (Shumway-Cook et al., 1997). Equally alarming is the group difference of 0.15 m/s for usual walking speed, which well exceeds the threshold of 0.10 m/s that is considered a clinically meaningful change in older adults (Perera et al., 2006). The importance of MT1 relative to other plantar sites is further confirmed by the absence of significant differences in mobility function between subgroups at the other plantar sites.

Another interesting finding from this study is the distinct difference in the extent to which tactile perception is linked to Berg Balance score vs. walking speed. At sites GT, MT5 and H, there was a significant association between tactile perception and Berg Balance score, but not between tactile perception and walking speed. At site MT1, the strength of the association between tactile perception and Berg Balance score was significantly stronger than the association with maximal walking speed ($p < 0.05$) and there was a trend for a stronger association compared to usual walking speed ($p = 0.07$). The finding that somatosensation is more closely linked to balance is consistent with prior reports (Mold et al., 2004; Deshpande et al., 2008; Zhang and Li, 2013), although the reason remains unclear. It may be that processing of movement control for balance is less "automatic" than processing for walking, and relies more heavily on utilization of peripheral inputs to provide real-time information (Brandt et al., 1999; Jahn et al., 2004; Zwergal et al., 2012; Lau et al., 2014), such as for integration with the visual and vestibular systems. Another possible explanation is that there is an age-related increase in controlled processing of balance (Boisgontier et al., 2013) that is less pronounced for gait. It may also be that somatosensory information is more likely to be deficient during balance tasks. This is because activation thresholds of peripheral receptors are more likely to be reached during walking due to higher pressure and impact forces compared to balance tasks (Jonely et al., 2011).

Overall, the results of this study strongly agree with prior work demonstrating that impaired somatosensation is detrimental to mobility function (Resnick et al., 2000; Mold et al., 2004; Deshpande et al., 2008; Buchman et al., 2009). We have expanded on this knowledge by demonstrating site-specific differences in the association between tactile perception and mobility function. There are some methodological considerations that should be noted when interpreting the results of this study. We assessed somatosensation of the plantar surface of the feet because they are the primary interface between ground and body, and because peripheral age-related neural impairments are most profound distally (Shaffer and Harrison, 2007). However, the relationship between somatosensation and mobility may also be affected by other types of somatosensory information (e.g., muscle spindles and joint receptors) from other lower extremity regions. We used a clinical assessment of somatosensation (monofilament) as opposed to more rigorous assessments (e.g., sensory thresholds). Accordingly, our data should be interpreted in the context of clinically detectable levels of impairment.

The findings from this research may have important implications for clinical care of older adults, such as in the design of footwear that is used to augment somatosensation. Our finding that mobility function is most closely associated with somatosensory function at MT1 warrants further research to examine whether insoles that preferentially or exclusively augment somatosensation at MT1 provide an advantage for enhancing functional outcomes. The potential importance of this topic is supported by evidence showing that the site of somatosensory stimulation on the plantar surface of the foot can yield different postural responses (Kavounoudias et al., 1998, 2001). Our findings also have implications for clinical assessment. An ideal assessment of somatosensory function would involve testing at multiple sites with multiple modalities (tactile, vibratory, proprioception, etc.). However, this rigorous level of assessment may be excessively time consuming and costly for use in regular screenings. Single-site assessment is more feasible and may encourage more widespread use of somatosensory screening in older adults. Although more research is warranted, our data suggest that assessment at MT1 may prove to be the most relevant site in the context of gauging risk for adverse mobility outcomes.

AUTHOR CONTRIBUTIONS

This study was designed by David J. Clark and Evangelos A. Christou. Data collection was conducted by Mieniecia L. Black and David J. Clark. Data analysis was conducted by Yenisel Cruz-Almeida and David J. Clark. The content of the manuscript was prepared by Yenisel Cruz-Almeida, Mieniecia L. Black, Evangelos A. Christou and David J. Clark.

ACKNOWLEDGMENTS

This work was supported by the National Institute on Aging (2P30-AG028740-06 to David J. Clark and Evangelos A. Christou; AG039659-02S1 to Yenisel Cruz-Almeida). Support was also provided by the U.S. Department of Veterans Affairs Rehabilitation Research and Development Service (B7176-W to David J. Clark).

REFERENCES

Berg, K., Wood-Dauphinee, S., Williams, J. I., and Gayton, D. (1989). Measuring balance in the elderly: preliminary development of an instrument. *Physiother Can* 41, 304–311. doi: 10.3138/ptc.41.6.304

Boisgontier, M. P., Beets, I. A., 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

Brandt, T., Strupp, M., and Benson, J. (1999). You are better off running than walking with acute vestibulopathy. *Lancet* 354, 746. doi: 10.1016/s0140-6736(99)03179-7

Buchman, A. S., Wilson, R. S., Leurgans, S., and Bennett, D. A. (2009). Vibratory thresholds and mobility in older persons. *Muscle Nerve* 39, 754–760. doi: 10.1002/mus.21263

Curran-Everett, D. (2000). Multiple comparisons: philosophies and illustrations. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 279, R1–R8.

Deshpande, N., Ferrucci, L., Metter, J., Faulkner, K. A., Strotmeyer, E., Satterfield, S., et al. (2008). Association of lower limb cutaneous sensitivity with gait speed in the elderly: the health ABC study. *Am. J. Phys. Med. Rehabil.* 87, 921–928. doi: 10.1097/phm.0b013e31818a5556

Donoghue, D., Physiotherapy Research and Older People (PROP) Group, Stokes, E. K. (2009). How much change is true change? The minimum detectable change of the Berg Balance Scale in elderly people. *J. Rehabil. Med.* 41, 343–346. doi: 10.2340/16501977-0337

Fallon, J. B., Bent, L. R., McNulty, P. A., and Macefield, V. G. (2005). Evidence for strong synaptic coupling between single tactile afferents from the sole of the foot and motoneurons supplying leg muscles. *J. Neurophysiol.* 94, 3795–3804. doi: 10.1152/jn.00359.2005

Hartmann, A., Murer, K., de Bie, R. A., and de Bruin, E. D. (2010). The effect of a training program combined with augmented afferent feedback from the feet using shoe insoles on gait performance and muscle power in older adults: a randomised controlled trial. *Disabil. Rehabil.* 32, 755–764. doi: 10.3109/09638280903295441

Hatton, A. L., Dixon, J., Martin, D., and Rome, K. (2009). The effect of textured surfaces on postural stability and lower limb muscle activity. *J. Electromyogr. Kinesiol.* 19, 957–964. doi: 10.1016/j.jelekin.2008.04.012

Hatton, A. L., Dixon, J., Rome, K., Newton, J. L., and Martin, D. J. (2012). Altering gait by way of stimulation of the plantar surface of the foot: the immediate effect of wearing textured insoles in older fallers. *J. Foot Ankle Res.* 5:11. doi: 10.1186/1757-1146-5-s1-o21

Hatton, A. L., Rome, K., Dixon, J., Martin, D. J., and McKeon, P. O. (2013). Footwear interventions: a review of their sensorimotor and mechanical effects on balance performance and gait in older adults. *J. Am. Podiatr. Med. Assoc.* 103, 516–533.

Inglis, J. T., Kennedy, P. M., Wells, C., and Chua, R. (2002). The role of cutaneous receptors in the foot. *Adv. Exp. Med. Biol.* 508, 111–117. doi: 10.1007/978-1-4615-0713-0_14

Jahn, K., Deutschlander, A., Stephan, T., Strupp, M., Wiesmann, M., and Brandt, T. (2004). Brain activation patterns during imagined stance and locomotion in functional magnetic resonance imaging. *Neuroimage* 22, 1722–1731. doi: 10.1016/j.neuroimage.2004.05.017

Jonely, H., Brismee, J. M., Sizer, P. S. Jr., and James, C. R. (2011). Relationships between clinical measures of static foot posture and plantar pressure during static standing and walking. *Clin. Biomech. (Bristol, Avon)* 26, 873–879. doi: 10.1016/j.clinbiomech.2011.04.008

Kavounoudias, A., Roll, R., and Roll, J. P. (1998). The plantar sole is a 'dynamometric map' for human balance control. *Neuroreport* 9, 3247–3252. doi: 10.1097/00001756-199810050-00021

Kavounoudias, A., Roll, R., and Roll, J. P. (2001). Foot sole and ankle muscle inputs contribute jointly to human erect posture regulation. *J. Physiol.* 532(Pt. 3), 869–878. doi: 10.1111/j.1469-7793.2001.0869e.x

Kennedy, P. M., and Inglis, J. T. (2002). Distribution and behaviour of glabrous cutaneous receptors in the human foot sole. *J. Physiol.* 538(Pt. 3), 995–1002. doi: 10.1113/jphysiol.2001.013087

Lau, T. M., Gwin, J. T., and Ferris, D. P. (2014). Walking reduces sensorimotor network connectivity compared to standing. *J. Neuroeng. Rehabil.* 11:14. doi: 10.1186/1743-0003-11-14

Melai, T., Schaper, N. C., Ijzerman, T. H., de Lange, T. L., Willems, P. J., Meijer, K., et al. (2013). Increased forefoot loading is associated with an increased plantar flexion moment. *Hum. Mov. Sci.* 32, 785–793. doi: 10.1016/j.humov.2013.05.001

Mold, J. W., Vesely, S. K., Keyl, B. A., Schenk, J. B., and Roberts, M. (2004). The prevalence, predictors, and consequences of peripheral sensory neuropathy in older patients. *J. Am. Board Fam. Pract.* 17, 309–318. doi: 10.3122/jabfm.17.5.309

Palluel, E., Nougier, V., and Olivier, I. (2008). Do spike insoles enhance postural stability and plantar-surface cutaneous sensitivity in the elderly? *Age (Dordr.)* 30, 53–61. doi: 10.1007/s11357-008-9047-2

Palluel, E., Olivier, I., and Nougier, V. (2009). The lasting effects of spike insoles on postural control in the elderly. *Behav. Neurosci.* 123, 1141–1147. doi: 10.1037/a0017115

Perera, S., Mody, S. H., Woodman, R. C., and Studenski, S. A. (2006). Meaningful change and responsiveness in common physical performance measures in older adults. *J. Am. Geriatr. Soc.* 54, 743–749. doi: 10.1111/j.1532-5415.2006.00701.x

Priplata, A. A., Niemi, J. B., Harry, J. D., Lipsitz, L. A., and Collins, J. J. (2003). Vibrating insoles and balance control in elderly people. *Lancet* 362, 1123–1124. doi: 10.1016/s0140-6736(03)14470-4

Qiu, F., Cole, M. H., Davids, K. W., Hennig, E. M., Silburn, P. A., Netscher, H., et al. (2012). Enhanced somatosensory information decreases postural sway in older people. *Gait Posture* 35, 630–635. doi: 10.1016/j.gaitpost.2011.12.013

Resnick, H. E., Vinik, A. I., Schwartz, A. V., Leveille, S. G., Brancati, F. L., Balfour, J., et al. (2000). Independent effects of peripheral nerve dysfunction on lower-extremity physical function in old age: the Women's Health and Aging Study. *Diabetes Care* 23, 1642–1647. doi: 10.2337/diacare.23.11.1642

Richardson, J. K., and Hurvitz, E. A. (1995). Peripheral neuropathy: a true risk factor for falls. *J. Gerontol. A Biol. Sci. Med. Sci.* 50, M211–M215. doi: 10.1093/gerona/50a.4.m211

Shaffer, S. W., and Harrison, A. L. (2007). Aging of the somatosensory system: a translational perspective. *Phys. Ther.* 87, 193–207. doi: 10.2522/ptj.20060083

Shumway-Cook, A., Baldwin, M., Polissar, N. L., and Gruber, W. (1997). Predicting the probability for falls in community-dwelling older adults. *Phys. Ther.* 77, 812–819.

Soriano, T. A., DeCherrie, L. V., and Thomas, D. C. (2007). Falls in the community-dwelling older adult: a review for primary-care providers. *Clin. Interv. Aging* 2, 545–554.

Sorock, G. S., and Labiner, D. M. (1992). Peripheral neuromuscular dysfunction and falls in an elderly cohort. *Am. J. Epidemiol.* 136, 584–591.

Stephen, D. G., Wilcox, B. J., Niemi, J. B., Franz, J. R., Kerrigan, D., and D'Andrea, S. E. (2012). Baseline-dependent effect of noise-enhanced insoles on gait variability in healthy elderly walkers. *Gait Posture* 36, 537–540. doi: 10.1016/j.gaitpost.2012.05.014.

Zhang, S., and Li, L. (2013). The differential effects of foot sole sensory on plantar pressure distribution between balance and gait. *Gait Posture* 37, 532–535. doi: 10.1016/j.gaitpost.2012.09.012

Zwergal, A., Linn, J., Xiong, G., Brandt, T., Strupp, M., and Jahn, K. (2012). Aging of human supraspinal locomotor and postural control in fMRI. *Neurobiol. Aging* 33, 1073–1084. doi: 10.1016/j.neurobiolaging.2010.09.022

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

Received: 15 August 2013; accepted: 27 March 2014; published online: 11 April 2014.
Citation: Cruz-Almeida Y, Black ML, Christou EA and Clark DJ (2014) Site-specific differences in the association between plantar tactile perception and mobility function in older adults. Front. Aging Neurosci. ***6****:68. doi: 10.3389/fnagi.2014.00068*
This article was submitted to the journal Frontiers in Aging Neuroscience.

frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 25 August 2014
doi: 10.3389/fnagi.2014.00217

Utilization of central nervous system resources for preparation and performance of complex walking tasks in older adults

David J. Clark[1,2]*, Dorian K. Rose[1,3], Sarah A. Ring[1,2] and Eric C. Porges[2]

[1] Brain Rehabilitation Research Center, Malcom Randall VA Medical Center, North Florida/South Georgia Veterans Health System, Gainesville, FL, USA
[2] Department of Aging and Geriatric Research, University of Florida, Gainesville, FL, USA
[3] Department of Physical Therapy, University of Florida, Gainesville, FL, USA

Edited by:
Brian C. Clark, Ohio University, USA

Reviewed by:
Sue Lord, Newcastle University, UK
Chia-Cheng Lin, University of Pittsburgh, USA

***Correspondence:**
David J. Clark, Brain Rehabilitation Research Center (151A), Malcom Randall VA Medical Center, North Florida/South Georgia Veterans Health System, 1601 SW Archer Road, Gainesville, FL 32608, USA
e-mail: davidclark@ufl.edu

Introduction: Walking in the home and community often involves performance of complex walking tasks. Understanding the control of such tasks is crucial to preserving independence and quality of life in older adults. However, very little research has been conducted in this area. Here, we assess the extent to which two measures of central nervous system (CNS) activity are responsive to the challenges posed by preparation and performance of complex walking tasks. Prefrontal cortical activity was measured by functional near-infrared spectroscopy (fNIRS) and sympathetic nervous system arousal was measured by skin conductance level (SCL).

Materials and methods: Sixteen older men and women (age: 77.2 ± 5.6 years) with mild mobility deficits participated in this study. Participants walked at their preferred speed without distractions along an unobstructed, well-lit course (*control* task) and also walked on the same course under five separate challenging conditions: performing a cognitive verbal fluency task (*verbal* task), dim lighting (*dim* task), carrying a tray (*carry* task), negotiating obstacles (*obstacles* task) and wearing a weighted vest (*vest* task). Mean prefrontal activation and SCL were calculated during the preparation and performance phases of each task. Gait spatiotemporal measurements were acquired by an instrumented gait mat.

Results: Prefrontal cortical activity and SCL were elevated during the preparation phase of complex walking tasks relative to the control task. During the performance phase, prefrontal activity remained elevated to a similar level as during task preparation. In contrast, SCL continued to increase beyond the level observed during task preparation. A larger increase in prefrontal activity was found to be linked to preserved quality of gait during complex walking tasks.

Discussion: These findings indicate that availability and utilization of CNS resources are important for optimizing performance of complex walking tasks in older adults.

Keywords: walking, aging, motor control, near infrared spectroscopy, skin conductance

INTRODUCTION

Walking in the home and community environment often involves performance of complex tasks (Patla and Shumway-Cook, 1999; Frank and Patla, 2003; Lord et al., 2010). Such tasks can encompass a variety of different conditions such as walking over obstacles, in low-lighting and while multi-tasking. Compared to typical steady-state walking, these tasks require heightened demand on motor and/or cognitive resources. A study of over 1200 older adults by Shumway-Cook et al. (2007) demonstrated that age-related performance decrements are more severe for complex walking tasks than for typical steady-state walking. Furthermore, age-related mobility disability has been shown to be characterized in part by avoidance of environments that require performance of complex walking tasks (Shumway-Cook et al., 2002, 2003). There is a crucial need for enhanced understanding of the control of complex walking tasks in older adults. This knowledge will contribute to the development of novel mobility assessments and to the design of new therapeutic interventions that seek to preserve independent ambulation in the home and community.

Very little research has been conducted to understand the central nervous system (CNS) determinants of complex walking task performance, especially in older adults. The present study sought to advance this area of research by examining prefrontal cortical activity and sympathetic nervous system (SNS) arousal during the preparation and performance phases of various complex walking tasks. Prefrontal cortical activity was quantified by functional near-infrared spectroscopy (fNIRS). fNIRS is a relatively new technology that non-invasively assesses tissue metabolic activity using near-infrared light, which is able to pass through bone and other biological tissues (Bunce et al., 2006). Metabolic activity is estimated based on the characteristic properties of infrared light absorption by oxygenated hemoglobin and deoxygenated hemoglobin (markers of oxygen delivery and utilization) (Bunce et al., 2006). Prefrontal activation has been shown to be broadly linked to the amount of attention/intention directed toward cognitive and motor tasks, including walking (Okamoto et al., 2004; Herrmann et al., 2006; Suzuki et al., 2008; Atsumori et al., 2010; Kaneko et al., 2011; Koenraadt et al., 2014). In some studies, higher levels of prefrontal activity have been linked to better performance under novel task conditions (Ohsugi et al., 2013; Ishikuro et al., 2014).

SNS arousal was quantified by skin conductance level (SCL), which measures the electrical conductance of the skin. SCL is affected by sweat gland activity, which is under the control of the SNS (Sato et al., 1989). One function of the SNS is to mobilize physiological resources (e.g., increase blood flow and glucose release) under physically or psychologically challenging conditions (Bear et al., 2007). It has been proposed to up-regulate the gain of the entire CNS to increase responsiveness (Sibley et al., 2010). Although increased arousal can be beneficial to task performance under certain conditions, excessive arousal is known to compromise performance (Yerkes and Dodson, 1908). The extent to which this may affect mobility performance in older adults remains unclear. It is possible that fear of falling due to the challenge of walking with an aged CNS and musculoskeletal system could lead to excessively heightened arousal. For instance, heightened arousal/anxiety due to fear of falling has previously been linked to abnormal responses for posture (Adkin et al., 2002; Carpenter et al., 2004) and gait (Brown et al., 2002; Hadjistavropoulos et al., 2012).

Our primary objective was to assess the extent to which prefrontal activity and SCL were responsive to the increased utilization of CNS resources that is expected to occur when preparing for and executing complex walking tasks. Our secondary objective was to assess the potential link between CNS responses and gait quality during performance of the complex walking tasks. We hypothesized that prefrontal activity (interpreted as utilization and availability of cognitive resources) would be increased during preparation and performance of complex walking tasks, and that higher responses would be linked to better gait performance. We also hypothesized that SCL (interpreted as cognitive load and arousal) would be increased during preparation and performance of complex walking tasks, but that higher responses would be linked to poorer gait performance.

MATERIALS AND METHODS

PARTICIPANTS

Men and women between the ages of 65–85 years with mild mobility deficits were recruited for this study. Mild mobility deficits were defined as 400 m walking speed less than 1.1 m/s and agreement with the statement “You find it physically tiring to walk a quarter mile, or climb two flights of stairs, or perform household chores.” Preliminary screening of inclusion/exclusion criteria was conducted by telephone. Exclusion criteria included use of an assistive device for walking (cane, crutch, walker, brace, etc.); lower extremity pain while walking; involuntary weight gain or loss exceeding 10 pounds within the past six months; myocardial infarction or symptomatic cardiovascular disease in the past year; bone fracture in the past year; injury or illness to the CNS; uncontrolled hypertension exceeding 160 systolic and/or 95 diastolic; or terminal illness. Volunteers who met these criteria were invited to our research center for further screening. Additional inclusion criteria applied at the onsite visit were Berg Balance Scale (BBS, Berg et al., 1989) score $\geq$ 41, Mini-Mental State Exam (MMSE, Folstein et al., 1975) score $\geq$ 21, and body mass index (BMI) within the range of 19–35. All study procedures were approved by the University of Florida Institutional Review Board. All individuals provided their written informed consent at time of enrollment.

PROTOCOL AND EQUIPMENT

The assessments described here are a subset from a larger experimental protocol (PI: David J. Clark) that tested motor control of walking in older adults. The study was conducted over three separate visits to our research center. The first day consisted of functional assessments and questionnaires. This included the screening items mentioned in the prior section (BBS and MMSE) as well as the Activities-Specific Balance Confidence Scale (ABC Scale). The second and third day involved mechanistic assessments of walking including fNIRS of the prefrontal cortex, SCL and spatiotemporal gait measurement. The overground walking course consisted of five consecutive laps around an 18 m course in our laboratory, for a total walking distance of 90 m. The floor surface was smooth tile with the exception of the 5.2 m instrumented walkway, which has the texture of firm foam (GAITRite, CIR Systems, Sparta, NJ, USA). Participants walked at their preferred speed without distractions along an unobstructed, well-lit pathway (*control* task) and also walked on the same course while separately performing the following five additional challenging tasks on separate trials: cognitive verbal fluency task (“*verbal*”), dim lighting (“*dim*”), carrying a tray (“*carry*”), negotiating obstacles (“*obstacles*”) and wearing a weighted vest (“*vest*”). The *control*, *verbal*, *dim*, and *carry* tasks were conducted on the second visit to our center, and the *control*, *obstacle*, and *vest* tasks were conducted on the third visit. For the *verbal* task, participants were asked to say as many words as possible that began with a randomly selected letter. In order to maintain a comparable level of cognitive effort over the duration of the trial, a new letter was provided to the participant for each lap. For the *dim* task the lights in the laboratory were turned off and the windows were blocked, but some light entered through the door of an adjoining room. The participant’s eyes were allowed to adjust for approximately 2 min prior to starting the task. For the *carry* task, three rolls of athletic tape were stacked on the tray, and the participant was instructed to keep the tray stable to avoid having the stack fall over. For the *obstacle* task, the participant was instructed to step over six small obstacles (shoes) evenly spaced along the walking path. For the *vest* task, the participant wore an adjustable weighted vest with a load equal to 10% of body weight. The load was evenly distributed between the front and rear of the vest, and velcro straps were used to ensure that the vest remained snug against the body. Prior to performing each task, the participant stood quietly at the start of the course for about one minute to allow measurement of CNS activity during task preparation. The participants were given no specific instructions regarding how to perform or prioritize the objectives within each task, because our goal was to evaluate their natural/preferred walking behavior.

Metabolic activity of the left and right anterior prefrontal cortices (Brodmann Area 10) was evaluated with a commercially available fNIRS monitor (Niro 200NX, Hamamatsu Photonics, Japan). In accordance with prior studies, each set of probes (i.e., for left and right prefrontal cortices) were placed high on the forehead to avoid the temporalis muscle (but not over hair) and sufficiently lateral from the midline to avoid the superior sagittal sinus (Al-Rawi and Kirkpatrick, 2006; Tisdall et al., 2009). Optode spacing was 3 cm. fNIRS uses light of varying wavelengths to non-invasively record changes in blood flow and hemoglobin due to neuronal activation of cerebral cortex. SCL was measured using a commercially available data acquisition unit (Flexcomp Infiniti, Thought Technology Ltd., QC, Canada) and sensors (SA9309M, Thought Technology Ltd., QC, Canada). Sensors were secured to the proximal phalanges of the index and ring fingers using a velcro strap. SCL signals were acquired separately from both the left and right hands. fNIRS and SCL data were sampled at 2 and 32 Hz, respectively, and saved to a memory card in each data acquisition unit. Spatiotemporal gait data were acquired from the instrumented walkway.

DATA ANALYSIS

Raw data were converted into text files via each manufacturer's software, then analyzed with custom programs in Matlab version R2011b (The Mathworks, Natick, MA, USA). Prefrontal cortical activity was quantified as the tissue oxygenation index (TOI), which is the ratio (expressed as a percent) of oxygenated hemoglobin to total hemoglobin (sum of oxygenated and deoxygenated). TOI provides a real-time measure of the balance between cerebral oxygen delivery and utilization (Tisdall et al., 2009). For both TOI and SCL, the average magnitude was calculated for a 10-s epoch in which the participants were standing still immediately preceding task performance (preparation phase) and also for the full period of steady-state walking (performance phase). The transition periods for gait initiation and gait termination were excluded from the analysis. Gait variables extracted from the instrumented walkway included measures typically used to infer the use of a cautious gait pattern: decreased speed, increased stance width, increased double limb support time and increased variability (measured by standard deviation of step length and double support time).

STATISTICS

Statistical analysis was conducted with JMP Pro software (version 11.0.0). Two-way repeated-measures ANOVA models were used to assess task- and side-dependent differences in prefrontal TOI (task × hemisphere) and SCL (task × hand). Separate models were used for tasks that were assessed on the first day of evaluation (*control*, *verbal*, *dim* and *carry*) and the second day of evaluation (*control*, *obstacles*, and *vest*). Mauchly's sphericity test was used to test the assumption of sphericity in the ANOVA models. If sphericity was not achieved, the model was adjusted using the Huynh–Feldt correction (if $\epsilon > 0.75$) or the Greenhouse–Geisser correction (if $\epsilon < 0.75$). *Post hoc* testing of significant main effects was conducted using one-sided repeated-measures t-tests to test the hypothesis that complex walking tasks increased TOI and SCL relative to the preparation phase of each task and/or relative to performance of the *control* walking task. The false discovery rate procedure (Curran-Everett, 2000; Curran-Everett and Benos, 2004) was used to correct for multiple comparisons during *post hoc* testing. Secondary analyses were conducted to determine whether there was evidence to support a link between CNS responses and gait quality. For TOI, separate two-tailed t-tests were used to test the hypothesis that gait quality would be better in a high-response subgroup versus a low-response subgroup. For SCL, separate two-tailed t-tests were used to test the hypothesis that gait quality would be better in a low-response subgroup versus a high-response subgroup.

RESULTS

PARTICIPANTS

Sixteen older adults (8 male/8 female) participated in this study. The mean age of participants was 77.2 ± 5.6 years, with a range of 66–85 years. Additional information from clinical assessments is presented in **Table 1**.

fNIRS

Exemplar fNIRS data for one participant are shown in **Figure 1** and group average data are shown in **Figure 2**. For **Figure 2**, the TOI value shown for the performance phase of the control task is the average of the values from visit 1 and visit 2. These values did not differ significantly across visits (0.29 ± 1.13 versus 0.48 ± 1.24, respectively, $p = 0.38$).

Preparation for complex walking tasks

For TOI during the preparation phase preceding each walking task, there was a significant main effect of task ($p < 0.05$). The size of that effect across tasks is shown by the gray bars in **Figure 2**, which show the percent increase in TOI for the preparation phase of each complex walking task relative to the TOI for the preparation phase of the *control* task. *Post hoc* analysis revealed that, relative to $control_{\text{prepare}}$, TOI increased significantly for dim_{prepare} ($p = 0.003$), $carry_{\text{prepare}}$ ($p = 0.04$), $vest_{\text{prepare}}$ ($p = 0.006$) and $obstacles_{\text{prepare}}$ ($p = 0.001$). There was also a trend toward significance for $verbal_{\text{prepare}}$ ($p = 0.09$). The effects of hemisphere and task × hemisphere interaction were not significant.

Table 1 | Participant characteristics.

	Mean	Range
Body Mass Index (kg/m^2)	29.3 ± 2.7	24.3–33.8
Mini Mental State Exam	27.4 ± 1.7	24–30
Berg Balance Test	50.5 ± 3.9	42–56
400 m Walk speed (m/s)	0.92 ± 0.11	0.66–1.08
ABC Scale (% confidence)	83.0 ± 15.0	58–100

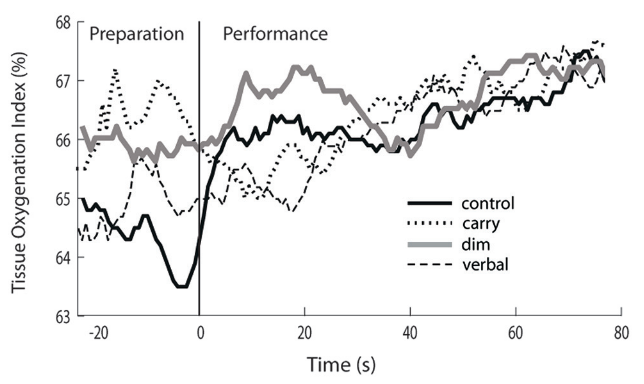


FIGURE 1 | Exemplar data demonstrating task-dependent differences in tissue oxygenation index (TOI). Prefrontal cortical activation, as indicated by TOI, for one study participant. Data are shown for walking along an unobstructed, well-lit pathway (*control* task; black solid line), walking while carrying a tray (*carry* task; dotted line), walking in dim lighting (*dim* task; gray solid line) and walking while performing a verbal fluency task (*verbal* task; dashed line). The participant is standing still for a short period of time at the start of the trial (preparation phase) and then walks at preferred speed (performance phase).

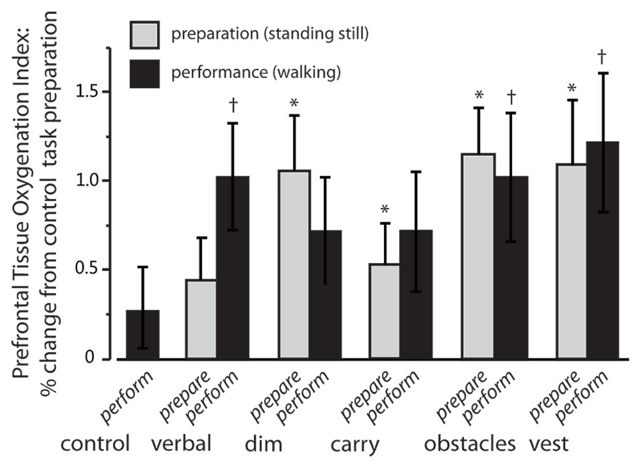


FIGURE 2 | Increase in prefrontal activation for complex tasks relative to preparation for control task. Gray bars indicate the average percentage increase in prefrontal activation during the preparation phase of each complex walking task relative to preparation for the *control* task. Significant changes are shown by an asterisk. Black bars indicate the percentage increase in prefrontal activation during the performance phase of each complex walking task relative to preparation for the *control* task. Significant changes are shown by a dagger. Error bars indicate group standard error.

Performance of complex walking tasks

For TOI during the performance phase of each task, a significant main effect of task was also found ($p < 0.05$). The size of that effect across tasks is indicated by the black bars of **Figure 2**, which show the percent increase in TOI for the performance phase of each complex walking task relative to the TOI for the preparation phase of the *control* task. *Post hoc* analysis revealed that, relative to $control_{\text{prepare}}$, TOI increased for $verbal_{\text{perform}}$ ($p = 0.006$), $vest_{\text{perform}}$ ($p = 0.005$), and $obstacles_{\text{perform}}$ ($p = 0.002$). There was a trend toward increased TOI during dim_{perform} ($p = 0.06$) and $\text{carry}_{\text{perform}}$ ($p = 0.11$). The effects of hemisphere and task × hemisphere interaction were not significant.

Within-task comparison of preparation versus performance

Also examined was whether TOI increased from the preparation phase to the performance phase within each task (i.e., comparing gray bars to black bars for each task in **Figure 2**). TOI for preparation versus performance did not increase significantly between dim_{prepare} and dim_{perform} ($p = 0.95$), between $carry_{\text{prepare}}$ and $carry_{\text{perform}}$ ($p = 0.16$), between $obstacles_{\text{prepare}}$ and $obstacles_{\text{perform}}$ ($p = 0.84$), or between $vest_{\text{prepare}}$ and $vest_{\text{perform}}$ ($p = 0.30$). However, there was a trend for increased TOI between $verbal_{\text{prepare}}$ and $verbal_{\text{perform}}$ ($p = 0.05$).

SKIN CONDUCTANCE LEVEL

Exemplar SCL data for one participant are shown in **Figure 3** and group average data are shown in **Figure 4**. For **Figure 4**, the SCL value shown for the performance phase of the control task is the average of the values from visit 1 and visit 2. These values did not differ significantly across visits (8.02 ± 11.48 versus 9.85 ± 10.74, respectively, $p = 0.65$).

Preparation for complex walking tasks

For SCL during the preparation phase of each task, there was a significant main effect of task ($p < 0.05$). The size of that effect across tasks is shown by the gray bars in **Figure 4**, which show the change in SCL for the preparation phase of each complex walking task relative to the TOI for the preparation phase of the *control* task. *Post hoc* analysis revealed that, relative to $control_{\text{prepare}}$, SCL increased significantly for $verbal_{\text{prepare}}$ ($p = 0.03$), dim_{prepare} ($p = 0.04$), $carry_{\text{prepare}}$ ($p = 0.02$), $obstacles_{\text{prepare}}$ ($p = 0.02$), and $vest_{\text{prepare}}$ ($p = 0.03$). The effects of side (right and left hands) and task × side interactions were not significant.

Performance of complex walking tasks

For SCL during the performance phase of each task, a significant main effect of task was also found ($p < 0.05$). The size of that effect across tasks is indicated by the black bars of **Figure 4**, which show the change in SCL for the performance phase of each complex walking task relative to the SCL for the preparation phase of the *control* task. *Post hoc* analysis revealed that, relative to $control_{\text{prepare}}$, SCL increased significantly for $verbal_{\text{perform}}$ ($p = 0.02$), dim_{perform} ($p = 0.04$), $carry_{\text{perform}}$ ($p = 0.01$), $obstacles_{\text{perform}}$ ($p = 0.02$), and $vest_{\text{perform}}$ ($p = 0.03$). The effects of side (right and left hands) and task × side interaction were not significant.

Within-task comparison of preparation versus performance

Also examined was whether SCL increased from the preparation phase to the performance phase within each task (i.e., comparing gray bars to black bars for each task in **Figure 4**). Preparation and performance for TOI increased significantly between dim_{prepare} to dim_{perform} ($p = 0.001$), between $verbal_{\text{prepare}}$ and $verbal_{\text{perform}}$ ($p < 0.001$), between $carry_{\text{prepare}}$ and $carry_{\text{perform}}$ ($p < 0.001$), between $vest_{\text{prepare}}$ and $vest_{\text{perform}}$ ($p < 0.001$), and between $obstacles_{\text{prepare}}$ and $obstacles_{\text{perform}}$ ($p < 0.001$).

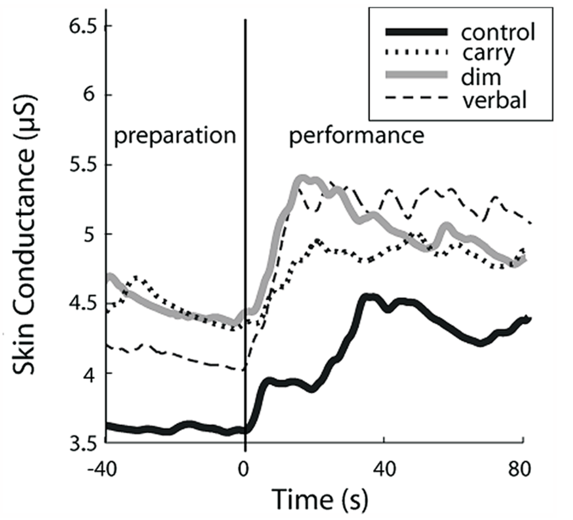


FIGURE 3 | Exemplar data demonstrating task-dependent differences in skin conductance level (SCL). Sympathetic nervous system (SNS) arousal, as indicated by SCL, for one study participant. Data are shown for walking along an unobstructed, well-lit pathway (*control* task; black solid line), walking while carrying a tray (*carry* task; dotted line), walking in dim lighting (*dim* task; gray solid line) and walking while performing a verbal fluency task (*verbal* task; dashed line). The participant is standing still for a short period of time at the start of the trial (preparation phase) and then walks at preferred speed (performance phase).

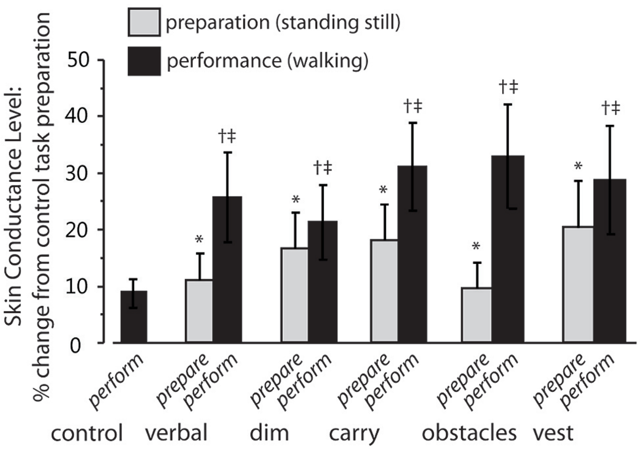


FIGURE 4 | Increase in skin conductance level (SCL) for complex tasks relative to preparation for control task. Gray bars indicate the average percentage increase in SCL during the preparation phase of each complex walking task relative to preparation for the *control* task. Significant changes are shown by an asterisk. Black bars indicate the percentage increase in SCL during the performance phase of each complex walking task relative to preparation for the *control* task. Significant changes are shown by a dagger. Significant within-task differences (preparation versus performance) are shows by a double dagger. Error bars indicate group standard error.

GAIT SPATIOTEMPORAL MEASUREMENTS

Gait spatiotemporal measurements were adversely affected by the complex walking tasks. Relative to *control*, walking speed was reduced for *carry* (−0.05 m/s, $p = 0.02$), *verbal* (−0.15 m/s, $p < 0.001$), *obstacles* (−0.15 m/s, $p < 0.001$) and tended to be reduced for *dim* (−0.02 m/s, $p = 0.09$). Base of support was increased for *carry* (0.89 cm, $p = 0.03$), *verbal* (0.82 cm, $p = 0.008$), and *dim* (0.94 cm, $p = 0.005$). Double support % was increased for *carry* (2.2%, $p = 0.002$), *verbal* (2.5%, $p < 0.001$), and *vest* (0.7%, $p = 0.02$). Variability of step length and double support time increased for *obstacles* (as expected due to the irregular terrain).

Secondary analyses were conducted to determine if the size of the response for prefrontal activation and/or SCL during the performance phase of complex walking tasks was related to the severity of the gait disturbance. For each CNS measure, the study sample was split in half to form two subgroups: low-response subgroup and high-response subgroup. For prefrontal activation, the "response" was calculated as the change in TOI that occurred between the preparation of the *control* task and the performance phase of each complex walking task. For each individual, the average response across all complex walking tasks was calculated. The low-response subgroup for TOI had an average change of −0.2 ± 1.1 percentage points (i.e., roughly unchanged prefrontal activity) and the high-response subgroup had a mean change in TOI of 2.1 ± 0.6 percentage points (i.e., increased prefrontal activity for complex tasks). For each TOI subgroup, average gait measurements during the *control* task are reported in **Table 2A**. The subgroups did not differ significantly for any *control* gait variable, with the exception of a trend for a wider base of support in the high-response subgroup. The subgroups also did not differ significantly for age, body mass index, or MMSE score (all p-values greater than 0.53). Significant differences between subgroups (or a trend) indicate that the high response subgroup had a smaller reduction of walking speed for *obstacles* ($p = 0.003$) and *vest* ($p = 0.001$); lower proportion of gait cycle spent in double limb support for *obstacles* ($p = 0.10$) and *vest* ($p = 0.04$); and less increase for step length variability for *carry* ($p = 0.02$), and *dim* ($p = 0.04$). Although the effect of complex walking tasks

Table 2 | Control task gait values for TOI and SCL response subgroups.

	High	Low	*p*
(A) TOI response subgroups			
Walking speed (m/s)	97.5 ± 9.5	102.5 ± 11.3	0.44
Base of support (cm)	12.5 ± 3.1	8.1 ± 2.7	0.04
Double support (% gait cycle)	34.1 ± 1.5	34.4 ± 2.8	0.85
Step length variability*	2.81 ± 2.10	1.66 ± 0.43	0.26
Double support time variability**	0.022 ± .009	0.021 ± .006	0.75
(B) SCL response subgroups			
Walking speed (m/s)	102.7 ± 14.0	95.9 ± 15.1	0.42
Base of support (cm)	9.9 ± 4.0	12.8 ± 3.0	0.18
Double support (% gait cycle)	34.5 ± 1.8	35.3 ± 3.5	0.59
Step length variability*	2.47 ± 2.04	2.4 ± 1.19	0.94
Double support time variability**	0.02 ± .009	0.026 ± .010	0.26

**Units are in cm SD. **Units are % gait cycle SD.*

Table 3 | Percentage change in gait variables for TOI response subgroups.

	High response	Low response	Effect size	p
Walking speed				
Carry	0.0 ± 7.3	−3.4 ± 5.5	0.51	0.40
Dim	0.6 ± 7.3	4.4 ± 5.3	0.61	0.35
Verbal	−13.6 ± 8.3	−12.5 ± 9.1	0.13	0.85
Obstacles	*−5.5 ± 6.2*	*−21.3 ± 5.8*	*1.72*	*0.003*
Vest	*7.0 ± 3.4*	*−5.3 ± 4.3*	*1.83*	*0.001*
Base of support				
Carry	6.9 ± 24.9	12.1 ± 15.8	0.28	0.69
Dim	11.1 ± 15.4	16.3 ± 18.3	0.34	0.63
Verbal	11.9 ± 9.8	0.7 ± 15.1	0.92	0.20
Obstacles	8.3 ± 24.0	6.8 ± 19.2	0.07	0.92
Vest	4.3 ± 20.0	−5.1 ± 18.3	0.54	0.46
Double support time				
Carry	1.0 ± 1.4	1.6 ± 2.7	0.27	0.67
Dim	0.9 ± 0.8	−0.1 ± 0.8	1.07	0.06
Verbal	2.1 ± 1.3	2.6 ± 2.5	0.26	0.69
Obstacles	−6.8 ± 1.9	−4.3 ± 2.2	1.16	0.10
Vest	*−0.2 ± 0.5*	*1.4 ± 1.2*	*1.36*	*0.04*
Step length variability				
Carry	*−4.3 ± 31.6*	*55.0 ± 37.7*	*1.39*	*0.02*
Dim	*−13.8 ± 35.8*	*16.2 ± 33.1*	*1.18*	*0.04*
Verbal	1.49 ± 50.6	63.6 ± 39.1	0.81	0.18
Obstacles	270.7 ± 184.1	376.9 ± 220.5	0.54	0.43
Vest	1.3 ± 42.6	20.0 ± 30.5	0.56	0.45
Double support time Variability				
Carry	−0.2 ± 30.1	44.8 ± 55.4	1.04	0.16
Dim	−0.5 ± 41.7	7.3 ± 37.9	0.22	0.75
Verbal	25.6 ± 47.2	65.9 ± 125.7	0.49	0.53
Obstacles	77.8 ± 77.3	91.6 ± 92.2	0.18	0.80
Vest	2.5 ± 33.8	13.7 ± 43.9	0.32	0.66

For each complex walking task, the percentage change for each gait variable is calculated relative to the control task. Results are shown for the subgroups determined by higher and lower response of prefrontal cortical activation. Italicized items indicate statistical significance as determined by two-tailed t-tests ($p < 0.05$). All values are mean ± SD.

was not statistically different between groups for most gait variables, it may be valuable to note that the direction of differences favored the high response subgroup as having less gait disturbance for 76% of the variables (19 out of 25; as indicated in **Table 3**). The mean effect size for this subset of gait variables was 0.76 ± 0.54.

The same type of exploratory subgroup analysis as just described was conducted for SCL. The low-response subgroup had an average change in SCL of −2.9 ± 4.2% (i.e., roughly unchanged SNS arousal) and the high-response subgroup had a mean change in SCL of 47.7 ± 29.7% (i.e., increased SNS arousal for complex tasks). For each SCL subgroup, average gait measurements during the *control* task are reported in **Table 2B**. The subgroups did not differ significantly for any *control* gait variable. The low and high SCL response subgroup differed significantly for age (73.6 versus 81.3 years, $p = 0.005$), but not for body mass index ($p = 0.24$) or MMSE score ($p = 0.74$). Accordingly, the gait variables were corrected for age prior to evaluating the effect of complex walking tasks. None of the age-corrected gait variables were found to differ significantly between the low and high SCL response subgroups (all p-values ≥ 0.23). Also examined was the potential association between the mean response size for prefrontal activity and the mean response size for SCL (means calculated across all tasks), in order to investigate the presence of a link between these physiological mechanisms. No association was found ($p = 0.90$).

DISCUSSION

Performance of complex walking tasks is adversely affected by aging (Shumway-Cook et al., 2007), which is concerning given the high relevance of such tasks to everyday ambulation in the home and community. Our choice of tasks was motivated by the "*person-environment interaction model*" of mobility proposed by Patla and Shumway-Cook (1999) and Shumway-Cook et al. (2002). This model describes multiple dimensions that must be mastered to attain successful community ambulatory function. Four dimensions are represented by the tasks in this study: terrain (*obstacles* task), physical load (*vest* task), ambient conditions (*dim* task), and attentional demands (*verbal* and *carry* tasks). The results of this study reveal that prefrontal cortical activity and SNS arousal are elevated during both the preparation and performance phases of complex walking tasks. Furthermore, the changes in prefrontal activity during performance of complex walking tasks were found to be linked to the quality of gait. These findings suggest that utilization of CNS resources is increased to optimize performance of complex walking tasks, and that a shortage of available resources contributes to performance decrements in some older adults.

Prefrontal cortical activation is important to complex walking tasks because of its role in preparing for and executing purposeful actions (Fuster, 2000; Jenkins et al., 2000; Tanji and Hoshi, 2001), including walking (Suzuki et al., 2008; Atsumori et al., 2010; Koenraadt et al., 2014). Our results show that prefrontal TOI increased bilaterally during preparation for all complex walking tasks with the exception of the *verbal* task. During the performance phase of the complex walking tasks, prefrontal TOI remained elevated but generally did not exceed the magnitude observed during the preparation phase. Again, the only notable exception was for *verbal*, where TOI was more strongly elevated during performance than during preparation. This is in agreement with the strongly increased demand for prefrontal resources that is associated with cognitive processing (Holtzer et al., 2011; Ohsugi et al., 2013). Our secondary analysis of subgroups with low versus high prefrontal response generally supported our hypothesis that a high response is linked to better gait performance. Most gait variables (19 out of the 25 when accounting for all tasks) seemed to favor the high-response subgroup, although only a small number were found to be statistically significantly because the analysis was underpowered. For these 19 variables, the average effect size was 0.76, which is considered to be a large effect (Cohen, 1988). Although these results are preliminary, the possible advantage for the high-response subgroup over the low-response subgroup provides encouraging rationale for pursuing this mechanistic finding in future research. We propose that a high response for prefrontal TOI indicates an available reserve supply of prefrontal resources that can contribute to control of complex walking tasks. This reserve supply helps to prevent against excessive competition for central neural resources, thereby preserving movement quality. This assertion is generally consistent with the "supply and demand framework" described by Seidler et al. (2010). These findings build upon prior work that has demonstrated an association between structural integrity of the cortex and gait performance under non-challenging walking conditions (Rosso et al., 2013; Holtzer et al., 2014). For instance, less cerebral gray matter volume of the prefrontal, medial temporal, frontoparietal and sensorimotor areas has been linked to walking decrements such as slow speed, shorter steps, and longer double support time (Rosano et al., 2007, 2008, 2012). The presence of cerebral white matter hyperintensities have also been shown to be linked to decrements in walking ability (Rosano et al., 2010; Wakefield et al., 2010; Viana-Baptista et al., 2011; Moscufo et al., 2012; Willey et al., 2013).

We quantified SNS arousal using the well-established measure of SCL. Our results show that SCL increases substantially when preparing for the complex walking tasks and increases even further when performing the complex walking tasks. However, our hypothesis of a link between SCL and gait performance during complex walking tasks was not supported. Future research is warranted to determine whether a link between SCL response and gait performance may be revealed by comparing cohorts with different characteristics (such as low versus high functioning elders). No association was found between the magnitude of SCL and prefrontal responses. The difference in SCL and prefrontal responses was also evident in the pattern of change that was observed across testing conditions. The elevation in SCL occurred in a stepwise manner, such that (1) SCL for complex task preparation increased over *control* task preparation, and (2) SCL for complex task performance increased over complex task preparation. In agreement with SCL, prefrontal TOI for complex task preparation increased over *control* task preparation. However, in contrast to SCL, no further increase was seen between complex task preparation and complex task performance. Cumulatively, our findings suggest that SCL and prefrontal TOI represent different functions of the CNS for control of walking.

An important finding from our data is that CNS assessments provide the advantage of being more broadly responsive to neurophysiological demand than any single spatiotemporal measure of gait performance. The spatiotemporal gait parameters that were affected by complex walking tasks differed depending on the task. Likewise, the gait parameters that were linked to prefrontal TOI response also differed depending on the task. This finding is not particularly surprising, because the gait modification that is adopted by an individual can be expected to depend on task objectives and also on what facet of performance is prioritized (Al-Yahya et al., 2009; Hobert et al., 2011; Oh-Park et al., 2013). For instance, if a person adopts a cautious gait pattern characterized by greater stance width, then it may be possible to preserve walking speed. In contrast, if a person adopts a slower walking speed, then it may be possible to preserve stance width. Therefore, caution should be used when attempting to interpret isolated gait parameters.

The relative supply and demand of CNS resources during complex walking tasks can be expected to differ among different people (Seidler et al., 2010). This is because the relative challenge of each task will be highly dependent on the specific motor, sensory, and/or cognitive capabilities of the individual. These capabilities were not thoroughly quantified for our participants, so explaining the precise reasons for heightened CNS activity and/or diminished gait quality during complex walking tasks is outside the scope of the present study. However, we did institute a number of exclusion criteria pertaining to medical history (as described in the section "Methods"). These criteria help to ensure that our findings are not overly influenced by the presence of overt health conditions. For instance, we excluded individuals with evidence of more than mild cognitive impairment, based on the MMSE. Cognitive impairment is well known to compromise performance on tasks requiring heightened attentional demand, and may therefore strongly affect task performance. We also screened out individuals who are considered to have a heightened fall risk due to balance impairment, as indicated by the Berg Balance Test. Based on the cumulative criteria employed by our study, it is reasonable to conclude that the observed demand for CNS resources is typical of what can be expected in pre-frail older adults who are free from major medical conditions. Another factor that is known to influence performance on complex tasks is the instructions given to the participants, and the resultant prioritization of different aspects of task performance. For the present study, we gave the participants no specific information regarding how performance would be evaluated, and no instructions regarding prioritization of dual tasks. The rationale for this approach was to observe each participants natural/preferred behavior in order to maximize the relevance of our findings to actual home and community ambulation.

In summary, preparation and performance of complex walking tasks requires heightened utilization of CNS resources in older adults. The findings from this study warrant additional investigation into the role of the CNS in loss of mobility function. The non-invasive measures presented here may be valuable for identifying individuals who are at risk of adverse mobility outcomes and falls, and for gauging the effectiveness of various rehabilitation approaches.

AUTHOR CONTRIBUTIONS

This study was designed by David J. Clark. Data collection was conducted by David J. Clark and Sarah A. Ring. Data analysis was conducted by David J. Clark and Eric C. Porges. Data interpretation was conducted by David J. Clark, Dorian K. Rose, and Eric C. Porges. The content of the manuscript was prepared by David J. Clark, Sarah A. Ring, Dorian K. Rose, and Eric C. Porges.

ACKNOWLEDGMENTS

This work was supported by the North Florida/South Georgia Veterans Health System Rehabilitation Research and Development Service (B7176W, B6862W, B6793C, and 0512BRRC-3), by the

National Institute on Aging via the University of Florida Claude Pepper Older Americans Independence Center (2P30AG028740-06) and by the University of Florida McKnight Brain Research Foundation endowment to the Cognitive Aging and Memory Clinical Translational Research Program.

REFERENCES

Adkin, A. L., Frank, J. S., Carpenter, M. G., and Peysar, G. W. (2002). Fear of falling modifies anticipatory postural control. *Exp. Brain Res.* 143, 160–170. doi: 10.1007/s00221-001-0974-8

Al-Rawi, P. G., and Kirkpatrick, P. J. (2006). Tissue oxygen index: thresholds for cerebral ischemia using near-infrared spectroscopy. *Stroke* 37, 2720–2725. doi: 10.1161/01.STR.0000244807.99073.ae

Al-Yahya, E., Dawes, H., Collett, J., Howells, K., Izadi, H., Wade, D. T., et al. (2009). Gait adaptations to simultaneous cognitive and mechanical constraints. *Exp. Brain Res.* 199, 39–48. doi: 10.1007/s00221-009-1968-1

Atsumori, H., Kiguchi, M., Katura, T., Funane, T., Obata, A., Sato, H., et al. (2010). Noninvasive imaging of prefrontal activation during attention-demanding tasks performed while walking using a wearable optical topography system. *J. Biomed. Opt.* 15, 046002. doi: 10.1117/1.3462996

Bear, M. F., Connors, B. W., and Paradiso, M. A. (2007). *Neuroscience: Exploring the Brain*, 3rd Edn. Philadelphia: Lippincott Williams & Wilkins.

Berg, K., Wood-Dauphinee, S., Williams, J. I., and Gayton, D. (1989). Measuring balance in the elderly: preliminary development of an instrument. *Physiother. Can.* 41, 304–311. doi: 10.3138/ptc.41.6.304

Brown, L. A., Gage, W. H., Polych, M. A., Sleik, R. J., and Winder, T. R. (2002). Central set influences on gait. Age-dependent effects of postural threat. *Exp. Brain Res.* 145, 286–296. doi: 10.1007/s00221-002-1082-0

Bunce, S. C., Izzetoglu, M., Izzetoglu, K., Onaral, B., and Pourrezaei, K. (2006). Functional near-infrared spectroscopy. *IEEE Eng. Med. Biol. Mag.* 25, 54–62. doi: 10.1109/MEMB.2006.1657788

Carpenter, M. G., Frank, J. S., Adkin, A. L., Paton, A., and Allum, J. H. (2004). Influence of postural anxiety on postural reactions to multi-directional surface rotations. *J. Neurophysiol.* 92, 3255–3265. doi: 10.1152/jn.01139.2003

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences*, 2nd Edn. Hillsdale, NJ: Lawrence Erlbaum.

Curran-Everett, D. (2000). Multiple comparisons: philosophies and illustrations. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 279, R1–R8.

Curran-Everett, D., and Benos, D. J. (2004). Guidelines for reporting statistics in journals published by the American Physiological Society. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 287, R247–R249. doi: 10.1152/ajpregu.00346.2004

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

Frank, J. S., and Patla. A. E. (2003). Balance and mobility challenges in older adults: implications for preserving community mobility. *Am. J. Prev. Med.* 25(3 Suppl. 2), 157–163. doi: 10.1016/S0749-3797(03)00179-X

Fuster, J. M. (2000). Executive frontal functions. *Exp. Brain Res.* 133, 66–70. doi: 10.1007/s002210000401

Hadjistavropoulos, T., Carleton, R. N., Delbaere, K., Barden, J., Zwakhalen, S., Fitzgerald, B., et al. (2012). The relationship of fear of falling and balance confidence with balance and dual tasking performance. *Psychol. Aging* 27, 1–13. doi: 10.1037/a0024054

Herrmann, M. J., Walter, A., Ehlis, A. C., and Fallgatter, A. J. (2006). Cerebral oxygenation changes in the prefrontal cortex: effects of age and gender. *Neurobiol. Aging* 27, 888–894. doi: 10.1016/j.neurobiolaging.2005.04.013

Hobert, M. A., Niebler, R., Meyer, S. I., Brockmann, K., Becker, C., Huber, H., et al. (2011). Poor trail making test performance is directly associated with altered dual task prioritization in the elderly–baseline results from the TREND study. *PLoS ONE* 6:e27831. doi: 10.1371/journal.pone.0027831

Holtzer, R., Epstein, N., Mahoney, J. R., Izzetoglu, M., and Blumen, H. M. (2014). Neuroimaging of mobility in aging: a targeted review. *J. Gerontol. A Biol. Sci. Med. Sci.* doi: 10.1093/gerona/glu052

Holtzer, R., Mahoney, J. R., Izzetoglu, M., Izzetoglu, K., Onaral, B., and Verghese, J. (2011). fNIRS study of walking and walking while talking in young and old individuals. *J. Gerontol. A Biol. Sci. Med. Sci.* 66, 879–887. doi: 10.1093/gerona/glr068

Ishikuro, K,. Urakawa, S., Takamoto, K., Ishikawa, A., Ono, T., and Nishijo, H. (2014). Cerebral functional imaging using near-infrared spectroscopy during repeated performances of motor rehabilitation tasks tested on healthy subjects. *Front. Hum. Neurosci.* 8:292. doi: 10.3389/fnhum.2014.00292

Jenkins, I. H., Jahanshahi, M., Jueptner, M., Passingham, R. E., and Brooks, D. J. (2000). Self-initiated versus externally triggered movements. II. The effect of movement predictability on regional cerebral blood flow. *Brain* 123(Pt 6), 1216–1228. doi: 10.1093/brain/123.6.1216

Kaneko, H., Yoshikawa, T., Nomura, K., Ito, H., Yamauchi, H., Ogura, M., et al. (2011). Hemodynamic changes in the prefrontal cortex during digit span task: a near-infrared spectroscopy study. *Neuropsychobiology* 63, 59–65. doi: 10.1159/000323446

Koenraadt, K. L., Roelofsen, E. G., Duysens, J., and Keijsers, N. L. (2014). Cortical control of normal gait and precision stepping: an fNIRS study. *Neuroimage* 85(Pt 1), 415–422. doi: 10.1016/j.neuroimage.2013.04.070

Lord, S. E., Weatherall, M., and Rochester, L. (2010). Community ambulation in older adults: which internal characteristics are important? *Arch. Phys. Med. Rehabil.* 91, 378–383. doi: 10.1016/j.apmr.2009.11.008

Moscufo, N., Wolfson, L., Meier, D., Liguori, M., Hildenbrand, P. G., Wakefield, D., et al. (2012). Mobility decline in the elderly relates to lesion accrual in the splenium of the corpus callosum. *Age* 34, 405–414. doi: 10.1007/s11357-011-9242-4

Oh-Park, M., Holtzer, R., Mahoney, J., Wang, C., Raghavan, P., and Verghese, J. (2013). Motor dual-task effect on gait and task of upper limbs in older adults under specific task prioritization: pilot study. *Aging Clin. Exp. Res.* 25, 99–106. doi: 10.1007/s40520-013-0014-0

Ohsugi, H., Ohgi, S., Shigemori, K., and Schneider, E. B. (2013). Differences in dual-task performance and prefrontal cortex activation between younger and older adults. *BMC Neurosci.* 14:10. doi: 10.1186/1471-2202-14-10

Okamoto, M., Dan, H., Shimizu, K., Takeo, K., Amita, T., Oda, I., et al. (2004). Multimodal assessment of cortical activation during apple peeling by NIRS and fMRI. *Neuroimage* 21, 1275–1288. doi: 10.1016/j.neuroimage.2003.12.003

Patla, A. E., and Shumway-Cook, A. (1999). Dimensions of mobility: defining the complexity and difficulty associated with community mobility. *J. Aging Phys. Act.* 7, 7–19.

Rosano, C., Aizenstein, H., Brach, J., Longenberger, A., Studenski, S., and Newman, A. B. (2008). Special article: gait measures indicate underlying focal gray matter atrophy in the brain of older adults. *J. Gerontol. A Biol. Sci. Med. Sci.* 63, 1380–1388. doi: 10.1093/gerona/63.12.1380

Rosano, C., Aizenstein, H. J., Studenski, S., and Newman, A. B. (2007). A regions-of-interest volumetric analysis of mobility limitations in community-dwelling older adults. *J. Gerontol. A Biol. Sci. Med. Sci.* 62, 1048–1055. doi: 10.1093/gerona/62.9.1048

Rosano, C., Bennett, D. A., Newman, A. B., Venkatraman, V., Yaffe, K., Harris, T., et al. (2012). Patterns of focal gray matter atrophy are associated with bradykinesia and gait disturbances in older adults. *J. Gerontol. A Biol. Sci. Med. Sci.* 67, 957–962. doi: 10.1093/gerona/glr262

Rosano, C., Sigurdsson, S., Siggeirsdottir, K., Phillips, C. L., Garcia, M., Jonsson, P. V., et al. (2010). Magnetization transfer imaging, white matter hyperintensities, brain atrophy and slower gait in older men and women. *Neurobiol. Aging* 31, 1197–1204. doi: 10.1016/j.neurobiolaging.2008.08.004

Rosso, A. L., Studenski, S. A., Chen, W. G., Aizenstein, H. J., Alexander, N. B., Bennett, D. A., et al. (2013). Aging, the central nervous system, and mobility. *J. Gerontol. A Biol. Sci. Med. Sci.* 68, 1379–1386. doi: 10.1093/gerona/glt089

Sato, K., Kang, W. H., Saga, K., and Sato, K. T. (1989). Biology of sweat glands and their disorders. I. Normal sweat gland function. *J. Am. Acad. Dermatol.* 20, 537–563. doi: 10.1016/S0190-9622(89)70063-3

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

Shumway-Cook, A., Guralnik, J. M., Phillips, C. L., Coppin, A. K., Ciol, M. A., Bandinelli, S., et al. (2007). Age-associated declines in complex walking task performance: the Walking InCHIANTI toolkit. *J. Am. Geriatr. Soc.* 55, 58–65. doi: 10.1111/j.1532-5415.2006.00962.x

Shumway-Cook, A., Patla, A., Stewart, A., Ferrucci, L., Ciol, M. A., and Guralnik, J. M. (2003). Environmental components of mobility disability in community-living older persons. *J. Am. Geriatr. Soc.* 51, 393–398. doi: 10.1046/j.1532-5415.2003.51114.x

Shumway-Cook, A., Patla, A. E., Stewart, A., Ferrucci, L., Ciol, M. A., and Guralnik, J. M. (2002). Environmental demands associated with community mobility in older adults with and without mobility disabilities. *Phys. Ther.* 82, 670–681.

Sibley, K. M., Mochizuki, G., Frank, J. S., and McIlroy, W. E. (2010). The relationship between physiological arousal and cortical and autonomic responses to postural instability. *Exp. Brain Res.* 203, 533–540. doi: 10.1007/s00221-010-2257-8

Suzuki, M., Miyai, I., Ono, T., and Kubota, K. (2008). Activities in the frontal cortex and gait performance are modulated by preparation. An fNIRS study. *Neuroimage* 39, 600–607. doi: 10.1016/j.neuroimage.2007.08.044

Tanji, J., and Hoshi, E. (2001). Behavioral planning in the prefrontal cortex. *Curr. Opin. Neurobiol.* 11, 164–170. doi: 10.1016/S0959-4388(00)00192-6

Tisdall, M. M., Taylor, C., Tachtsidis, I., Leung, T. S., Elwell, C. E., and Smith, M. (2009). The effect on cerebral tissue oxygenation index of changes in the concentrations of inspired oxygen and end-tidal carbon dioxide in healthy adult volunteers. *Anesth. Analg.* 109, 906–913. doi: 10.1213/ane.0b013e3181aedcdc

Viana-Baptista, M., Bugalho, P., Jordao, C., Ribeiro, O., Esperanca-Pina, J. A., and Ferro, J. (2011). Motor dysfunction correlates with frontal white matter ischemic changes in patients with leukoaraiosis. *J. Aging Res.* 2011, 950341. doi: 10.4061/2011/950341

Wakefield, D. B., Moscufo, N., Guttmann, C. R., Kuchel, G. A., Kaplan, R. F., Pearlson, G., et al. (2010). White matter hyperintensities predict functional decline in voiding, mobility, and cognition in older adults. *J. Am. Geriatr. Soc.* 58, 275–281. doi: 10.1111/j.1532-5415.2009.02699.x

Willey, J. Z., Scarmeas, N., Provenzano, F. A., Luchsinger, J. A., Mayeux, R., and Brickman, A. M. (2013). White matter hyperintensity volume and impaired mobility among older adults. *J. Neurol.* 260, 884–890. doi: 10.1007/s00415-012-6731-z

Yerkes, R. M., and Dodson, J. D. (1908). The relation of strength of stimulus to rapidity of habit formation. *J. Comp. Neurol. Psychol.* 18, 459–482. doi: 10.1002/cne.920180503

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

Received: 19 June 2014; accepted: 04 August 2014; published online: 25 August 2014.
Citation: Clark DJ, Rose DK, Ring SA and Porges EC (2014) Utilization of central nervous system resources for preparation and performance of complex walking tasks in older adults. Front. Aging Neurosci. ***6****:217. doi: 10.3389/fnagi.2014.00217*
This article was submitted to the journal Frontiers in Aging Neuroscience.

frontiers in
AGING NEUROSCIENCE

REVIEW ARTICLE
published: 05 February 2014
doi: 10.3389/fnagi.2014.00014

Development and decline of upright gait stability

Marco Iosa*, Augusto Fusco, Giovanni Morone and Stefano Paolucci

Clinical Laboratory of Experimental Neurorehabilitation, Fondazione Santa Lucia, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Rome, Italy

Edited by:
Brian C. Clark, Ohio University, USA

Reviewed by:
Shinichi Amano, Ohio University, USA
Jacob Sosnoff, University of Illinois at Urbana-Champaign, USA

****Correspondence:***
Marco Iosa, Clinical Laboratory of Experimental Neurorehabilitation, Fondazione Santa Lucia, IRCCS, Via Ardeatina 306, Rome 00179, Italy
e-mail: m.iosa@hsantalucia.it

Upright gait is a peculiar characteristic of humans that requires the ability to manage upper body dynamic balance while walking, despite the perturbations that are generated by movements of the lower limbs. Most of the studies on upright gait stability have compared young adults and the elderly to determine the effects of aging. In other studies, the comparison was between healthy subjects and patients to examine specific pathologies. Fewer researches have also investigated the development of upright gait stability in children. This review discusses these studies in order to provide an overview of this relevant aspect of human locomotion. A clear trend from development to decline of upright gait stability has been depicted across the entire lifespan, from toddlers at first steps to elderly. In old individuals, even if healthy, the deterioration of skeletal muscle, combined with sensorial and cognitive performance, reduces the ability to maintain an upright trunk during walking, increasing the instability and the risk of falls. Further, the pathological causes of altered development or of a sudden loss of gait stability, as well as the environmental influence are investigated. The last part of this review is focused on the control of upper body accelerations during walking, a particularly interesting topic for the recent development of low-cost wearable accelerometers.

Keywords: locomotion, walking, balance, falls, accelerometry, motor control, aging, neuromuscular diseases

INTRODUCTION

An experience of great pleasure for a person is surely when his/her child begins to walk independently. Those first few unstable steps are considered a fundamental stage of human development. Arguably, the child's clear pronunciation of his first word rivals this milestone.

Differently from other animals, human children need more time to develop independent gait (Garwicz et al., 2009). Fourteen months are in mean needed (Bosch et al., 2007) because baby's rudimentary lower limb flexion–extension movements evolve into sophisticated coordination that permits upright walking (Dominici et al., 2011). Upright walking was not only a fundamental stage in the ontogenesis of a child but also a basic step in phylogenetic human evolution that about 1.5 million years ago evolved to *Homo erectus*. Erectus should not be considered a synonym of bipedal walking but as a stable, upright upper body posture during walking.

The expression "stable gait" may refer to a step-to-step repeatable walking (Ingwell and Marin, 2006), to a gait resilient to external and internal perturbations (Terrier and Dériaz, 2011), or to the ability of maintaining upright balance during walking (Menz et al., 2003). A recent review identified 92 different linear and non-linear quantitative measures of "gait stability" obtained using five different categories of devices and mainly related to spatio-temporal gait parameters, lower limb joint kinematics, and upper body kinematics (Hamacher et al., 2011). About this latter aspect, "upright gait stability" refers to the capacity of humans to minimize oscillations during walking, in a progressive way from the lower to upper levels of the human body, with the head moved on a straight line at quite constant speed (Cappozzo, 1981; Inman et al., 1981). The stabilization of the head during human gait allows steadying the optic flow and increasing the control of equilibrium with more effective processing of vestibular system signals (Berthoz and Pozzo, 1994; Spoor et al., 1994). These and other advantages, such as keeping the hands free and seeing farther, might have spurred the development of upright walking in humans (Friedman, 2006). In general, both exploratory and performative activities can benefit from the upright posture maintained also during gait (Reed, 1996).

The purpose of this review was to investigate the development and the decline of upright gait stability during the lifespan, both in unimpaired and impaired subjects. In the second part of this review, particular attention was deserved to the upright gait stability, i.e., to the upper body dynamic balance evaluated in terms of the capacity of smoothing accelerations during walking.

DEVELOPMENT OF UPRIGHT GAIT STABILITY

PHYSIOLOGICAL DEVELOPMENT

In typical development, gait mechanism becomes predominantly functional and efficient by the age of 2 years [walking speed (WS) close to 0.8 stature/s (Sutherland et al., 1980) and 60% of energy recovery (Ivanenko et al., 2004)]. However, children may need more time to achieve a stable gait and to manage the emerging instability that accompanies the progressive increase in WS (Iosa et al., 2012f). The beginning of independent walking, averaging at 14 months (Bosch et al., 2007) is characterized by extensive trunk oscillations and a wide base of support, which help the control of instability in new walkers (Ivanenko et al., 2007). At this age, both motor and somatosensory systems need to be developed in order to improve balance and dynamic equilibrium control (Bosch and

Rosenbaum, 2010). Unlike the adults, the lateral component of kinetic energy of the center of mass is not negligible, compared to its sagittal components, in toddlers (Ivanenko et al., 2004).

Upper limbs play an important role in this scenario. Healthy adults move their upper and lower limbs in a contralaterally synchronized fashion, to reduce the moment of inertia and maintain upright gait stability (Sparrow and Newell, 1994). At the early stages of gait development, however, healthy toddlers keep their upper limbs high, similar to the spastic limbs observed in children with cerebral palsy. During development, children lower this "high guard" position of the upper limbs, increasing their WS (Kubo and Ulrich, 2006a). The interaction between arm posture and upper trunk position creates a variety of changes in forces and torque between individuals that can be explained by the need for healthy toddlers to explore their dynamics and gait stability in the early stages of gait development (Pozzo et al., 1990).

From age 7, upper body gait stability is related to the adoption of head stabilization (Pozzo et al., 1990), which appears to be more difficult in the latero-lateral (LL) compared to the antero-posterior (AP) direction (Assaiante and Amblard, 1993; Mazzà et al., 2010). At age 9, children show upper body stability, similar to that of adults (Mazzà et al., 2010). Unfortunately, few data are available about individuals between 10 and 20 years of age, preventing a detailed examination on what occurs in teenagers: in this age, cultural habits and psychological features may be also have an impact on functional development and anthropometric growth.

ALTERED DEVELOPMENT

In children with impaired development, such as those with cerebral palsy, the ability to walk at a proper speed is limited in the first phase of independent walking, even if they are not severely affected (Iosa et al., 2012f). Later, they develop a faster speed, implying high trunk instability (Iosa et al., 2012f). Higher vertical oscillations in these children are likely related to their equinus foot or crouch gait, two typical features of cerebral palsy (Perry, 1992; Gage, 1993). Along LL direction, an increased distance has been found between the body center of mass and the center of pressure under the foot of standing leg in children with diplegia due to cerebral palsy during single support phase of gait (Hsue et al., 2009a,b). This could be due to three possibly concomitant reasons: (1) hip muscle weakness (see Gait Instability and Risk of Fall for details); (2) facilitating contralateral foot lift; (3) facilitating the control of forward progression by transferring part of forward momentum to lateral momentum.

The high trunk accelerations and gait asymmetry that are observed in children with cerebral palsy are likely to be related to certain compensatory mechanisms that facilitate walking at a speed that is similar to that of unimpaired children (Meyns et al., 2012). Greater arm swing on the unaffected side is often required to compensate for the reduced movement on the affected side and to counteract the substantial increases in angular momentum that are generated by functional asymmetry in the legs (Bruijn et al., 2011). Thus, it is conceivable that this compensatory strategy destabilizes gait patterns (Bruijn et al., 2011), reducing upright gait stability (Iosa et al., 2012f).

In children with Down syndrome, the development of independent walking usually occurs approximately 1 year later than in children who undergo typical development (Henderson, 1986). At the early stages of walking, children with Down syndrome have similar gait spatio-temporal patterns as typically developed toddlers but appear to be less able to manage the coupling of AP–LL oscillations at the level of the center of mass, i.e., at the lower trunk level (Kubo and Ulrich, 2006b).

The altered development of upright gait stability is an interesting topic, and further studies are needed to examine the development of gait stability in toddlers with and without developmental disability. The possibility of easily assessing gait related features by wearable devices (rather than with more complex stereophotogrammetric systems) might be helpful for early clinical analysis and, in general, for a greater understanding of this processes (Masci et al., 2013).

DECLINE OF UPRIGHT GAIT STABILITY

PHYSIOLOGICAL DECLINE WITH AGING

Many studies reported a decline of gait stability in the elderly. Experimental evidence shows that this reduction in the ability to stabilize the upper body during walking is due to the loss of skeletal muscle strength (Doherty, 2003) and a reduction in the ability to detect and process proprioceptive and sensorial information (Scaglioni et al., 2003).

From a motor point of view, after the age of 50, approximately 1–2% of muscle mass is lost per year. This muscle mass and strength reduction, called sarcopenia, is also accompanied by intramuscular fat accumulation, muscle atrophy (especially the type IIa fibers), decreased satellite cell proliferation and differentiation capacity, and reduction in motor unit number (Muscaritoli et al., 2013). The loss in body mass density, which is related to muscle weakness, is greater in women compared to men aged 60 years and older (Daly et al., 2013). From a skeletal point of view, the age-related degradation of joints, including articular cartilage and bone epiphysis, especially at knee level, can cause gait impairments, especially when it suddenly degenerates in pathological osteoarthritis (van Baar et al., 1998).

A recent study had also suggested that vitamin D may be involved in gait stability. Vitamin D metabolism is in fact involved in muscular contraction speed and one of the consequence of its concentration reduction, typically occurring in the elderly, was found to be an increased stride-to-stride duration variability that is related to a reduction of gait stability and hence to an increased risk of fall (Beauchet et al., 2011).

Aging implies not only a loss in musculoskeletal functioning, but also a decline in vision, reaction time, peripheral and vestibular sensations: all of which can reduce upper body stability during walking (Menz et al., 2003). The vestibular system becomes impaired with age, altering the vestibulospinal reflex function (Allum et al., 1997). With regard to the chief function of the vestibular system in upright gait stability, it is noteworthy that the inner ear of *Homo erectus* was more developed than in earlier hominids, who possessed ape-like inner ears (Spoor et al., 1994).

Considering these reduction in sensorimotor ability, older persons have a more conservative gait pattern, characterized by reduced velocity that is a result of a shorter step length and accompanied by increased variability in step timing (Menz et al., 2003). These differences are particularly pronounced when they walk on irregular surfaces (Menz et al., 2003; Marigold and Patla, 2008). The conservative basic gait patterns, evident in older people, might be a compensatory strategy to ensure adequate stabilization of the upper body (Menz et al., 2003). It has been proposed that these gait patterns in older people are attributed in part to a decline in leg strength and a reluctance to walk quickly, so that their upper body accelerations do not increase (Menz et al., 2003). Notably, the elderly experience an abrupt increase in instability in the LL direction. These results are also supported by the excessive lateral momentum found in balance-impaired during gait (Kaya et al., 1998) and by the increased center of mass – center of pressure inclination angle measured in lateral direction (frontal plane) (Lee and Chou, 2006) that were both found as sensitive measures of loss of equilibrium in elderly during gait. Lateral trunk bending has been described as a typical compensation mechanism for hip abductor weakness: lateral trunk movements toward the stance limb align the body's center of mass over the hip joint center, supporting the body in the single stance when the hip abductor muscles are weak (Perry, 1992). This trunk bending strategy, helpful for compensation hip muscle weakness, is typical not only of old age, but also of many pathologies (as described below), including children with cerebral palsy with lateral excessive trunk bending, as reported above.

Not only motor and sensorial impairment have been shown to affect upright gait stability in the elderly. Indeed, physiological reduction of cognitive functions might also have a significant role, as suggested by studies that reported decreased gait stability in subjects with cognitive impairment (see Pathological Loss of Gait Stability) (Lamoth et al., 2011; Ijmker and Lamoth, 2012). This topic appears rather controversial, as the study entitled "walking without thinking" (Ruchinskas et al., 2000) questions the role of cognitive function on gait control, observing that, while it could affect the overall geriatric rehabilitation course, it may not predict walking or stair climbing ability. It must be remembered, however that cognitive status and thinking are two different things. Another study, in fact, observed that in elderly persons without cognitive impairment, gait patterns were altered when subjects were asked to walk and perform a cognitive naming task simultaneously (Lamoth et al., 2011). In response to dual tasking, subjects decreased their WS by increasing stride time. Despite the lower speed, trunk acceleration patterns were more irregular and variable, and local stability declined in the dual task condition. These results highlight the importance to take into account the control of functional resource allocation, with a reduction in upright gait stability when subjects are asked to walk and perform a cognitive task simultaneously, as occurs often in everyday life.

Finally, upright gait stability has been found adversely associated to subclinical cerebrovascular lesions. Silent infarcts (detectable in 7.2–28% of the general population, i.e., in the absence of a history of clinical stroke), cerebral microbleedings (occurring in 4.7–23.5% of the general population), and cerebral white matter microlesions (present in 90% of people aged >60 years) affect gait ability and stability in elderly (Choi et al., 2012).

GAIT INSTABILITY AND RISK OF FALL

All the difficulties described above in controlling dynamic balance during walking in the elderly have also been associated with the risk of falls (Marigold and Patla, 2008; Senden et al., 2012). There are currently over 400 known risk factors for falls, broadly classified into environmental, task-related, and personal factors (Masud and Morris, 2001). Age is one of the most important risk factor, and many other personal factors may be related to age: among others, muscular strength, reaction time, visual ability, use of drugs and medications, living alone, sedentary behavior, psychological status, and impaired cognition and foot problems (Hamacher et al., 2011). As above reported, most of them are also associated to higher upper body accelerations and higher step-by-step gait variability.

Environmental, task-related, and personal factors may also increase the risk of fall. For example, this risk increases when older individuals can not reduce their WS by controlling their trunk acceleration. This event may occur when they want to cross a street and must time their gait speed with the traffic lights, which usually requires a mean speed of at least 0.9 m/s (Hesse et al., 2009), higher than what many older subjects can attain (see **Table 1**; Mazzà et al., 2008; Lamoth et al., 2011; Senden et al., 2012). For example, in UK, such as in other Western countries, 1.2 m/s is the value of theoretical WS utilized to set the crossing timing of traffic lights (Asher et al., 2012). However, the comfortable speed of many elderly is lower than these values (Asher et al., 2012). A speed lower than 0.8 m/s has been defined as a pathological gait velocity and resulted associated with repeated falls, even when observed in healthy elderly (without any specific pathology) (Montero-Odasso et al., 2004). But a low steady speed is not the only factor affecting the safety in road crossing. The presence of obstacles (Hahn and Chou, 2004), the visual attention and the time-to-arrival estimation (Dommes and Cavallo, 2011), the fear of falling (Avineri et al., 2012), the time spent in selecting the proper motor strategy (Sueur et al., 2013), as well as the management of accelerations (for example in the start of walking, or for further increasing speed if traffic green light is going to expire or if a car is arriving) or deceleration for terminating road crossing (Bollard and Fleming, 2013) are all factors that can reduce gait stability and increase the risk of fall or of an accident.

Regarding acceleration, upper body cranio-caudal (CC) accelerations were found significantly increased in elderly with balance impairment compared to elderly without balance impairment (Senden et al., 2012). Furthermore, it has been reported that the harmonicity of trunk movements (assessed by analysis of trunk accelerations in the domain of frequency) is a reliable predictor of the risk of falls in elderly, independently of their physical performance, in 1 year after the assessment (Doi et al., 2013) (for details about these last two studies, see Assessment of Dynamic Equilibrium by Trunk Accelerations).

A recent review analyzed the available kinematic measures for assessing gait stability, taking into account old versus young subjects' comparisons and fallers versus no-fallers comparisons (Hamacher et al., 2011). The authors found that, regarding the 92 different outcome measures identified in literature, linear measures of gait stability showed a higher sensitivity concerning age-related differences than non-linear measures. In detail,

Table 1 | Healthy subject trunk accelerations during walking ordered by age.

Authors (year)	Age (years)	WS (m/s)	Gender	Trunk level	*n*	RMS_{AP} (m/s^2)	RMS_{LL} (m/s^2)	RMS_{CC} (m/s^2)
Iosa et al. (2012f)	4 ± 1	0.94 ± 0.22	M and F	L2–L3	8	2.23 ± 0.60	2.14 ± 0.47	2.95 ± 0.81
	7 ± 2	1.09 ± 0.13	M and F	L2–L3	9	1.72 ± 0.40	1.54 ± 0.48	2.44 ± 0.86
Mazzà et al. (2010)	9 ± 1	1.34 ± 0.14	M	Pelvis	15	1.93 ± 0.31	1.76 ± 0.23	2.90 ± 0.67
	9 ± 1	1.32 ± 0.16	F	Pelvis	15	1.97 ± 0.31	1.79 ± 0.31	2.93 ± 0.85
Mazzà et al. (2009)	23 ± 2	1.33 ± 0.13	M	Pelvis	20	1.91 ± 0.40	1.57 ± 0.36	2.70 ± 0.72
	23 ± 3	1.34 ± 0.09	F	Pelvis	20	2.06 ± 0.40	1.90 ± 0.22	2.88 ± 0.13
Moe-Nilssen (1998)	23 ± 2	1.2[a]	M and F	L3	19	1.57 ± 0.18	1.33 ± 0.17	2.06 ± 0.23
Kavanagh (2009)	23 ± 3	1.32 ± 0.18	M and F	L3	13	1.63 ± 0.17	1.23 ± 0.16	1.91 ± 0.23
Iosa et al. (2012b)	28 ± 5	1.12 ± 0.11	M and F	L2–L3	28	1.72 ± 0.28	1.51 ± 0.36	2.76 ± 0.56
Iosa et al. (2010)	31 ± 9	1.25 ± 0.08	M and F	Pelvis	13	1.53 ± 0.25	0.56 ± 0.07	1.79 ± 0.35
Henriksen et al. (2004)	35	1.35[a]	M and F	L3	20	1.75 ± 0.20	1.35 ± 0.25	2.47 ± 0.24
Iosa et al. (2012d)	63 ± 10	1.17 ± 0.18	M and F	L2–L3	10	1.49 ± 0.30	1.02 ± 0.22	2.21 ± 0.70
Iosa et al. (2012e)	29 ± 5	1.13 ± 0.11	M and F	L2–L3	15	1.75 ± 0.35	1.57 ± 0.39	2.87 ± 0.65
	65 ± 9	1.02 ± 0.16	M and F		15	1.37 ± 0.26	0.96 ± 0.22	1.94 ± 0.54
Mazzà et al. (2008)	24 ± 4	1.30 ± 0.28	F	Pelvis	16	1.41 ± 0.23	0.48 ± 0.18	1.66 ± 0.92
	72 ± 4	0.97 ± 0.18	F	Pelvis	20	1.06 ± 0.24	0.48 ± 0.14	0.99 ± 0.32
Kavanagh et al. (2004)	23 ± 4	1.28 ± 0.15	M and F	L2–L3	8	1.47 ± 0.98	1.10 ± 0.78	1.77 ± 1.17
	74 ± 3	1.23 ± 0.15		L2–L3	8	1.37 ± 0.98	1.10 ± 0.69	1.77 ± 1.10
Marigold and Patla (2008)	26 ± 5	1.0[a]	M and F	Iliac crests	10	0.95 ± 0.10	0.57 ± 0.09	1.65 ± 0.21
	74 ± 7				10	1.05 ± 0.16	0.74 ± 0.13	1.56 ± 0.17
Ijmker and Lamoth (2012)	64 ± 3	1.19 ± 0.08	M and F	L3	12	1.40 ± 0.16	1.28 ± 0.19	Not eval.
	77 ± 4	1.14 ± 0.11			14	0.84 ± 0.32	0.95 ± 0.31	
Lamoth et al. (2011)	79 ± 5	0.95 ± 0.21	M and F	L3	13	1.04 ± 0.23	0.96 ± 0.18	Not eval.
Menz et al. (2003)	29 ± 4	1.33 ± 0.19	M and F	Pelvis	30	1.86 ± 0.39	1.86 ± 0.39	2.55 ± 0.69
	79 ± 3	1.17 ± 0.16		Pelvis	30	1.67 ± 0.29	1.57 ± 0.49	1.96 ± 0.49
Senden et al. (2012)	74 ± 5	1.23 ± 0.22	M and F	Sacrum	50	Not eval.	Not eval.	2.45 ± 0.69
	79 ± 6	0.86 ± 0.26			50			1.57 ± 0.69

The columns report authors and year of publication, the reference number for each study, the mean age (±SD) of groups of subjects, walking speed ([a] in some studies a reference value of WS has been used to identify trunk acceleration from interpolant curves), gender, analyzed level of trunk (in many of these studies, other parts of the body are analyzed), number of subjects enrolled (n), and mean acceleration RMS along the antero-posterior (AP), latero-lateral (LL), and cranio-caudal (CC) axis. In some of the original studies, accelerations were reported in g, in which case they were transformed to m/s^2, or reported in terms of mean and standard error of the mean, in which case they were transformed to mean ± SD. For study Henderson (1986), the data are related to the first 6 min of walking. Finally, not all studies evaluated accelerations along all three body axes.

variability of step width and stride velocity were capable of distinguishing between old and young subjects, whereas variability of stride, stance, and swing between fallers and non-fallers. Step width variability had higher discriminative power in the comparison between elderly and young subjects than in the faller versus non-faller comparisons, suggesting that although it may increase with age, it is not necessarily a dominant factor in fall risk. This suggestion has also been supported by the fact that differences between fit and frail older adults were better highlighted by interstride trunk acceleration variability, than by step width variability (Moe-Nilssen and Helbostad, 2005). Another study reported increased trunk acceleration and trunk roll variability along LL direction in elderly walking, despite having similar step width of the control group formed by younger subjects (Marigold and Patla, 2008).

According to all these studies, the increased LL trunk acceleration observed in advanced age seems to be a particularly important risk of fall given its association with gait instability. Moreover, hip fractures occur most frequently in association with lateral falls.

PATHOLOGICAL LOSS OF GAIT STABILITY

The loss of stability can be abrupt when a pathological event occurs, wherein more severe pathologies affect a greater loss of upright gait stability.

Upright gait stability has been studied extensively in subjects after stroke. In these patients, upper body accelerations are significantly lower than in age-matched healthy controls in all axes due to the reducing WS. However, acceleration root mean square (RMS) values that have been normalized by speed are higher than in healthy subjects along all body axes in subjects with chronic (Mizuike et al., 2009) and subacute stroke (Iosa et al., 2012e). As shown in **Table 1**, the mean WS of young healthy adults was about 1.3 m/s. Although WS in stroke patients (reported in **Table 2**) declines by approximately 50% versus young healthy adults, their CC acceleration (in terms of its RMS), their AP and LL accelerations do not. Yet, in patients with stroke, trunk control is a prognostic factor for gait recovery (Masiero et al., 2007; Di Monaco et al., 2010): their trunk asymmetries are more marked than their

Table 2 | Gait stability data of subjects with a pathology or healthy subjects walking on uneven floor or without vision support, with respect to reference values obtained as the average of means (±SDMs) reported in studies on young healthy adults.

Condition	Reference	Age (years)	WS (m/s)	Trunk level	*n*	RMS_{AP} (m/s^2)	RMS_{LL} (m/s^2)	RMS_{CC} (m/s^2)
Cerebral palsy	Iosa et al. (2012f)	4 ± 1	0.76 ± 0.19	L2–L3	11	2.29 ± 0.78	2.26 ± 0.93	3.04 ± 1.43
		7 ± 2	1.15 ± 0.09	L2–L3	6	2.86 ± 0.91	2.50 ± 0.68	4.29 ± 1.31
Stroke	Iosa et al. (2012e)	61 ± 15	0.60 ± 0.29	L2–L3	15	0.98 ± 0.33	0.80 ± 0.24	1.16 ± 0.50
	Iosa et al. (2012d)	64 ± 13	0.55 ± 0.31	L2–L3	20	0.91 ± 0.37	0.87 ± 0.41	1.13 ± 0.61
Dystrophy	Iosa et al. (2010)	39 ± 11	1.04 ± 0.15	Pelvis	13	1.31 ± 0.36	0.59 ± 0.16	1.30 ± 0.40
Dementia	Lamoth et al. (2011)	83 ± 4	0.88 ± 0.27	L3	13	1.03 ± 0.26	0.82 ± 0.18	Not eval.
	Ijmker and Lamoth (2012)	82 ± 6	0.67 ± 0.21	L3	15	0.56 ± 0.22	0.59 ± 0.21	Not eval.
Uneven floor	Moe-Nilssen (1998)	23 ± 2	1.2[a]	L3	19	1.72 ± 0.22	1.57 ± 0.18	2.28 ± 0.23
No vision	Iosa et al. (2012b)	28 ± 5	0.83 ± 0.18	L2–L3	28	1.32 ± 0.36	1.23 ± 0.36	1.87 ± 0.68
Reference values	Mazzà et al. (2009), Iosa et al. (2012e), Menz et al. (2003), Kavanagh et al. (2004), Moe-Nilssen (1998), Henriksen et al. (2004), Marigold and Patla (2008)	26 ± 4	1.26 ± 0.10	Lower trunk	183	1.67 ± 0.30	1.40 ± 0.39	2.36 ± 0.47

[a] *A reference value of WS from interpolant curve.*

asymmetries with regard to step length and single support timing (Hodt-Billington et al., 2008).

Overexertion and fatigue can compromise the control of gait stability following stroke. Two alternative strategies have been highlighted in these patients for prolonged (6-min) walking. Some subjects maintain their speed during long-lasting walking, despite a slight but progressive reduction in upper body stability. Other subjects apply a compensatory strategy, based on a reduction in WS for maintaining low upper body accelerations (Iosa et al., 2012d).

Patients with Parkinson's disease show increased stride time variability, reduced trunk rotation, reduced arm swing as signs of gait impairments as well as increased time spent in the double support phase that is probably due to the need of improving dynamic equilibrium during gait (Horak and Mancini, 2013). L-DOPA reduces stride time variability, decreases double support time, and increases gait speed, all consistent with improvements in gait dynamic balance (Rebula et al., 2013). Interesting studies showed a reduced coordination between the rhythmic processes of the two legs in these patients (Plotnik et al., 2007). In particular, reduced inter-lower limb coordination and higher stride time variability can expose these subjects to a higher risk of falls. Furthermore, during the execution of a cognitive task while walking, gait symmetry was reduced in these patients (Plotnik et al., 2011).

Subjects who are affected by muscular impairment, such as dystrophy, have wider and less symmetrical upper body oscillations than healthy controls in the AP and LL directions. Further, the ability of these subjects to attenuate accelerations from the lower body to the head is weakened. It has been suggested that these features are related not only to upper body muscle impairments but also indirectly to the above described strategy that compensates for hip muscle weakness (Iosa et al., 2010).

As above mentioned, increased LL trunk bending, as described in the elderly, is a typical compensatory mechanism for hip abductor weakness also in other pathologies, such as dystrophy (Iosa et al., 2010), myelomeningocele (Gutierrez et al., 2005), and spinal muscular atrophy (Armand et al., 2005).

Upright gait stability in patients with vestibular deficits is a notable area of study. However, most researches on such patients have investigated their postural standing stability, instead of gait dynamic stability. Nevertheless, one of the few studies on upper body stability during walking in persons with vestibular hypofunction reported lower regularity of upper body movements compared with healthy subjects, consistent with the function of the vestibular system in controlling the dynamic stability of walking (Sylos-Labini et al., 2012). Also, in patients with small vestibular schwannomas and an apparently normal gait who are asked to walk without vision support, gait variability increases, reducing their gait steadiness (Yin et al., 2011). After unilateral vestibular neurotomy, used as curative surgery in patients with Menière syndrome, robust walking deviations develop toward the damaged side on walking with the eyes closed (Borel et al., 2004).

Another sensorial impairment that affects gait stability is altered vision (Perry et al., 2001). However, few studies have examined upright gait stability in a population with visual impairment. Yet, significant differences exist between subjects with and without visual impairments and between conditions of full vision and no vision. Further, these differences reflect a more cautious walking strategy and adaptive changes under challenging conditions. In particular, subjects with visual impairments undergo adaptations that are related to a shorter stride length and prolonged plantar foot contact. These patterns might reflect a strategy to overcome the problems that arise from sensory deprivation, compensated by the use of the feet to probe the ground for haptic exploration, to maintain adequate upper body stability (Hallemans et al., 2010).

In less disabling pathologies, such as low back pain, subjects exhibit altered coordination of the pelvis and trunk, resulting in a less harmonic and less stable gait (Lamoth et al., 2002).

Finally, reductions in cognitive functions, such as those that are related to dementia (Allali et al., 2008; Lamoth et al., 2011; Ijmker and Lamoth, 2012) and Alzheimer disease (Sheridan et al., 2003), contribute to changes in the variability and stability of the gait pattern when the task becomes more challenging, increasing the risk of falls.

OTHER FACTORS INFLUENCING UPRIGHT GAIT STABILITY

Upright gait stability also depends on the capacity of subjects to exploit information on the orientation of the swaying body during walking with respect to the environment. This information is provided primarily by the vestibular system, lower-extremity mechanoreceptors, and vision (Lee, 1980; Perry et al., 2001), but also environmental features can affect upright gait stability (Iosa et al., 2012b) and hence the risk of fall (Hamacher et al., 2011). For example, under impaired physical conditions, subjects usually adopt a strategy to reduce velocity in challenging environments, decreasing upper body accelerations.

A typical situation is when one walks on uneven ground, implying greater upper body acceleration, even in young healthy adults (Moe-Nilssen, 1998). Also, a sudden reduction in environmental light implies an increase in trunk accelerations and inter-step trunk acceleration variability (Moe-Nilssen et al., 2006). Conversely, optic flow can alter locomotion parameters (Pailhous et al., 1990) and mediates the maintenance of a steady gait (Pailhous and Bonnard, 1992).

When vision is blocked completely, the stability, in terms of normalized accelerations, decrease drastically and the harmony of movements in the AP direction falls significantly (Iosa et al., 2012b). These findings demonstrated the fundamental role of vision in upright gait stability, confirming that vestibular, proprioceptive, acoustic, and tactile information can not fully compensate for the loss of visual information to produce a normal gait pattern (Hallemans et al., 2009; Iosa et al., 2012b). There is also a slight difference between walking outdoors and indoors, with higher AP accelerations outdoors, a difference that increases in the absence of visual feedback (Iosa et al., 2012b). It has been suggested that when visual information is lacking, the memorized environment acts as a selective tuner between various walking strategies that is based more on sensory feedback versus on an internal representation of the own body and the external world (Iosa et al., 2012c).

Upper body stability during walking can be also affected by cultural habits, as already suggested (Mazzà et al., 2009), but this relationship has not been investigated in detail. Walking with books over the head was a common exercise for young aristocratic ladies. Certain gender differences in upright gait stability have recently been studied: females have better control strategy, allowing them to reach head accelerations that are equivalent to those of males, despite having higher LL pelvis accelerations (Mazzà et al., 2009). However, this difference was not found significant at the level of L2–L3 (Iosa et al., 2012b), of shoulders and head (Mazzà et al., 2008). Furthermore, the most of the studies did not separate data between males and females. Nevertheless, gender-related features of upright gait stability are reported and the absence of visual feedback exacerbates these gender-based differences in LL movements (Iosa et al., 2012b). The development of upright gait could have had sexual implications: it has even been suggested that permanent sexuality that replaced female estrus, was an effect of the phylogenetic development of upright gait (Graslund, 1995).

Finally, it is noteworthy that in some areas of the world that lack a transportation infrastructure, people routinely carry extraordinary loads supported by their heads, for example the sherpa of the Himalayas and the women of East Africa. It needs a very stable head during walking and it is a result of a greater conservation of mechanical energy resulting from an improved gait control (Heglund et al., 1995).

Thus, it is conceivable that differences in upright stable gait could be related not only to differences in motor abilities, but also to the dictates of social and cultural prescriptions specific for each phase of life and probably also to geographical differences. These hypotheses, however, are unconfirmed and should be further investigated.

THE CONTROL OF UPPER BODY ACCELERATIONS DURING GAIT

ASSESSMENT OF DYNAMIC EQUILIBRIUM BY TRUNK ACCELERATIONS

In the early 1990s, gait analysis was focused on hip, knee, and ankle angular kinematics, and the mainstream idea was that the upper body was a static passenger unit of a locomotor apparatus that was located primarily at the lower limb level (Perry, 1992). This idea was then challenged by empirical evidence. In fact, many following studies confirmed as the trunk plays a fundamental dynamic role during walking, attenuating acceleration, ensuring the upright posture, and stabilizing the optic flow and vestibular signals (Winter, 1995; Menz et al., 2003; Kavanagh et al., 2004). This stability is achieved through a combination of passive mechanical damping and active feed-forward control of paraspinal muscles (Prince et al., 1994).

According to these studies, interest in upper body movements during walking has even increased in the past decade. A large and growing body of literature has investigated movements of the pelvis, center of mass, trunk, shoulder, and head during walking, primarily for two reasons: the function of upper body during gait and the development of wearable wireless accelerometers for quantifying gait stability. Accelerometers are usually small, lightweight, wireless, and wearable, allowing subjects to walk relatively unrestricted and without the limitations of the test environment of a laboratory (Kavanagh and Menz, 2008; Iosa et al., 2012a).

The second part of this review is mainly focused on the stability of upper body during gait in terms of control of upper body accelerations during gait.

In a 2008 review, Kavanagh and Menz (2008) analyzed 33 reports on the use of accelerometry for gait analysis, noting that the most common location for these devices was the lower trunk (12 of 33 studies, 36%), followed by head (21%) and lower limbs (21%). The authors concluded that the available literature indicates accelerometry as an accurate and reliable measure of basic spatio-temporal gait parameters and segmental accelerations of the body when walking, and a suitable measure for highlighting age-related differences in dynamic balance control during gait in people with movement disorders.

Examples of accelerometric signals that are obtained during walking are reported in **Figure 1** for a child, an adult, and an elderly subject along the AP direction. It is possible to observe how upper body AP acceleration was higher and less repeatable in the child and elderly, whereas it was lower and less variable in the young adult.

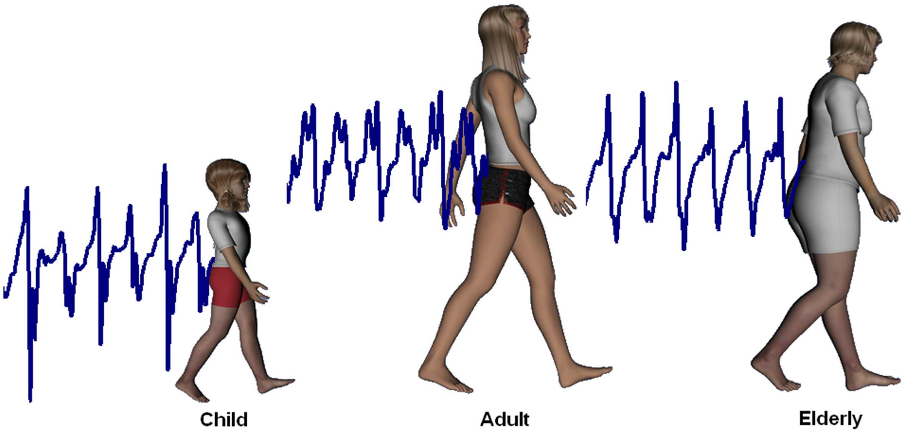


FIGURE 1 | Upper body accelerations. Upper body accelerations along the antero-posterior direction in a child (data obtained for a 2-year-old female), an adult (35 years, female), and an elderly subject (69 years, female).

The root mean square of an acceleration signal is the most commonly used parameter in assessing upper body stability using accelerometric-based gait analysis (Menz et al., 2003; Kavanagh et al., 2004; Marigold and Patla, 2008; Mazzà et al., 2008; Mizuike et al., 2009; Lamoth et al., 2011; Iosa et al., 2012e). It simply corresponds to the standard deviation of acceleration signals at which it has been removed its mean, indicating the dispersion of acceleration. Triaxial accelerometers allow one to measure accelerations along the three body axes: AP, LL, and CC, so the RMS can be evaluated along each one of the three body axes (RMS_{AP}, RMS_{LL}, RMS_{CC}, respectively).

Since the 90s, it has been suggested that RMS of accelerations could be a valid parameter for assessing balance during walking, differentiating between subjects with and without balance impairment or between walking on solid and soft terrains (Moe-Nilssen, 1998). These results were then confirmed by two studies of Menz et al. In the first one, the authors showed the age-related differences in walking stability measured using accelerometers fixed to head and trunk of subjects (Menz et al., 2003). In the second one, they showed as the RMS of pelvis accelerations increases when subjects were asked to walk on irregular surfaces (Menz et al., 2003). Subsequently, many other studies showed as acceleration RMS was a suitable parameter for discriminating between patients with unstable gait and healthy subjects (Mizuike et al., 2009; Lamoth et al., 2011; Iosa et al., 2012e). High reliability of three dimensional accelerometric approach at head, neck, trunk, and shank level was found in test–retest conditions (a mean coefficient of multiple determination across all conditions of 0.87) (Kavanagh et al., 2006).

Senden et al., enrolled 100 elderly subjects that were divided into two groups: with and without unspecific balance disorders clinically assessed by Tinetti scale. Many gait parameters were found correlated with the score of Tinetti scale, but only WS, step length, and acceleration RMS showed moderate to strong correlations and high discriminative power to classify elderly according to their clinical balance assessment. As reported in Section "Gait Instability and Risk of Fall," another study conducted using an accelerometric-based gait analysis found that the harmonic ratio of trunk acceleration (a parameter extracted by frequency analysis on accelerometric signals) may predict the risk of falls in elderly, independently of their physical performance, in 1 year after the accelerometric assessment (Doi et al., 2013). The harmonic ratio of trunk acceleration was taken into account also in the study of Senden et al. It showed moderate association with the Tinetti score, but did not enter into the final regression model for identifying subjects with unstable gait (Senden et al., 2012). All these studies showed as the analysis of trunk accelerations can be informative about the excessive and disperse trunk movements strictly interconnected with upright gait instabilities. The relationship between gait harmony and risk of falls needs further studies, however it has recently been suggested that the involuntary control of locomotion can be favored by the intrinsic gait temporal harmony, implying that its lost can increase the difficulties in controlling gait (Iosa et al., 2013).

Several studies have advocated normalizing upper body acceleration as a function of gait speed (Marigold and Patla, 2008; Kavanagh, 2009; Iosa et al., 2012e). In fact, increasing or decreasing gait speed effects a corresponding quadratic rise or decline in acceleration amplitude, thus, RMS values need to be normalized between subjects and populations at different walk speeds to assess only the upper body dynamic instabilities that are imputable to some balance impairment suitably (Mizuike et al., 2009; Iosa et al., 2012e). To take into account the relationship between acceleration RMS and WS, many different methods have been suggested (Moe-Nilssen and Helbostad, 2004; Marigold and Patla, 2008; Mizuike et al., 2009; Iosa et al., 2012e,f). Clinicians should hence keep clearly in mind that an increase in upper body accelerations could be attributed to an unsteady speed due to gait instabilities or a rise in WS, in absence of a suitable normalization of accelerometric values (Iosa et al., 2012e).

In this last part of the review, we summarize the results of the studies that compared upright gait stability between elderly and young adults or between subjects with a specific pathology or impairment and age-matched healthy controls, providing an overview of the development and the decline of upright gait stability in terms of upper body acceleration control.

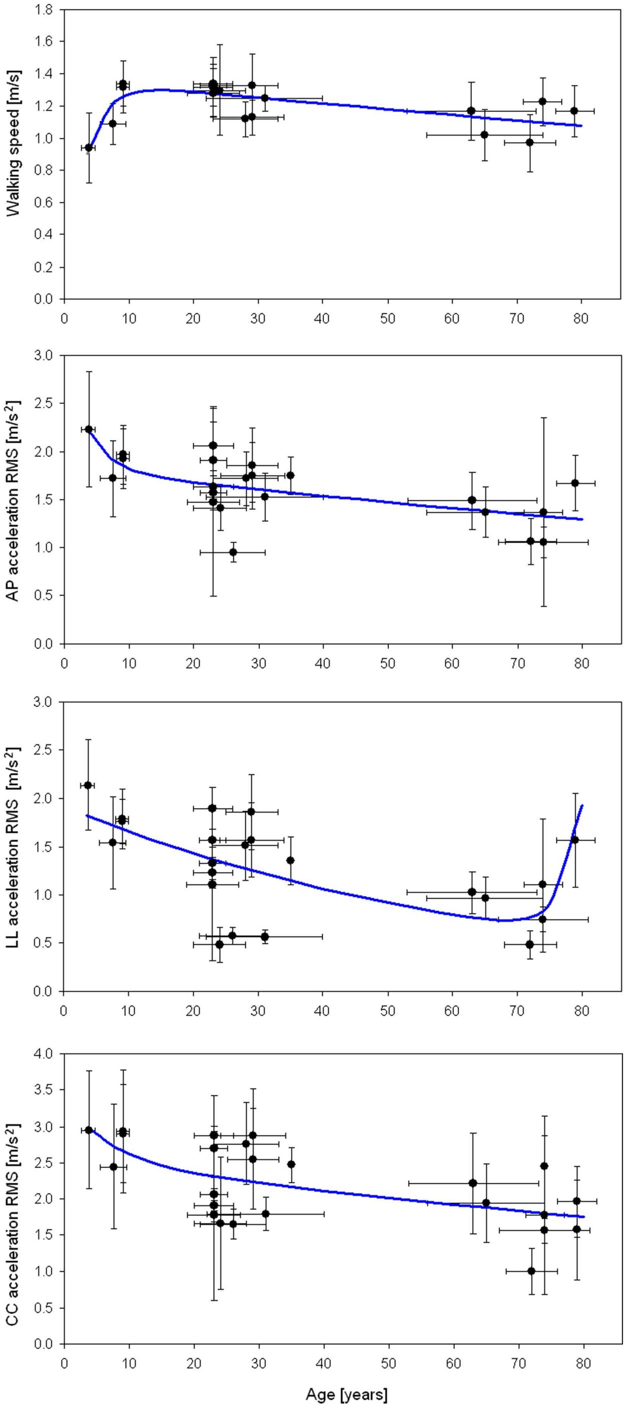


FIGURE 2 | Walking speed and acceleration RMSs. Mean (±SD) of walking speed, AP, LL, and CC acceleration RMSs with respect to mean (±SD) age for the studies in **Table 1**. Regression lines (in blue) were obtained with a bi-exponential fit.

DEVELOPMENT AND DECLINE OF UPPER BODY ACCELERATION CONTROL DURING GAIT

Table 1 reports the results of 15 studies regarding the measurements of upper body accelerations in 552 healthy subjects during walking. Only the data related to healthy subjects enrolled in these studies are reported in the table, and they were ordered by age. Most of these studies used accelerometers to assess upper body gait stability; two studies used stereophotogrammetry (Mazzà et al., 2008; Iosa et al., 2010) and one used an optoelectronic system (Marigold and Patla, 2008). The stereophotogrammetric analysis studies generated lower values of acceleration RMS along the LL direction compared with other studies, probably because analyzing a virtual point inside of the body, rendering them less sensitive to rotations around the CC axis.

Many of these studies compared upper body accelerations between healthy subjects (reported in **Table 1**) and patients. **Figure 2** graphs the results of the studies in **Table 1**. WS and RMSs were found significantly correlated with age (Pearson correlation: $p = 0.031$ for WS, $p < 0.001$ for RMS$_{AP}$, $p = 0.013$ for RMS$_{LL}$, $p = 0.003$ for RMS$_{CC}$). However, bi-exponential curves better fitted the data than linear regression fits (mean coefficient of determination 0.43 versus 0.30). The equation of the bi-exponential fit, applied using the least mean square method, was: $y = a \cdot e^{-\frac{x}{\tau_1}} + b \cdot e^{-\frac{x}{\tau_2}} + c$, with WS and accelerations as dependent variable y and age as independent variable x (**Figure 2**).

As expected, WS increased quickly in the first years of life, based on the rise in anthropometric dimensions, and slowly decreasing for the remainder of life after the teenage years. In details, RMS$_{AP}$ declined rapidly in the first years of life, then being progressively reduced, despite an increase toward the end of life. RMS$_{CC}$ decreased in childhood, becoming progressive and smooth for the remainder of life. The coefficient of determinations (R^2) of all four fits graphed in **Figure 2** was between 0.34 and 0.53, showing goodness of fits from moderate to good (Cohen, 1988). The lower value was for the RMS$_{LL}$. In this case, in fact, the bi-exponential trend lacks to fit the initial abrupt decrement occurred in childhood, well matching the data only after 7 years. It is noteworthy that lateral acceleration rose again in persons older than 70 toward values similar to those of children.

Because most studies have compared two groups of subjects, usually young versus elderly persons, little attention has been paid to the ages between 10–20 and 35–60 years. Nevertheless, we noted clear trends of rapid improvement in upright gait stability in the first period of life (reduction of RMS) despite the improvements in WS, and a loss of stability (increase of RMS) in older ages.

Because the quadratic relationship between WS and the three RMSs (Menz et al., 2003), a linear relationship exists between WS^2 and RMSs as shown by Mazzà et al. (2008). Hence, more regular quadrilateral shapes are expected for healthy subjects than for toddlers or patients for the plots reported in **Figure 3A** and formed by the mean values of WS^2 and of the three RMS values (obtained averaging the values over studies). On the left plot of this figure these quadrangles were reported for healthy subjects aged 1.5–5, 5–15, 20–30, 60–70, and over 70 years. Five of the studies in **Table 1** were not taken into account in generating this figure [two due to the instruments that were used (Mazzà et al., 2008; Iosa et al.,

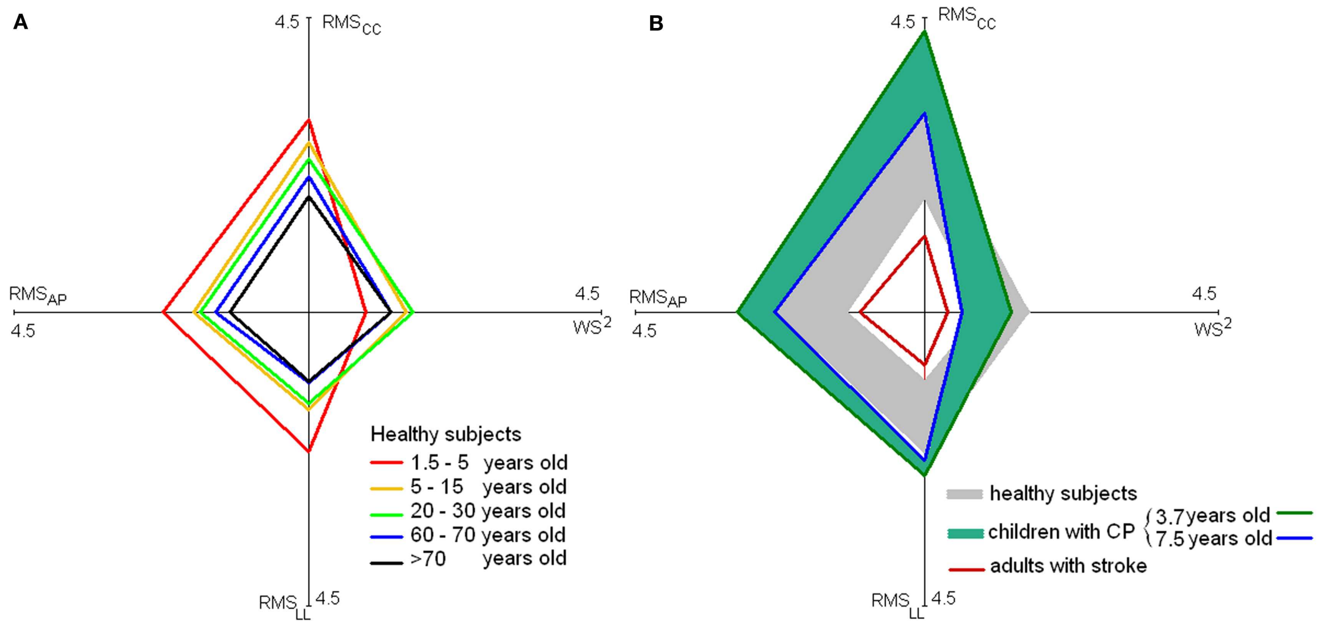


FIGURE 3 | Stability and velocity of walking. Values of mean RMSs [along the antero-posterior (AP), latero-lateral, (LL) and cranio-caudal (CC) axes] and WS^2 for healthy subjects at various ages [**(A)**, on the left] and for children with cerebral palsy and adults with stroke [**(B)**, on the right]. In the latter graph, the large gray rhomboidal area is formed by joining the extremes of values of healthy subjects [reported in **(A)**], and blue–green rhomboidal area by joining the extremes of values of children with cerebral palsy.

2010), two due to the absence of data along all the three body axes (Lamoth et al., 2011; Senden et al., 2012), and one due to subjects with a mean age of 35 years (Henriksen et al., 2004)].

The quadrilateral shape of younger children trended toward higher acceleration and lower speed. Older children and young adults generated a more rhomboidal shape, with lower acceleration and increased speed. Finally, elderly showed a reduction both in terms of speed and accelerations.

The reduction of gait instability was fast both along AP- and LL-axes during gait development, followed by a slight sloped trend, positive along AP and negative along LL-axis. Finally, after 65 years of age, an abrupt increase of instability occurred. Unfortunately, only sporadic data are available for age ranges between 10 and 20 years and between 40 and 60 years included; thus, upright gait stability in these ranges requires further investigation. On the right side of **Figure 3**, on the quadrilateral shape of healthy subjects were superimposed those of children with cerebral palsy (a range was shown to take into account the different ages) and subjects with stroke extracting the data by the relevant studies reported in **Table 2**.

CONCLUSION

Upright gait is a peculiar characteristic of human beings. This feature usually needs approximately 1 year to evolve but continues to improve during development. Body growth implies the possibility of increasing WS and the need to manage higher instabilities. In challenging environments or with existing physical impairments, the easiest solution to maintain upright gait stability is to reduce WS. This approach is also used by elderly subjects to compensate for the effects of aging on sensorimotor and cognitive functions.

The decline of upright gait stability with age is a slow but progressive process that increased drastically after 70 years. Pathologies can abruptly increase this loss proportionally to the severity of the impairment. The increase in upper body accelerations may be a direct effect of the impairment or a mixed result of impairment and compensatory strategies, as in children with atypical development (such as those with cerebral palsy) and persons with a progressively impairing pathology (such as muscular dystrophy).

A decrease in upright gait stability also exposes subjects to the risk of falls, which is particularly dangerous in the elderly. The development of low-cost and easy-to-use wearable sensors can facilitate the introduction of instrumented movement analysis in clinical settings (Iosa et al., 2012e). The clinical monitoring of upper body accelerations may provide a quantitative and hence objective outcome measure of the benefit of a rehabilitative pathway, evaluating the same parameters measured by vestibular system for maintaining balance.

Wireless and wearable technology have now provided us the possibility to quantify a feature, the importance of which was already noted in ancient time, when Aristotle wrote: “Man alone among all living beings walks erect, because his nature and his being are divine.”

AUTHOR CONTRIBUTIONS

Marco Iosa conceived this review, analyzed the data, and wrote the first draft. Augusto Fusco and Giovanni Morone provided a critical revision of manuscript for important clinical intellectual content. Stefano Paolucci supervised the entire work and obtained funding.

ACKNOWLEDGMENTS

This material is the result of work supported by and use of facilities at the Italian Ministry of Health (projects: assessment of altered motor schemas in the pathologies of central nervous system; inability and instability of gait in patients with stroke) and the Fondazione Santa Lucia, IRCCS (Santa Lucia Foundation, Scientific Institute for Research Hospitalization and Health Care), Rome, Italy. The authors would thank Claudine J. C. Lamoth, Daniel S. Marigold, and Justin J. Kavanagh for having provided the data of their studies in order to allow the analyses performed in this review. The authors would thank Francesca Fusco Lynch for English Editing of this manuscript.

REFERENCES

Allali, G., Assal, F., Kressig, R. W., Dubost, V., Herrmann, F. R., and Beauchet, O. (2008). Impact of impaired executive function on gait stability. *Dement. Geriatr. Cogn. Disord.* 26, 364–369. doi:10.1159/000162358

Allum, J. H., Gresty, M., Keshner, E., and Shupert, C. (1997). The control of head movements during human balance corrections. *J. Vestib. Res.* 7, 189–218. doi:10.1016/S0957-4271(97)00029-3

Armand, S., Mercier, M., Watelain, E., Patte, K., Pelissier, J., and Rivier, F. (2005). A comparison of gait in spinal muscular atrophy, type II and duchenne muscular dystrophy. *Gait Posture* 21, 369–378. doi:10.1016/j.gaitpost.2004.04.006

Asher, L., Aresu, M., Falaschetti, E., and Mindell, J. (2012). Most older pedestrians are unable to cross the road in time: a cross-sectional study. *Age Ageing* 41, 690–694. doi:10.1093/ageing/afs076

Assaiante, C., and Amblard, B. (1993). Ontogenesis of head stabilization in space during locomotion in children: influence of visual cues. *Exp. Brain Res.* 93, 499–515. doi:10.1007/BF00229365

Avineri, E., Shinar, D., and Susilo, Y. O. (2012). Pedestrians' behaviour in cross walks: the effects of fear of falling and age. *Accid. Anal. Prev.* 44, 30–34. doi:10.1016/j.aap.2010.11.028

Beauchet, O., Annweiler, C., Verghese, J., Fantino, B., Herrmann, F. R., and Allali, G. (2011). Biology of gait control: vitamin D involvement. *Neurology* **76**, 1617–1622. doi:10.1212/WNL.0b013e318219fb08

Berthoz, A., and Pozzo, T. (1994). "Head and body coordination during locomotion and complex movements," in *Interlimb Coordination*, eds S. Swinnen, H. Heuer, J. Massion, and P. Casaer (San Diego: Academic Press), 147–165.

Bollard, E., and Fleming, H. (2013). A study to investigate the walking speed of elderly adults with relation to pedestrian crossings. *Physiother. Theory Pract.* 29, 142–149. doi:10.3109/09593985.2012.703760

Borel, L., Harlay, F., Lopez, C., Magnan, J., Chays, A., and Lacour, M. (2004). Walking performance of vestibular-defective patients before and after unilateral vestibular neurotomy. *Behav. Brain Res.* 150, 191–200. doi:10.1016/S0166-4328(03)00257-2

Bosch, K., Gerss, J., and Rosenbaum, D. (2007). Preliminary normative values for foot loading parameters of the developing child. *Gait Posture* 26, 238–247. doi:10.1016/j.gaitpost.2006.09.014

Bosch, K., and Rosenbaum, D. (2010). Gait symmetry improves in childhood – a 4-year follow-up of foot loading data. *Gait Posture* 32, 464–468. doi:10.1016/j.gaitpost.2010.07.002

Bruijn, S. M., Meyns, P., Jonkers, I., Kaat, D., and Duysens, J. (2011). Control of angular momentum during walking in children with cerebral palsy. *Res. Dev. Disabil.* 32, 2860–2866. doi:10.1016/j.ridd.2011.05.019

Cappozzo, A. (1981). Analysis of the linear displacement of the head and trunk during walking at different speeds. *J. Biomech.* 14, 411–425. doi:10.1016/0021-9290(81)90059-2

Choi, P., Ren, M., Phan, T. G., Callisaya, M., Ly, J. V., Beare, R., et al. (2012). Silent infarcts and cerebral microbleeds modify the associations of white matter lesions with gait and postural stability: population-based study. *Stroke* 43, 1505–1510. doi:10.1161/STROKEAHA.111.647271

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, NJ: Lawrence Erlbaum Associates, Inc.

Daly, R. M., Rosengren, B. E., Alwis, G., Ahlborg, H. G., Sernbo, I., and Karlsson, M. K. (2013). Gender specific age-related changes in bone density, muscle strength and functional performance in the elderly: a-10 year prospective population-based study. *BMC Geriatr.* 13:71. doi:10.1186/1471-2318-13-71

Di Monaco, M., Trucco, M., Di Monaco, R., Tappero, R., and Cavanna, A. (2010). The relationship between initial trunk control or postural balance and inpatient rehabilitation outcome after stroke: a prospective comparative study. *Clin. Rehabil.* 24, 543–554. doi:10.1177/0269215509353265

Doherty, T. J. (2003). Invited review: aging and sarcopenia. *J. Appl. Physiol.* 95, 1717–1727. doi:10.1152/japplphysiol.00347.2003

Doi, T., Hirata, S., Ono, R., Tsutsumimoto, K., Misu, S., and Ando, H. (2013). The harmonic ratio of trunk acceleration predicts falling among older people: results of a 1-year prospective study. *J. Neuroeng. Rehabil.* 10, 7. doi:10.1186/1743-0003-10-7

Dominici, N., Ivanenko, Y. P., Cappellini, G., d'Avella, A., Mondí, V., Cicchese, M., et al. (2011). Locomotor primitives in newborn babies and their development. *Science* 334, 997–999. doi:10.1126/science.1210617

Dommes, A., and Cavallo, V. (2011). The role of perceptual, cognitive, and motor abilities in street-crossing decisions of young and older pedestrians. *Ophthalmic Physiol. Opt.* 31, 292–301. doi:10.1111/j.1475-1313.2011.00835.x

Friedman, M. J. (2006). *The Evolution of Hominid Bipedalism.* Honors Projects, Wesleyan University, Bloomington.

Gage, J. R. (1993). Gait analysis. An essential tool in the treatment of cerebral palsy. *Clin. Orthop. Relat. Res.* 288, 126–134.

Garwicz, M., Christensson, M., and Psouni, E. (2009). A unifying model for timing of walking onset in humans and other mammals. *Proc. Natl. Acad. Sci. U.S.A.* 106, 21889–21893. doi:10.1073/pnas.0905777106

Graslund, B. (1995). *Early Humans and Their World.* Abingdon: Routledge.

Gutierrez, E. M., Bartonek, A., Haglund-Akerlind, Y., and Saraste, H. (2005). Kinetics of compensatory gait in persons with myelomeningocele. *Gait Posture* 21, 12–23. doi:10.1016/j.gaitpost.2003.11.002

Hahn, M. E., and Chou, L. S. (2004). Age-related reduction in sagittal plane center of mass motion during obstacle crossing. *J. Biomech.* 37, 837–844. doi:10.1016/j.jbiomech.2003.11.010

Hallemans, A., Beccu, S., Van Loock, K., Ortibus, E., Truijen, S., and Aerts, P. (2009). Visual deprivation leads to gait adaptations that are age- and context-specific: II. Kinematic parameters. *Gait Posture* 30, 307–311. doi:10.1016/j.gaitpost.2009.05.017

Hallemans, A., Ortibus, E., Meire, F., and Aerts, P. (2010). Low vision affects dynamic stability of gait. *Gait Posture* 32, 547–551. doi:10.1016/j.gaitpost.2010.07.018

Hamacher, D., Singh, N. B., Van Dieën, J. H., Heller, M. O., and Taylor, W. R. (2011). Kinematic measures for assessing gait stability in elderly individuals: a systematic review. *J. R. Soc. Interface* 8, 1682–1698. doi:10.1098/rsif.2011.0416

Heglund, N. C., Willems, P. A., Penta, M., and Lavagna, G. A. (1995). Energy-saving gait mechanics with head-supported loads. *Nature* 375, 52–54. doi:10.1038/375052a0

Henderson, S. E. (1986). "Some aspects of the development of motor control in Down's syndrome," in *Themes in Motor Development*, eds H. T. A. Whiting and M. G. Wade (Boston: Martinus Nijhoff), 147–186.

Henriksen, M., Lund, H., Moe-Nilssen, R., Bliddal, H., and Danneskiod-Samsøe, B. (2004). Test-retest reliability of trunk accelerometric gait analysis. *Gait Posture* 19, 288–297. doi:10.1016/S0966-6362(03)00069-9

Hesse, S., Welz, A., Assmann, E., Quentin, B., and Waldner, A. (2009). Pedestrians in Berlin after stroke. Recommendations for street and subway transit. *Nervenarzt* 80, 953–958. doi:10.1007/s00115-009-2700-x

Hodt-Billington, C., Helbostad, J. L., and Moe-Nilssen, R. (2008). Should trunk movement or footfall parameters quantify gait asymmetry in chronic stroke patients? *Gait Posture* 27, 552–558. doi:10.1016/j.gaitpost.2007.07.015

Horak, F. B., and Mancini, M. (2013). Objective biomarkers of balance and gait for Parkinson's disease using body-worn sensors. *Mov. Disord.* 28, 1544–1551. doi:10.1002/mds.25684

Hsue, B. J., Miller, F., and Su, F. C. (2009a). The dynamic balance of the children with cerebral palsy and typical developing during gait. Part I: spatial relationship between COM and COP trajectories. *Gait Posture* 29, 465–470. doi:10.1016/j.gaitpost.2008.11.007

Hsue, B. J., Miller, F., and Su, F. C. (2009b). The dynamic balance of the children with cerebral palsy and typical developing during gait. Part II: instantaneous velocity and acceleration of COM and COP and their relationship. *Gait Posture* 29, 471–476. doi:10.1016/j.gaitpost.2008.11.008

Ijmker, T., and Lamoth, C. J. (2012). Gait and cognition: the relationship between gait stability and variability with executive function in persons with and without dementia. *Gait Posture* 35, 126–130. doi:10.1016/j.gaitpost.2011.08.022

Ingwell, J. B., and Marin, L. C. (2006). Kinematic variability and local dynamic stability of upper body motions when walking at different speeds. *J. Biomech.* 39, 444–452. doi:10.1016/j.jbiomech.2004.12.014

Inman, V. T., Ralston, H. J., and Todd, F. (1981). *Human Walking*. Baltimore: Williams & Wilkins.

Iosa, M., Fusco, A., Marchetti, F., Morone, G., Caltagirone, C., Paolucci, S., et al. (2013). The golden ratio of gait harmony: repetitive proportions of repetitive gait phases. *Biomed Res. Int.* 2013, 918642. doi:10.1155/2013/918642

Iosa, M., Mazzà, C., Pecoraro, F., Aprile, I., Ricci, E., and Cappozzo, A. (2010). Control of the upper body movements during level walking in patients with facioscapulohumeral dystrophy. *Gait Posture* 31, 68–72. doi:10.1016/j.gaitpost.2009.08.247

Iosa, M., Morone, G., Fusco, A., Bragoni, M., Coiro, P., Multari, M., et al. (2012a). Seven capital devices for the future of stroke rehabilitation. *Stroke Res. Treat.* 2012, 187965. doi:10.1155/2012/187965

Iosa, M., Fusco, A., Morone, G., and Paolucci, S. (2012b). Effects of visual deprivation on gait dynamic stability. *ScientificWorldJournal* 2012, 974560. doi:10.1100/2012/974560

Iosa, M., Fusco, A., Morone, G., and Paolucci, S. (2012c). Walking there: environmental influence on walking-distance estimation. *Behav. Brain Res.* 226, 124–132. doi:10.1016/j.bbr.2011.09.007

Iosa, M., Morone, G., Fusco, A., Pratesi, L., Bragoni, M., Coiro, P., et al. (2012d). Effects of walking endurance reduction on gait stability in patients with stroke. *Stroke Res. Treat.* 2012, 810415. doi:10.1155/2012/810415

Iosa, M., Fusco, A., Morone, G., Pratesi, L., Coiro, P., Venturiero, V., et al. (2012e). Assessment of upper body dynamic stability during walking in patients with subacute stroke. *J. Rehabil. Res. Dev.* 49, 439–450. doi:10.1682/JRRD.2011.03.0057

Iosa, M., Marro, T., Paolucci, S., and Morelli, D. (2012f). Stability and harmony of gait in children with cerebral palsy. *Res. Dev. Disabil.* 33, 129–135. doi:10.1016/j.ridd.2011.08.031

Ivanenko, Y. P., Dominici, N., Cappellini, G., Dan, B., Cheron, G., and Lacquaniti, F. (2004). Development of pendulum mechanism and kinematic coordination from the first unsupported steps in toddlers. *J. Exp. Biol.* 207, 3797–3810. doi:10.1242/jeb.01214

Ivanenko, Y. P., Dominici, N., and Lacquaniti, F. (2007). Development of independent walking in toddlers. *Exerc. Sport Sci. Rev.* 35, 67–73. doi:10.1249/JES.0b013e31803eafa8

Kavanagh, J. J. (2009). Lower trunk motion and speed-dependence during walking. *J. Neuroeng. Rehabil.* 9, 6–9. doi:10.1186/1743-0003-6-9

Kavanagh, J. J., Barrett, R. S., and Morrison, S. (2004). Upper body accelerations during walking in healthy young and elderly men. *Gait Posture* 20, 291–298. doi:10.1016/j.gaitpost.2003.10.004

Kavanagh, J. J., and Menz, H. B. (2008). Accelerometry: a technique for quantifying movement patterns during walking. *Gait Posture* 28, 1–15. doi:10.1016/j.gaitpost.2007.10.010

Kavanagh, J. J., Morrison, S., James, D. A., and Barrett, R. (2006). Reliability of segmental accelerations measured using a new wireless gait analysis system. *J. Biomech.* 39, 2863–2872. doi:10.1016/j.jbiomech.2005.09.012

Kaya, B. K., Krebs, D. E., and Riley, P. O. (1998). Dynamic stability in elders: momentum control in locomotor ADL. *J. Gerontol. A Biol. Sci. Med. Sci.* 53, M126–M134. doi:10.1093/gerona/53A.2.M126

Kubo, M., and Ulrich, B. D. (2006a). A biomechanical analysis of the "high guard" position of arms during walking in toddlers. *Infant Behav. Dev.* 29, 509–517. doi:10.1016/j.infbeh.2006.05.001

Kubo, M., and Ulrich, B. D. (2006b). Early stage of walking: development of control in mediolateral and antoposterior directions. *J. Mot. Behav.* 38, 229–237. doi:10.3200/JMBR.38.3.229-237

Lamoth, C. J., Meijer, O. G., Wuisman, P. I., van Dieen, J. H., Levin, M. F., and Beek, P. J. (2002). Pelvis-thorax coordination in the transverse plane during walking in persons with nonspecific low back pain. *Spine* 27, E92–E99. doi:10.1097/00007632-200202150-00016

Lamoth, C. J., van Deudekom, F. J., van Campen, J. P., Appels, B. A., de Vries, O. J., and Pijnappels, M. (2011). Gait stability and variability measures show effects of impaired cognition and dual tasking in frail people. *J. Neuroeng. Rehabil.* 8, 2. doi:10.1186/1743-0003-8-2

Lee, D. N. (1980). The optic flow field: the foundation of vision. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 290, 169–179. doi:10.1098/rstb.1980.0089

Lee, H. J., and Chou, L. S. (2006). Detection of gait instability using the center of mass and center of pressure inclination angles. *Arch. Phys. Med. Rehabil.* 87, 569–575. doi:10.1016/j.apmr.2005.11.033

Marigold, D. S., and Patla, A. E. (2008). Age-related changes in gait for multi-surface terrain. *Gait Posture* 27, 696696. doi:10.1016/j.gaitpost.2007.09.005

Masci, I., Vannozzi, G., Bergamini, E., Pesce, C., Getchell, N., and Cappozzo, A. (2013). Assessing locomotor skills development in childhood using wearable inertial sensor devices: the running paradigm. *Gait Posture* 37, 570–574. doi:10.1016/j.gaitpost.2012.09.017

Masiero, S., Avesani, R., Armani, M., Verena, P., and Ermani, M. (2007). Predictive factors for ambulation in stroke patients in the rehabilitation setting: a multivariate analysis. *Clin. Neurol. Neurosurg.* 109, 763–769. doi:10.1016/j.clineuro.2007.07.009

Masud, T., and Morris, R. O. (2001). Epidemiology of falls. *Age Ageing* 30, 3–7. doi:10.1093/ageing/30.suppl_4.3

Mazzà, C., Iosa, M., Pecoraro, F., and Cappozzo, A. (2008). Control of the upper body accelerations in young and elderly women during level walking. *J. Neuroeng. Rehabil.* 5, 30. doi:10.1186/1743-0003-5-30

Mazzà, C., Iosa, M., Picerno, P., and Cappozzo, A. (2009). Gender differences in the control of the upper body accelerations during level walking. *Gait Posture* 29, 300–303. doi:10.1016/j.gaitpost.2008.09.013

Mazzà, C., Zok, M., and Cappozzo, A. (2010). Head stabilization in children of both genders during level walking. *Gait Posture* 31, 429–432. doi:10.1016/j.gaitpost.2010.01.012

Menz, H. B., Lord, S. R., and Fitzpatrick, R. C. (2003). Acceleration patterns of the head and pelvis when walking on level and irregular surfaces. *Gait Posture* 18, 35–46. doi:10.1016/S0966-6362(02)00159-5

Meyns, P., Van Gestel, L., Bruijn, S. M., Desloovere, K., Swinnen, S. P., and Duysens, J. (2012). Is interlimb coordination during walking preserved in children with cerebral palsy? *Res. Dev. Disabil.* 33, 1418–1428. doi:10.1016/j.ridd.2012.03.020

Mizuike, C., Ohgi, S., and Morita, S. (2009). Analysis of stroke patient walking dynamics using a tri-axial accelerometer. *Gait Posture* 30, 60–64. doi:10.1016/j.gaitpost.2009.02.017

Moe-Nilssen, R. (1998). Test-retest reliability of trunk accelerometry during standing and walking. *Arch. Phys. Med. Rehabil.* 79, 1377–1385. doi:10.1016/S0003-9993(98)90231-3

Moe-Nilssen, R., and Helbostad, J. L. (2004). Estimation of gait cycle characteristics by trunk accelerometry. *J. Biomech.* 37, 121–126. doi:10.1016/S0021-9290(03)00233-1

Moe-Nilssen, R., and Helbostad, J. L. (2005). Interstride trunk acceleration variability but not step width variability can differentiate between fit and frail older adults. *Gait Posture* 21, 164–170. doi:10.1016/j.gaitpost.2004.01.013

Moe-Nilssen, R., Helbostad, J. L., Akra, T., Birdedal, L., and Nygaard, H. A. (2006). Modulation of gait during visual adaptation to dark. *J. Mot. Behav.* 38, 118–125. doi:10.3200/JMBR.38.2.118-125

Montero-Odasso, M., Schapira, M., Varala, C., Pitteri, C., Soriano, E. R., Kaplan, R., et al. (2004). Gait velocity in senior people. An easy test for detecting mobility impairment in community elderly. *J. Nutr. Health Aging* 8, 340–343. doi:10.1093/brain/117.4.715

Muscaritoli, M., Lucia, S., Molfino, A., Cederholm, T., and Rossi Fanelli, F. (2013). Muscle atrophy in aging and chronic diseases: is it sarcopenia or cachexia? *Intern. Emerg. Med.* 8, 553–560. doi:10.1007/s11739-012-0807-8

Pailhous, J., and Bonnard, M. (1992). Steady-state fluctuations of human walking. *Behav. Brain Res.* 47, 181–189. doi:10.1016/S0166-4328(05)80124-X

Pailhous, J., Ferrandez, A. M., Flückiger, M., and Baumberger, B. (1990). Unintentional modulations of human gait by optical flow. *Behav. Brain Res.* 38, 275–281. doi:10.1016/0166-4328(90)90181-D

Perry, J. (1992). *Gait Analysis: Normal and Pathological Function.* Thorofare, NJ: Slack Incorporated.

Perry, S. D., Santos, L. C., and Patla, A. E. (2001). Contribution of vision and cutaneous sensation to the control of centre of mass (COM) during gait termination. *Brain Res.* 913, 27–34. doi:10.1016/S0006-8993(01)02748-2

Plotnik, M., Giladi, N., Dagan, Y., and Hausdorff, J. M. (2011). Postural instability and fall risk in Parkinson's disease: impaired dual tasking, pacing, and bilateral coordination of gait during the "ON" medication state. *Exp. Brain Res.* 210, 529–538. doi:10.1007/s00221-011-2551-0

Plotnik, M., Giladi, N., and Hausdorff, J. M. (2007). A new measure for quantifying the bilateral coordination of human gait: effects of aging and Parkinson's disease. *Exp. Brain Res.* 181, 561–570. doi:10.1007/s00221-007-0955-7

Pozzo, T., Berthoz, A., and Lefort, L. (1990). Head stabilization during various locomotor tasks in humans. I. Normal subjects. *Exp. Brain Res.* 82, 97–106. doi:10.1007/BF00230842

Prince, F., Winter, D. A., Stergiou, P., and Walt, S. E. (1994). Anticipatory control of upper body balance during human locomotion. *Gait Posture* 2, 19–25. doi:10.1371/journal.pone.0056313

Rebula, J. R., Ojeda, L. V., Adamczyk, P. G., and Kuo, A. D. (2013). Measurement of foot placement and its variability with inertial sensors. *Gait Posture* 38, 974–980. doi:10.1016/j.gaitpost.2013.05.012

Reed, E. S. (1996). *Encountering the World: Toward an Ecological Psychology*. New York: Oxford University Press.

Ruchinskas, R. A., Singer, H. K., and Repetz, N. K. (2000). Cognitive status and ambulation in geriatric rehabilitation: walking without thinking? *Arch. Phys. Med. Rehabil.* 81, 1224–1228. doi:10.1053/apmr.2000.6976

Scaglioni, G., Narici, M. V., Maffiuletti, N. A., Pensini, M., and Martin, A. (2003). Effect of ageing on the electrical and mechanical properties of human soleus motor units activated by the H reflex and M wave. *J. Physiol.* 548, 649–661. doi:10.1113/jphysiol.2002.032763

Senden, R., Savelberg, H. H., Grimm, B., Heyligers, I. C., and Meijer, K. (2012). Accelerometry-based gait analysis, an additional objective approach to screen subjects at risk for falling. *Gait Posture* 36, 296–300. doi:10.1016/j.gaitpost.2012.03.015

Sheridan, P. L., Solomont, J., Kowall, N., and Hausdorff, J. M. (2003). Influence of executive function on locomotor function: divided attention increases gait variability in Alzheimer's disease. *J. Am. Geriatr. Soc.* 51, 1633–1637. doi:10.1046/j.1532-5415.2003.51516.x

Sparrow, W. A., and Newell, K. M. (1994). The coordination and control of human creeping with increases in speed. *Behav. Brain Res.* 63, 151–158. doi:10.1016/0166-4328(94)90086-8

Spoor, F., Wood, B., and Zonneveld, F. (1994). Implications of early hominid labyrinthine morphology for evolution of human bipedal locomotion. *Nature* 369, 645–648. doi:10.1038/369645a0

Sueur, C., Class, B., Hamm, C., Meyer, X., and Pelé, M. (2013). Different risk thresholds in pedestrian road crossing behaviour: a comparison of French and Japanese approaches. *Accid. Anal. Prev.* 58, 59–63. doi:10.1016/j.aap.2013.04.027

Sutherland, D. H., Olshen, R., Cooper, L., and Woo, S. L. (1980). The development of mature gait. *J. Bone Joint Surg. Am.* 62, 336–353.

Sylos-Labini, F., Meli, A., Ivanenko, Y. P., and Tufarelli, D. (2012). Recurrence quantification analysis of gait in normal and hypovestibular subjects. *Gait Posture* 35, 48–55. doi:10.1016/j.gaitpost.2011.08.004

Terrier, P., and Dériaz, O. (2011). Kinematic variability, fractal dynamics and local dynamic stability of treadmill walking. *J. Neuroeng. Rehabil.* 8, 12. doi:10.1186/1743-0003-8-12

van Baar, M. E., Dekker, J., Lemmens, J. A., Oostendorp, R. A., and Bijlsma, J. W. (1998). Pain and disability in patients with osteoarthritis of hip or knee: the relationship with articular, kinesiological, and psychological characteristics. *J. Rheumatol.* 25, 125–133.

Winter, D. A. (1995). Human balance and posture control during standing and walking. *Gait Posture* 3, 193–214. doi:10.1016/0966-6362(95)99069-W

Yin, M., Ishikawa, K., Omi, E., Saito, T., Itasaka, Y., and Angunsuri, N. (2011). Small vestibular schwannomas can cause gait instability. *Gait Posture* 34, 25–28. doi:10.1016/j.gaitpost.2011.02.026

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

Received: 02 October 2013; accepted: 22 January 2014; published online: 05 February 2014.

Citation: Iosa M, Fusco A, Morone G and Paolucci S (2014) Development and decline of upright gait stability. Front. Aging Neurosci. ***6****:14. doi: 10.3389/fnagi.2014.00014*

This article was submitted to the journal Frontiers in Aging Neuroscience.

frontiers in
AGING NEUROSCIENCE

REVIEW ARTICLE
published: 11 August 2014
doi: 10.3389/fnagi.2014.00208

The neuromuscular junction: aging at the crossroad between nerves and muscle

Marta Gonzalez-Freire[1,2]*, Rafael de Cabo[1], Stephanie A. Studenski[1,2] and Luigi Ferrucci[1,2]

[1] Translational Gerontology Branch, National Institute on Aging, Intramural Research Program, National Institutes of Health, Baltimore, MD, USA
[2] Longitudinal Studies Section, Baltimore Longitudinal Study of Aging, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA

Edited by:
Brian C. Clark, Ohio University, USA

Reviewed by:
David J. Clark, Malcom Randall VA Medical Center, USA
David W. Russ, Ohio University, USA
Michael R. Deschenes, College of William and Mary, USA

***Correspondence:**
Marta Gonzalez-Freire, Translational Gerontology Branch, National Institute on Aging, BRC Room 09C506, 251 Bayview Blvd Baltimore, MD 21224, USA
e-mail: marta.gonzalezfreire@nih.gov

Aging is associated with a progressive loss of muscle mass and strength and a decline in neurophysiological functions. Age-related neuromuscular junction (NMJ) plays a key role in musculoskeletal impairment that occurs with aging. However, whether changes in the NMJ precede or follow the decline of muscle mass and strength remains unresolved. Many factors such as mitochondrial dysfunction, oxidative stress, inflammation, changes in the innervation of muscle fibers, and mechanical properties of the motor units probably perform an important role in NMJ degeneration and muscle mass and strength decline in late life. This review addresses the primary events that might lead to NMJ dysfunction with aging, including studies on biomarkers, signaling pathways, and animal models. Interventions such as caloric restriction and exercise may positively affect the NMJ through this mechanism and attenuate the age-related progressive impairment in motor function.

Keywords: aging, denervation, motor unit, neuromuscular junction, sarcopenia

INTRODUCTION

Autopsy studies in persons who died of acute trauma while relatively healthy have shown that aging is associated with a gradual loss of motor neurons (Valdez et al., 2010; Rowan et al., 2012). The mechanism that leads to neuronal loss with aging is still unclear and may involve both impaired trophic signaling from the central nervous system (CNS), local degeneration, and feedback from dysfunctional muscle. Indeed, individuals over 65 years of age exhibit reduced activity in motor brain areas, increased oxidative stress in motor neurons and impaired energetic metabolism in muscle fibers (Deschenes et al., 2010; Ferrucci et al., 2012; Reid et al., 2012, 2014; Manini et al., 2013). However, there is evidence that this decrease in muscle energetic metabolism is not solely affected by aging but also by the levels of physical activity, suggesting that energetic changes are more likely to be a function of activity, and not time (Tevald et al., 2010; Russ and Lanza, 2011).

Regardless of the cause, when a motor neuron is lost, fibers previously innervated by that neuron, globally defined as a motor unit, are no longer controlled by the nervous system and fail to contribute to the force generated during a volitional muscle contraction. In the attempt to counteract the functional consequence of this process, denervated orphan fibers express proteins and produce chemotactic signals that stimulate the sprouting of new dendrites from residual motor neurons. This process leads re-innervation by the expansion of pre-existing motor units and is aimed at returning to function previously denervated muscle fibers. This dynamic denervation–re-innervation cycle successfully compensates for neuronal loss, with little decline in global strength and only slightly reduced control. However, there is evidence that this compensatory mechanism starts failing with aging. Some denervated fibers are not successfully re-innervated, become apoptotic, and are not replaced by new fibers. It is hypothesized that this phenomenon contributes to a progressive decline in muscle mass and strength with aging.

The reason for a progressive impairment of the re-innervation process with aging is unknown, but some lines of evidence point to changes that occur with aging in the neuromuscular junction (NMJ), which is the synaptic interface between a branch of a motor neuron and muscle cells. The NMJ is composed of three elements: pre-synaptic (motor nerve terminal), intrasynaptic (synaptic basal lamina), and post-synaptic part (muscle fiber and muscle membrane) (Punga and Ruegg, 2012). When an action potential reaches the pre-synaptic element, voltage-dependent calcium channels open allowing calcium to enter the neuron and trigger the delivery of acetylcholine (ACh) in the synaptic cleft. Acetylcholine triggers nicotin acetylcholine receptors (nAChR) located in the post-synaptic membrane to produce an action potential, which in turn, activates voltage-gated dihydropyridine receptors (DHPRs) located in the sarcolemma and by induction, ryanodine receptors (RyRs). Of note, the post-synaptic membrane presents folds that expand its area. Calcium released from the sarcoplasmic reticulum through the RyRs binds to troponin C and allows cross-bridge cycling and force production (**Figure 1**).

Over the last decade, age-associated degeneration of the NMJ has been reported. It has been proposed that such changes may be causally related to the decline in muscle mass and function that occurs in most aging individuals. However, whether changes in the NMJ precede or follow the decline of muscle mass and strength remains unresolved. Understanding whether the primary event in the pathway to sarcopenia is muscle denervation, NMJ fragmentation or muscle fiber degeneration is important because the identification of the source of the primary event influences strategies to delay the onset of age-related muscle dysfunction. In this report, we review our current understanding of the events that lead to NMJ dysfunction with aging, including studies on biomarkers,

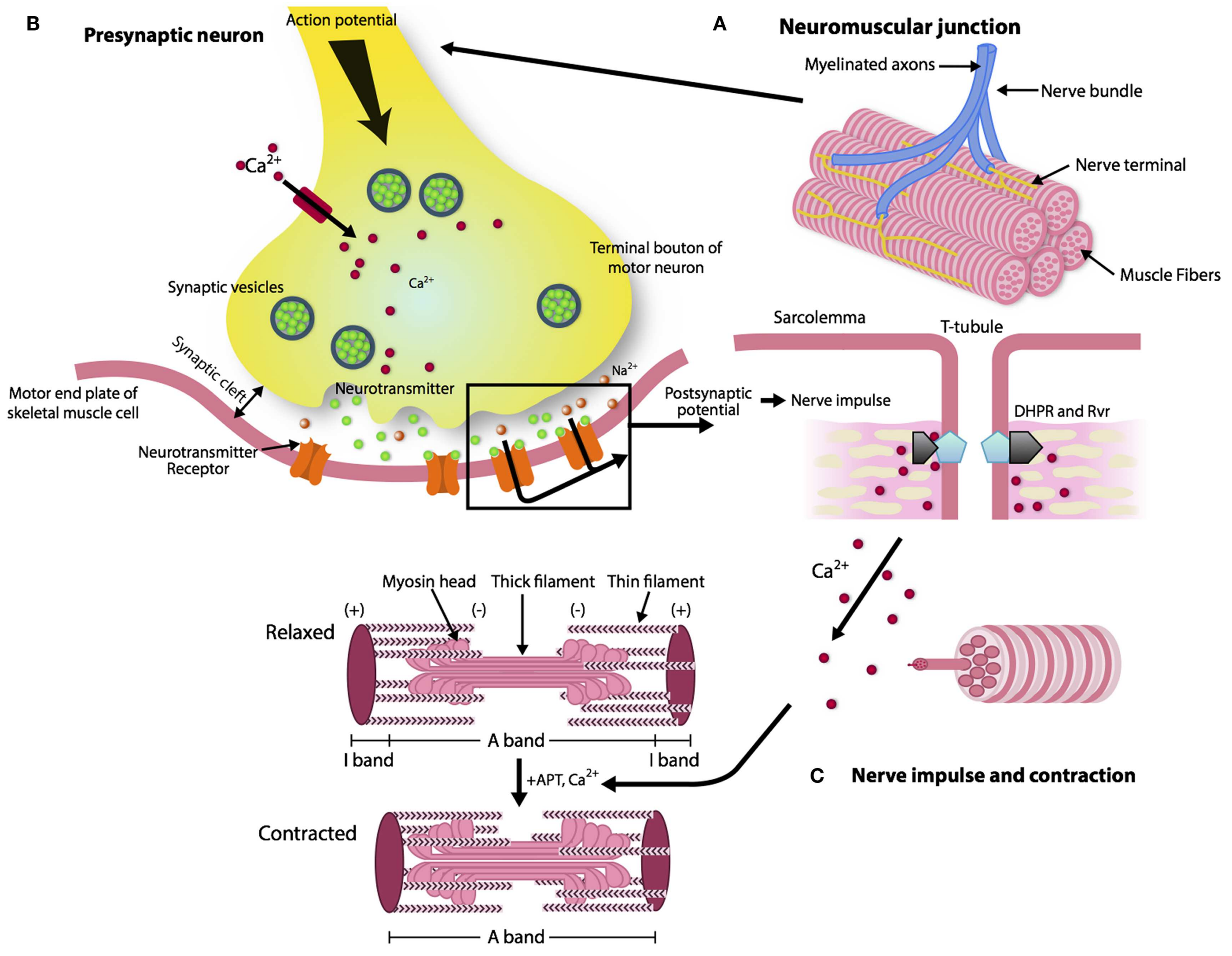


FIGURE 1 | The architecture of a neuromuscular junction (NMJ). (A, B) The NMJ is composed of three elements: pre-synaptic (motor nerve terminal), intrasynaptic (synaptic basal lamina), and post-synaptic component (muscle fiber and muscle membrane) (Punga and Ruegg, 2012). When the action potential reaches the motor nerve terminal the calcium channels open and the calcium enters in the neuron and delivers ACh in the synaptic cleft. **(C)** AChR activates the DHPRs located in the sarcolemma and by induction the RyRs. Calcium released from the sarcoplasmic reticulum through the RyRs binds to troponin C and allows cross-bridge cycling and force production.

signaling pathways, and animal models. We propose that interventions aimed at preventing the deterioration of the NMJ should be aimed at reversing the mechanisms that lead to NMJ degeneration with aging. It is important to underline that our comprehension of the global mechanism that lead to NJM impairment with aging is still patchy. Some of the elements emerging in the literature will be described and their relationship with aging explored. However, it is worth noticing that how these different parts participate and interact within a unique global mechanism and cause NMJ dysfunction with aging is not understood.

THE AGED NEUROMUSCULAR JUNCTION

CHANGES THAT OCCUR WITH AGING IN THE NMJ

The structure of the NMJ varies depending on the muscle fiber innervated and potentially on the level of muscle activity (Smith and Rosenheimer, 1982; Rosenheimer and Smith, 1985; Arrowsmith, 2007). There is strong evidence that changes in end-plate morphology and NMJ remodeling occur with aging and precede loss of fast motor units. Morphologically, both the nerve terminal area and the number of post-synaptic folds are reduced leading to a functional impairment in the post-synaptic response of the NMJ (i.e., motor nerve conduction velocity becomes slower and the amplitude of compound muscle action potential (CMAP) decreases) (Kurokawa et al., 1999). Mitochondria in the plaque region are numerically reduced and tend to show signs of degeneration. In particular, some authors have described dramatic alterations in mitochondrial morphology in axon terminals, including cristae disruption, swelling, and formation of megamitochondria due to multiple fusions between adjacent mitochondria (Garcia et al., 2013). Studies of pre-synaptic plaque changes with aging have found high levels of oxidative damage, decreased number of synaptic vesicles, and lower quantities of neurotransmitter released during depolarization (**Figure 2**). These changes have been correlated with denervation of muscle fibers and muscle atrophy occurring in a fiber dependent manner (Banker et al., 1983; Jang and Van Remmen, 2011; Rowan et al., 2012). Hypothesized mechanisms include (1) progressively reduced capacity of motor neurons to re-innervate muscle fibers that are denervated or regenerating; (2) impaired excitation–contraction coupling; and (3) age-associated decline in satellite cell proliferation (Clark and Fielding, 2012; Rosso et al., 2013) (**Figure 3**). In particular, Clark and Fielding (2012) suggest that the NMJ activation of muscle agonists is impaired in some older adults in whom weakness is more prominent than reduced muscle mass.

As mentioned previously, some studies (Li et al., 2011) suggest that in mice, NMJ changes follow degeneration and regeneration of individual muscle fibers, while others suggest that muscle denervation might be a consequence of high energetic demand in skeletal muscle fibers, as found in human mutant SOD1 (mSOD1) mice who develop amyotrophy and muscle denervation (Dupuis et al., 2004, 2009, 2011).

Mitochondrial dysfunction and oxidative stress in NMJ dysfunction

Mitochondria play a critical role in regulating energy production, metabolism, signal transduction, and apoptosis and are also the primary source of oxygen free radicals generated by the dislocation of electrons traveling across the respiratory chain (Peterson et al., 2012). The numerous mitochondria in the axon not only provide energy but also buffer the large calcium ion loads which are essential for excite–contraction coupling (Barrett et al., 2011). Decline in number and function of mitochondria as well as frequent modification of their morphological structure with aging has been described in many tissues, including skeletal muscle. Dysfunctional mitochondria are often found with aging, characterized by increased levels of oxidation and nitrosylation products and decreased enzymatic activity. It has been hypothesized that the diffusion of mitochondrial nitric oxide (NO) and hydrogen peroxide (H_2O_2) to the cytosol is decreased in the aged brain and may impair mitochondrial biogenesis (Navarro and Boveris, 2009). Since neurons and muscle fibers are highly metabolically active, it is rational to hypothesize that they are affected by even minor mitochondrial dysfunction (Li et al., 2013; Baines et al., 2014). Indeed, it has been recently shown in sarcopenic rats with NMJ disruption that the expression of genes implicated in mitochondrial energy metabolism is down regulated (Ibebunjo et al., 2013). However, the role of oxidative stress in peripheral nervous system aging and pathology remains poorly understood (Lin and Beal, 2006; Garcia et al., 2013). Reduced ATP production and impaired calcium buffering in the subsarcolemmal mitochondria located near the NMJ may impair both neurotransmission and vesicular recycling (Deschenes, 2011).

Changes in the innervation of muscle fibers and motor units

Neuron loss (cell death) that occurs with aging is progressive and, as far as we know, irreversible. Loss of motor units in young adults results in re-innervation of denervated fibers by sprouting from other motor neurons and in death of fibers that are not successfully re-innervated. The details of this process have been studied mostly in animal models. Chai et al. (2011) have shown that in mice, while the size and number of alpha motor neurons in the

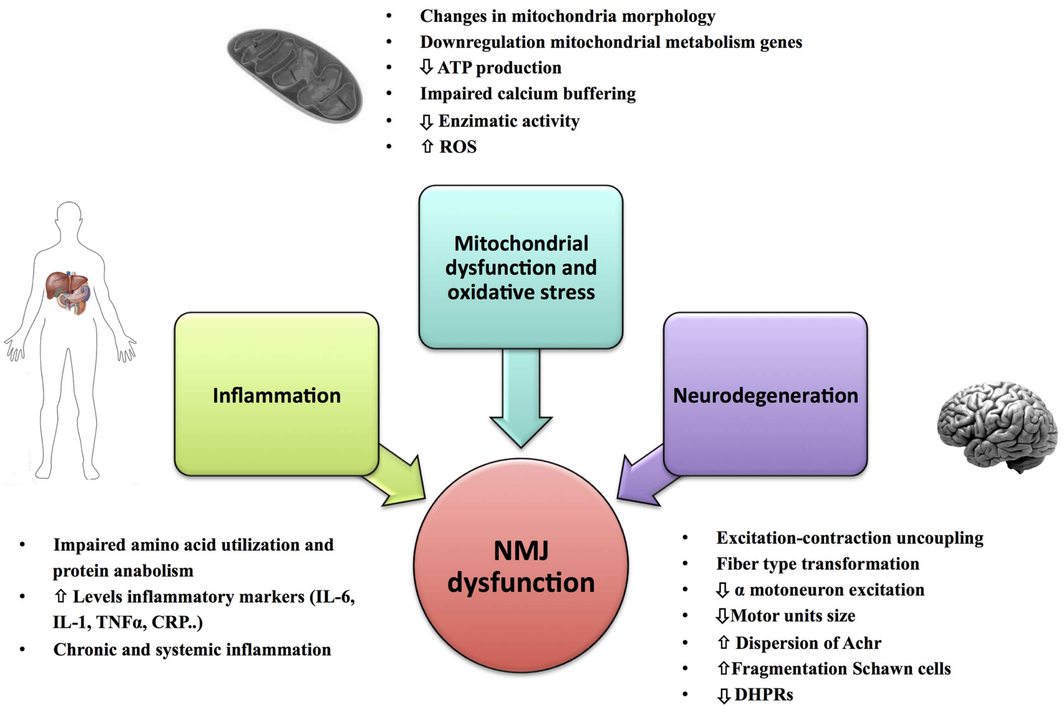


FIGURE 2 | Primary causes of NMJ dysfunction during aging. Factors such as mitochondrial dysfunction, oxidative stress, inflammation, and changes in the innervation of muscle fiber and mechanical properties of the motor units could play an important role in the NMJ degeneration and development of sarcopenia.

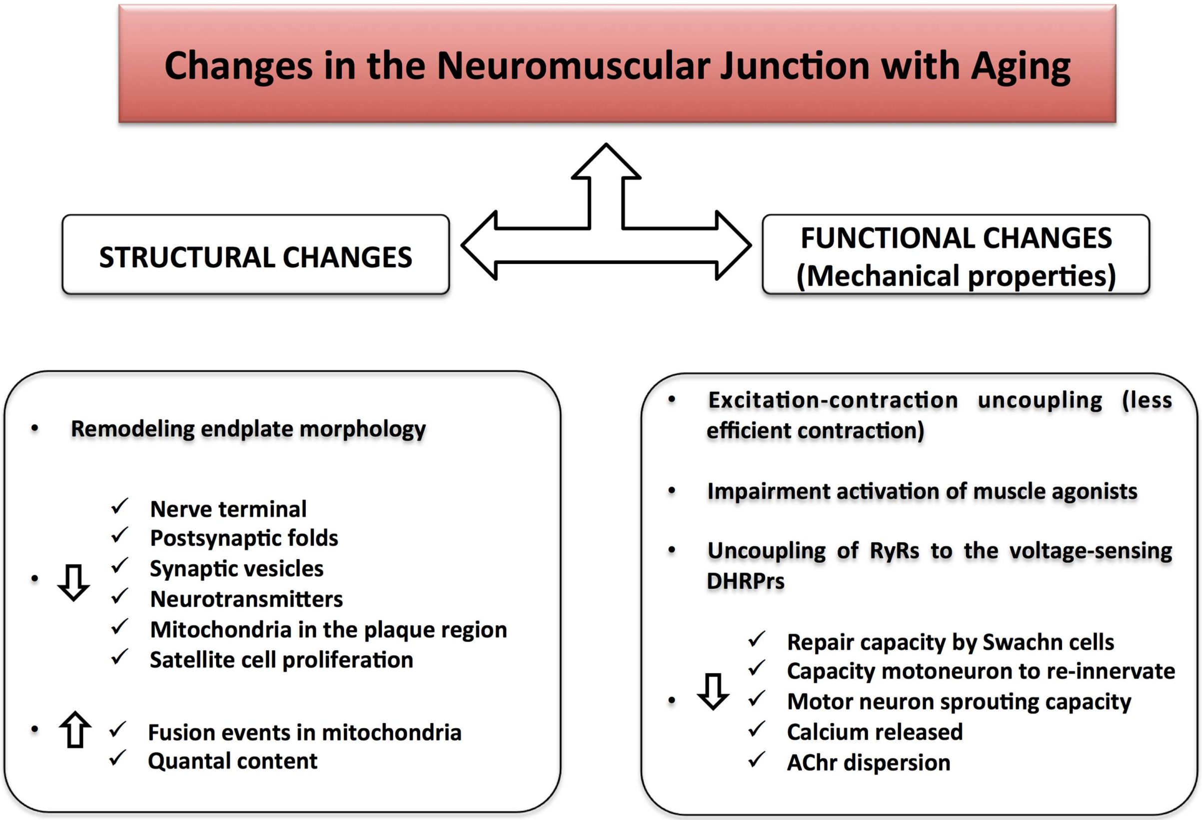


FIGURE 3 | Changes in the neuromuscular junction with aging. Structural changes together with functional alterations result in a NMJ impairment during aging. The excitation–contraction uncoupling leads to a loss of communication between the nervous and muscular system, causing a decline in skeletal muscle strength and muscle mass.

spinal cord do not change until very late in life, profound earlier change is observed at the NMJ. In very late life, motor neurons show impaired capacity to sprout and re-innervate denervated fibers, and as a consequence, larger motor units become smaller, and more fatigable and there is a considerable atrophy of muscle fibers (Luff, 1998; Roubenoff, 2000; Glass and Roubenoff, 2010). Macroscopic age-associated muscle atrophy is due to a combination of individual fiber atrophy and a decrease in the total number of type II fibers (fast and glycolytic muscle fibers) (Lexell, 1995, 1997; Andersen, 2003; Suetta et al., 2012). These alterations in morphologic remodeling in the aged NMJ result in more dispersed AChR, with greater spatial uncoupling between ACh vesicle clusters and receptor clusters. These events together induce physiological adaptations (i.e., changes of a quantal level) in the aged NMJ that have been extensively reviewed by Deschenes (2011).

According to current views, Schwann cells (cells that myelinate axons) play an critical role in synaptic repair following denervation, through their ability to direct axonal regrowth, re-myelinate, and allow functional recovery by secreting trophic and growth factors (Rangaraju et al., 2009; Rangaraju and Notterpek, 2011; Kim et al., 2013). Impairment in these cells, such as increased fragmentation, damage, or denervation may contribute to ineffective re-innervation and neuromuscular dysfunction in aging (Verge et al., 1996; Kawabuchi et al., 2001, 2011; Gordon et al., 2009).

Changes that occur at the NMJ with aging are paralleled by a progressive uncoupling of the excitation–contraction in the skeletal muscle (Delbono et al., 1995, 1997; Delbono, 2003). It has been hypothesized that age-related muscle uncoupling is due to a mismatch between DHPR and RyR. In particular RyR would be more numerous than DHPR. This uncoupling reduces calcium release after an action potential, resulting in less efficient contraction (Wang et al., 2004; Shear and Martyn, 2009). It has been shown that insulin-like growth factor-I (IGF-1) could prevent the age-related decline in the number of DHPRs, therefore preventing the changes in nerve terminal and NMJ (Delbono, 2000, 2003; Zheng et al., 2002). These findings suggest that overexpression of IGF-1 may have a role in preventing muscle strength decline with aging.

Inflammation in aging (inflammaging)

Aging is characterized by high circulating levels of inflammatory markers such as interleukin 6 (IL-6), interleukin 1 (IL-1), tumor necrosis factor alpha (TNF-alpha), and C-reactive protein (CRP) in blood and tissues, often without a clear cause. This chronic low-grade inflammation in older persons has been defined by

Franceschi et al. (2007) as "inflammaging." Epidemiological studies have consistently demonstrated that "inflammaging" is a risk factor for accelerated decline of muscle mass and strength with aging, and that these changes in muscle performance may be a critical mediating step in the causal pathway between "inflammaging" and mobility disability (Ferrucci et al., 1999, 2005). In addition, medical conditions characterized by chronic overt inflammation often cause muscle wasting and weakness (Saini et al., 2007, 2009; Degens, 2010; Ferrucci et al., 2013). The mild pro-inflammatory state of aging may affect muscle performance and maintenance in many ways. For example, Schwann cell senescence has been associated with overexpression of IL-6, suggesting a role of inflammation in the age-related alterations in axonal regeneration (Saheb-Al-Zamani et al., 2013). Chronic inflammation down regulates the production of IGF-1 and blunts its biological activity. Inflammation is associated with impaired amino acid (Aa) utilization and protein anabolism, especially in critical periods such as after a meal or after a bout of exercise.

BIOMARKERS OF NMJ IN AGING AND SIGNALING PATHWAYS

The direct study of the NMJ in human beings presents challenges that are almost insurmountable. The NMJ is seldom detected in muscle needle biopsies and requires open surgery biopsies that are only done for diagnostic purposes. Newly emerging neurophysiological techniques may be used in the future to study the NMJ but they are still at an early stage of development. One of the most promising areas of investigation and perhaps the one with the strongest translational potential is the study of circulating biomarkers, such as neurotrophic factors, muscle anabolic hormones, and growth factors that are known to have a role in NMJ dysfunction. Although most of the biomarkers addressed in this section are known to change with aging, whether they modulate the causal pathway from aging to NMJ impairment with aging is not fully established. Nevertheless, correlational studies may provide knowledge that in the future may help reconstructing a general model of the mechanism leading to NMJ degeneration with aging.

NEUROTROPHIC FACTORS

Neurotrophins are a family of proteins implicated in neural development, maintenance, and maturation that also play a role in neurotransmission. Changes in production and response to neurotrophins with aging may contribute to reduced axonal regeneration, and dysfunction at multiple levels, including motor axons, post-synaptic membrane, and Schwann cells. One of the most studied neurotrophic factors is brain-derived neurotrophic factor (BDNF), which plays a critical role in neural plasticity and facilitates synaptic function by increasing pre-synaptic depolarization at the NMJ (Seeburger and Springer, 1993; Springer et al., 1995; Huang and Reichardt, 2001; Lipsky and Marini, 2007; Jiang et al., 2008; Gomez-Pinilla, 2011) and maintaining AChR clustering in the NMJ (Gomez-Pinilla et al., 2002; Peng et al., 2003). Interestingly, there is some initial evidence that production of glia cell-derived neurotrophic factor (GDNF) declines with aging (Li et al., 1995). Denervation leads to an up regulation of GDNF in rat and human skeletal muscle (Lie and Weis, 1998). Consistently, *in vitro* studies have found that GDNF is a potent trophic factor for motor neuron survival and a potent regulator of pre- and post-synaptic plasticity (Lin et al., 1993; Nguyen et al., 1998). Moreover, GDNF protein content in aged rat skeletal muscle might be controlled by stretching the muscle and the membrane depolarization of AChR acts to decrease GDNF protein content (McCullough et al., 2011).

There is evidence that short-term exercise increases levels of GDNF in the skeletal muscle and spinal cord of young and old rats (McCullough et al., 2013). Gyorkos et al. (2014) found increased GDNF protein levels at the end plate in the soleus and extensor digitorum longus muscles following training, supporting the idea that GDNF is activity dependent. Different models of exercise type and intensity could have varying effects on GDNF protein content in slow- and fast-twitch muscle fibers. The authors concluded that GDNF may play a role in remodeling of the NMJ in slow and fast-twitch muscle fibers.

INSULIN-LIKE GROWTH FACTOR 1

Insulin-like growth factor 1 is a pleiotropic growth factor with many functions, including a neutrotrophic effect, promotion of motor neuron survival, maintenance of muscle mass and strength, and protection from oxidative stress (Yuan et al., 2000; Maggio et al., 2006, 2013; Apel et al., 2010). Many studies have found that circulating IGF-1 declines with aging and such decline may contribute to NMJ degeneration and motor unit denervation (Delbono, 2003; Messi and Delbono, 2003). In accordance with this hypothesis, in mouse models, the overexpression of muscle-specific IGF-1 reverses sarcopenia (Musaro et al., 2001), prevents the age-dependent decrease in type IIB and increase in type IIA fibers (Messi and Delbono, 2003), and also leads to improved nerve regeneration by acting on axons, Schwann cells, and the NMJ. Systemic administration of IGF-1 decreased motor neuron cell death and promoted muscle re-innervation after injury in young animals, suggesting that the decline in IGF-1 with aging may impair the ability of aging animals to repair and maintain the integrity of NMJ (Vergani et al., 1998). IGF-1 sensitivity may not decrease with age, so that IGF-1 could promote regeneration after nerve injury even in older individuals. Overexpression of muscle-specific IGF-1 in mice increases the size of NMJ without substantial changes in muscle fiber size suggesting that preservation of specific force in aged animals overexpressing IGF-1 in muscle is achieved, in part, by improved motor neurons-muscle coupling (Payne et al., 2006).

AGRIN-MuSK SIGNALING PATHWAY

Acetylcholine receptors clustering on the post-synaptic membrane is a main event in the differentiation of NMJ. This process requires the presence of neural agrin, a basal lamina proteoglycan that activates a muscle-specific kinase (MuSK), which is essential for AChR clustering.

Agrin is transported along the axons and finally released into synaptic basal lamina where it is inactivated by cleavage from neurotrypsin, a synaptic protease, which produces a soluble 22 kDa C-terminal agrin fragment (CAF). Importantly, CAF can be easily detected and measured in human serum (Bolliger et al., 2010; Butikofer et al., 2011). The destabilization of the NMJ by proteolysis of agrin results in precocious sarcopenia (Drey et al., 2013; Hettwer et al., 2013). This is consistent with findings in experiments with transgenic mice overexpressing neurotrypsin in spinal motoneurons that shown the full sarcopenia phenotype (Butikofer et al., 2011).

Wnt SIGNALING PATHWAY

There is wide evidence, both in animals models and in humans, the Wnt signaling pathway is down regulated with aging and contributes to the progressive reduction in muscle regeneration and repair capacity (Conboy and Rando, 2012). Wnt proteins are a large family (19 members in humans) of secreted glycoproteins that are highly evolutionary conserved. Wnt signaling modulates the formation and the function of synapses and is involved in maintenance and function of many tissues including muscle and nerve. Wnt deregulation produces many neurodegenerative and mental diseases (Okerlund and Cheyette, 2011; Mulligan and Cheyette, 2012; Stamatakou and Salinas, 2013).

The role of WNT signaling on the NMJ is complex. Canonical and non-canonical Wnt pathways exert opposite effects on the formation of the vertebrate NMJ (Korkut and Budnik, 2009). The non-canonical Wnt cascade has a positive role on post-synaptic development. In contrast, activation of the canonical Wnt pathway has a negative effect on NMJ formation. Thus, while the role of Wnt signaling on NMJ development and in muscle regeneration impairment with aging is well established, evidence for a direct effect of Wnt on NMJ plasticity, maintenance, and repair is lacking and requires further investigation.

VOLTAGE-GATED SODIUM CHANNEL: $Na_V1.5$

The Na_V channel gene family ($Na_V1.1$–$Na_V1.9$, NaVX) codes for voltage-gated sodium channels (NaChs), which are essential for the initiation and propagation of action potentials in both nerve and muscle (Young and Caldwell, 2005). Adult skeletal muscle expresses two isoforms of Nav (Nav1.4 and Nav1.5) (Rannou et al., 2011; Kraner et al., 2012). The isoform $Na_V1.5$ is particularly relevant to aging because it is mainly expressed in adult muscle following denervation (Kallen et al., 1990; Morel et al., 2010). Consistently, fibers positive for tetrodotoxin resistant (TTX-R) $Na_V1.5$ channels are more prevalent in muscles from old compared with young mice, suggesting a potential biomarker for muscle denervation during aging (Wang et al., 2005; Rowan et al., 2012).

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA COACTIVATOR 1-ALPHA (PGC-1α)

Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) is a transcription factor that promotes mitochondrial biogenesis. Studies have consistently shown that PGC-1α decline with aging and in many age-related chronic diseases suggesting that such decline may explain the progressive mitochondrial dysfunction with aging.

Recent studies using muscle-specific PGC-1α knockout and PGC-1α overexpressing mice have suggested that PGC-1α is a key protein involved in NMJ integrity, and the decline in PGC-1α may cause NMJ degeneration with aging by a mechanism that is separate from the effect of PGC-1α on mitochondrial biogenesis (Handschin et al., 2007; Wenz et al., 2009; Liang et al., 2011; Gouspillou et al., 2013). There is recent strong evidence that elevated activity of the co-activator PGC-1α in skeletal muscle contributes to the efficient pre- and post-synaptic remodeling of the NMJ (Arnold et al., 2014).

Gouspillou et al. (2013) hypothesized that the denervation and innervation cycle observed with aging is under the control of PGC-1α expression and proposed that the aging-related decline in PGC-1α may be a central mechanism promoting instability of the NMJ and consequently aging-related alterations of myofiber innervation in sarcopenia. Interestingly, the decline in muscle PGC-1α levels with aging is attenuated by caloric restriction (CR) and exercise (Derbre et al., 2012; Garcia-Valles et al., 2013).

PROTEIN DEGRADATION PATHWAYS: MAFbx AND MuRF1

The ubiquitin–proteasome and the autophagic-lysosomal pathways are activated during disease-related muscle atrophy and, perhaps, during the development of age-related sarcopenia. The ubiquitin–proteasome system is required to remove sarcomeric proteins, either because they are damaged or in response to decline in muscle activity. Two main enzymes at the core of this system, the ubiquitin ligases muscle atrophy f-box (Atrogin1/MAFbx) and muscle ring finger-1 (MuRF1), increase significantly in muscular atrophy, in part due to enhanced expression of tumor necrosis factor alpha (TNF-α). Mice lacking both are resistant to atrophy induced by denervation (Bodine et al., 2001; Lecker et al., 2004; Nordquist et al., 2007; Furlow et al., 2013). There is some evidence that MuRF1 could play a role in NMJ control by regulating AChR lifetime, implicating a role of MuRF1 in membrane protein turnover during aging (Rudolf et al., 2013; Franke et al., 2014; Khan et al., 2014).

THE STUDY OF NMJ IN AGING: ANIMALS MODELS

The NMJ is the best model to study synaptogenesis, because, at least in animals, it is experimentally accessible in a living organism. The mechanisms that lead to differentiation and maturation of the NMJ have been studied extensively while changes that occur with aging and lead to impairment of the NMJ are not fully understood. Most of the studies conducted in this field focused on early development (i.e., the KO mice for synaptic regulators such as rapsyn, agrin, MuSK, and AChR) (Yampolsky et al., 2010; Witzemann et al., 2013). Mouse models that were originally developed to study neuromuscular diseases [i.e., amyotrophic lateral sclerosis (ALS)] could be used to explore the effect of aging on the NMJ. The prototype of these models is the $Sod1^{-/-}$ mice.

$Sod1^{-/-}$ MICE

The homozygous deletion of Cu/Zn superoxide dismutase (Cu/Zn SOD) leads to age-dependent muscle atrophy with alterations in NMJ similar to, but more severe than aging-related muscle atrophy (Sakellariou et al., 2011, 2014). This model is of great interest because the main function of SOD is to scavenge free oxygen radicals, being the oxidative stress, one of the landmarks of aging.

The $Sod1^{-/-}$ mice were originally created to study ALS and addresses pathological events in the spinal cord, peripheral axons, and muscle. However, the neuromuscular sarcopenic phenotypes exhibited by this mouse share several characteristics with age-related sarcopenia, namely shift from fast to slow fiber type, mitochondrial dysfunction, and increased mitochondrial ROS generation (Jang and Van Remmen, 2009, 2011). In particular, the mitochondrial dysfunction might contribute to early motor terminal death in these mice (Muller et al., 2007). Rocha et al. (2013) have shown that the Sod1$^{-/-}$ mice undergo cycles of denervation/re-innervation by mixed NMJ populations (Sod1a, Sod1b) supporting morphological evidence for two populations of motor units in Sod1$^{-/-}$ mice (Schaefer et al., 2005). All together these data suggest that the impairment in neuromuscular transmission follows post-synaptic changes.

MRF4-NULL MICE

Muscle regulatory factor 4 (MRF4) is a member of the family of myogenic transcription factors (MyoD, myogenin, and myf-5) necessary for the differentiation of skeletal muscle (Weis et al., 2000). MRF4-null mice express genes encoding nAChR subunits and contractile proteins at normal levels, but express myogenin at dramatically increased levels. These mice have normal morphology and fiber-type composition (Zhang et al., 1995) and reduced expression of the Na_V 1.4 NaCh (Snow et al., 2005). Denervation leads to a rapid increase of MRF4 protein in myofiber and satellite cell nuclei in all muscle fiber types, suggesting that MRF4 might mediates the earliest responses to denervation and muscle damage (Weis et al., 2000). The NMJs in these mice at older age show higher levels of synaptic vesicle glycoprotein 2B (SV2B) a marker of synaptic vesicles and a decrease in MRF4 expression, suggesting an age-related loss of vesicles in the pre-synaptic terminal of MRF4-null mice that could lead to NMJ dysfunction (Wang et al., 2011). These authors propose MRF4 as a good therapeutic target to restoring and maintaining NMJ in aging and diseases.

INTERVENTIONS TO IMPROVE NMJ DYSFUNCTION IN AGING

Caloric restriction and exercise attenuate age-related declines in most physiological systems including the neuromuscular system (McKiernan et al., 2004; Gillette-Guyonnet and Vellas, 2008; Valdez et al., 2010; Mercken et al., 2012; Chistiakov et al., 2014). It has been shown that CR, but not exercise, blunts age-related loss of motor neurons and muscle fibers (Deschenes, 2011). Aging '*per se*' limits the capacity of a person to adapt to an exercise training program since muscle plasticity is reduced with aging (Degens, 2010). Because the NMJ could be impaired during aging, with a reduced capacity to adapt to fatigue, CR and exercise are candidate interventions to delay the onset of age-related NMJ dysfunction and sarcopenia.

CALORIC RESTRICTION

Caloric restriction has long been shown to be the most effective, non-genetic intervention to extend lifespan and delay the onset of age-related diseases (McCay et al., 1935; Fontana et al., 2010; Anderson and Weindruch, 2012; Gouspillou and Hepple, 2013). Valdez et al. (2010) found that CR from 4 to 24 months of age led to sparing of many NMJs in the tibialis anterior (TA) muscle in mice. The frequencies of fragmented and denervated post-synaptic sites were all significantly lower in these calorically restricted mice than in controls. The authors concluded that CR reduced the incidence of axonal atrophy and attenuated the deleterious effects of age on the structure of the NMJ. Other authors have found that dietary restriction (40% of *ad libitum* fed diet) attenuates age-associated muscle atrophy by lowering oxidative stress in Sod1$^{-/-}$ mice and up-regulating manganese superoxide dismutase (MnSOD), the main mitochondrial antioxidant enzyme responsible for scavenging superoxide produced by the mitochondrial electron transport chain (ETC). These data suggest that the CR model may be useful to identify mechanisms and targets for interventions aimed at preservation of NMJ with aging (Jang et al., 2012). Furthermore, Mayhew et al. (1998) propose that CR preserves the mechanical properties of aging skeletal muscles in rats through an increased expression of DHPRs.

EXERCISE

Voluntary physical activity declines with aging in humans and in most other animal species. The consequent reduction in fitness leads to reduced resistance to fatigue, lower muscle strength, and increased risk of frailty (Degens and Alway, 2006; Ferrucci et al., 2008; Afilalo et al., 2014). Neuromuscular fatigue (progressively impaired transduction of action potentials through the NMJ during exercise) has been identified as a factor constraining exercise intensity and duration, and a contributor to reduced response to exercise training during aging (Belluardo et al., 2001; Deschenes, 2011). A recent review highlighted the beneficial effects of exercise on the maintenance and regeneration of NMJs (Nishimune et al., 2014). Exercise induces NMJ hypertrophy and improves recovery from peripheral nerve injuries, while decreased physical activity results in NMJ degeneration and nerve terminal sprouting (Wilson and Deschenes, 2005; Nishimune et al., 2012, 2014). Clark et al. (2013) suggest that voluntary neuromuscular activation declines with advancing age, contributing to a reduction in power production, and precedes the decline of mobility function. Aging limit the capacity of NMJ to adapt to endurance training (Deschenes et al., 2010; Valdez et al., 2010). These findings suggest that in the presence of mitochondrial DNA (mtDNA) mutation induced by ROS, strength training (ST) can reverse the loss of muscle function and altered muscle morphology associated with age and can promote the normalization of dysfunctional mitochondria (Hurley et al., 2011). Voluntary running exercise begun in late middle-age is sufficient to preserve much of the endplate nerve terminal area (Cheng et al., 2013). In mice, endurance training reduced muscle fiber size in young adults even as NMJ size increased (Deschenes, 2011). Also, in mice, Fahim (1997) showed that if the exercise training is introduced during old age, the age-related expansion of NMJ is minimized and modulated at a lower level compared with sedentary controls, indicating that the mouse NMJ undergoes a process of physiological and morphological remodeling during aging, and such plasticity could be modulated differently by endurance exercise.

CONCLUSION AND FUTURE DIRECTIONS

Age-related NMJ dysfunction seems to be a key to understanding musculoskeletal impairment during aging. Morphological changes together with physiological alterations result in a remodeling of the motor unit and in a decline of the number of motor neurons, particularly the type II muscle fiber. These changes lead to excitation–contraction uncoupling, and a loss of communication between the nervous and muscular system, causing a decline in skeletal muscle strength and muscle mass. Despite the extensive evidence about muscle denervation in older persons, because the direct study of NMJ in humans remains extremely challenging, it remains unclear whether denervation precedes sarcopenia or vice versa. Understanding the molecular basis of NMJ dysfunction is essential and the study of biomarker is essential both to make scientific progress in this area and translating such research in search for new treatment. Not only new structural and molecular studies, but also novel animal models to clarify what really happens to this key connection between brain and muscle are needed.

ACKNOWLEDGMENTS

This review was supported entirely by the Intramural Research Program of the NIH, National Institute on Aging.

REFERENCES

Afilalo, J., Alexander, K. P., Mack, M. J., Maurer, M. S., Green, P., Allen, L. A., et al. (2014). Frailty assessment in the cardiovascular care of older adults. *J. Am. Coll. Cardiol.* 63, 747–762. doi:10.1016/j.jacc.2013.09.070

Andersen, J. L. (2003). Muscle fibre type adaptation in the elderly human muscle. *Scand. J. Med. Sci. Sports* 13, 40–47. doi:10.1034/j.1600-0838.2003.00299.x

Anderson, R. M., and Weindruch, R. (2012). The caloric restriction paradigm: implications for healthy human aging. *Am. J. Hum. Biol.* 24, 101–106. doi:10.1002/ajhb.22243

Apel, P. J., Ma, J., Callahan, M., Northam, C. N., Alton, T. B., Sonntag, W. E., et al. (2010). Effect of locally delivered IGF-1 on nerve regeneration during aging: an experimental study in rats. *Muscle Nerve* 41, 335–341. doi:10.1002/mus.21485

Arnold, A. S., Gill, J., Christe, M., Ruiz, R., McGuirk, S., St-Pierre, J., et al. (2014). Morphological and functional remodelling of the neuromuscular junction by skeletal muscle PGC-1alpha. *Nat Commun* 5, 3569. doi:10.1038/ncomms4569

Arrowsmith, J. E. (2007). The neuromuscular junction. *Surgery* (Oxford) 25, 105–111. doi:10.1016/j.mpsur.2007.02.001

Baines, H. L., Turnbull, D. M., and Greaves, L. C. (2014). Human stem cell aging: do mitochondrial DNA mutations have a causal role? *Aging Cell* 13, 201–205. doi:10.1111/acel.12199

Banker, B. Q., Kelly, S. S., and Robbins, N. (1983). Neuromuscular transmission and correlative morphology in young and old mice. *J. Physiol.* 339, 355–377.

Barrett, E. F., Barrett, J. N., and David, G. (2011). Mitochondria in motor nerve terminals: function in health and in mutant superoxide dismutase 1 mouse models of familial ALS. *J. Bioenerg. Biomembr.* 43, 581–586. doi:10.1007/s10863-011-9392-1

Belluardo, N., Westerblad, H., Mudo, G., Casabona, A., Bruton, J., Caniglia, G., et al. (2001). Neuromuscular junction disassembly and muscle fatigue in mice lacking neurotrophin 4. *Mol. Cell. Neurosci.* 18, 56–67. doi:10.1006/mcne.2001.1001

Bodine, S. C., Latres, E., Baumhueter, S., Lai, V. K., Nunez, L., Clarke, B. A., et al. (2001). Identification of ubiquitin ligases required for skeletal muscle atrophy. *Science* 294, 1704–1708. doi:10.1126/science.1065874

Bolliger, M. F., Zurlinden, A., Luscher, D., Butikofer, L., Shakhova, O., Francolini, M., et al. (2010). Specific proteolytic cleavage of agrin regulates maturation of the neuromuscular junction. *J. Cell Sci.* 123(Pt 22), 3944–3955. doi:10.1242/jcs.072090

Butikofer, L., Zurlinden, A., Bolliger, M. F., Kunz, B., and Sonderegger, P. (2011). Destabilization of the neuromuscular junction by proteolytic cleavage of agrin results in precocious sarcopenia. *FASEB J.* 25, 4378–4393. doi:10.1096/fj.11-191262

Chai, R. J., Vukovic, J., Dunlop, S., Grounds, M. D., and Shavlakadze, T. (2011). Striking denervation of neuromuscular junctions without lumbar motoneuron loss in geriatric mouse muscle. *PLoS ONE* 6:e28090. doi:10.1371/journal.pone.0028090

Cheng, A., Morsch, M., Murata, Y., Ghazanfari, N., Reddel, S. W., and Phillips, W. D. (2013). Sequence of age-associated changes to the mouse neuromuscular junction and the protective effects of voluntary exercise. *PLoS ONE* 8:e67970. doi:10.1371/journal.pone.0067970

Chistiakov, D. A., Sobenin, I. A., Revin, V. V., Orekhov, A. N., and Bobryshev, Y. V. (2014). Mitochondrial Aging and Age-Related Dysfunction of Mitochondria. *BioMed. Res. Int.* 2014, 238463. doi:10.1155/2014/238463

Clark, D. J., and Fielding, R. A. (2012). Neuromuscular contributions to age-related weakness. *J Gerontol A. Biol. Sci. Med. Sci.* 67, 41–47. doi:10.1093/gerona/glr041

Clark, D. J., Pojednic, R. M., Reid, K. F., Patten, C., Pasha, E. P., Phillips, E. M., et al. (2013). Longitudinal decline of neuromuscular activation and power in healthy older adults. *J. Gerontol.* 68, 1419–1425. doi:10.1093/gerona/glt036

Conboy, I. M., and Rando, T. A. (2012). Heterochronic parabiosis for the study of the effects of aging on stem cells and their niches. *Cell Cycle (Georgetown, Tex.)* 11, 2260–2267. doi:10.4161/cc.20437

Degens, H. (2010). The role of systemic inflammation in age-related muscle weakness and wasting. *Scand. J. Med. Sci. Sports* 20, 28–38. doi:10.1111/j.1600-0838.2009.01018.x

Degens, H., and Alway, S. E. (2006). Control of muscle size during disuse, disease, and aging. *Int. J. Sports Med.* 27, 94–99. doi:10.1055/s-2005-837571

Delbono, O. (2000). Regulation of excitation contraction coupling by insulin-like growth factor-1 in aging skeletal muscle. *J. Nutr. Health Aging* 4, 162–164.

Delbono, O. (2003). Neural control of aging skeletal muscle. *Aging Cell* 2, 21–29. doi:10.1046/j.1474-9728.2003.00011.x

Delbono, O., O'Rourke, K. S., and Ettinger, W. H. (1995). Excitation-calcium release uncoupling in aged single human skeletal muscle fibers. *J. Memb. Biol.* 148, 211–222. doi:10.1007/BF00235039

Delbono, O., Renganathan, M., and Messi, M. L. (1997). Excitation-Ca2+ release-contraction coupling in single aged human skeletal muscle fiber. *Muscle Nerve Suppl.* 5, S88–S92. doi:10.1002/(SICI)1097-4598(1997)5+<88::AID-MUS21>3.0.CO;2-U

Derbre, F., Gomez-Cabrera, M. C., Nascimento, A. L., Sanchis-Gomar, F., Martinez-Bello, V. E., Tresguerres, J. A., et al. (2012). Age associated low mitochondrial biogenesis may be explained by lack of response of PGC-1alpha to exercise training. *Age* (Dordr) 34, 669–679. doi:10.1007/s11357-011-9264-y

Deschenes, M. R. (2011). Motor unit and neuromuscular junction remodeling with aging. *Curr Aging Sci* 4, 209–220. doi:10.2174/1874609811104030209

Deschenes, M. R., Roby, M. A., Eason, M. K., and Harris, M. B. (2010). Remodeling of the neuromuscular junction precedes sarcopenia related alterations in myofibers. *Exp. Gerontol.* 45, 389–393. doi:10.1016/j.exger.2010.03.007

Drey, M., Sieber, C. C., Bauer, J. M., Uter, W., Dahinden, P., Fariello, R. G., et al. (2013). C-terminal agrin fragment as a potential marker for sarcopenia caused by degeneration of the neuromuscular junction. *Exp. Gerontol.* 48, 76–80. doi:10.1016/j.exger.2012.05.021

Dupuis, L., Gonzalez de Aguilar, J.-L., Echaniz-Laguna, A., Eschbach, J., Rene, F., Oudart, H., et al. (2009). Muscle mitochondrial uncoupling dismantles neuromuscular junction and triggers distal degeneration of motor neurons. *PLoS ONE* 4:e5390. doi:10.1371/journal.pone.0005390

Dupuis, L., Oudart, H., Rene, F., Gonzalez de Aguilar, J. L., and Loeffler, J. P. (2004). Evidence for defective energy homeostasis in amyotrophic lateral sclerosis: benefit of a high-energy diet in a transgenic mouse model. *Proc. Natl. Acad. Sci. U S A.* 101, 11159–11164. doi:10.1073/pnas.0402026101

Dupuis, L., Pradat, P. F., Ludolph, A. C., and Loeffler, J. P. (2011). Energy metabolism in amyotrophic lateral sclerosis. *Lancet Neurol.* 10, 75–82. doi:10.1016/S1474-4422(10)70224-6

Fahim, M. A. (1997). Endurance exercise modulates neuromuscular junction of C57BL/6NNia aging mice. *J. Appl. Physiol.* 83, 59–66.

Ferrucci, L., Baroni, M., Ranchelli, A., Lauretani, F., Maggio, M., Mecocci, P., et al. (2014). Interaction between bone and muscle in older persons with mobility limitations. *Curr. Pharm. Des.* 20, 3178–3197. doi:10.2174/13816128113196660690

Ferrucci, L., Corsi, A., Lauretani, F., Bandinelli, S., Bartali, B., Taub, D. D., et al. (2005). The origins of age-related proinflammatory state. *Blood* 105, 2294–2299. doi:10.1182/blood-2004-07-2599

Ferrucci, L., de Cabo, R., Knuth, N. D., and Studenski, S. (2012). Of Greek heroes, wiggling worms, mighty mice, and old body builders. *J Gerontol. A. Biol. Sci. Med. Sci.* 67, 13–16. doi:10.1093/gerona/glr046

Ferrucci, L., Giallauria, F., and Schlessinger, D. (2008). Mapping the road to resilience: novel math for the study of frailty. *Mech. Ageing Dev.* 129, 677–679. doi:10.1016/j.mad.2008.09.007

Ferrucci, L., Harris, T. B., Guralnik, J. M., Tracy, R. P., Corti, M. C., Cohen, H. J., et al. (1999). Serum IL-6 level and the development of disability in older persons. *J. Am. Geriatr. Soc.* 47, 639–646.

Fontana, L., Partridge, L., and Longo, V. D. (2010). Extending healthy life span – from yeast to humans. *Science* 328, 321–326. doi:10.1126/science.1172539

Franceschi, C., Capri, M., Monti, D., Giunta, S., Olivieri, F., Sevini, F., et al. (2007). Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. *Mech Ageing Dev* 128, 92–105. doi:10.1016/j.mad.2006.11.016

Franke, B., Gasch, A., Rodriguez, D., Chami, M., Khan, M. M., Rudolf, R., et al. (2014). Molecular basis for the fold organization and sarcomeric targeting of the muscle atrogin MuRF1. *Open Biol.* 4, 130172. doi:10.1098/rsob.130172

Furlow, J. D., Watson, M. L., Waddell, D. S., Neff, E. S., Baehr, L. M., Ross, A. P., et al. (2013). Altered gene expression patterns in muscle ring finger 1 null mice during denervation- and dexamethasone-induced muscle atrophy. *Physiol. Genomics* 45, 1168–1185. doi:10.1152/physiolgenomics.00022.2013

Garcia, M. L., Fernandez, A., and Solas, M. T. (2013). Mitochondria, motor neurons and aging. *J. Neurol. Sci.* 330, 18–26. doi:10.1016/j.jns.2013.03.019

Garcia-Valles, R., Gomez-Cabrera, M. C., Rodriguez-Manas, L., Garcia-Garcia, F. J., Diaz, A., Noguera, I., et al. (2013). Life-long spontaneous exercise does not prolong lifespan but improves health span in mice. *Longev. Healthspan* 2, 14. doi:10.1186/2046-2395-2-14

Gillette-Guyonnet, S., and Vellas, B. (2008). Caloric restriction and brain function. *Curr. Opin. Clin. Nutr. Metab. Care* 11, 686–692. doi:10.1097/MCO.0b013e328313968f

Glass, D., and Roubenoff, R. (2010). Recent advances in the biology and therapy of muscle wasting. *Ann. N Y Acad. Sci.* 1211, 25–36. doi:10.1111/j.1749-6632.2010.05809.x

Gomez-Pinilla, F. (2011). The combined effects of exercise and foods in preventing neurological and cognitive disorders. *Prev. Med.* 52(Suppl. 1), S75–S80. doi:10.1016/j.ypmed.2011.01.023

Gomez-Pinilla, F., Ying, Z., Roy, R. R., Molteni, R., and Edgerton, V. R. (2002). Voluntary exercise induces a BDNF-mediated mechanism that promotes neuroplasticity. *J. Neurophysiol.* 88, 2187–2195. doi:10.1152/jn.00152.2002

Gordon, T., Udina, E., Verge, V. M. K., and de Chaves, E. I. P. (2009). Brief electrical stimulation accelerates axon regeneration in the peripheral nervous system and promotes sensory axon regeneration in the central nervous system. *Motor Control* 13, 412–441.

Gouspillou, G., and Hepple, R. T. (2013). Facts and controversies in our understanding of how caloric restriction impacts the mitochondrion. *Exp. Gerontol.* 48, 1075–1084. doi:10.1016/j.exger.2013.03.004

Gouspillou, G., Picard, M., Godin, R., Burelle, Y., and Hepple, R. T. (2013). Role of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1alpha) in denervation-induced atrophy in aged muscle: facts and hypotheses. *Longev. Healthspan* 2, 13. doi:10.1186/2046-2395-2-13

Gyorkos, A. M., McCullough, M. J., and Spitsbergen, J. M. (2014). Glial cell line-derived neurotrophic factor (GDNF) expression and NMJ plasticity in skeletal muscle following endurance exercise. *Neuroscience* 257, 111–118. doi:10.1016/j.neuroscience.2013.10.068

Handschin, C., Kobayashi, Y. M., Chin, S., Seale, P., Campbell, K. P., and Spiegelman, B. M. (2007). PGC-1alpha regulates the neuromuscular junction program and ameliorates Duchenne muscular dystrophy. *Genes Dev.* 21, 770–783. doi:10.1101/gad.1525107

Hettwer, S., Dahinden, P., Kucsera, S., Farina, C., Ahmed, S., Fariello, R., et al. (2013). Elevated levels of a C-terminal agrin fragment identifies a new subset of sarcopenia patients. *Exp. Gerontol.* 48, 69–75. doi:10.1016/j.exger.2012.03.002

Huang, E. J., and Reichardt, L. F. (2001). Neurotrophins: roles in neuronal development and function. *Ann. Rev. Neurosci.* 24, 677–736. doi:10.1146/annurev.neuro.24.1.677

Hurley, B. F., Hanson, E. D., and Sheaff, A. K. (2011). Strength training as a countermeasure to aging muscle and chronic disease. *Sports Med.* 41, 289–306. doi:10.2165/11585920-000000000-00000

Ibebunjo, C., Chick, J. M., Kendall, T., Eash, J. K., Li, C., Zhang, Y., et al. (2013). Genomic and proteomic profiling reveals reduced mitochondrial function and disruption of the neuromuscular junction driving rat sarcopenia. *Mol. Cel. Biol.* 33, 194–212. doi:10.1128/MCB.01036-12

Jang, Y. C., Liu, Y., Hayworth, C. R., Bhattacharya, A., Lustgarten, M. S., Muller, F. L., et al. (2012). Dietary restriction attenuates age-associated muscle atrophy by lowering oxidative stress in mice even in complete absence of CuZnSOD. *Aging Cell* 11, 770–782. doi:10.1111/j.1474-9726.2012.00843.x

Jang, Y. C., and Van Remmen, H. (2009). The mitochondrial theory of aging: insight from transgenic and knockout mouse models. *Exp. Gerontol.* 44, 256–260. doi:10.1016/j.exger.2008.12.006

Jang Y. C., and Van Remmen, H. (2011). Age-associated alterations of the neuromuscular junction. *Exp. Gerontol.* 46, 193–198. doi:10.1016/j.exger.2010.08.029

Jiang, X., Tian, F., Du, Y., Copeland, N. G., Jenkins, N. A., Tessarollo, L., et al. (2008). BHLHB2 controls Bdnf promoter 4 activity and neuronal excitability. *J. Neurosci.* 28, 1118–1130. doi:10.1523/JNEUROSCI.2262-07.2008

Kallen, R. G., Sheng, Z. H., Yang, J., Chen, L. Q., Rogart, R. B., and Barchi, R. L. (1990). Primary structure and expression of a sodium channel characteristic of denervated and immature rat skeletal muscle. *Neuron* 4, 233–242. doi:10.1016/0896-6273(90)90098-Z

Kawabuchi, M., Tan, H., and Wang, S. (2011). Age affects reciprocal cellular interactions in neuromuscular synapses following peripheral nerve injury. *Ageing Res. Rev.* 10, 43–53. doi:10.1016/j.arr.2010.10.003

Kawabuchi, M., Zhou, C. J., Wang, S., Nakamura, K., Liu, W. T., and Hirata, K. (2001). The spatio temporal relationship among Schwann cells, axons and post-synaptic acetylcholine receptor regions during muscle reinnervation in aged rats. *Anat. Rec.* 264, 183–202. doi:10.1002/ar.1159

Khan, M. M., Strack, S., Wild, F., Hanashima, A., Gasch, A., Brohm, K., et al. (2014). Role of autophagy, SQSTM1, SH3GLB1, and TRIM63 in the turnover of nicotinic acetylcholine receptors. *Autophagy* 10, 123–136. doi:10.4161/auto.26841

Kim, H. A., Mindos, T., and Parkinson, D. B. (2013). Plastic fantastic: Schwann cells and repair of the peripheral nervous system. *Stem Cells Transl. Med.* 2, 553–557. doi:10.5966/sctm.2013-0011

Korkut, C., and Budnik, V. (2009). WNTs tune up the neuromuscular junction. *Nat. Rev. Neurosci.* 10, 627–634. doi:10.1038/nrn2681

Kraner, S. D., Novak, K. R., Wang, Q., Peng, J., and Rich, M. M. (2012). Altered sodium channel-protein associations in critical illness myopathy. *Skelet. Muscle* 2, 17. doi:10.1186/2044-5040-2-17

Kurokawa, K., Mimori, Y., Tanaka, E., Kohriyama, T., and Nakamura, S. (1999). Age-related change in peripheral nerve conduction: compound muscle action potential duration and dispersion. *Gerontology* 45, 168–173. doi:10.1159/000022081

Lecker, S. H., Jagoe, R. T., Gilbert, A., Gomes, M., Baracos, V., Bailey, J., et al. (2004). Multiple types of skeletal muscle atrophy involve a common program of changes in gene expression. *FASEB J.* 18, 39–51.

Lexell, J. (1995). Human aging, muscle mass, and fiber type composition. *J Gerontol. A. Biol. Sci. Med. Sci.* 50 Spec No, 11–16.

Lexell, J. (1997). Evidence for nervous system degeneration with advancing age. *J. Nutr.* 127, 1011S–1013S.

Li, H., Kumar Sharma, L., Li, Y., Hu, P., Idowu, A., Liu, D., et al. (2013). Comparative bioenergetic study of neuronal and muscle mitochondria during aging. *Free Rad. Biol. Med.* 63, 30–40. doi:10.1016/j.freeradbiomed.2013.04.030

Li, L., Wu, W., Lin, L. F., Lei, M., Oppenheim, R. W., and Houenou, L. J. (1995). Rescue of adult mouse motoneurons from injury-induced cell death by glial cell line-derived neurotrophic factor. *Proc. Natl. Acad. Sci.U S A* 92, 9771–9775. doi:10.1073/pnas.92.21.9771

Li, Y., Lee, Y. I., and Thompson, W. J. (2011). Changes in aging mouse neuromuscular junctions are explained by degeneration and regeneration of muscle fiber segments at the synapse. *J. Neurosci.* 31, 14910–14919. doi:10.1523/JNEUROSCI.3590-11.2011

Liang, H., Ward, W. F., Jang, Y. C., Bhattacharya, A., Bokov, A. F., Li, Y., et al. (2011). PGC-1alpha protects neurons and alters disease progression in an amyotrophic lateral sclerosis mouse model. *Muscle Nerve* 44, 947–956. doi:10.1002/mus.22217

Lie, D. C., and Weis, J. (1998). GDNF expression is increased in denervated human skeletal muscle. *Neurosci. Lett.* 250, 87–90. doi:10.1016/S0304-3940(98)00434-0

Lin, L. F., Doherty, D. H., Lile, J. D., Bektesh, S., and Collins, F. (1993). GDNF: a glial cell line-derived neurotrophic factor for midbrain dopaminergic neurons. *Science* 260, 1130–1132. doi:10.1126/science.8493557

Lin, M. T., and Beal, M. F. (2006). Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature* 443, 787–795. doi:10.1038/nature05292

Lipsky, R. H., and Marini, A. M. (2007). Brain-derived neurotrophic factor in neuronal survival and behavior-related plasticity. *Ann. NY Acad. Sci* 1122, 130–143. doi:10.1196/annals.1403.009

Luff, A. R. (1998). Age-associated changes in the innervation of muscle fibers and changes in the mechanical properties of motor units. *Ann. N. Y. Acad. Sci.* 854, 92–101. doi:10.1111/j.1749-6632.1998.tb09895.x

Maggio, M., Ble, A., Ceda, G. P., and Metter, E. J. (2006). Decline in insulin-like growth factor-I levels across adult life span in two large population studies. *J. Gerontol. A Biol. Sci. Med. Sci.* 61, 182–183. doi:10.1093/gerona/61.2.182

Maggio, M., De Vita, F., Lauretani, F., Butto, V., Bondi, G., Cattabiani, C., et al. (2013). IGF-1, the cross road of the nutritional, inflammatory and hormonal pathways to frailty. *Nutrients* 5, 4184–4205. doi:10.3390/nu5104184

Manini, T. M., Hong, S. L., and Clark, B. C. (2013). Aging and muscle: a neuron's perspective. *Curr. Opin. Clin. Nutr. Metab. Care* 16, 21–26. doi:10.1097/MCO.0b013e32835b5880

Mayhew, M., Renganathan, M., and Delbono, O. (1998). Effectiveness of caloric restriction in preventing age-related changes in rat skeletal muscle. *Biochem. Biophys. Res. Commun.* 251, 95–99. doi:10.1006/bbrc.1998.9438

McCay, C. M., Crowell, M. F., and Maynard, L. A. (1935). The effect of retarded growth upon the length of life span and upon the ulti- mate body size. *J. Nutr.* 10, 63–79.

McCullough, M. J., Gyorkos, A. M., and Spitsbergen, J. M. (2013). Short-term exercise increases GDNF protein levels in the spinal cord of young and old rats. *Neuroscience* 240, 258–268. doi:10.1016/j.neuroscience.2013.02.063

McCullough, M. J., Peplinski, N. G., Kinnell, K. R., and Spitsbergen, J. M. (2011). Glial cell line-derived neurotrophic factor protein content in rat skeletal muscle is altered by increased physical activity in vivo and in vitro. *Neuroscience* 174, 234–244. doi:10.1016/j.neuroscience.2010.11.016

McKiernan, S. H., Bua, E., McGorray, J., and Aiken, J. (2004). Early-onset calorie restriction conserves fiber number in aging rat skeletal muscle. *FASEB J.* 18, 580–581.

Mercken, E. M., Carboneau, B. A., Krzysik-Walker, S. M., and de Cabo, R. (2012). Of mice and men: the benefits of caloric restriction, exercise, and mimetics. *Ageing Res. Rev.* 11, 390–398. doi:10.1016/j.arr.2011.11.005

Messi, M. L., and Delbono, O. (2003). Target-derived trophic effect on skeletal muscle innervation in senescent mice. *J. Neurosci.* 23, 1351–1359.

Morel, J., Rannou, F., Talarmin, H., Giroux-Metges, M. A., Pennec, J. P., Dorange, G., et al. (2010). Sodium channel Na(V)1.5 expression is enhanced in cultured adult rat skeletal muscle fibers. *J. Membr. Biol.* 235, 109–119. doi:10.1007/s00232-010-9262-5

Muller, F. L., Song, W., Jang, Y. C., Liu, Y., Sabia, M., Richardson, A., et al. (2007). Denervation-induced skeletal muscle atrophy is associated with increased mitochondrial ROS production. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 293, R1159–R1168. doi:10.1152/ajpregu.00767.2006

Mulligan, K. A., and Cheyette, B. N. R. (2012). Wnt signaling in vertebrate neural development and function. *J. Neuroimmune Pharmacol.* 7, 774–787. doi:10.1007/s11481-012-9404-x

Musaro, A., McCullagh, K., Paul, A., Houghton, L., Dobrowolny, G., Molinaro, M., et al. (2001). Localized IGF-1 transgene expression sustains hypertrophy and regeneration in senescent skeletal muscle. *Nat. Genet.* 27, 195–200. doi:10.1038/84839

Navarro, A., and Boveris, A. (2009). Brain mitochondrial dysfunction and oxidative damage in Parkinson's disease. *J. Bioenerg. Biomembr* 41, 517–521. doi:10.1007/s10863-009-9250-6

Nguyen, Q. T., Parsadanian, A. S., Snider, W. D., and Lichtman, J. W. (1998). Hyperinnervation of neuromuscular junctions caused by GDNF overexpression in muscle. *Science* 279, 1725–1729. doi:10.1126/science.279.5357.1725

Nishimune, H., Numata, T., Chen, J., Aoki, Y., Wang, Y., Starr, M. P., et al. (2012). Active zone protein Bassoon co-localizes with presynaptic calcium channel, modifies channel function, and recovers from aging related loss by exercise. *PLoS ONE* 7:e38029. doi:10.1371/journal.pone.0038029

Nishimune, H., Stanford, J. A., and Mori, Y. (2014). Role of exercise in maintaining the integrity of the neuromuscular junction. *Muscle & Nerve* 49, 315–324. doi:10.1002/mus.24095

Nordquist, J., Hoglund, A. S., Norman, H., Tang, X., Dworkin, B., and Larsson, L. (2007). Transcription factors in muscle atrophy caused by blocked neuromuscular transmission and muscle unloading in rats. *Mol. Med.* 13, 461–470. doi:10.2119/2006-00066

Okerlund, N. D., and Cheyette, B. N. (2011). Synaptic Wnt signaling; a contributor to major psychiatric disorders? *J. Neurodev. Disord.* 3, 162–174. doi:10.1007/s11689-011-9083-6

Payne, A. M., Zheng, Z., Messi, M. L., Milligan, C. E., Gonzalez, E., and Delbono, O. (2006). Motor neurone targeting of IGF-1 prevents specific force decline in ageing mouse muscle. *J. Physiol.* 570(Pt 2), 283–294. doi:10.1113/jphysiol.2005.100032

Peng, H. B., Yang, J. F., Dai, Z., Lee, C. W., Hung, H. W., Feng, Z. H., et al. (2003). Differential effects of neurotrophins and Schwann cell-derived signals on neuronal survival/growth and synaptogenesis. *J. Neurosci.* 23, 5050–5060.

Peterson, C. M., Johannsen, D. L., and Ravussin, E. (2012). Skeletal muscle mitochondria and aging: a review. *J. Aging Res.* 2012, 194821. doi:10.1155/2012/194821

Punga, A. R., and Ruegg, M. A. (2012). Signaling and aging at the neuromuscular synapse: lessons learnt from neuromuscular diseases. *Curr. Opin. Pharmacol.* 12, 340–346. doi:10.016/j.coph.2012.02.002

Rangaraju, S., Hankins, D., Madorsky, I., Madorsky, E., Lee, W. H., Carter, C. S., et al. (2009). Molecular architecture of myelinated peripheral nerves is supported by calorie restriction with aging. *Aging Cell* 8, 178–191. doi:10.1111/j.1474-9726.2009.00460.x

Rangaraju, S., and Notterpek, L. (2011). Autophagy aids membrane expansion by neuropathic Schwann cells. *Autophagy* 7, 238–239. doi:10.4161/auto.7.2.14278

Rannou, F., Pennec, J.-P., Morel, J., Gueret, G., Leschiera, R., Droguet, M., et al. (2011). Na v1.4 and Na v1.5 are modulated differently during muscle immobilization and contractile phenotype conversion. *J. Appl. Physiol.* 111, 495–507. doi:10.1152/japplphysiol.01136.2010

Reid, K. F., Doros, G., Clark, D. J., Patten, C., Carabello, R. J., Cloutier, G. J., et al. (2012). Muscle power failure in mobility-limited older adults: preserved single fiber function despite lower whole muscle size, quality and rate of neuromuscular activation. *Eur J. Appl. Physiol.* 112, 2289–2301. doi:10.1007/s00421-011-2200-0

Reid, K. F., Pasha, E., Doros, G., Clark, D. J., Patten, C., Phillips, E. M., et al. (2014). Longitudinal decline of lower extremity muscle power in healthy and mobility-limited older adults: influence of muscle mass, strength, composition, neuromuscular activation and single fiber contractile properties. *Eur. J. Appl. Physiol.* 114, 29–39. doi:10.1007/s00421-013-2728-2

Rocha, M. C., Pousinha, P. A., Correia, A. M., Sebastiao, A. M., and Ribeiro, J. A. (2013). Early changes of neuromuscular transmission in the SOD1(G93A) mice model of ALS start long before motor symptoms onset. *PLoS ONE* 8:e73846. doi:10.1371/journal.pone.0073846

Rosenheimer, J. L., and Smith, D. O. (1985). Differential changes in the end-plate architecture of functionally diverse muscles during aging. *J. Neurophysiol.* 53, 1567–1581.

Rosso, A. L., Studenski, S. A., Chen, W. G., Aizenstein, H. J., Alexander, N. B., Bennett, D. A., et al. (2013). Aging, the central nervous system, and mobility. *J Gerontol. A. Biol. Sci. Med. Sci.* 68, 1379–1386. doi:10.1093/gerona/glt089

Roubenoff, R. (2000). Sarcopenia and its implications for the elderly. *Eur. J. Clin. Nutr.* 54(Suppl. 3), S40–S47. doi:10.1038/sj.ejcn.1601024

Rowan, S. L., Rygiel, K., Purves-Smith, F. M., Solbak, N. M., Turnbull, D. M., and Hepple, R. T. (2012). Denervation causes fiber atrophy and myosin heavy chain co-expression in senescent skeletal muscle. *PLoS ONE* 7:e29082. doi:10.1371/journal.pone.0029082

Rudolf, R., Bogomolovas, J., Strack, S., Choi, K. R., Khan, M. M., Wagner, A., et al. (2013). Regulation of nicotinic acetylcholine receptor turnover by MuRF1 connects muscle activity to endo/lysosomal and atrophy pathways. *Age (Dordr)* 35, 1663–1674. doi:10.1007/s11357-012-9468-9

Russ, D. W., and Lanza, I. R. (2011). The impact of old age on skeletal muscle energetics: supply and demand. *Curr. Aging Sci.* 4, 234–247. doi:10.2174/1874609811104030234

Saheb-Al-Zamani, M., Yan, Y., Farber, S. J., Hunter, D. A., Newton, P., Wood, M. D., et al. (2013). Limited regeneration in long acellular nerve allografts is associated with increased Schwann cell senescence. *Exp. Neurol.* 247, 165–177. doi:10.1016/j.expneurol.2013.04.011

Saini, A., Faulkner, S., Al-Shanti, N., and Stewart, C. (2009). Powerful signals for weak muscles. *Ageing Res. Rev.* 8, 251–267. doi:10.1016/j.arr.2009.02.001

Saini, A., Nasser, A. S., and Stewart, C. E. (2007). Waste management – cytokines, growth factors and cachexia. *Cytokine Growth Factor Rev.* 17, 475–486. doi:10.1016/j.cytogfr.2006.09.006

Sakellariou, G. K., Davis, C. S., Shi, Y., Ivannikov, M. V., Zhang, Y., Vasilaki, A., et al. (2014). Neuron-specific expression of CuZnSOD prevents the loss of muscle mass and function that occurs in homozygous CuZnSOD-knockout mice. *FASEB J.* 28, 1666–1681. doi:10.1096/fj.13-240390

Sakellariou, G. K., Pye, D., Vasilaki, A., Zibrik, L., Palomero, J., Kabayo, T., et al. (2011). Role of superoxide-nitric oxide interactions in the accelerated age-related loss of muscle mass in mice lacking Cu,Zn superoxide dismutase. *Aging Cell* 10, 749–760. doi:10.1111/j.1474-9726.2011.00709.x

Schaefer, A. M., Sanes, J. R., and Lichtman, J. W. (2005). A compensatory subpopulation of motor neurons in a mouse model of amyotrophic lateral sclerosis. *J. Comparat. Neurol.* 490, 209–219. doi:10.1002/cne.20620

Seeburger, J. L., and Springer, J. E. (1993). Experimental rationale for the therapeutic use of neurotrophins in amyotrophic lateral sclerosis. *Exp. Neurol.* 124, 64–72. doi:10.1006/exnr.1993.1176

Shear, T. D., and Martyn, J. A. J. (2009). Physiology and biology of neuromuscular transmission in health and disease. *J. Crit. Care* 24, 5–10. doi:10.1016/j.jcrc.2008.08.002

Smith, D. O., and Rosenheimer, J. L. (1982). Decreased sprouting and degeneration of nerve terminals of active muscles in aged rats. *J. Neurophysiol.* 48, 100–109.

Snow, L. M., McLoon, L. K., and Thompson, L. V. (2005). Adult and developmental myosin heavy chain isoforms in soleus muscle of aging Fischer Brown Norway rat. *Anat. Rec. A. Discov. Mol. Cell. Evol. Biol.* 286, 866–873. doi:10.1002/ar.a.20218

Springer, J. E., Seeburger, J. L., He, J., Gabrea, A., Blankenhorn, E. P., and Bergman, L. W. (1995). cDNA sequence and differential mRNA regulation of two forms of glial cell line-derived neurotrophic factor in Schwann cells and rat skeletal muscle. *Exp. Neurol.* 131, 47–52. doi:10.1016/0014-4886(95)90006-3

Stamatakou, E., and Salinas, P. C. (2013). Postsynaptic assembly: a role for Wnt signaling. *Dev. Neurobiol.* doi:10.1002/dneu.22138

Suetta, C., Frandsen, U., Jensen, L., Jensen, M. M., Jespersen, J. G., Hvid, L. G., et al. (2012). Aging affects the transcriptional regulation of human skeletal muscle disuse atrophy. *PLoS ONE* 7:e51238. doi:10.1371/journal.pone.0051238

Tevald, M. A., Foulis, S. A., Lanza, I. R., and Kent-Braun, J. A. (2010). Lower energy cost of skeletal muscle contractions in older humans. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 298, R729–R739. doi:10.1152/ajpregu.00713.2009

Valdez, G., Tapia, J. C., Kang, H., Clemenson, G. D., Gage, F. H., Lichtman, J. W., et al. (2010). Attenuation of age-related changes in mouse neuromuscular synapses by caloric restriction and exercise. *Proc. Natl. Acad. Sci.* U S A 107, 14863–14868. doi:10.1073/pnas.1002220107

Vergani, L., Di Giulio, A. M., Losa, M., Rossoni, G., Muller, E. E., and Gorio, A. (1998). Systemic administration of insulin-like growth factor decreases motor neuron cell death and promotes muscle reinnervation. *J. Neurosci. Res.* 54, 840–847. doi:10.1002/(SICI)1097-4547(19981215)54:6<840::AID-JNR12>3.3.CO;2-C

Verge, V. M., Gratto, K. A., Karchewski, L. A., and Richardson, P. M. (1996). Neurotrophins and nerve injury in the adult. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 351, doi:10.1098/rstb.1996.0038

Wang, Q., Hebert, S. L., Rich, M. M., and Kraner, S. D. (2011). Loss of synaptic vesicles from neuromuscular junctions in aged MRF4-null mice. *Neuroreport* 22, 185–189. doi:10.1097/WNR.0b013e328344493c

Wang, X., Engisch, K. L., Li, Y., Pinter, M. J., Cope, T. C., and Rich, M. M. (2004). Decreased synaptic activity shifts the calcium dependence of release at the mammalian neuromuscular junction in vivo. *J. Neurosci.* 24, 10687–10692. doi:10.1523/JNEUROSCI.2755-04.2004

Wang, Z. M., Zheng, Z., Messi, M. L., and Delbono, O. (2005). Extension and magnitude of denervation in skeletal muscle from ageing mice. *J. Physiol.* 565(Pt 3), 757–764. doi:10.1113/jphysiol.2005.087601

Weis, J., Kaussen, M., Calvo, S., and Buonanno, A. (2000). Denervation induces a rapid nuclear accumulation of MRF4 in mature myofibers. *Dev. Dyn.* 218, 438–451. doi:10.1002/1097-0177(200007)

Wenz, T., Rossi, S. G., Rotundo, R. L., Spiegelman, B. M., and Moraes, C. T. (2009). Increased muscle PGC-1alpha expression protects from sarcopenia and metabolic disease during aging. *Proc. Natl. Acad. Sci.* U S A. 106, 20405–20410. doi:10.1073/pnas.0911570106

Wilson, M. H., and Deschenes, M. R. (2005). The neuromuscular junction: anatomical features and adaptations to various forms of increased, or decreased neuromuscular activity. *Int. J. Neurosci.* 115, 803–828. doi:10.1080/00207450590882172

Witzemann, V., Chevessier, F., Pacifici, P. G., and Yampolsky, P. (2013). The neuromuscular junction: selective remodeling of synaptic regulators at the nerve/muscle interface. *Mech. Dev.* 130, 402–411. doi:10.1016/j.mod.2012.09.004

Yampolsky, P., Pacifici, P. G., and Witzemann, V. (2010). Differential muscle-driven synaptic remodeling in the neuromuscular junction after denervation. *Eur. J. Neurosci.* 31, 646–658. doi:10.1111/j.1460-9568.2010.07096.x

Young, K. A., and Caldwell, J. H. (2005). Modulation of skeletal and cardiac voltage-gated sodium channels by calmodulin. *J. Physiol.* 565(Pt 2), 349–370. doi:10.1113/jphysiol.2004.081422

Yuan, Q., Wu, W., So, K. F., Cheung, A. L., Prevette, D. M., and Oppenheim, R. W. (2000). Effects of neurotrophic factors on motoneuron survival following axonal injury in newborn rats. *Neuroreport* 11, 2237–2241. doi:10.1097/00001756-200007140-00035

Zhang, W., Behringer, R. R., and Olson, E. N. (1995). Inactivation of the myogenic bHLH gene MRF4 results in up-regulation of myogenin and rib anomalies. *Genes Dev.* 9, 1388–1399. doi:10.1101/gad.9.11.1388

Zheng, Z., Wang, Z. M., and Delbono, O. (2002). Insulin-like growth factor-1 increases skeletal muscle dihydropyridine receptor alpha1s transcriptional activity by acting on the camp-response element-binding protein element of the promoter region. *J. Biol. Chem.* 277, 50535–50542. doi:10.1074/jbc.M210526200

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

Received: 27 May 2014; accepted: 25 July 2014; published online: 11 August 2014.
Citation: Gonzalez-Freire M, de Cabo R, Studenski SA and Ferrucci L (2014) The neuromuscular junction: aging at the crossroad between nerves and muscle. Front. Aging Neurosci. ***6****:208. doi: 10.3389/fnagi.2014.00208*
This article was submitted to the journal Frontiers in Aging Neuroscience.

frontiers
in Aging Neuroscience

ORIGINAL RESEARCH
published: 23 June 2015
doi: 10.3389/fnagi.2015.00097

Elderly use proprioception rather than visual and vestibular cues for postural motor control

*Isabella Katharina Wiesmeier, Daniela Dalin and Christoph Maurer**

Klinik für Neurologie und Neurophysiologie, Universität Freiburg, Freiburg, Germany

Multiple factors have been proposed to contribute to the deficits of postural control in the elderly. They were summarized as sensory, motor, and higher-level adaptation deficits. Using a model-based approach, we aimed to identify which of these deficits mainly determine age-related changes in postural control. We analyzed postural control of 20 healthy elderly people with a mean age of 74 years. The findings were compared to data from 19 healthy young volunteers (mean age 28 years) and 16 healthy middle-aged volunteers (mean age 48 years). Postural control was characterized by spontaneous sway measures and measures of perturbed stance. Perturbations were induced by pseudorandom anterior–posterior tilts of the body support surface. We found that spontaneous sway amplitude and velocity were significantly larger, and sway frequencies were higher in elderly compared to young people. Body excursions as a function of tilt stimuli were clearly different in elderly compared to young people. Based on simple feedback model simulations, we found that elderly favor proprioceptive over visual and vestibular cues, other than younger subjects do. Moreover, we identified an increase in overall time delay challenging the feedback systems stability, and a decline in the amplitude of the motor feedback, probably representing weakness of the motor system. In general, these parameter differences between young and old may result from both deficits and compensation strategies in the elderly. Our model-based findings correlate well with deficits measured with clinical balance scores, which are widely used in clinical practice.

Keywords: elderly, postural control, proprioception, vestibular, model

Edited by:
S. Lee Hong,
Ohio University, USA

Reviewed by:
Breanna Erin Studenka,
Utah State University, USA
Kristina Anne Neely,
The Pennsylvania State University, USA
Leslie Marion Decker,
Université de Caen Basse-Normandie, France

****Correspondence:***
Christoph Maurer,
Klinik für Neurologie und Neurophysiologie, Universität Freiburg, Breisacherstr. 64, Freiburg 79106, Germany
christoph.maurer@uniklinik-freiburg.de

Received: *18 February 2015*
Accepted: *07 May 2015*
Published: *23 June 2015*

Citation:
Wiesmeier IK, Dalin D and Maurer C (2015) Elderly use proprioception rather than visual and vestibular cues for postural motor control. Front. Aging Neurosci. 7:97. doi: 10.3389/fnagi.2015.00097

Introduction

Postural control in elderly people is impaired by numerous factors [for an overview, see, e.g., Shumway-Cook and Woollacott (2001) and Iosa et al. (2014)]. Changes in sensory systems include a reduced joint position sense at the ankle (Horak et al., 1989; Goble et al., 2009), paralleled by a higher perception threshold for vibration (Tang and Woollacott, 1996; Hilz et al., 1998; Lin et al., 2005; Shaffer and Harrison, 2007). Moreover, visual function (visual acuity, contour and depth perception, contrast sensitivity, peripheral vision) is reduced, partly due to structural changes of the eye. In addition, a decrease of vestibular function has been described (Bergström, 1973; Rosenhall, 1973; Merchant et al., 2000; Park et al., 2001; Rauch et al., 2001; Shumway-Cook and Woollacott, 2001; Nag and Wadhwa, 2012; Grossniklaus et al., 2013).

Impairments of the motor system in the elderly have numerously been reported [e.g., Doherty (2003), Macaluso and De Vito (2004), and Reeves et al. (2006)]. For example, a 40% reduction of the lower body muscle strength was found when compared to young healthy adults (Shumway-Cook and Woollacott, 2001). During balance corrections, elderly people display an altered muscle response organization (Shumway-Cook and Woollacott, 2001; Tsai et al., 2014) and more frequent coactivations of antagonist muscles (Shumway-Cook and Woollacott, 2001; Macaluso and De Vito, 2004; Klass et al., 2007; Papegaaij et al., 2014).

Some authors proposed deficits in higher-level adaptive systems [e.g., Shumway-Cook and Woollacott (2001)]. They suggested that elderly people's ability to adapt to external perturbations is diminished (Horak et al., 1989; Peterka and Black, 1990; Mansfield and Maki, 2009). Elderly people react with longer onset latencies to external perturbations than young adults do (Woollacott et al., 1988; Horak et al., 1989; Woollacott and Shumway-Cook, 1990; Tsai et al., 2014). In addition, elderly people seem to have difficulties in sensory reweighting (Horak et al., 1989; Teasdale and Simoneau, 2001; Eikema et al., 2012, 2014). The term "sensory reweighting" was established by Nashner et al. (1982) to describe a process of scaling the relative importance of sensory cues (visual, vestibular, and proprioceptive) for motor control (Nashner et al., 1982; Jeka et al., 2006). However, the sensory weighting process itself seems to be unimpaired in elderly people (Allison et al., 2006; Jeka et al., 2006), indicating that differences in sensory weights between elderly and young people are related to different sensory preferences.

Measures of human postural control are usually segregated into spontaneous sway measures and measures of motor behavior induced by external perturbations. Age-related differences in spontaneous sway mainly concern increases in mean velocity (MV) and mean frequency (MF) (Maki et al., 1990; Hytönen et al., 1993; Baloh et al., 1994; Collins et al., 1995; Prieto et al., 1996; Maurer and Peterka, 2005; Qu et al., 2009).

During perturbed stance, somatosensory cues affect postural control in young people differently than in elderly people [e.g., Peterka and Black (1990), Speers et al. (2002), Fransson et al. (2004), Ghulyan et al. (2005), and Maitre et al. (2013)]. In general, stance of elderly people is reported to be less stable with absent or altered proprioceptive, vestibular, and visual information (Peterka and Black, 1990; Whipple et al., 1993; Speers et al., 2002; Rosengren et al., 2007; Liaw et al., 2009; Pierchała et al., 2012; Maitre et al., 2013; Eikema et al., 2014), leading to larger body excursions. Some authors evaluated the relationship between the perturbation and the induced body motion in terms of transfer functions [see Materials and Methods, see also Nashner and McCollum (1985), Ishida et al. (1997), Van der Kooij et al. (2001), Peterka (2002), Maurer and Peterka (2005), Masani et al. (2006), Maurer et al. (2006a), Vette et al. (2010), Davidson et al. (2011), Nishihori et al. (2012), and Van der Kooij and Peterka (2011)]. Transfer functions are frequently interpreted using a model-based approach. These models usually involve inverted pendulum bodies, a neural controller including a proportional (stiffness of the system) and a derivative feedback gain (damping of the system), and a feedback time delay. The proportional gain is proportional to the sensory error signal and the derivative gain is proportional to the time derivative of the sensory error signal. Both factors are added up as a motor output to provide corrective ankle torque, thereby stabilizing the inverted pendulum and reducing oscillations (Peterka, 2002; Vette et al., 2010). The feedback time delay represents the lumped time delays of sensory, central, and motor transduction (Peterka, 2002). The sensory weighting mechanism of the model scales the gains of the sensory cues (proprioceptive, vestibular, and visual) in terms of relative contributions to the overall feedback gain (Maurer et al., 2006a; Van der Kooij and Peterka, 2011; Engelhart et al., 2014).

Recently, some authors applied the model-based approach to postural control data of elderly people (Cenciarini et al., 2009, 2010; Davidson et al., 2011; Nishihori et al., 2012; Maurer and Peterka, 2005). During quiet stance, elderly people seem to have an increased proportional gain of the sensorimotor control system (Maurer and Peterka, 2005; Nishihori et al., 2012). During external perturbations, an increased derivative gain of the system has been reported (Cenciarini et al., 2009, 2010; Davidson et al., 2011), whereas reports of the system's proportional gain were controversial (Cenciarini et al., 2009, 2010; Davidson et al., 2011), depending, for example, on the direction of sway.

In the current study, we aimed to find out whether we are able to detect sensory, motor, and higher-level adaptation deficits mentioned above in postural control behavior of the elderly. In addition, we aimed to identify which of these contributors most significantly influence postural control in the elderly. For that, we assessed both, spontaneous sway parameters and applied external perturbations in young, middle-aged, and elderly people. The subjects' reactions to anterior–posterior platform tilts were analyzed at 11 frequencies with eyes closed or open, using different amplitudes, with the purpose to simultaneously identify the major components of the sensorimotor control system and their modifications as a function of age. We hypothesized that degradations of sensory, motor, and higher-level adaptation deficits in elderly could be extracted from postural control behavior. As our model-based approach is highly sensitive to changes in the sensory-motor system, it might be valuable in future for differentiating between age-related and pathology-related impairments of postural control, and for evaluating therapeutic interventions that ameliorate postural control in elderly.

Materials and Methods

Subjects were tested by recording spontaneous sway as well as motor reactions to platform tilts (perturbed stance). In addition, elderly subjects were tested using relevant standardized clinical tests.

Subjects

In this study, we measured postural control of elderly people (60–80 years group) and compared their data with data from middle-aged (40–59 years group) and young (20–39 years group) people.

The group of elderly subjects consisted of 20 participants with a mean age of 74 ± 3.4 years (Mean ± SD, 10 female, 10 male). We excluded elderly people suffering from any disease that may interact with postural control. For that, each subject was carefully examined by a senior consultant neurologist. In addition, we specifically tested for vestibular function using Frenzel goggles on a turning chair. We thereby quantified the function of the vestibular–ocular reflex. Moreover, we evaluated proprioceptive function, which is related to deep sensibility, by testing for position sense and by quantifying vibration sense using a vibrating tuning fork. Further exclusion criteria included any acute or chronic disease that may influence the general condition of health.

Elderly subjects were also assessed using the timed up and go test (TUG, Enkelaar et al., 2013) and the functional reach test (FRT, Enkelaar et al., 2013). Our emphasis was to monitor elderly people's balance function with widely accepted clinical tests. Furthermore, we correlated those relevant clinical tests with our postural control measurements to evaluate whether functional impairments shown by one of our parameters may be linked to abnormalities in clinical tests.

For comparison, we analyzed data of 16 healthy volunteers (middle-aged group) between 36 and 58 years with a mean age of 48.2 ± 5.3 years (9 female, 7 male) who had been measured in our laboratory during the previous years. In addition, data of 19 healthy volunteers (20–39 years group) between 22 and 34 years with a mean age of 27.6 ± 3.7 years (10 female, 9 male) were acquired.

Procedures

Spontaneous sway and perturbed stance were measured on a custom-built motion platform (Cnyrim et al., 2009; **Figure 1**). For that, participants were told to stand upright in a relaxed position on the platform, wearing their normal shoes. Stance width was predetermined within a marked area (maximum 30 cm). For safety reasons, participants held two ropes hanging from the ceiling in a way they were not able to attain any orientation cues (Cnyrim et al., 2009). However, no subject fell, probably due to the small stimulus amplitudes. Spontaneous sway was measured on the non-moving platform with eyes open and with eyes closed. Each trial lasted 1 min. Between each trial, a short break was taken according to the participants needs.

We measured center-of-pressure (COP) sway paths and 3-D angular positions of the body in order to calculate spontaneous sway measures (parameters) and measures of perturbed stance. The COP sway path was detected with the help of a force transducing platform (Kistler platform type 9286, Winterthur, Switzerland, **Figure 1**). 3-D angular positions (Angular excursions) of the body (hip-to-ankle, shoulder-to-hip) and the platform in space were measured using an optoelectronic motion-measuring device with markers attached to shoulder, hip, and a rigid bar solely fixed to the platform (Optotrak 3020, Waterloo, ON, Canada). Each marker consisted of three light-emitting diodes fixed to a rigid triangle. 3-D angular positions of the triangles were used to calculate marker positions (Maurer et al., 2006b). Optotrak® and Kistler® output signals as well as the stimulus signals were transferred online to a computer system (IBM compatible Pentium®) via an analog-digital converter at a sampling rate of 100 Hz. We recorded all data with software programed in LabView® (National Instruments, Austin, TX, USA). Center of mass (COM) height above the ankle joints was calculated according to tables from Winter (1995) using the measured heights of hip and shoulder markers. A detailed description of the experimental setup has been published previously (Maurer et al. 2003, 2006a, 2006b; Cnyrim et al., 2009).

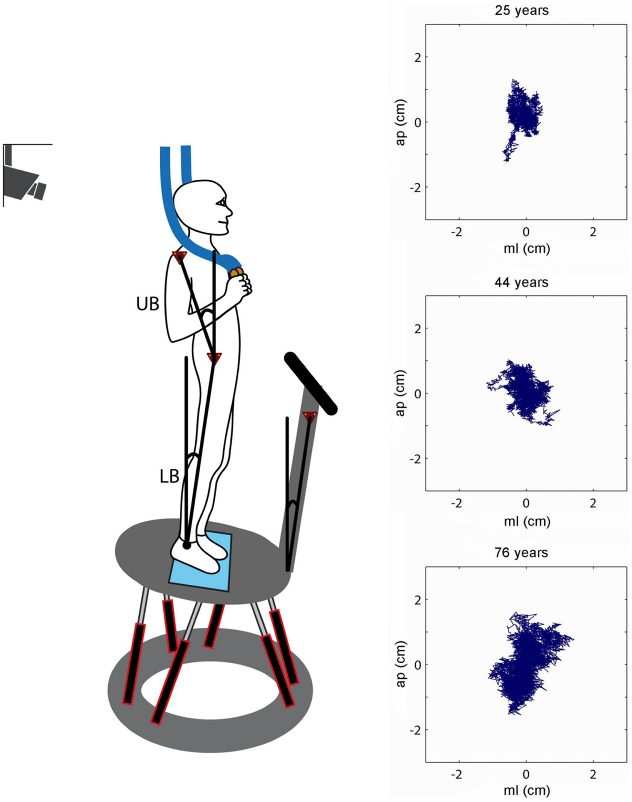


FIGURE 1 | Experimental setup. Scheme of a participant who stands on the platform in an upright position. The six linear motors rotated the platform in the sagittal plane about the axis of the ankle joints. Angular excursions of the upper body (UB) and lower body (LB) and the platform in space were measured using an optoelectronic motion-measuring device with markers attached to shoulder, hip, and platform. Sway paths of a young (25 years), middle-aged (44 years), and elderly person (76 years) are shown on the right (ap, anterior–posterior; ml, medio-lateral).

Perturbed stance was measured on the moving platform with eyes open and with eyes closed (**Figure 2**). The rotational tilt is characterized by a platform rotation in the sagittal plane with the tilt axis passing through the participant's ankle joints (Maurer et al., 2006a,b; Cnyrim et al., 2009). Platform rotations were designed as pseudorandom stimuli (PRTS, pseudorandom ternary sequence) with 2 peak angular displacements (0.5° and 1°) at 11 frequencies (0.05, 0.15, 0.3, 0.4, 0.55, 0.7, 0.9, 1.1, 1.35, 1.75, and 2.2 Hz).

Data Analysis

Data analysis was performed off-line with custom-made software programed in MATLAB® (The MathWorks Inc., Natick, MA, USA; Maurer et al., 2003, 2006b; Cnyrim et al., 2009). From the lower and upper body excursions and COP over time in anterior–posterior (and medio-lateral directions), we calculated root mean square (RMS) around the mean COP position

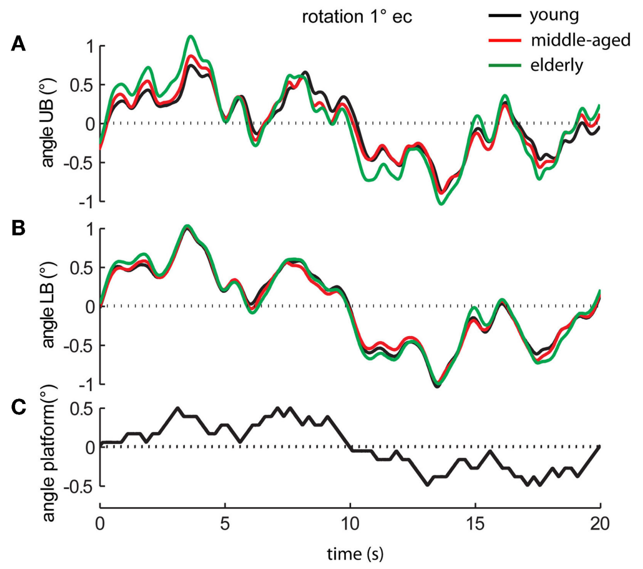


FIGURE 2 | Platform movements and motor reactions of the human body over time. Motor reactions of the three age groups' **(A)** upper body (UB) and **(B)** lower body (LB) at 1° stimulus amplitude with eyes closed (ec) and **(C)** platform movement (black bottom line).

(Prieto et al., 1996; Maurer et al., 2003).

$$\mathrm{RMS} = \mathrm{SD} = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\left(x_{\mathrm{COP}}(i)\right)^{2}}$$

Mean velocity is the average of the absolute COP velocity (Maurer and Peterka, 2005). It was calculated by differentiating the corresponding time series.

$$\mathrm{MV} = \frac{1}{n-1}\sum_{\mathrm{i}=1}^{\mathrm{n}-1}\left|\dot{x}_{\mathrm{COP}}(i)\right|$$

Mean frequency was computed as the ratio of MV and mean distance (MD).

$$\mathrm{MFREQ} = \frac{\mathrm{MV}}{4\cdot\sqrt{2}\cdot\mathrm{MD}}$$

Further details on spontaneous sway measures can be found in Maurer and Peterka (2005).

Transfer functions from stimulus–response data were calculated by a discrete Fourier transform (Peterka, 2002; Cnyrim et al., 2009). Fourier coefficients of stimulus and response time series are used to determine GAIN and PHASE with respect to stimulus frequencies (Maurer et al., 2006a). GAIN (response sensitivity) shows the relationship between the platform angle (stimulus amplitude) and the lower body or upper body response amplitude (Peterka, 2002; Maurer et al., 2006a; Cnyrim et al., 2009). PHASE is the relative delay between the stimulus and the reaction of the body. The transfer functions were used as the experimental data basis for model simulations using a predefined model of upright stance (see **Figure 3**).

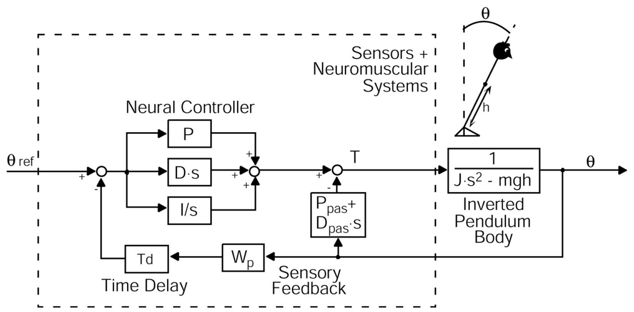


FIGURE 3 | Modified postural control model describing perturbed stance. The model consists of a body represented by an inverted pendulum with the mass concentrated at the center of mass (COM) of the body and the sensors and neuromuscular systems including a Neural Controller. θ, body sway angle; h, height of the COM above the ankle joints; θ ref, external stimulus; P, proportional gain (stiffness factor), D, derivative gain (damping factor), I, integral gain of the neural controller; Ppas, passive stiffness factor; Dpas, passive damping factor; Wp, proprioceptive sensory weight; Td, feedback time delay; T, control torque; J, moment of inertia of the body; mgh, body mass × gravitational constant × height of the COM from the ankle joint; s, Laplace transform variable.

Statistics were performed using Microsoft Excel and statistic programs (JMP® and Statview by SAS Institute Inc., Cary, NC, USA). Statistical significance was tested by a two-level analysis of variance (ANOVA) unless stated otherwise. The between-subjects factor was age, the within-subjects factors were visual condition, sway direction, stimulus amplitude, stimulus frequency, and body segment (hip, shoulder). The level of statistical significance was set at $p = 0.05$. For the elderly group, relationships between clinical test parameters and parameters obtained from platform experiments were analyzed using a Pearson Correlation [see Maurer and Peterka (2005)]. We created a matrix of correlation coefficients, which depicts the strength of linear relationships between each pair of parameters.

The study was performed according to the ethical standards of the Declaration of Helsinki. It was approved by the ethics committee of the University of Freiburg. All participants gave their written informed consent prior to study participation.

Model Simulations

We used a specific modification of an established postural control model (Van der Kooij et al., 2001; Mergner et al., 2002, 2003; Peterka, 2002; Maurer et al., 2004, 2006a; Cnyrim et al., 2009; Engelhart et al., 2014) to extract relevant parameters of postural control. This model includes a negative feedback loop that relates body excursion detected by visual, vestibular, and proprioceptive sensors to a corrective torque via a neural controller with proportional [P], derivative [D], and integral [I] contributions (PDI-controller, **Figure 3**). Neural controller gains are, in part, determined by mass and height of the COM of the individual subject [see Peterka (2002) and Cenciarini et al. (2010)]. Because our elderly group displayed lower masses and heights, we had to correct neural controller gains for this effect. That is why we give numbers for [P/mgh], [D/mgh], and [I/mgh], where (mgh) represents the gravitational pull (body mass) × (gravitational constant) × (height of COM from the ankle joint). [P/mgh] and [D/mgh] represent the stiffness and damping of our model. The proportional gain [P/mgh], the derivative gain [D/mgh], and the integral gain [I/mgh] simulate the regulatory activity of the central nervous system to perturbations of stance (Nishihori et al., 2012).

Moreover, the model contains a lumped time delay [Td], which represents the time interval between the stimulus and the motor reaction. In addition, the model includes a sensory weighting mechanism [Wp], which represents the coordinate frame of the body excursion (visual and vestibular coordinates vs. platform coordinates). [Wp] describes the contribution of proprioception to the sensory feedback (Peterka, 2002). A decrease in [Wp] signifies that people tend to rely less on proprioception and more on vestibular and/or visual feedback. The biomechanics part represents the passive elasticity [Ppas] and passive damping factor [Dpas] of the muscles and tendons (**Figure 3**). With the help of an optimization procedure (fmincon/Matlab, Mathworks), we fit the model-derived transfer functions to the experimental transfer functions (GAIN and PHASE values) under different stimulus amplitudes and visual conditions. Subsequently, the set of model parameters representing the optimal fit were read out.

Results

Spontaneous Sway

The RMS of the elderly group [0.56 ± 0.011 cm, (Mean ± Standard Error)] was significantly larger than the RMS of the middle-aged (0.452 ± 0.011 cm) and young group (0.447 ± 0.011 cm, $F = 22.98$, $p < 0.0001$, see **Figure 4A** for the COP-derived measures). Across all age groups, RMS was larger in the anterior–posterior (a–p) direction (0.60 ± 0.01 cm) than in the medio-lateral (m–l) direction (0.38 ± 0.01 cm; $F = 187.5$, $p < 0.0001$), and significantly larger with eyes closed (ec, 0.52 ± 0.01 cm) than with eyes open (eo, 0.45 ± 0.01 cm; $F = 19.3$, $p < 0.0001$). In general, RMS of the shoulder (0.55 ± 0.011 cm) was significantly larger than RMS of the hip (0.42 ± 0.011 cm, $F = 66.12$, $p < 0.0001$). There were no significant interactions between age group and sway direction ($F = 0.97$, $p = 0.38$), visual condition ($F = 1.38$, $p = 0.25$), and body segments ($F = 1.52$, $p = 0.22$).

As with RMS, MV of the elderly group was significantly higher (0.7 ± 0.018 cm/s) than MV of the middle-aged (0.46 ± 0.02 cm/s) and young group (0.41 ± 0.018 cm/s, $F = 66.8$, $p < 0.0001$, see **Figure 4B** for the COP-derived measures). Across all age groups, MV was larger in the a–p direction (0.65 ± 0.015 cm/s) than in the m-l direction (0.4 cm/s; $F = 122.7$, $p < 0.0001$), and significantly larger with eyes closed (0.6 ± 0.015 cm/s) than with eyes open (0.45 ± 0.015 cm/s; $F = 38.7$, $p < 0.0001$). In addition, across all age groups, MV of the shoulder was significantly larger (0.4 ± 0.019 cm/s) than MV of the hip (0.3 ± 0.019 cm/s, $F = 47.5$, $p < 0.0001$). Age group and sway direction significantly interacted, representing the fact that the MV difference between age groups was much larger in the a–p than in the m-l direction ($F = 4.2$, $p = 0.0153$). Furthermore, there were no significant interactions between age group and visual condition ($F = 1.93$, $p = 0.146$), or between age group and body segments ($F = 1.3$, $p = 0.285$).

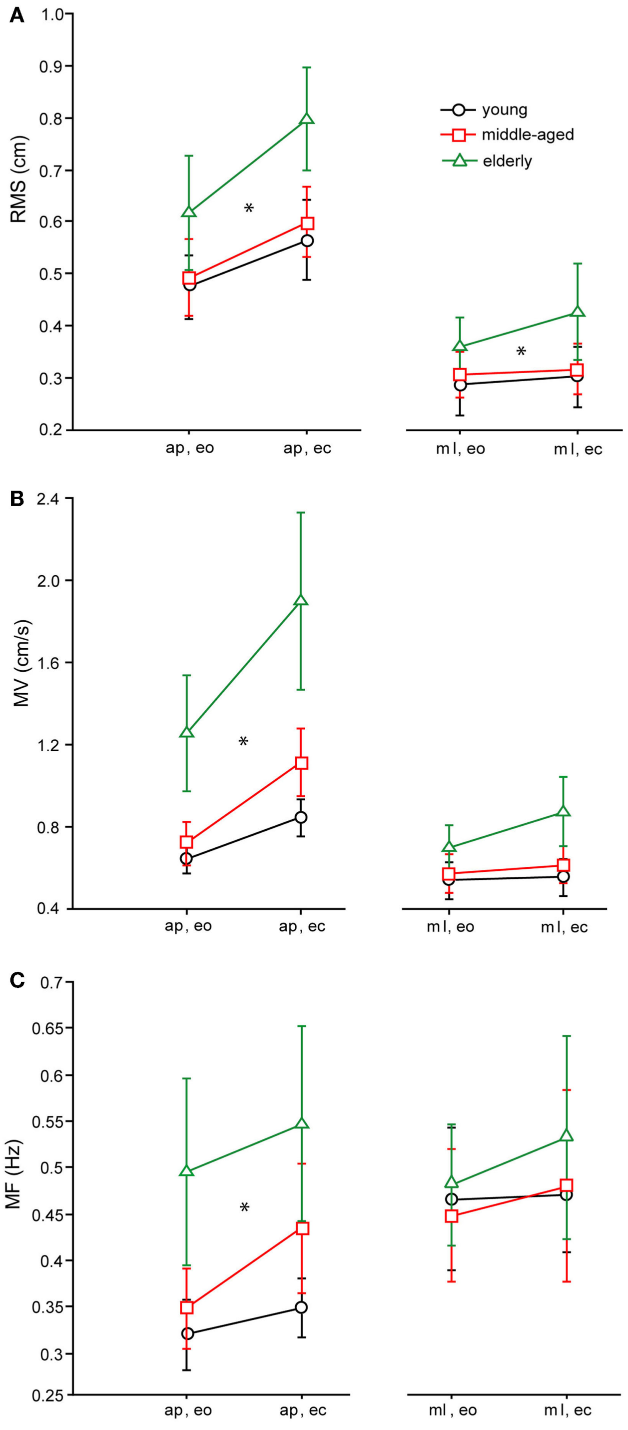


FIGURE 4 | Spontaneous sway parameters derived from COP traces. **(A)** Root mean square (RMS) of the three age groups, **(B)** mean velocity (MV) of the THREE age groups, **(C)** mean frequency (MF) of the three age groups. a–p, anterior–posterior; ml, medio-lateral; eo, eyes open; ec, eyes closed.

Effects on MF were similar to the effects on MV (see **Figure 4C** for the COP-derived measures). The MF of the elderly group was significantly higher (0.3 ± 0.007 Hz) than the MF of the middle-aged (0.25 ± 0.007 Hz) and the young group (0.24 ± 0.007 Hz, $F = 16.97$, $p < 0.0001$). Across all age groups, MF was larger in the m-l direction (0.28 ± 0.006 Hz) than in the a–p direction (0.25 ± 0.006 Hz, $F = 3.4$, $p = 0.035$), and significantly larger with eyes closed (0.28 ± 0.006 Hz) than with eyes open (0.25 Hz; $F = 9.18$, $p = 0.003$). In general, MF of hip (0.17 ± 0.007 Hz) and shoulder (0.17 ± 0.007 Hz) were nearly equal, which was not statistically significant ($F = 0.2$, $p = 0.620$). Age group and sway direction significantly interacted ($F = 3.4$, $p = 0.035$), representing the fact that the MF difference between age groups was much larger in the a–p than in the m-l direction. In addition, we found no significant interaction between age group and body segments ($F = 0.1$, $p = 0.887$) or between age group and visual condition ($F = 1.9$, $p = 0.157$).

Externally Perturbed Stance

We characterize the participants' sway behavior as a function of external perturbation by a transfer function in the frequency domain over 11 frequencies (0.05–2.2 Hz, see Procedures). The transfer function consists of a gain and a phase curve. For didactic reasons, we display GAIN effects of the middle-aged and elderly group also as GAINFACTOR with respect to a reference group (young group). GAINFACTOR is the percentage gain of the two elder groups with respect to the young reference group.

We found significant differences in GAIN between the three age groups ($F = 327.5$, $p < 0.0001$). In the young group, GAIN was lowest (1.66 ± 0.022) whereas it was highest in the elderly group (2.42 ± 0.021). Across all groups, GAIN was on average 37.6% higher with eyes closed than with eyes open ($F = 621.2$, $p < 0.0001$). GAIN significantly depended on stimulus amplitudes (0.5°: 2.21 ± 0.018, 1°: 1.80 ± 0.018, $F = 249.3$, $p < 0.0001$), on stimulus frequencies ($F = 394.9$, $p < 0.0001$), and on body segments (hip: 1.62 ± 0.018, shoulder: 2.40 ± 0.018, $F = 878.3$, $p < 0.0001$). Age group significantly interacted with frequency ($F = 9.52$, $p < 0.0001$). The major GAIN difference between age groups appeared to be in the lower frequency range, except for the lowest frequency value (see GAIN and GAINFACTOR plots in **Figures 5** and **6**). Moreover, age group significantly interacted with body segments ($F = 170.7$, $p < 0.0001$). This represents the fact that GAIN of the shoulder in the elderly group was almost twice as large as that of the hip, whereas in the young group, shoulder GAIN was 20% larger than hip GAIN (**Figure 7A**). Finally, age group significantly interacted with visual conditions ($F = 3.17$, $p = 0.042$), representing the finding that GAIN with eyes closed was about 50% larger than with eyes open in the young group, whereas the GAIN increase with closing the eyes was only 25% in the elderly group (**Figure 7B**). There was no significant interaction between age group and stimulus amplitude ($F = 0.9$, $p = 0.39$).

Across all age groups, PHASE was mainly determined by frequency ($F = 849.2$, $p < 0.0001$). PHASE differed significantly between the three age groups (young: $-123.45 \pm 1.52°$, middle-aged: $-131.82 \pm 1.65°$, elderly: $-122.77 \pm 1.48°$; $F = 9.9$, $p = < 0.0001$). More specifically, the PHASE profile as a function of frequency was different between the age groups. While the young group showed a moderate slope of the PHASE as a function of stimulus frequencies, the middle-aged and the elderly group presented a steeper relationship between PHASE and frequencies (see **Figures 5** and **6**). Interestingly, the PHASE profile difference between the middle-aged and the elderly group mainly consisted of a downward shift (reduction of phase lag) that was consistent across all frequencies (LAGPHASE plots in **Figures 5** and **6**). In general, the effect of age on PHASE as a function of frequency was characterized by a significant interaction between age and frequency ($F = 3.5$, $p < 0.0001$). Across all age groups, phase lag was found to be significantly smaller with eyes closed ($-121.82 \pm 1.27°$) than with eyes open ($-129.44 \pm 1.27°$, $F = 17.6$, $p < 0.0001$), significantly smaller at the hip ($-101.26 \pm 1.27°$) than at the shoulder level ($-150.01 \pm 1.27°$, $F = 761.5$, $p < 0.0001$), but was not significantly different across different stimulus amplitudes ($F = 0.02$, $p = 0.87$). Age group significantly interacted with body segment ($F = 27.1$, $p < 0.0001$) representing the fact that phase difference between shoulder and hip decreases with age (see **Figure 7C**). There was no significant interaction between age group and visual condition ($F = 0.5$, $p = 0.6002$).

Model Parameters

The model parameter/stiffness factor [P/mgh] is the proportional gain of the neural controller. We found significant differences of [P/mgh] across the three age groups ($F = 9.3$, $p = 0.0001$, see **Figure 8A**). This parameter was highest in the young group ($1.43\,\mathrm{rad}^{-1}$) and lowest in the elderly group ($1.29\,\mathrm{rad}^{-1}$). Across all age groups, [P/mgh] was significantly higher at a stimulus amplitude of 1°($1.41\,\mathrm{rad}^{-1}$) than of 0.5°($1.33\,\mathrm{rad}^{-1}$, $F = 6.7$, $p = 0.01$), representing a slight amplitude non-linearity of the system. Visual conditions did not significantly influence [P/mgh] ($F = 0.7$, $p = 0.42$). The age group did not significantly interact with visual condition ($F = 0.9$, $p = 0.39$) or stimulus amplitude ($F = 0.02$, $p = 0.98$).

The derivative gain or damping factor, [D/mgh], did not significantly vary with age ($F = 0.1$, $p = 0.87$, **Figure 8A**). This parameter was nearly equal in the three age groups (young: $0.372\,\mathrm{s} \times \mathrm{rad}^{-1}$, middle-aged: $0.370\,\mathrm{s} \times \mathrm{rad}^{-1}$, elderly: $0.365\,\mathrm{s} \times \mathrm{rad}^{-1}$). ([D/mgh] was significantly higher with eyes closed ($0.37\,\mathrm{s} \times \mathrm{rad}^{-1}$) than with eyes open ($0.35\,\mathrm{s} \times \mathrm{rad}^{-1}$, $F = 9.34$, $p = 0.0025$). Stimulus amplitude had a significant effect on [D/mgh] (0.5°: $0.36\,\mathrm{s} \times \mathrm{rad}^{-1}$, 1°: $0.38\,\mathrm{s} \times \mathrm{rad}^{-1}$, $F = 4.4$, $p = 0.04$). The age group did not have a significant interaction with visual condition ($F = 0.47$, $p = 0.62$) or stimulus amplitude ($F = 0.23$, $p = 0.79$) considering their effect on [D/mgh]).

The integral gain, [I/mgh], was significantly higher in the young and the middle-aged group (young: $0.118\,\mathrm{s}^{-1} \times \mathrm{rad}^{-1}$, middle-aged: $0.120\,\mathrm{s}^{-1} \times \mathrm{rad}^{-1}$) than in the elderly group ($0.097\,\mathrm{s}^{-1} \times \mathrm{rad}^{-1}$, $F = 9.4$, $p = 0.0001$, **Figure 8A**). Visual condition had a significant effect on [I/mgh] (eo: $0.118\,\mathrm{s}^{-1} \times \mathrm{rad}^{-1}$, ec: $0.104\,\mathrm{s}^{-1} \times \mathrm{rad}^{-1}$, $F = 8.8$, $p = 0.0033$), while stimulus amplitude did not ($F = 0.02$, $p = 0.88$). The age was found to interact significantly with visual condition ($F = 1.1$, $p = 0.34$) or stimulus amplitude ($F = 0.2$, $p = 0.86$) in their effect on [I/mgh].

The age group was found to have a significant effect on the passive stiffness factor [Ppas/mgh] ($F = 9.9$, $p < 0.0001$, see **Figure 8B**). [Ppas/mgh] was smallest in the elderly group (0.109) and larger in the other two age groups (young: 0.130, middle-aged: 0.135). [Ppas/mgh] was significantly higher with eyes open (0.135) than with eyes closed (0.113, $F = 19.02$, $p < 0.0001$). Stimulus amplitude did not significantly influence [Ppas/mgh] ($F = 0.6$, $p = 0.45$). The age group was not found to significantly interact with visual condition ($F = 0.5$, $p = 0.62$) or stimulus amplitude ($F = 0.3$, $p = 0.72$) with respect to [Ppas/mgh].

[Dpas/mgh], the passive damping factor, decreased significantly with age ($F = 9.07$, $p = 0.0002$, **Figure 8B**). It was highest in

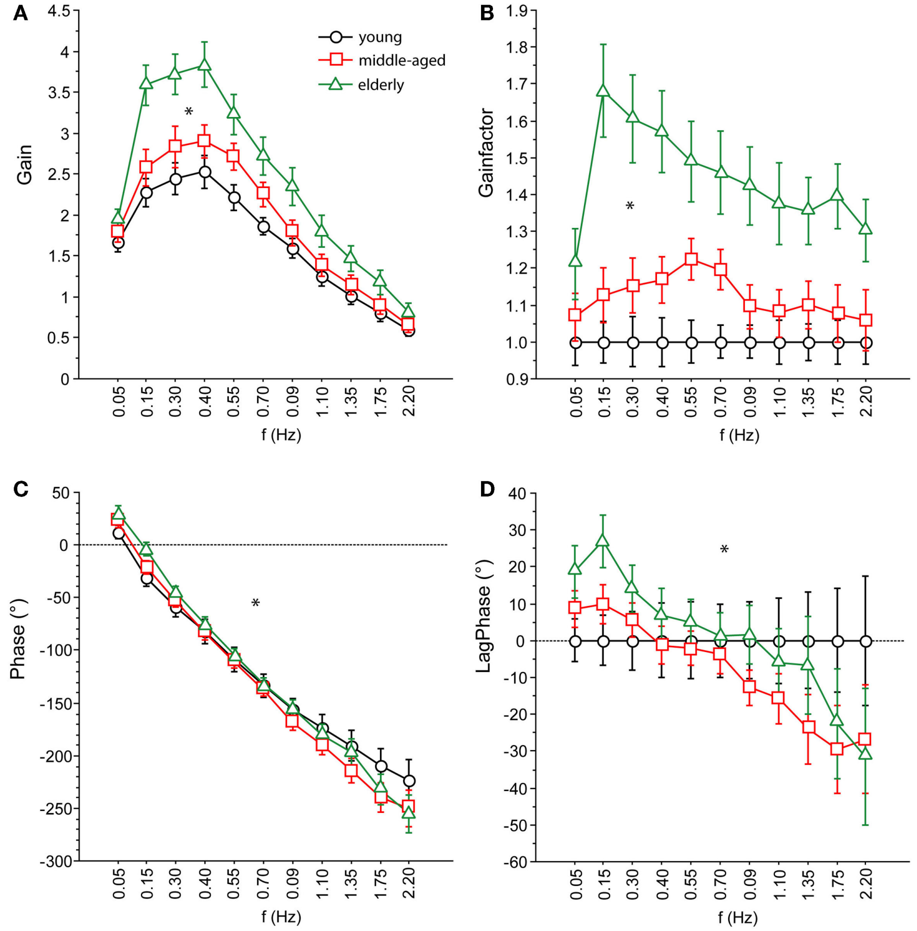


FIGURE 5 | Parameters of perturbed stance. **(A)** GAIN, **(B)** GAINFACTOR, **(C)** PHASE, **(D)** LAGPHASE of the three age groups across all stimulus amplitudes and visual conditions. GAINFACTOR is the percental quotient between the GAIN of the middle-aged and elderly group and the young group as a comparison group. The time difference between PHASE of the middle-aged and elderly group and the young group as a comparison group is named LAGPHASE. Its unit is degrees (°).

the young group (0.089) and lowest in the elderly group (0.074). [Dpas/mgh] was significantly higher with eyes open (0.089) than with eyes closed (0.078, $F = 10.9$, $p = 0.0011$). Stimulus amplitude had no significant influence on [Dpas/mgh] ($F = 0.3$, $p = 0.61$). The age group was not observed to have a significant interaction with visual condition ($F = 0.14$, $p = 0.87$) or stimulus amplitude ($F = 0.1$, $p = 0.89$) with respect to [Dpas/mgh].

Time delay, [Td], significantly increased with age ($F = 14.1$, $p < 0.0001$, **Figure 8C**). It was lowest in the young group (0.153 ± 0.003 s) and highest in the elderly group (0.177 ± 0.003 s). Neither visual condition ($F = 0.9$, $p = 0.34$) nor stimulus amplitude ($F = 2.9$, $p = 0.09$) had a significant effect on [Td]. Moreover, age group did not significantly interact with visual condition ($F = 0.2$, $p = 0.85$) or stimulus amplitude ($F = 0.88$, $p = 0.42$) with respect to [Td].

The proprioceptive sensory weight, [Wp], increased significantly with increasing age ($F = 7.2$, $p = 0.0009$, see **Figure 8D**). Being lowest in the young group (0.64 ± 0.018) and highest in the elderly group (0.74 ± 0.018), [Wp] was 35% higher with eyes closed (0.8 ± 0.015) than with eyes open (0.59 ± 0.015), and this difference was significant ($F = 93.5$, $p < 0.0001$). The stimulus amplitude significantly affected [Wp] (0.5°: 0.74 ± 0.015, 1°: 0.65 ± 0.015, $F = 18.7$, $p < 0.0001$), resulting in a 14% increase. The age group did not significantly interact with visual condition ($F = 1.8$, $p = 0.16$) or stimulus amplitude ($F = 0.3$, $p = 0.77$) in their effect on [Wp]. In addition to [Wp], we show a figure of [Wspace] (**Figure 8E**). [Wspace] is 1-[Wp] and it reflects vestibular weight with eyes closed and visual and vestibular weight with eyes open.

Clinical Tests

The elderly group performed also two clinical tests: the TUG and the FRT. The average results were for the FRT a reach distance of 28.2 ± 6.4 cm and for the TUG 8.48 ± 1.2 s.

In the following, we report significant correlations between our experimental spontaneous sway measures and measures of perturbed stance, derived model parameters, and the results of clinical tests in the elderly group (see **Figure 9**; **Table 1**). However, we calculated the correlation matrix only between measures (spontaneous and perturbed sway measures) and parameters that

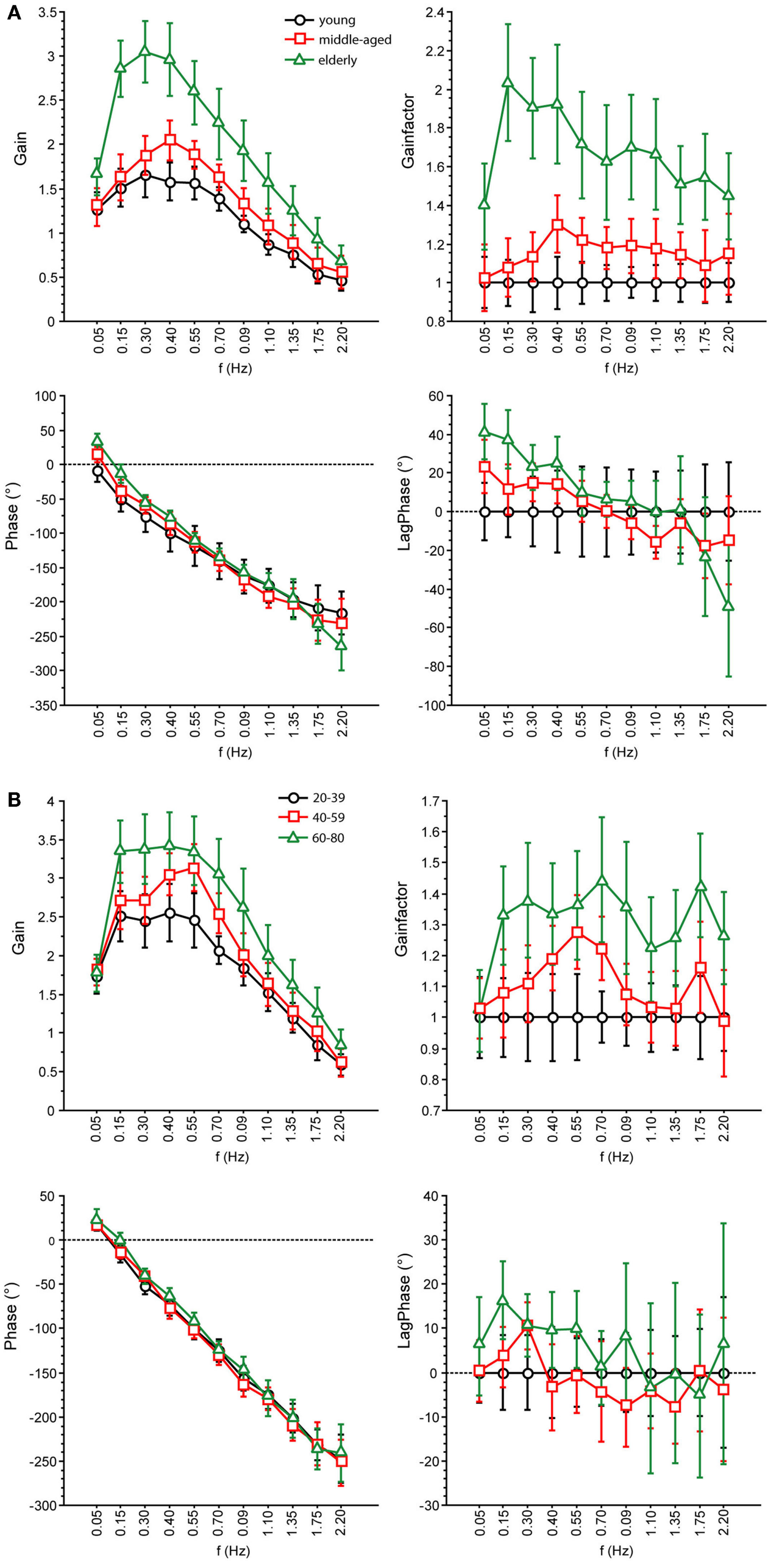


FIGURE 6 | Parameters of perturbed stance. GAIN, GAINFACTOR, PHASE, LAGPHASE of the three age groups at 1° with eyes open **(A)** and eyes closed **(B)**.

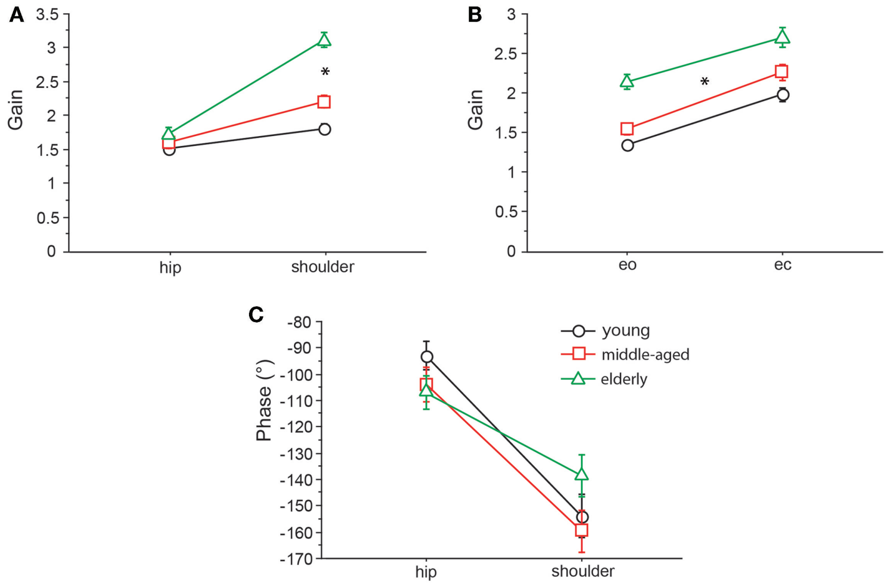


FIGURE 7 | GAIN interaction between age and body segments and age and visual condition, and PHASE interaction between age and body segments. GAIN of the three age groups with respect to body segment **(A)** and visual condition **(B)** and PHASE of the three age groups with respect to body segment **(C)**. eo, eyes open; ec, eyes closed.

were significantly different from young subjects. PHASE, MF, MV, [P/mgh], and TUG all correlated significantly with each other. In addition, PHASE correlated significantly with [Td], [Td] correlated with [Wp], [Wp] correlated with GAIN and GAIN correlated with TUG. By contrast, RMS correlated only with MF and FRT correlated only with TUG.

Discussion

We analyzed postural control of elderly people (60–80 years) and compared their data to the data of two younger groups (20–39 and 40–59 years). Postural control was characterized by spontaneous sway measures and measures of perturbed stance between 0.05 and 2.2 Hz. Perturbations were induced by a pseudorandom platform tilt stimulus. Stimulus–response data were interpreted on the basis of a simple negative feedback model (Peterka, 2002; Maurer et al., 2006a; Engelhart et al., 2014).

Among the spontaneous sway measures, RMS, MV, and MF were significantly higher in elderly people (elderly group) than in young people (young group). These results are in line with previous studies (Maki et al., 1990; Hytönen et al., 1993; Baloh et al., 1994; Collins et al., 1995; Prieto et al., 1996; Tang and Woollacott, 1996; Maurer and Peterka, 2005). The effect on MV had the highest significance. The high sensitivity of the MV effect as compared to other spontaneous sway measures to detect abnormalities was reported earlier (Prieto et al., 1996; Maurer and Peterka, 2005; Ruhe et al., 2010; Delignières et al., 2011; Moghadam et al., 2011). In previous work by our group (Maurer and Peterka, 2005) and others (Maki et al., 1990; Prieto et al., 1996), higher MV of elderly people was interpreted as a higher amount of regulatory balancing activity. Furthermore, MV was different from other spontaneous sway parameters as the age effect significantly interacted with sway direction (a–p vs. m-l). The interaction with sway direction was based on the fact that elderly's MV in the a–p direction was much larger (+36%) than in m-l direction, whereas this directional effect was much weaker in the younger groups. As already shown in other studies, a–p sway might be more sensitive to any impairment (Collins et al., 1995; Prieto et al., 1996; Tia et al., 2012), due to the fact that balance in a–p direction follows the rules of an unstable inverted pendulum.

Mean velocity of the middle-aged and elderly group increased about 30% (elderly: 26%, middle-aged 36%) across all body segments when closing the eyes. In the young group, this increase amounted to only 18%. Independently of age, the increase of MV when closing the eyes has been described before [e.g., Era and Heikkinen (1985), Horak et al. (1989), Teasdale et al. (1991), Hytönen et al. (1993), Prieto et al. (1996), Accornero et al. (1997), Schieppati et al. (1999), and Shumway-Cook and Woollacott (2001)]. It is still controversial whether this increase is more or less pronounced in elderly than in young subjects. Peterka and Black (1990) and Teasdale et al. (1991) observed as well no significant age-related increase in spontaneous sway with eyes closed. Hytönen et al. (1993) found an increased difference of sway velocity between eyes closed and eyes open in their eldest group (76–90 years).

In general, spontaneous sway measures in our study seemed to mirror age-dependent changes of postural control in a reliable way. However, the variance across scores of different spontaneous sway measures is known to be covered by only two principal components, even if one analyzes up to 14 different measures [see Maurer and Peterka (2005)]. That might be the reason why measuring spontaneous sway does not allow for detecting specific constituents of postural control deficits (Horak et al., 1989; Maki et al., 1990; Tang and Woollacott, 1996;

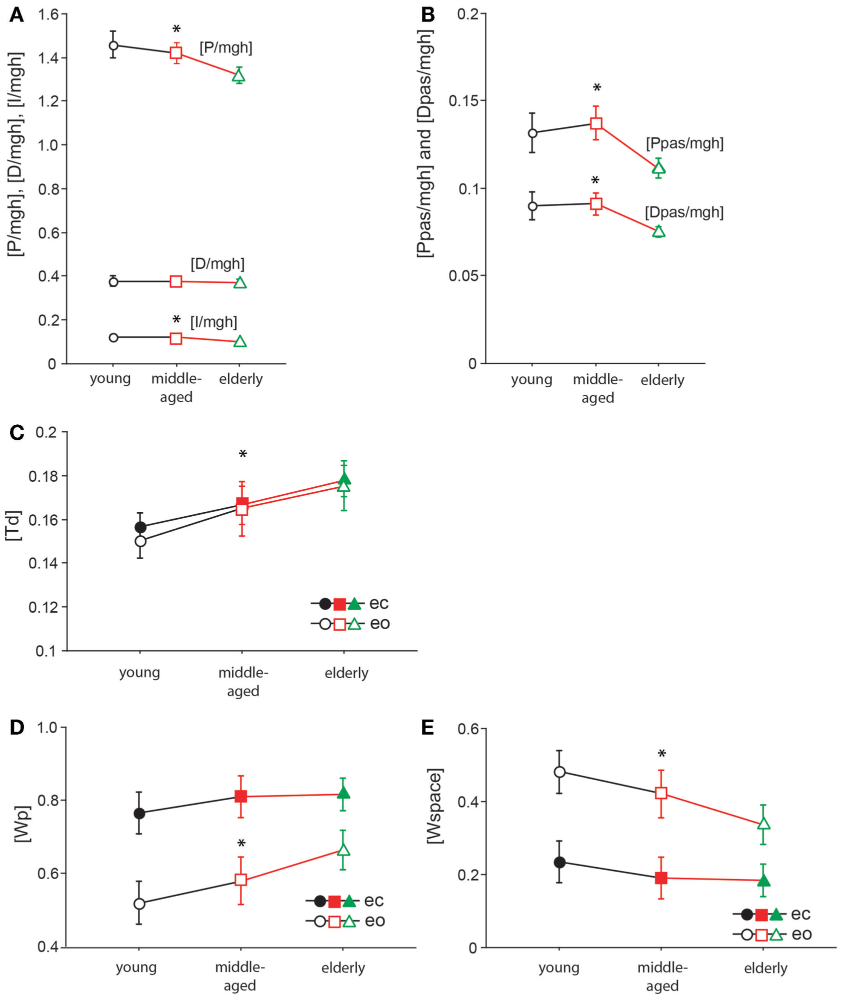


FIGURE 8 | Model parameters. [P/mgh] in rad^{-1} **(A)**, [D/mgh] in s × rad^{-1} **(A)**, [I/mgh] in s^{-1} × rad^{-1} **(A)**, [Ppas/mgh] **(B)**, [Dpas/mgh] **(B)**, [Td] in s **(C)**, [Wp] **(D)**, and [Wspace] **(E)** of the three age groups. The three different age groups are shown on the *x*-axis; eo, eyes open; ec, eyes closed.

Kuo et al., 1998; Black, 2001; Ghulyan et al., 2005). From a model-based perspective, many different sources of postural control deficits like, e.g., increased feedback time delay, too strong or too weak feedback gain, increased sensory noise level, and abnormal weighting of sensory inputs may all lead to increased sway or sway velocity (Maurer and Peterka, 2005). For a more specific analysis of postural control deficits, an external perturbation is required (Engelhart et al., 2014). Consequently, we characterized subjects' behavior as a function of external perturbations, i.e., anterior–posterior platform tilts, by transfer functions in the frequency domain. Transfer functions consist of gain and phase curves. We first discuss GAIN and PHASE findings separately before we integrate the findings using our model-based approach.

GAIN was highest in elderly and lowest in young people, which is in line with earlier findings [e.g., Ghulyan et al. (2005) during sinusoidal platform translations]. Across all age groups, GAIN significantly depended on visual conditions, stimulus amplitudes, stimulus frequencies, and on body segments. Moreover, we found significant interactions between age, on one hand, and frequency, visual condition, and body segments, on the other. The interaction between age and frequency represents the fact that the major GAIN difference between age groups appeared in the lower frequency range. The interaction between age and visual condition is due to the fact that the GAIN increase was about 48% when closing the eyes in the youngest group and only 26% in the elderly group. The significant interaction between age and body segments is related to the relatively larger shoulder GAIN (almost twice as large as the hip GAIN) in elderly people, whereas in young people, shoulder GAIN was 20% larger than hip GAIN. This finding is in line with the fact that elderly people are known to have a tendency to engage hip flexion/extension when stance is perturbed (Kuo et al., 1998; Shumway-Cook and Woollacott, 2001).

PHASE as a function of frequency was significantly different between the three age groups. The PHASE decreased with increasing frequency in all age groups; however, the middle-aged and the elderly group displayed a steeper relationship between PHASE and frequencies. Age significantly interacted with body segment, representing the fact that PHASE differences between shoulder and hip decreases with age.

In order to interpret the numerous findings concerning GAIN and PHASE curves, we fitted subjects' data by a simple feedback system that is known to adequately describe body motion as a function of sensory inputs [e.g., Mergner et al. (2002, 2003), Vette et al. (2010), Van der Kooij and Peterka (2011), and Engelhart et al. (2014)]. A very basic version consists of the body represented by mass and height, a neural controller including stiffness factor and damping factor, a feedback time delay, and sensory weighting mechanism that integrates proprioceptive, vestibular, and visual cues (Maurer et al., 2006a; Van der Kooij and Peterka, 2011). We had to reject our hypothesis that elderly people show a general decline in sensory, motor, and higher-level adaptation systems. The most significant differences between age groups relate to the sensory weighting, the feedback gain of the neural controller, and the overall time delay of the motor reaction: Across all stimulus conditions, elderly people weigh proprioceptive cues ([Wp]) higher than visual and vestibular cues. This finding suggests that elderly people tend to stabilize and orient their body relative to the support surface and, therefore, rely more on proprioceptive than on vestibular or visual cues, which is related to the larger GAIN across all frequencies. Abnormalities in the use of sensory cues have already been reported by others (Nishihori et al., 2012; Maitre et al., 2013). All subjects weigh proprioceptive cues relatively stronger when they close their eyes, i.e., one space reference cue (visual) is missing. This relates to the larger GAIN observed with eyes closed than with eyes open. The vestibular cue as another space cue does not fully compensate for the lack of the visual cue as also reported by others (Ishida et al., 1997). This is in line with the experience of other laboratories that other cues fill in when sensory cues are missing (Van der Kooij and Peterka, 2011).

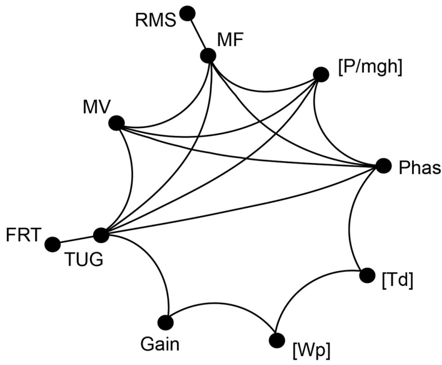


FIGURE 9 | Correlation of clinical tests and measurements of spontaneous and perturbed stance. Correlation matrix between clinical test parameters and parameters obtained from platform measures. The correlation revealed a group of parameters that all significantly correlate with each other (MF, MV, PHASE, [P/mgh], and TUG). Some of the measures mentioned above significantly correlate with additional measures and parameters. Only correlations with $R > 0.47$ and $p < 0.05$ are shown.

Although not being significant, elderly people tend to down-regulate proprioceptive cues when opening the eyes less than young people do. Then again, all age groups similarly down-regulate their proprioceptive weights with increasing stimulus amplitude, representing the fact that with larger disturbances of the support surface, stabilization in space becomes advantageous to avoid large body sway (Peterka, 2002; Van der Kooij and Peterka, 2011). This might indicate that the reliability of the sensory weighting process is not impaired in elderly people as a result of aging.

Elderly people display an overall time delay that is about 24 ms longer than that of young people. Our results are almost identical to the results of Davidson et al. (2011) in which the time delay of

TABLE 1 | Significance of correlations in terms of *p*-values ($p < 0.05$) and the associated *R*-values between experimental spontaneous sway measures and measures of perturbedstance, derived model parameters, and the results of the clinical tests in the elderly group.

	Phase	[P/mgh]	MF	RMS	MV	TUG	FRT	GAIN	[Wp]	[Td]
Phase										
[P/mgh]	$p = 0.0008$ $R = 0.72$									
MF	$p = 0.0001$ $R = 0.79$	$p = 0.0001$ $R = 0.88$								
RMS	n.s.	n.s.	$p = 0.0307$ $R = -0.51$							
MV	$p = 0.0012$ $R = 0.70$	$p = 0.0028$ $R = 0.66$	$p = 0.0052$ $R = 0.63$	n.s.						
TUG	$p = 0.0369$ $R = 0.49$	$p = 0.002$ $R = 0.68$	$p = 0.0353$ $R = 0.50$	n.s.	$p = 0.0464$ $R = 0.47$					
FRT	n.s.	n.s.	n.s.	n.s.	n.s.	$p = 0.0433$ $R = -0.48$				
GAIN	n.s.	n.s.	n.s.	n.s.	n.s.	$p = 0.0461$ $R = 0.48$	n.s.			
[Wp]	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	$p = 0.0001$ $R = 0.78$		
[Td]	$p = 0.0343$ $R = -0.51$	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	$p = 0.0331$ $R = 0.50$	

n.s., not significant; MF, mean frequency; RMS, root mean square; TUG, timed up and go test; FRT, functional reach test; Td, time delay.

the motor reaction in elderly people was found to be 23 ms higher than in the young people when perturbing stance with jolts of a ballistic pendulum. A large time delay endangers stability of the system through an enlarged oscillation tendency (Peterka, 2000; Van der Kooij and Peterka, 2011). Since a high-proportional feedback gain increases oscillation tendencies, too, a lower feedback gain in elderly might represent a compensation strategy to reduce oscillations (Peterka, 2002; Van der Kooij and Peterka, 2011). In fact, we identified smaller feedback gain parameters (active proportional, [P/mgh]; passive proportional, [Ppas/mgh]; passive damping factor, [Dpas/mgh]) in elderly compared to young subjects.

Everyday postural control is usually assessed by simple clinical tests and scales such as the TUG (Podsiadlo and Richardson, 1991; Enkelaar et al., 2013) and the FRT (Duncan et al., 1990; Enkelaar et al., 2013). In order to relate our findings to established measures of postural control, our elderly subjects performed FRT and TUG. The FRT revealed an average reach distance of 28.2 cm in the elderly group. The reach distance of our elderly group is similar to data of Duncan et al. (1990) who evaluated the FRT in 128 volunteers between 21 and 87 years. Their group of elderly people aged between 70 and 87 years attained a reach distance of 25.0 cm whereas the younger group (20–40ys) showed a distance of 39.8 ± 5.2 cm. In our study, the TUG in the elderly group amounted to 8.48 s. The TUG scores of the elderly group are similar to the one reported by Buatois et al. (2006); (9.6–10.2 s), Nagy et al. (2007); (8.9–10.3 s), Enkelaar et al. (2013); (9.3 s), and Bohannon (2006); (9.2 s).

The correlation analysis between clinical scales (FRT, TUG) and our experimental findings in the elderly group revealed a group of parameters that all significantly correlated with each other, consisting of two spontaneous sway measures (MF, MV), one measure of perturbed stance (PHASE), one model-derived parameter ([P/mgh]), and the clinical measure of TUG (see **Table 1**). This could be explained by the fact that all those parameters may be influenced by systems stability. Why would a clinical score like TUG, which involves walking and transitioning between straight walking, turning, sit-to-stand and stand-to-sit motions, correlate with parameters that describe human postural control? We assume that stability of the postural control system also affects more complex postural tasks such as walking or certain transitions.

Furthermore, there was a significant correlation between PHASE and [Td], which are both related to the timing of a response following a stimulus. [Wp] correlated significantly with GAIN and this is consistent with [Wp] being responsible for a uniform scaling of the gain curves across all frequencies.

It was interesting to find that the FRT correlated only with the TUG. The fact that the FRT seems to correlate with other clinical balance measures has been reported by others (Granacher et al., 2009; Enkelaar et al., 2013: moderate correlation). However, it is not clear why a stance parameter related to the amount of forward voluntary lean is related to a complex dynamic movement task as the TUG. We deem it likely, however, that the endangered stability of the postural control system described above, might influence both, voluntary lean and more complex movement tasks. Further investigations are needed to explain this finding. Furthermore, RMS correlated significantly solely with MF, while MF correlated with many other measures of perturbed sway analogously to MV, supporting our view that spontaneous sway measures are gross measures related to balance control and that the information contained in those measures is highly correlated and possibly redundant (Maurer and Peterka, 2005). More specifically, sway amplitude, represented by RMS, might be less crucial for the postural stability than velocity related measures such as MV and MF.

In summary, the perturbation-based approach presented here gives us more insight about postural control mechanisms of elderly people than measures of spontaneous sway do. In addition, it allows for a model-based interpretation of the experimental data, which provide valuable information of underlying mechanisms of the whole postural control system. We were able to identify basic parameters of the postural control system that are related to aging, i.e., the increased reliance of elderly people on proprioception, the decreased feedback loop gain, and the increased closed loop feedback time delay between the sensory perception and the motor reaction. Understanding the postural changes during aging is crucial for the development of new therapies that improve postural control in the elderly population. Our approach is highly sensitive even to small changes in postural control. Accordingly, it might be also suited to monitor therapeutic interventions, which aim to improve postural stability in the elderly.

Acknowledgments

We would like to thank Anja Wehrle and Jörg Dietterle for their support during the measurements. In addition, we thank Dr. Massimo Cenciarini for proofreading. CM was partially funded by a European Union FP7 grant (EMBALANCE: Grant Agreement no. 610454), the Brainlinks-Braintools Cluster of Excellence funded by the German Research foundation (DFG, grant no. ADV139), and by DFG (MA 2543/3-1).

References

Accornero, N., Capozza, M., Rinalduzzi, S., and Manfredi, G. W. (1997). Clinical multisegmental posturography: age-related changes in stance control. *Electroencephalogr. Clin. Neurophysiol.* 105, 213–219. doi:10.1016/S0924-980X(97)96567-X

Allison, L. K., Kiemel, T., and Jeka, J. J. (2006). Multisensory reweighting of vision and touch is intact in healthy and fall-prone older adults. *Exp. Brain Res.* 175, 342–352. doi:10.1007/s00221-006-0559-7

Baloh, R. W., Fife, T. D., Zwerling, L., Socotch, T., Jacobson, K., Bell, T., et al. (1994). Comparison of static and dynamic posturography in young and older normal people. *J. Am. Geriatr. Soc.* 42, 405–412. doi:10.1111/j.1532-5415.1994.tb07489.x

Bergström, B. (1973). Morphology of the vestibular nerve: II. the number of myelinated vestibular nerve fibers in man at various ages. *Acta Otolaryngol.* 76, 173–179. doi:10.3109/00016487309121496

Black, F. O. (2001). What can posturography tell us about vestibular function? *Ann. N. Y. Acad. Sci.* 942, 446–464. doi:10.1111/j.1749-6632.2001.tb03765.x

Bohannon, R. (2006). Reference values for the timed up and go test: a descriptive meta-analysis. *J. Geriatr. Phys. Ther.* 29, 64–68. doi:10.1519/00139143-200608000-00004

Buatois, S., Gueguen, R., Gauchard, G. C., Benetos, A., and Perrin, P. P. (2006). Posturography and risk of recurrent falls in healthy non-institutionalized persons aged over 65. *Gerontology* 52, 345–352. doi:10.1159/000094983

Cenciarini, M., Loughlin, P. J., Sparto, P. J., and Redfern, M. S. (2009). "Medial-lateral postural control in older adults exhibits increased stiffness and damping," in *Conference Proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society. Annual Conference, 2009* (Minneapolis, Minnesota: IEEE Engineering in Medicine and Biology Society), 7006–7009.

Cenciarini, M., Loughlin, P. J., Sparto, P. J., and Redfern, M. S. (2010). Stiffness and damping in postural control increase with age. *IEEE Trans. Biomed. Eng.* 57, 267–275. doi:10.1109/TBME.2009.2031874

Cnyrim, C., Mergner, T., and Maurer, C. (2009). Potential roles of force cues in human stance control. *Exp. Brain Res.* 194, 419–433. doi:10.1007/s00221-009-1715-7

Collins, J. J., De Luca, C. J., Burrows, A., and Lipsitz, L. A. (1995). Age-related changes in open-loop and closed-loop postural control mechanisms. *Exp. Brain Res.* 104, 480–492. doi:10.1007/BF00231982

Davidson, B. S., Madigan, M. L., Southward, S. C., and Nussbaum, M. A. (2011). Neural control of posture during small magnitude perturbations: effects of aging and localized muscle fatigue. *IEEE Trans. Biomed. Eng.* 58, 1546–1554. doi:10.1109/TBME.2010.2095500

Delignières, D., Torre, K., and Bernard, P. (2011). Transition from persistent to anti-persistent correlations in postural sway indicates velocity-based control. *PLoS Comput. Biol.* 7:e1001089. doi:10.1371/journal.pcbi.1001089

Doherty, T. J. (2003). Invited review: aging and sarcopenia. *J. Appl. Physiol.* 95, 1717–1727. doi:10.1152/japplphysiol.00347.2003

Duncan, P. W., Weiner, D. K., Chandler, J., and Studenski, S. (1990). Functional reach: a new clinical measure of balance. *J. Gerontol.* 45, M192–M197. doi:10.1093/geronj/45.6.M192

Eikema, D. J., Hatzitaki, V., Tzovaras, D., and Papaxanthis, C. (2012). Age-dependent modulation of sensory reweighting for controlling posture in a dynamic virtual environment. *Age* 34, 1381–1392. doi:10.1007/s11357-011-9310-9

Eikema, D. J., Hatzitaki, V., Tzovaras, D., and Papaxanthis, C. (2014). Application of intermittent galvanic vestibular stimulation reveals age-related constraints in the multisensory reweighting of posture. *Neurosci. Lett.* 561, 112–117. doi:10.1016/j.neulet.2013.12.048

Engelhart, D., Pasma, J. H., Schouten, A. C., Meskers, C. G. M., Maier, A. B., Mergner, T., et al. (2014). Impaired standing balance in elderly: a new engineering method helps to unravel causes and effects. *J. Am. Med. Dir. Assoc.* 15, .e1–.e6. doi:10.1016/j.jamda.2013.09.009

Enkelaar, L., Smulders, E., van Schrojenstein Lantman-de Valk, H., Weerdesteyn, V., and Geurts, A. C. H. (2013). Clinical measures are feasible and sensitive to assess balance and gait capacities in older persons with mild to moderate intellectual disabilities. *Res. Dev. Disabil.* 34, 276–285. doi:10.1016/j.ridd.2012.08.014

Era, P., and Heikkinen, E. (1985). Postural sway during standing and unexpected disturbance of balance in random samples of men of different ages. *J. Gerontol.* 40, 287–295. doi:10.1093/geronj/40.3.287

Fransson, P.-A., Kristinsdottir, E. K., Hafström, A., Magnusson, M., and Johansson, R. (2004). Balance control and adaptation during vibratory perturbations in middle-aged and elderly humans. *Eur. J. Appl. Physiol.* 91, 595–603. doi:10.1007/s00421-003-1013-1

Ghulyan, V., Paolino, M., Lopez, C., Dumitrescu, M., and Lacour, M. (2005). A new translational platform for evaluating aging or pathology-related postural disorders. *Acta Otolaryngol.* 125, 607–617. doi:10.1080/00016480510026908

Goble, D. J., Coxon, J. P., Wenderoth, N., van Impe, A., and Swinnen, S. P. (2009). Proprioceptive sensibility in the elderly: degeneration, functional consequences and plastic-adaptive processes. *Neurosci. Biobehav. Rev.* 33, 271–278. doi:10.1016/j.neubiorev.2008.08.012

Granacher, U., Gruber, M., and Gollhofer, A. (2009). Resistance training and neuromuscular performance in seniors. *Int. J. Sports Med.* 30, 652–657. doi:10.1055/s-0029-1224178

Grossniklaus, H. E., Nickerson, J. M., Edelhauser, H. F., Bergman, L. A. M. K., and Berglin, L. (2013). Anatomic alterations in aging and age-related diseases of the eye. *Invest. Ophthalmol. Vis. Sci.* 54, ORSF23–ORSF27. doi:10.1167/iovs.13-12711

Hilz, M. J., Axelrod, F. B., Hermann, K., Haertl, U., Duetsch, M., and Neundörfer, B. (1998). Normative values of vibratory perception in 530 children, juveniles and adults aged 3-79 years. *J. Neurol. Sci.* 159, 219–225. doi:10.1016/S0022-510X(98)00177-4

Horak, F. B., Shupert, C. L., and Mirka, A. (1989). Components of postural dyscontrol in the elderly: a review. *Neurobiol. Aging* 10, 727–738. doi:10.1016/0197-4580(89)90010-9

Hytönen, M., Pyykkö, I., Aalto, H., and Starck, J. (1993). Postural control and age. *Acta Otolaryngol.* 113, 119–122. doi:10.3109/00016489309135778

Iosa, M., Fusco, A., Morone, G., and Paolucci, S. (2014). Development and decline of upright gait stability. *Front. Aging Neurosci.* 6:14. doi:10.3389/fnagi.2014.00014

Ishida, A., Imai, S., and Fukuoka, Y. (1997). Analysis of the posture control system under fixed and sway-referenced support conditions. *IEEE Trans. Biomed. Eng.* 44, 331–336. doi:10.1109/10.568908

Jeka, J., Allison, L., Saffer, M., Zhang, Y., Carver, S., and Kiemel, T. (2006). Sensory reweighting with translational visual stimuli in young and elderly adults: the role of state-dependent noise. *Exp. Brain Res.* 174, 517–527. doi:10.1007/s00221-006-0502-y

Klass, M., Baudry, S., and Duchateau, J. (2007). Voluntary activation during maximal contraction with advancing age: a brief review. *Eur. J. Appl. Physiol.* 100, 543–551. doi:10.1007/s00421-006-0205-x

Kuo, A., Speers, R., Peterka, R., and Horak, F. (1998). Effect of altered sensory conditions on multivariate descriptors of human postural sway. *Exp. Brain Res.* 122, 185–195. doi:10.1007/s002210050506

Liaw, M.-Y., Chen, C.-L., Pei, Y.-C., Leong, C.-P., and Lau, Y.-C. (2009). Comparison of the static and dynamic balance performance in young, middle-aged, and elderly healthy people. *Chang Gung Med. J.* 32, 297–304.

Lin, Y.-H., Hsieh, S.-C., Chao, C.-C., Chang, Y.-C., and Hsieh, S.-T. (2005). Influence of aging on thermal and vibratory thresholds of quantitative sensory testing. *J. Peripher. Nerv. Syst.* 10, 269–281. doi:10.1111/j.1085-9489.2005.10305.x

Macaluso, A., and De Vito, G. (2004). Muscle strength, power and adaptations to resistance training in older people. *Eur. J. Appl. Physiol.* 91, 450–472. doi:10.1007/s00421-003-0991-3

Maitre, J., Gasnier, Y., Bru, N., Jully, J.-L., and Paillard, T. (2013). Discrepancy in the involution of the different neural loops with age. *Eur. J. Appl. Physiol.* 113, 1821–1831. doi:10.1007/s00421-013-2608-9

Maki, B. E., Holliday, P. J., and Fernie, G. R. (1990). Aging and postural control. A comparison of spontaneous- and induced-sway balance tests. *J. Am. Geriatr. Soc.* 38, 1–9. doi:10.1111/j.1532-5415.1990.tb01588.x

Mansfield, A., and Maki, B. E. (2009). Are age-related impairments in change-in-support balance reactions dependent on the method of balance perturbation? *J. Biomech.* 42, 1023–1031. doi:10.1016/j.jbiomech.2009.02.007

Masani, K., Vette, A. H., and Popovic, M. R. (2006). Controlling balance during quiet standing: proportional and derivative controller generates preceding motor command to body sway position observed in experiments. *Gait Posture* 23, 164–172. doi:10.1016/j.gaitpost.2005.01.006

Maurer, C., Mergner, T., and Peterka, R. J. (2004). Abnormal resonance behavior of the postural control loop in Parkinson's disease. *Exp. Brain Res.* 157, 369–376. doi:10.1007/s00221-004-1852-y

Maurer, C., Mergner, T., and Peterka, R. J. (2006a). Multisensory control of human upright stance. *Exp. Brain Res.* 171, 231–250. doi:10.1007/s00221-005-0256-y

Maurer, C., Schweigart, G., and Mergner, T. (2006b). Pronounced overestimation of support surface tilt during stance. *Exp. Brain Res.* 168, 41–50. doi:10.1007/s00221-005-0087-x

Maurer, C., Mergner, T., Xie, J., Faist, M., Pollak, P., and Lücking, C. H. (2003). Effect of chronic bilateral subthalamic nucleus (STN) stimulation on postural control in Parkinson's disease. *Brain* 126, 1146–1163. doi:10.1093/brain/awg100

Maurer, C., and Peterka, R. J. (2005). A new interpretation of spontaneous sway measures based on a simple model of human postural control. *J. Neurophysiol.* 93, 189–200. doi:10.1152/jn.00221.2004

Merchant, S. N., Velázquez-Villaseñor, L., Tsuji, K., Glynn, R. J., Wall, C III., and Rauch, S. D. (2000). Temporal bone studies of the human peripheral vestibular system. Normative vestibular hair cell data. *Ann. Otol. Rhinol. Laryngol. Suppl.* 181, 3–13.

Mergner, T., Maurer, C., and Peterka, R. J. (2002). Sensory contributions to the control of stance: a posture control model. *Adv. Exp. Med. Biol.* 508, 147–152. doi:10.1007/978-1-4615-0713-0_18

Mergner, T., Maurer, C., and Peterka, R. J. (2003). A multisensory posture control model of human upright stance. *Prog. Brain Res.* 142, 189–201. doi:10.1016/S0079-6123(03)42014-1

Moghadam, M., Ashayeri, H., Salavati, M., Sarafzadeh, J., Taghipoor, K., Saeedi, A., et al. (2011). Reliability of center of pressure measures of postural stability in healthy older adults: effects of postural task difficulty and cognitive load. *Gait Posture* 33, 651–655. doi:10.1016/j.gaitpost.2011.02.016

Nag, T. C., and Wadhwa, S. (2012). Ultrastructure of the human retina in aging and various pathological states. *Micron* 43, 759–781. doi:10.1016/j.micron.2012.01.011

Nagy, E., Feher-Kiss, A., Barnai, M., Domján-Preszner, A., Angyan, L., and Horvath, G. (2007). Postural control in elderly subjects participating in balance training. *Eur. J. Appl. Physiol.* 100, 97–104. doi:10.1007/s00421-007-0407-x

Nashner, L. M., Black, F. O., and Wall, C. III (1982). Adaptation to altered support and visual conditions during stance: patients with vestibular deficits. *J. Neurosci.* 2, 536–544.

Nashner, L. M., and McCollum, G. (1985). The organization of human postural movements: a formal basis and experimental synthesis. *Behav Brain Sci.* 8, 135–150. doi:10.1017/S0140525X00020008

Nishihori, T., Aoki, M., Jiang, Y., Nagasaki, S., Furuta, Y., and Ito, Y. (2012). Effects of aging on lateral stability in quiet stance. *Aging Clin. Exp. Res.* 24, 162–170. doi:10.3275/7626

Papegaaij, S., Taube, W., Baudry, S., Otten, E., and Hortobágyi, T. (2014). Aging causes a reorganization of cortical and spinal control of posture. *Front. Aging Neurosci.* 6:28. doi:10.3389/fnagi.2014.00028

Park, J. J., Tang, Y., Lopez, I., and Ishiyama, A. (2001). Age-related change in the number of neurons in the human vestibular ganglion. *J. Comp. Neurol.* 431, 437–443. doi:10.1002/1096-9861(20010319)431:4<437::AID-CNE1081>3.0.CO;2-P

Peterka, R. J. (2000). Postural control model interpretation of stabilogram diffusion analysis. *Biol. Cybern.* 82, 335–343. doi:10.1007/s004220050587

Peterka, R. J. (2002). Sensorimotor integration in human postural control. *J. Neurophysiol.* 88, 1097–1118. doi:10.1152/jn.00605.2001

Peterka, R. J., and Black, F. O. (1990). Age-related changes in human posture control: sensory organization tests. *J. Vestib. Res.* 1, 73–85.

Pierchała, K., Lachowska, M., Morawski, K., and Niemczyk, K. (2012). Sensory organization test outcomes in young, older and elderly healthy individuals – preliminary results. *Otolaryngol. Pol.* 66, 274–279. doi:10.1016/j.otpol.2012.05.005

Podsiadlo, D., and Richardson, S. (1991). The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J. Am. Geriatr. Soc.* 39, 142–148. doi:10.1111/j.1532-5415.1991.tb01616.x

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

Qu, X., Nussbaum, M. A., and Madigan, M. L. (2009). Model-based assessments of the effects of age and ankle fatigue on the control of upright posture in humans. *Gait Posture* 30, 518–522. doi:10.1016/j.gaitpost.2009.07.127

Rauch, S. D., Velázquez-Villaseñor, L., Dimitri, P. S., and Merchant, S. N. (2001). Decreasing hair cell counts in aging humans. *Ann. N. Y. Acad. Sci.* 942, 220–227. doi:10.1111/j.1749-6632.2001.tb03748.x

Reeves, N. D., Narici, M. V., and Maganaris, C. N. (2006). Myotendinous plasticity to ageing and resistance exercise in humans. *Exp. Physiol.* 91, 483–498. doi:10.1113/expphysiol.2005.032896

Rosengren, K. S., Rajendran, K., Contakos, J., Chuang, L.-L., Peterson, M., Doyle, R., et al. (2007). Changing control strategies during standard assessment using computerized dynamic posturography with older women. *Gait Posture* 25, 215–221. doi:10.1016/j.gaitpost.2006.03.009

Rosenhall, U. (1973). Degenerative patterns in the aging human vestibular neuro-epithelia. *Acta Otolaryngol.* 76, 208–220. doi:10.3109/00016487309121501

Ruhe, A., Fejer, R., and Walker, B. (2010). The test–retest reliability of centre of pressure measures in bipedal static task conditions – a systematic review of the literature. *Gait Posture* 32, 436–445. doi:10.1016/j.gaitpost.2010.09.012

Schieppati, M., Tacchini, E., Nardone, A., Tarantola, J., and Corna, S. (1999). Subjective perception of body sway. *J. Neurol. Neurosurg. Psychiatr.* 66, 313–322. doi:10.1136/jnnp.66.3.313

Shaffer, S. W., and Harrison, A. L. (2007). Aging of the somatosensory system: a translational perspective. *Phys. Ther.* 87, 193–207. doi:10.2522/ptj.20060083

Shumway-Cook, A., and Woollacott, M. (2001). "Chapter 9: aging and postural control," in *Motor Control: Theory and Practical Applications*, 2nd Edn, ed. M. Biblis (Philadelphia, PA: Lippincott Williams & Wilkins), 222–247.

Speers, R. A., Kuo, A. D., and Horak, F. B. (2002). Contributions of altered sensation and feedback responses to changes in coordination of postural control due to aging. *Gait Posture* 16, 20–30. doi:10.1016/S0966-6362(02)00003-6

Tang, P., and Woollacott, M. (1996). "Balance control in the elderly," in *Clinical Disorders of Balance, Posture and Gait*, eds A. Bronstein, T. Brandt, and M. Woollacott (London: Arnold), 268–286.

Teasdale, N., and Simoneau, M. (2001). Attentional demands for postural control: the effects of aging and sensory reintegration. *Gait Posture* 14, 203–210. doi:10.1016/S0966-6362(01)00134-5

Teasdale, N., Stelmach, G. E., and Breunig, A. (1991). Postural sway characteristics of the elderly under normal and altered visual and support surface conditions. *J. Gerontol.* 46, B238–B244. doi:10.1093/geronj/46.6.B238

Tia, B., Paizis, C., Mourey, F., and Pozzo, T. (2012). Do equilibrium constraints modulate postural reaction when viewing imbalance? *Brain Cogn.* 79, 89–95. doi:10.1016/j.bandc.2012.02.008

Tsai, Y.-C., Hsieh, L.-F., and Yang, S. (2014). Age-related changes in posture response under a continuous and unexpected perturbation. *J. Biomech.* 47, 482–490. doi:10.1016/j.jbiomech.2013.10.047

Van der Kooij, H., Jacobs, R., Koopman, B., and van der Helm, F. (2001). An adaptive model of sensory integration in a dynamic environment applied to human stance control. *Biol. Cybern.* 84, 103–115. doi:10.1007/s004220000196

Van der Kooij, H., and Peterka, R. J. (2011). Non-linear stimulus-response behavior of the human stance control system is predicted by optimization of a system with sensory and motor noise. *J. Comput. Neurosci.* 30, 759–778. doi:10.1007/s10827-010-0291-y

Vette, A. H., Masani, K., Nakazawa, K., and Popovic, M. R. (2010). Neural-mechanical feedback control scheme generates physiological ankle torque fluctuation during quiet stance. *IEEE Trans. Neural. Syst. Rehabil. Eng.* 18, 86–95. doi:10.1109/TNSRE.2009.2037891

Whipple, R., Wolfson, L., Derby, C., Singh, D., and Tobin, J. (1993). Altered sensory function and balance in older persons. *J. Gerontol.* 48, 71–76. doi:10.1093/geronj/48.Special_Issue.71

Winter, D. (1995). Human balance and posture control during standing and walking. *Gait Posture* 3, 193–214. doi:10.1016/0966-6362(95)99069-W

Woollacott, M., Inglin, B., and Manchester, D. (1988). Response preparation and posture control neuromuscular changes in the older adult. *Ann. N. Y. Acad. Sci.* 515, 42–53. doi:10.1111/j.1749-6632.1988.tb32964.x

Woollacott, M. H., and Shumway-Cook, A. (1990). Changes in posture control across the life span – a systems approach. *Phys. Ther.* 70, 799–807.

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

frontiers

EPFL Innovation Park · Building I · 1015 Lausanne · Switzerland
T +41 21 510 17 00 · info@frontiersin.org · frontiersin.org