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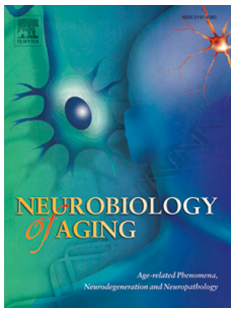

Supplementary motor area—primary motor cortex facilitation in younger but not older adults

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Running head: Reduced SMA—M1 connectivity in older adults.

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Abstract

Growing evidence implicates a decline in white matter integrity in the age-related decline in motor control. Functional neuroimaging studies show significant associations between functional connectivity in the cortical motor network, including the supplementary motor area (SMA), and motor performance. Dual-coil transcranial magnetic stimulation (TMS) studies show facilitatory connections between SMA and the primary motor cortex (M1) in younger adults. Here, we investigated whether SMA—M1 facilitation is affected by age, and whether the strength of SMA—M1 facilitation is associated with bilateral motor control. Dual-coil TMS was used to measure SMA—M1 connectivity in younger (N=20) and older adults (N=18), and bilateral motor control was measured with the assembly sub-test of the Purdue Pegboard and clinical measures of dynamic balance. SMA—M1 facilitation was seen in younger but not older adults, and a significant positive association was found between SMA—M1 facilitation and bimanual performance. These results show that SMA—M1 facilitation is reduced in older adults compared to younger adults, and provide evidence of the functional importance of SMA—M1 facilitation.

Keywords

Supplementary motor area; motor control; aging; transcranial magnetic stimulation; functional connectivity; facilitation

1. Introduction

Aging is accompanied by a decline in motor control across a wide spectrum of gross and finely controlled movements. Older adults are poorer at object manipulation and dexterous control than younger adults (Carmeli et al., 2003). In addition, older adults walk more slowly and have greater variability in gait length and rhythm than younger adults (Hollman et al., 2011). Such declines in voluntary motor control substantially increase the likelihood of a fall (Seidler et al., 2010).

Growing evidence implicates age-related structural and functional changes throughout the cerebral cortex in age-related decline in motor control. Structurally, aging is associated with changes in gray matter and white matter in motor areas of the brain (for review see: Seidler et al., 2010). It is well established that older adults have reduced gray matter volume compared to younger adults (Salat et al., 2004, Good et al., 2001, Raz et al., 1997, Sowell et al., 2003), including greater ventricular (Good et al., 2001) and cerebrospinal fluid volume (Courchesne et al., 2000). Gray matter atrophy is evident in both the pre- and post-central gyri (Good et al., 2001, Salat et al., 2004), with an association between sensorimotor volume and gait characteristics in older adults (Rosano et al., 2008). In addition, older adults have reduced white matter quantity and quality than younger adults, evidenced by reduced axonal and myelin integrity (Ota et al., 2006, Jernigan et al., 2001, Sullivan et al., 2010, Zahr et al., 2009). Age-related decline in the size of the corpus callosum, the white matter tract connecting the two hemispheres (Salat et al., 2005, Sullivan et al., 2010, Ota et al., 2006), has been shown to affect activity within motor areas of the brain, including the supplementary motor area (Stancak et al., 2003). The decline in white matter is important because it affects information transfer between brain regions, or ‘functional connectivity’ (Bruijn et al., 2014, Wu, 2005, Zahr et al., 2009).

Functional neuroimaging studies show a significant positive association between functional connectivity within the cortical motor network, including the supplementary motor area (SMA), and voluntary motor control (Wu et al., 2007, Bernard et al., 2013, Marchand et al., 2011). Three lines of evidence strongly suggest a role of SMA in bilateral voluntary movement. First, SMA plays a major role in planning and executing rhythmic bilateral movements of the upper and lower limbs (Nachev et al., 2008, Hanakawa et al., 1999, Malouin et al., 2003, Rojkova et al., 2016). Second, SMA has a major inhibitory role for preventing execution of an inappropriate motor plan, switching to an appropriate motor plan, and modifying existing motor plans based on feedback (Sumner et al., 2007, Kasess et al., 2008). Third, SMA is crucial for timing and rhythm production (Pastor et al., 2004, Rao et al., 1997). All of these processes are important for coordination of upper- and lower-limb movements in gait.

Functional magnetic resonance imaging (fMRI) has shown increased coupling of SMA and the primary motor cortex (M1) during bimanual movements (Grefkes et al., 2008), suggesting a key role of SMA-M1 interactions in the cortical motor network implicated in bimanual movements. However, it is not possible from these studies to determine whether the associations between SMA and M1 are mediated by direct connectivity between SMA and M1, or whether the connectivity is inhibitory or facilitatory. Therefore, the functional nature and importance of connectivity between SMA and M1 is not well characterised. The SMA, which lies anterior to M1, is densely connected with M1 (Dum and Strick, 2002). Electrical stimulation of SMA, in non-human primates, evokes short-latency responses in M1 (Tokuno and Nambu, 2000). Similarly, SMA stimulation evokes short-latency responses in M1 in epilepsy patient data, gathered via subdural electrodes implanted in the lateral and medial

frontal cortex (Matsumoto et al., 2007). Pharmacological studies provide support for glutamatergic anatomical connections between SMA and M1 (Shima and Tanji, 1998).

Transcranial magnetic stimulation is a non-invasive method for stimulating the brain. A brief, high current electrical pulse is delivered through a handheld coil placed over the scalp, which induces a magnetic field that passes through the scalp and skull with little attenuation. The magnetic field induces current flow in the underlying brain tissue, and if the stimulation is sufficiently intense, will result in depolarisation of the neurons (Hallett, 2007, Barker et al., 1985). A single suprathreshold intensity *test* TMS pulse delivered to M1 elicits a motor evoked potential (MEP) in the muscle(s) controlled by the cortical representation(s) over which the pulse was delivered. The MEP is the result of TMS activating motor cortical output cells and evoking a complex descending corticospinal volley that is composed of a series of components known as direct (D) and indirect (I) waves. The D-wave is thought to reflect direct activation of the corticospinal output cells, while the later I-waves reflect trans-synaptic activation of the output cells (Di Lazzaro et al., 2012). Therefore, the MEP amplitude provides a measure of corticospinal system excitability (Hallett, 2007). Furthermore, single-pulse TMS can also be used to determine the threshold for producing an MEP, known as the resting motor threshold (RMT), which reflects membrane excitability (Ziemann, 2004). A large body of literature using pharmacological intervention has shown that short- and long-interval intracortical inhibition (SICI; LICI) and short-interval intracortical facilitation (ICF)—all of which are measured using paired-pulse TMS—are mediated by GABAergic and glutamatergic transmission, respectively (for review see: Ziemann, 2004, Nitsche et al., 2012).

Dual-coil TMS can be used to measure functionally relevant connections in the cortical motor network (Rothwell, 2011), including connectivity between SMA and M1 (Arai et al., 2012, Arai et al., 2011). When a *conditioning* TMS pulse delivered to the SMA precedes a *test* TMS pulse delivered to M1 at appropriate intervals, the MEP elicited by the test TMS pulse is facilitated in younger adults (Arai et al., 2012, Arai et al., 2011). The facilitatory effect of SMA stimulation on M1 is suggested to be due to activation of excitatory networks between SMA and M1 (Arai et al., 2012), mediated by direct glutamatergic connectivity (Muakkassa and Strick, 1979, Luppino et al., 1993, Shima and Tanji, 1998)

The evidence suggesting an important role of SMA—M1 interactions in bilateral motor control (for review see: Nachev et al., 2008), together with the well-characterised age-related decline in bilateral motor control and white matter integrity (for review see: Seidler et al., 2010), led us to hypothesise that facilitatory connectivity between SMA and M1 declines with age. Here, we investigated whether the facilitatory interaction between SMA and M1 in younger adults persists in community ambulant older adults, and whether the strength of SMA—M1 connectivity is associated with bilateral motor control. Dual-coil TMS was used to measure SMA—M1 connectivity in younger and older adults, and bilateral motor control was measured with the assembly sub-test of the Purdue Pegboard (upper limb) and clinical measures of dynamic balance (lower limb).

2. Methods

2.1 Subjects

Twenty right handed younger (12 male, $M = 25 \pm 4.6$ years, range 19-35 years) and 18 older adults (11 male, $M = 70 \pm 6.2$ years, range 61-84 years) participated in this study. The older adults were recruited from group exercise classes that were organized by local retirement

villages (in which people aged over 55 years live independently). None of the participants were taking any medication at the time of testing, or required walking aids. Handedness was determined using the Edinburgh Handedness Inventory - short version (Veale, 2014) which revealed that all were strongly right-handed with laterality quotients (M = 93.16, SD = 8.81). All subjects were screened for conditions that would contraindicate TMS (Rossi et al., 2009, Rossi et al., 2011). The study was approved by the Murdoch University Human Research Ethics Committee (2014/247) and all subjects gave written informed consent prior to testing.

2.2 Physical performance measures

The Purdue Pegboard task, a validated measure of manual dexterity, was used to assess bimanual performance (Lafayette instrument company, USA); following the standardized testing procedure, participants used alternating hands to pick-up and insert four items (a peg, a washer, a collar, and a second washer) to assemble an object, into a hole on the pegboard (in 60 s). The timed up and go (TUG) test was used to measure functional mobility (Shumway-Cook et al., 2000); participants started in a seated position on a standard chair (46 cm seat height), stood, walked 3 metres as quickly as possible, turned, and walked to return to the seated position. The four square step test (FSST) was used to assess dynamic balance (Dite and Temple, 2002); participants stepped into four quadrants, first clockwise, and then anti-clockwise. Time taken to complete the TUG and FSST was recorded. All tasks were performed as quickly as possible. The order of testing for the physical performance tasks was randomised across individuals.

2.3 Transcranial magnetic stimulation

Electromyographic (EMG) activity was recorded from the relaxed first dorsal interosseous (FDI) muscle of the (dominant) right hand using surface electrodes placed in a belly-tendon

montage. The EMG signal was amplified (x1000; Cambridge Electronic Design (CED) 1902 amplifier), band pass filtered (20-1000 Hz) and digitized at a sampling rate of 2 kHz (CED 1401 interface). Dual-coil TMS was delivered through two Magstim 200^2 stimulators (Magstim Co., Whitland, Dyfedd, UK), each connected to a figure-of-eight coil (50-mm diameter).

M1 stimulation was delivered with the coil placed tangentially to the scalp with the handle pointing backwards 45° away from the midline to induce a posterior-anterior current in the cortex. To determine the optimal stimulation site, suprathreshold pulses were delivered at a number of sites to identify the site from which MEPs were consistently evoked in the target FDI. M1 stimulation was set to the intensity that elicited MEPs of ~1 mV in FDI (SI_{1mV}).

SMA stimulation was delivered with the coil placed on the midline, with the handle pointing forward. The centre of the coil was placed 4 cm anterior to Cz (the mid point between the nasion-inion and interaural plane; International 10-20 System) as per previous research using dual-coil TMS to measure SMA—M1 connectivity (Arai et al., 2012, Arai et al., 2011). In both of these previous studies, individual MRIs and neuronavigation used in a sub-sample of the participants confirmed that positioning the coil 4 cm anterior to Cz aligns with anatomical landmarks that identify SMA. SMA stimulation was set at 140% active motor threshold (AMT). AMT was defined as the minimum stimulus intensity (as a percentage of maximum stimulator output; MSO) required to elicit MEPs of at least 0.2 mV in at least 3 out of 5 consecutive trials during an isometric contraction of 10% maximum voluntary contraction (Goldsworthy et al., 2012, Hordacre et al., 2017, Di Lazzaro et al., 2007, Hamada et al., 2013, Arai et al., 2012, Arai et al., 2011). AMT was determined at the optimal stimulation site for M1 with the coil used for SMA stimulation.

Blocks of stimuli comprised single-pulse trials delivered to M1 (SI_{1mV}) and dual-coil paired-pulse trials. There were three dual-coil paired-pulse conditions: (1) SMA (140% AMT) preceding M1 (SI_{1mV}) by a 6 ms inter-stimulus interval (ISI); (2) SMA (140% AMT) preceding M1 (SI_{1mV}) by an 8 ms ISI; and (3) pre-SMA (140% AMT) preceding M1 (SI_{1mV}) by a 6 or 8 ms ISI (counterbalanced across individuals). The two ISIs were tested because previous research showed significant facilitation of M1 by SMA at a 6 ms ISI but not a 3 ms or 15 ms ISI (Arai et al., 2012, Arai et al., 2011); we included the 8 ms ISI here as a first step to test whether there were latency differences in SMA—M1 facilitation between younger and older adults. The pre-SMA stimulation was included as a control condition because previous research has shown no facilitation of M1 following pre-SMA stimulation (Arai et al., 2012, Arai et al., 2011), consistent with the absence of direct anatomical connections between pre-SMA and M1 (Luppino et al., 1993, Johansen-Berg et al., 2004, Kim et al., 2010). For pre-SMA stimulation, the coil was placed 7 cm anterior to Cz (Arai et al., 2012, Arai et al., 2011). Each condition consisted of 30 trials. The order of testing for the three dual-coil conditions was randomised across individuals. For half the subjects, TMS measures were obtained before the physical performance measures, for the remaining half, TMS was obtained after (order counter-balanced across participants).

2.4 Data Analysis

Trials in which pre-TMS EMG activity exceeded 30 μV (peak-to-peak) were excluded from analysis. Peak-to-peak MEP amplitude in mV was obtained for 50-ms of EMG starting 10-ms after the test stimulus for both single- and dual-coil paired-pulse trials. The mean MEP amplitude for each dual-coil paired-pulse condition was expressed as a ratio of the mean

MEP amplitude for single-pulse TMS. The ratios were log-transformed prior to analysis to normalise the distributions, and back-transformed means are reported.

A multivariate analysis of variance (MANOVA) was performed to test for differences in scores on the physical performance tasks (Purdue, TUG, FSST) between younger and older adults. Conditional on a significant main effect, univariate *F*-tests comparing scores of the physical performance tasks between younger and older adults were conducted. Two-way repeated measures analyses of variance (ANOVA) were performed to test for differences in SMA—M1 connectivity, with within-subject factor of CONDITION (2 levels: 6 ms ISI, 8 ms ISI), and between-subject factor of AGE (2 levels: younger, older). Conditional on significant main effects or an interaction, post hoc independent samples *t*-tests comparing SMA-M1 ratios between younger and older adults were conducted for the different conditions. Correlational analyses were performed to examine associations between SMA–M1 connectivity and physical performance measures using Pearson's correlation coefficient.

3. Results

Figure 1 shows Mean AMT, SI_{1mV}, and MEP amplitude elicited by SI_{1mV} for younger and older adults. There were no significant differences in AMT, SI_{1mV}, or MEP amplitude elicited by SI_{1mV} between younger and older adults (all t_{36} <0.53, all p > .602). Figure 2 shows SMA—M1 connectivity in younger and older adults (top) and associations between SMA—M1 connectivity and performance on the behavioural tasks (bottom). MEP amplitude following SMA—M1 stimulation with a 6 ms ISI was greater than the MEP following M1-alone stimulation for younger but not older adults. A two way ANOVA performed on the SMA-M1 ratios showed no main effect of CONDITION ($F_{1,36}$ = 3.50, p = .069), but a main effect of GROUP ($F_{1,36}$ = 6.74, p = .014) and a GROUP*CONDITION interaction ($F_{1,36}$ =

4.85, p = .034). Post hoc t-tests showed a significant difference in SMA—M1 ratios between younger and older adults at the 6 ms ISI (independent t_{36} = 2.83, p = .008) but not the 8 ms ISI (independent t_{36} = 1.08, p = .287; Fig 2, panel B).

The independent samples t-test performed to compare pre-SMA—M1 ratios in younger and older adults showed no significant difference between groups (t_{36} = 0.66, p = .515).

The mean number of items placed for the Purdue Pegboard for older adults was 26.6 (5.9), which is consistent with normative data (26.6 ± 5.2; Agnew et al., 1988). The mean time taken to complete the FSST for older adults was 7.76 (1.36) seconds, which is consistent with normative data (8.7 seconds; Dite and Temple, 2002). The mean time taken to complete the TUG for older adults was 6.20 (0.96) seconds, which is consistent with, albeit slightly faster than, normative data (8.4 ± 1.7 seconds; Shumway-Cook et al., 2000). A MANOVA performed on the physical performance data showed a statistically significant difference in scores on the physical performance tasks based on age group ($F_{3,34}$ = 11.51, p < .001); post hoc univariate F-tests showed that younger adults performed significantly better than older adults on the Purdue, TUG, and FSST (all $F_{1,36}$ >10.78, all p < .002). The bottom row of Figure 2 shows associations between SMA—M1 ratio (6 ms ISI) and scores on the physical performance tasks. Greater SMA—M1 facilitation (i.e. ratio greater than 0) was associated with a greater number of objects assembled on the Purdue, and faster performance on the TUG and FSST. When using Bonferroni correction for multiple comparisons, the association between SMA—M1 connectivity and Purdue performance was statistically significant (r = 0.53, p < .001; 95% confidence limits: 0.25, 0.73; panel C); the associations between SMA—M1 connectivity and TUG (r = 0.38, p = .018; 95% confidence limits: 0.07, 0.62;

panel D) and FSST (r = 0.37, *p* = .022; 95% confidence limits: 0.06, 0.62; panel E) just failed to reach statistical significance.

4. Discussion

The current study has two key findings. First, the facilitatory interactions between SMA—M1 in younger adults is significantly reduced in older adults. Second, the magnitude of SMA—M1 facilitation is positively associated with bimanual performance. Together, these findings show that SMA—M1 facilitation is functionally relevant and is reduced in older adults compared to younger adults; this is important for understanding the neural correlates of age-related decline in voluntary movement.

Behaviourally, younger adults assembled more objects on the Purdue Pegboard task than older adults, and younger adults performed the TUG and FSST faster than older adults, consistent with published normative data for healthy older adults (Agnew et al., 1988, Desrosiers et al., 1995, Dite and Temple, 2002, Shumway-Cook et al., 2000, Steffen et al., 2002). These results show poorer performance for upper- and lower-limb bilateral movements in older adults compared to younger adults.

In younger adults, SMA stimulation facilitated M1 at an ISI of 6 ms, replicating previous research (Arai et al., 2012, Arai et al., 2011). Research using direct cortical stimulation in non-human primates, and human patients with implanted electrodes, suggests a cortical origin of the facilitatory effect of SMA on M1, likely mediated by glutamatergic connections (Dum and Strick, 2002, Tokuno and Nambu, 2000, Matsumoto et al., 2007, Shima and Tanji, 1998). In line with this, SMA—M1 facilitation is only evident when the M1 coil induces current in an antero-medial direction, suggesting that SMA—M1 facilitation is mediated by excitatory

interneurons in M1 (that generate the I1 wave) (Arai et al., 2011). However, we did not measure spinal excitability in the current study and, therefore, cannot rule out a spinal contribution to the SMA—M1 facilitation.

The novel finding here is that the SMA—M1 facilitation seen in younger adults is significantly reduced in older adults, suggesting that direct SMA—M1 connectivity is affected in older adults. This, taken together with the neuroimaging data that show a decline in white-matter integrity with age, particularly in the frontal cortex (Jernigan et al., 2001), suggests that the reduced SMA—M1 facilitation in older than younger adults is mediated by a decline in white matter. This fits with reports of reduced connectivity within frontal cortical networks in older compared to younger adults, measured using dual-coil TMS – specifically, reduced functional connectivity between dorsal premotor cortex and M1 (both contralateral and ipsilateral) and between dorsolateral prefrontal cortex and M1 (contralateral) in older adults compared to younger adults (Ni et al., 2015, Fujiyama et al., 2016, Hinder et al., 2012). Importantly, Fujiyama and colleagues (2016) showed a significant association between PMd—M1 connectivity measured using dual-coil TMS and fractional anisotropy between the two brain regions measured using diffusion tensor imaging. This further supports the suggestion that the decline in functional connectivity between frontal cortical regions is mediated by a decline in white matter infrastructure.

The current results show, for the first time, a significant association between bilateral motor performance and SMA—M1 facilitation. Specifically, greater SMA—M1 facilitation was associated with better performance on the bimanual assembly subtest of the Purdue Pegboard task. Previous research has shown that modulating the excitability of SMA with non-invasive brain stimulation affects bimanual performance (Serrien et al., 2002, Steyvers et al., 2003,

Carter et al., 2015); the current findings extend this, providing evidence that facilitatory connections between SMA and M1 are important for bimanual motor performance. In addition, the current results show moderate associations between SMA—M1 connectivity and dynamic balance. Specifically, greater facilitatory SMA—M1 connectivity was associated with faster completion of the TUG and the FSST. Although the associations were not statistically significant after correcting for multiple comparisons, the results do provide some evidence to suggest that connectivity measured between SMA and the hand representation of M1 reflect the connectivity between SMA and M1 more generally; this warrants further investigation.

In the current study, SMA—M1 facilitation was detected at the 6 ms ISI but not the 8 ms ISI, adding to previous research showing SMA facilitates M1 at an ISI of 6 ms but not 3 or 15 ms (Arai et al., 2012, Arai et al., 2011). Non-human primate research shows peak excitatory responses in M1 3-4 ms following SMA stimulation (Tokuno and Nambu, 2000); the facilitatory response in humans at 6 ms fits with these results given longer SMA—M1 conduction distance in humans (Arai et al., 2012, Arai et al., 2011). Future research should comprehensively investigate the ISIs at which SMA—M1 facilitation is present. In addition, there was no influence of pre-SMA stimulation on M1 at either the 6 ms or 8 ms ISI, either in younger or older adults. This is consistent with previous dual-coil TMS studies showing facilitation following SMA but not pre-SMA stimulation (Arai et al., 2012, Arai et al., 2011). Furthermore, this finding is consistent with studies in humans and non-human primates showing direct anatomical connections between SMA and M1 but not between pre-SMA and M1 (Luppino et al., 1993, Johansen-Berg et al., 2004, Kim et al., 2010).

It is important to note that aging is a process that occurs across the lifespan. Our primary aim was to examine whether SMA—M1 connectivity was associated with voluntary motor control in younger and older adults. Previous literature consistently shows a decline in motor control from the sixth decade of life: from 60 years, walking speed declines (Ferrucci et al., 2016), senile tremor emerges (Deuschl et al., 2015), saccade latency and velocity declines (Irving et al., 2006), and a meta-analysis shows that sensory disturbances largely occur from 60 years (Vrancken et al., 2006). However, structural imaging studies show fractional anisotropy reductions from middle-adulthood (Giorgio et al., 2010, Salat et al., 2005). Therefore, future research should measure SMA—M1 connectivity and voluntary motor control in middle age adults (30 – 60 years) to identify the timing of decline in connectivity and motor control. In line with this suggestion, future research should use structural imaging to characterise changes in brain volume, and identify the occurrence of vascular white matter lesions, including subcortical lesions. Although the effect of white matter lesions in older adults is not fully understood, it has been proposed that such lesions could affect brain connectivity and plasticity (Galluzzi et al., 2008). Support for this suggestion comes from research showing hyperexcitability of M1 evidenced by reduced motor thresholds and increased intracortical facilitation in vascular cognitive impairment (Bella et al., 2013, Pennisi et al., 2016, Pennisi et al., 2015, Lanza et al., 2017).

Structural imaging would also be valuable to confirm placement of the conditioning stimulus coil using neuronavigation. Although previous research has verified the International 10-20 system to identify SMA and pre-SMA using anatomical landmarks and neuronavigation, the lack of neuronavigation is a limitation of the current study. In fact, it has been suggested that

a functional approach, like the procedure used to identify the M1 hotspot should be combined with the anatomical approach of neuronavigation (Karabanov et al., 2013).

It is also worth noting that in the current study we only measured SMA—M1 facilitation with a single conditioning stimulus intensity. Given that resting motor threshold increases with age (Bhandari et al., 2016), and that conditioning stimulus intensity-dependent connectivity between PMd and M1 is influenced by age (Ni et al., 2015), future studies testing SMA—M1 connectivity with a range of conditioning stimulus intensities are warranted to fully characterise age-related changes in SMA—M1 connectivity. Similarly, future studies examining a larger range of ISI are warranted to determine whether precise timing of SMA—M1 facilitation is affected by age. Future research examining both cortico-cortical connectivity of this scope, combined with structural imaging, might provide insights into the value of dual-coil TMS measures of connectivity as a diagnostic tool for subclinical health problems, and for tracking the development of clinical abnormalities. Finally, the sample of older adults who participated were from physical activity groups, and we do not have demographic or clinical characteristics of the sample. Therefore, the conclusions from the present study are limited to physically active older adults; future work quantifying physical activity levels as well as demographic and clinical characteristics, including peripheral neuropathies, is warranted.

Conclusions

The current study shows that SMA—M1 facilitation is reduced in older adults compared to younger adults. This adds to the growing literature reporting age-related decline in connectivity and white matter in the cortical motor network. Furthermore, the current study

shows a significant association between SMA—M1 facilitation and bilateral movement, providing evidence of the functional importance of SMA—M1 facilitation. The current study contributes to our understanding of the complex age-related decline in voluntary movement, and provides a physiological basis for the development of interventions to improve bilateral movement. Finally, it is worth noting that dual-site TMS provides a valuable method for examining cortico-cortical connectivity, and thus has the potential to increase our understanding of the pathophysiology of neurological disorders such as Parkinson's disease and dementia.

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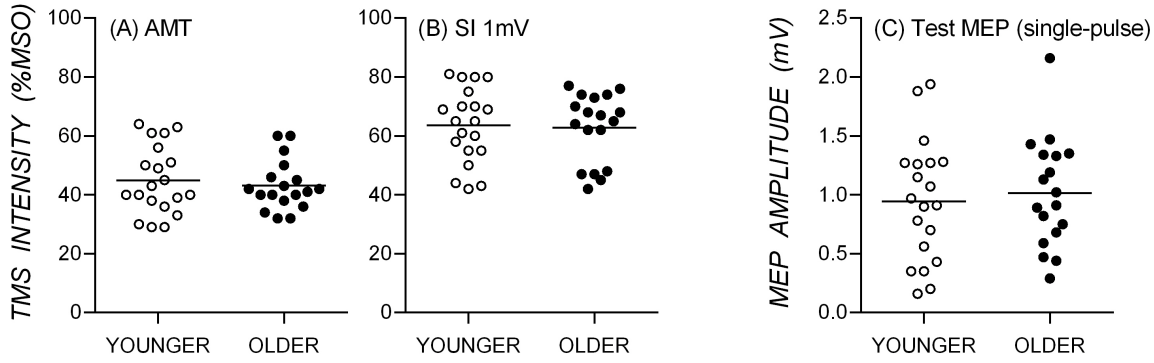
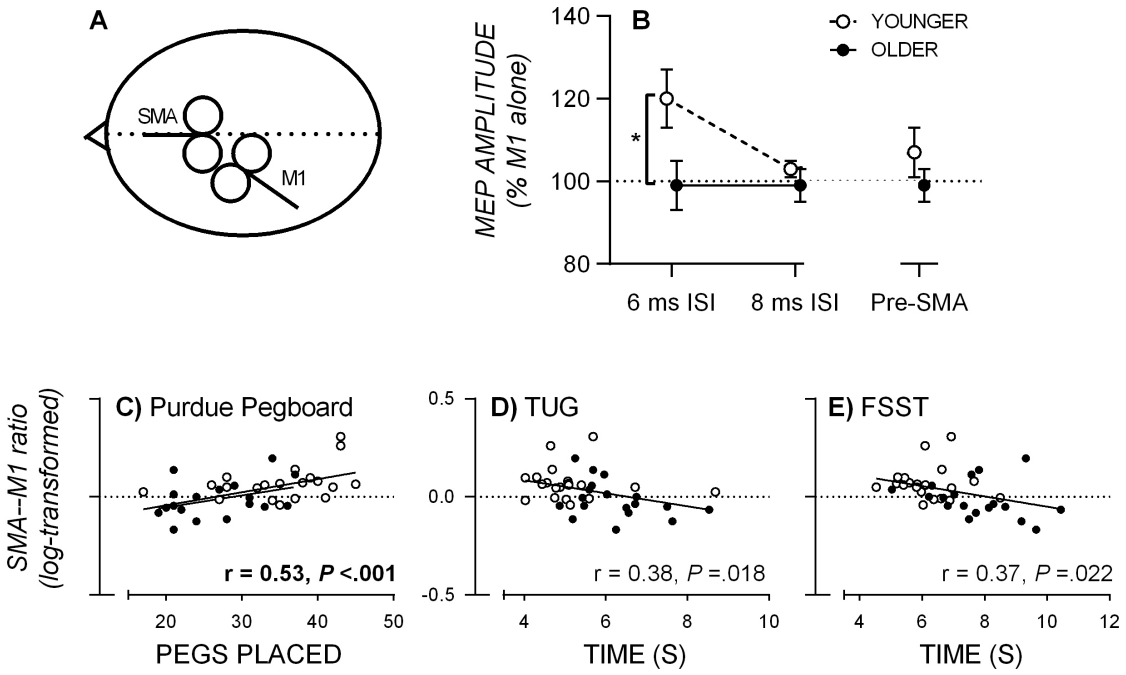
Figure 1. Column scatter graphs showing the TMS intensity of AMT (A) and SI_{1mV} (B), and the mean MEP amplitude to test-alone TMS trials (C) for younger (open symbols) and older adults (closed symbols).

Figure 2. SMA—M1 connectivity in younger and older adults. (A) paired-pulse dual-coil TMS setup to measure connectivity between SMA and M1. The conditioning stimulus was delivered to SMA, located 4 cm anterior to Cz; the test stimulus was delivered to M1, at the optimal site for eliciting MEPs in FDI. (B) Mean MEP amplitude from dual-coil conditions expressed as a percentage of mean MEP amplitude from the single pulse condition for younger (open symbols) and older adults (filled symbols). For the 6 ms ISI, younger but not older adults show significant MEP facilitation. * represents $p < .05$. (C-E) Associations between SMA-M1 connectivity and performance on the Purdue Pegboard task (C), TUG (D), and FSST (E). Bolded text represents $p < .017$ (Bonferroni corrected).





Highlights

- Decline in white matter implicated in age-related decline in motor control
- SMA—M1 facilitation evident in younger but not older adults
- SMA—M1 facilitation is positively associated with bimanual motor control