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ORIGINAL ARTICLE

You Are as Old as the Connectivity You Keep: Distinct Neurophysiological Mechanisms Underlying Age-Related Changes in Hand Dexterity and Strength

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Background. Aging can lead to a decline in motor control. While age-related motor impairments have been documented, the underlying changes in cortico-cortical interactions remain poorly understood.

Methods. We took advantage of the high temporal resolution of dual-site transcranial magnetic stimulation (dsTMS) to investigate how communication between higher-order rostral premotor regions and the primary motor cortex (M1) influences motor control in young and elderly adults. We assessed the dynamics of connectivity from the inferior frontal gyrus (IFG) or pre-supplementary motor area (preSMA) to M1, by testing how conditioning of the IFG/preSMA affected the amplitude of motor evoked potentials (MEPs) induced by M1 stimulation at different temporal intervals. Moreover, we explored how age-related changes in premotor-M1 interactions relate to motor performance.

Results. Our results show that both young and elderly adults had excitatory IFG-M1 and preSMA-M1 interactions, but the two groups' timing and strength differed. In young adults, IFG-M1 interactions were early and time-specific (8 ms), whereas in older individuals, they were delayed and more prolonged (12-16 ms). PreSMA-M1 interactions emerged early (6 ms) and peaked at 10-12 ms in young individuals but were attenuated in older individuals. Critically, a connectivity profile of the IFG-M1 circuit like that of the young cohort predicted better dexterity in older individuals, while preserved preSMA-M1 interactions predicted greater strength, suggesting that age-related motor decline is associated with specific changes in premotor-motor networks.

Conclusions. Preserving youthful motor network connectivity in older individuals is related to maintaining motor performance and providing information for interventions targeting aging effects on behavior.

Key Words: Aging, Brain connectome, Premotor cortex, Transcranial magnetic stimulation, Hand strength, Motor skills.

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Introduction

Aging can be associated with a progressive decay in motor control, leading to limitations in daily activities, independence, and well-being. Older adults often experience reduced motor performance in a variety of tasks. For instance, they exhibit longer response times (1,2) and increased movement duration than younger adults (3–6). Hand strength typically decreases, and its regulation becomes less efficient in older individuals (6,7). The reasons for this decline are multifactorial. Lifestyle factors, such as nutrition and physical activity, diseases, and peripheral changes involving muscles, receptors, and nerves, play a significant role in age-related decline. However, a growing body of research suggests that physiological changes in the central nervous system are also crucial (8–10).

Neuroimaging studies have demonstrated a correlation between poor motor performance and age-related structural and functional brain changes (9,11), including reduced gray and white matter volume in premotor and motor areas (11–13). The deterioration of white matter, is particularly noteworthy, as it may indicate reduced efficiency and functionality of brain networks (11,14,15). However, existing studies do not provide detailed information on the temporal dynamics of neural interactions between premotor and motor networks and whether effective connectivity in premotor-motor networks predicts motor decline in the elderly. To address this gap, we investigated the relationship between age-related changes in motor performance and neurophysiological indices of cortico-cortical connectivity strength using dual-site transcranial magnetic stimulation (dsTMS).

The dsTMS method allows the investigation of time-resolved effective connectivity by delivering two TMS pulses at varying interstimulus intervals (ISIs) over two cortical areas (16,17). A test stimulus (TS) to the primary motor cortex (M1) is used to record a motor-evoked potential (MEP) in peripheral muscles and to assess motor excitability. To quantify the effective connectivity between the M1 and a remote functionally connected target area, the TS is preceded in some trials by a conditioning stimulus (CS) delivered to the second site through another coil. The strength of the connectivity is measured by how much the CS affects M1 excitability, as reflected in the amplitude of the MEPs. The magnitude of this influence depends on the strength of the cortico-cortical projections from the conditioned site to M1. The dynamics of effective connectivity can be precisely mapped by systematically probing the ISIs between the CS and TS at several different values (16,18).

This method has been used in young adults to study influences on M1 from its contralateral homologue (19,20) and non-primary motor regions (21–25). In the elderly population, previous dsTMS studies have mainly focused on changes in interhemispheric interactions between the two M1s (26–30), while limited research has examined the interactions between the supplementary motor area (SMA) and M1 (31–33). However, information on age-related changes in rostral premotor-M1 intrahemispheric connectivity and their contribution to manual performance decline remains scarce.

Here, we focused on investigating the connectivity between M1 and two ventral/mesial rostral premotor sites involved in different functional motor streams (34,35): the left posterior inferior frontal gyrus (IFG, bordering the ventral premotor cortex) and the pre-supplementary motor area (preSMA; bordering the SMA itself). The IFG and the adjacent ventral premotor cortex have been widely related to externally triggered actions, playing a key role in sensorimotor transformations and visually guided actions, such as grasping and manipulating objects (36–40). The supplementary motor complex (which includes SMA and preSMA), on the other hand, is essential for the generation of self-initiated and endogenously guided movements, such as the execution of fixed motor sequences or intentional movements (41–44).

We assembled a battery of six manual tests that potentially depend on the IFG/preSMA connectivity with M1. Two of these tests measured peak whole hand and precision grip strength production. Previous studies suggest that manual strength is positively correlated with contralateral (to the effector) M1 engagement, but some evidence has also found an association between strength and increased motor-related activity in non-primary motor areas such as IFG (especially in precision grip tasks) and preSMA/SMA (27,45–48). The remaining four tasks require different degrees of fast and fine control of hand movements (49–52), which rely on ventral premotor-motor networks (36–40). Therefore, we hypothesized that neurophysiological markers of age-related decline in IFG-M1 and preSMA-M1 connectivity may help explain the behavioral decline in strength and manual dexterity in the elderly.

We used dsTMS to investigate the neural interactions between the left IFG and the preSMA and the ipsilateral M1 in young and elderly participants. We investigated the dynamics of cortico-cortical IFG-M1 and preSMA-M1 interactions by testing different ISIs within an early time window (4–20 ms). Moreover, we assessed motor performance using behavioral tests to probe fine hand motor control and strength generation. By examining the relationship between cortico-cortical modulations and hand motor performance, we aimed to identify neurophysiological markers associated with poor/efficient motor control in the elderly.

Materials and Methods

Participants

Thirty-seven healthy volunteers aged 20–83 years participated in the study after providing written informed

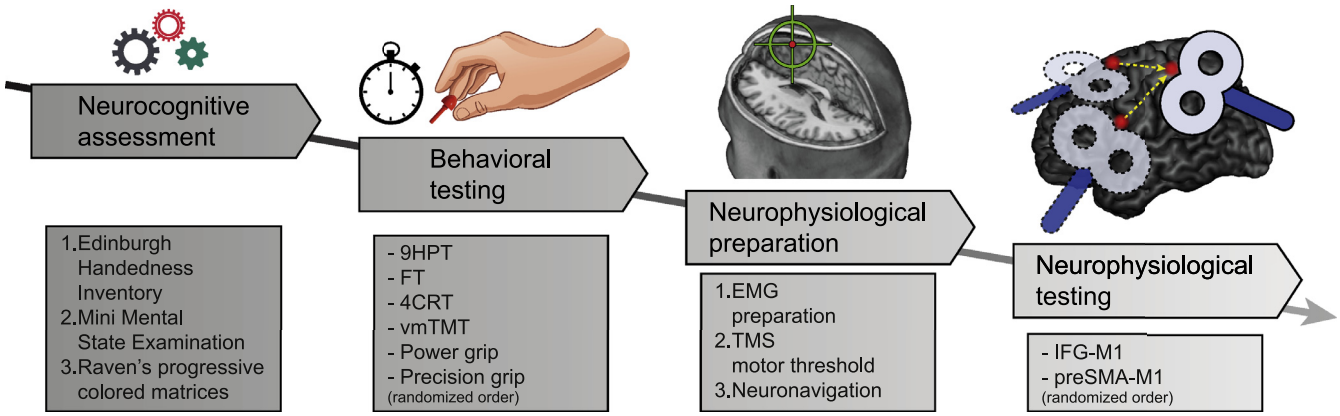

Figure 1. Study timeline; representation of the experimental procedure. The experiment began with handedness and neurocognitive assessments, including the Edinburgh Handedness Inventory, the Mini-Mental State Examination (MMSE), and the Raven's Colored Progressive Matrices (RCPM). Participants then performed six behavioral tasks in randomized order: the 9-hole pegboard test (9HPT), the finger tapping test (FT), the 4-choice reaction time task (4CRT), the visuomotor trail-making test (vmTMT), and a dynamometer assessment of power and pinch grip strength. Finally, after neurophysiological preparation, effective connectivity between the IFG or preSMA and M1 was assessed by dsTMS.

consent. Participants reported no history of neurological, cardiological, or psychiatric pathologies and were not taking any medications that could interact with the effects of TMS (53). Sample size was determined a priori by power analysis using G*Power (v. 3.1.9.4). Assuming a small-to-moderate effect size f (f = 0.18), an alpha probability of 5%, and a power of 95%, a two-group design (older and younger adults) with 14 repeated measures (seven ISIs for each of the two areas) would require a sample size of at least 32 participants. The experimental procedures were approved by the Bioethics Committee of the University of Bologna (2.6/07.12.16) and were conducted in accordance with the 1964 Declaration of Helsinki and subsequent amendments (54). Three participants did not complete the experimental session, as two elderly participants were excluded due to their inability to maintain muscle relaxation during the TMS test, and one elderly participant was excluded because reliable MEPs could not be elicited. The final sample consisted of 17 young adults (8 females, mean age 23 ± 2.3 years) and 17 older adults (9 females, mean age 70 ± 6.1 years). All participants, except one whose score did not indicate a specific preference, were right-handed according to the Edinburgh Handedness Inventory (EHI, mean score 84.8 ± 15.3, range 37-100). All participants had a normal cognitive performance as assessed by the Mini-Mental State Examination (MMSE, mean corrected score 26.6 ± 1, range 24.2-28.4) and the Raven's Colored Progressive Matrices (RCPM, mean corrected score 33.1 ± 3, range 29-39).

General Procedure

At the beginning of the study, we assessed the participants' laterality quotient for handedness using the EHI and their cognitive performance using the MMSE and RCPM tests. Next, we evaluated participants' behavioral performance through a series of six motor tasks, with the order of the tasks counterbalanced across participants. After completing the behavioral assessment, participants underwent preparation for TMS. This involved organizing the electromyographic (EMG) setup, locating the TMS target sites, and determining individual stimulation intensities. Two blocks of TMS were then administered, one for each conditioning site (IFG and preSMA), with the order counterbalanced across participants. In each block, a TS was delivered alone over M1 in single-pulse TMS (spTMS) trials or preceded by a CS in dsTMS trials. The CS could be delivered at 7 different ISIs: 4, 6, 8, 10, 12, 16, and 20 ms. Each block consisted of 162 trials, with 36 spTMS trials and 18 dsTMS trials (one for each ISI). The blocks were divided into two parts, with a short break in between. Each part consisted of 81 trials, including nine dsTMS trials for each ISI and 18 spTMS trials, administered in a pseudo-randomized order. The intertrial interval was randomly varied between 5.5 and 6.5 s in 250 ms steps (6 s on average). A schematic representation of the procedure is shown in Figure 1.

Motor Tasks

We evaluated participants' hand-motor performance using a set of tasks that measured dexterity, speed, and strength.

9-hole Pegboard Test (9HPT). This widely used test evaluates fine hand dexterity (3,55). Participants were required to shape their right hand to grasp, move, and manipulate the small pegs. The task required picking up nine pegs from a tray, one by one, and placing them in the narrow holes of a 3 × 3 board (distance between holes: 3.2 cm); then, participants had to remove the pegs one at a time and return them to the tray as quickly as possible (Figure 2A). The execution time to complete the entire pro-

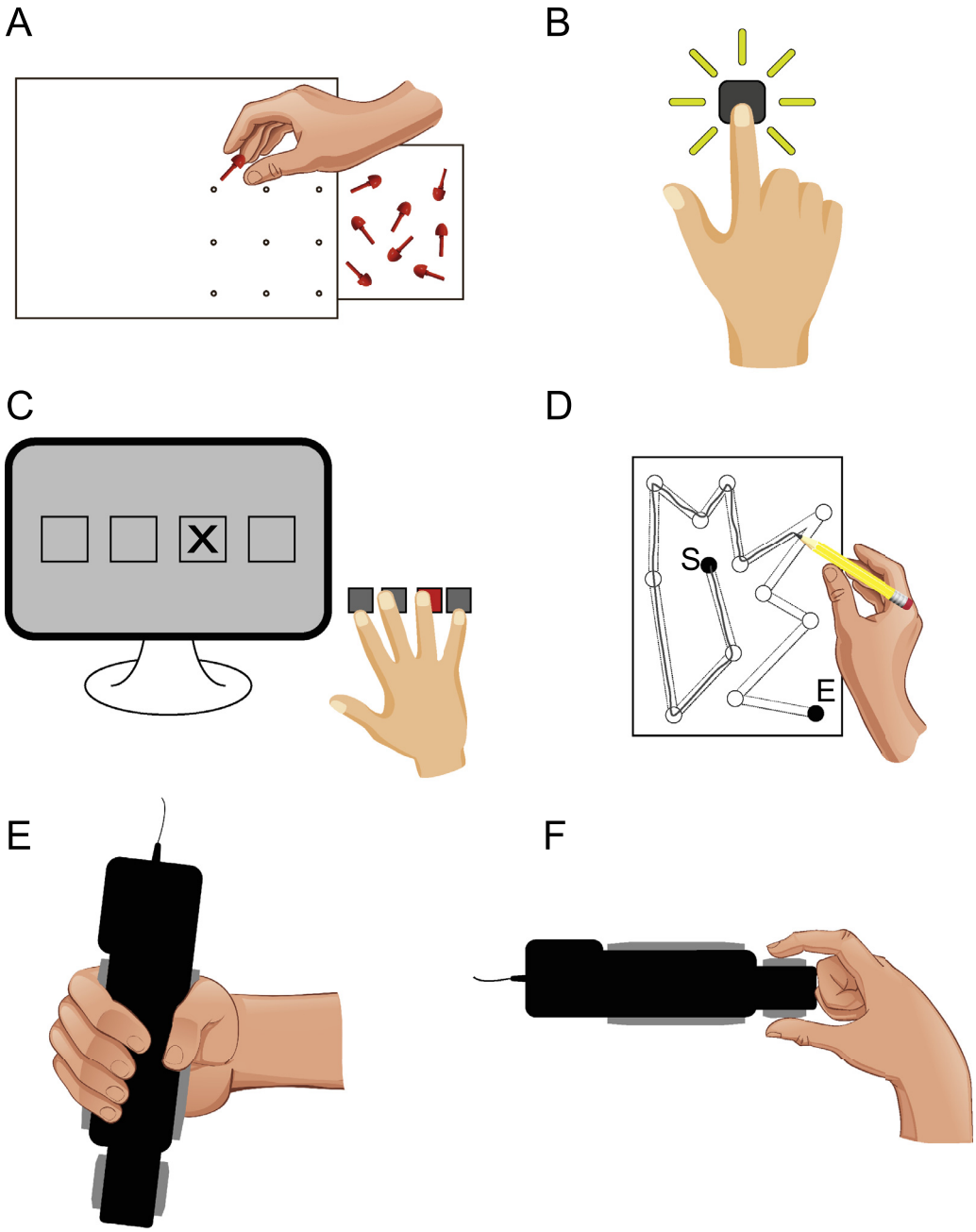

Figure 2. Schematic representation of the motor tasks. A, 9-hole peg test; B, finger tapping; C, 4-choice reaction time task; D, visuomotor trail-making test; E, power grip test; F, pinch grip test.

cedure was recorded as a measure of dexterity. Participants released the space bar on a computer keyboard to activate a MATLAB-controlled stopwatch at the start of each trial and pressed the space bar again when the last peg was replaced in the tray. The test consisted of one familiarization trial and five experimental trials. The trimmed mean of the five trials (excluding the fastest and the slowest trials) provided a robust estimate of central tendency (56).

Finger Tapping (FT). This task primarily evaluates motor speed. Participants were instructed to press a key on a computer keyboard with their right index finger as many times as possible within 5 s (57). They were asked to use only finger movements without using the wrist or forearm (Figure 2B). The test consisted of five experimental trials, and the trimmed mean was used for analysis (56).

Four-choice Reaction Time Task (4CRT). The 4CRT is considered a test of motor speed and general alertness (58). Participants sat in front of a monitor and placed their index, middle, ring, and little fingers on the keyboard. A target (cross) appeared on the screen in one of four

possible locations represented by four blank squares. Participants had to press the key corresponding to the location of the target as quickly as possible (Figure 2C). The task consisted of a 20-trial practice block followed by a 40-trial test block. The median response time (RT) of correct trials was calculated after excluding anticipations (RTs <100 ms) and late responses (RTs >2 s) (% of excluded trials = 3 ± 3%, range: 0-10%). The mean accuracy of the participants was 97 ± 2% (range: 92-100%).

Visuomotor Trail-making Test (vmTMT). This test was used to assess visuomotor abilities. Participants completed a series of 10 trials of increasing complexity. Each trail consisted of a sequence of circles connected by two parallel dotted lines, from a circle labeled "start" to a circle labeled "end" (50). Participants used a pencil to draw a line along the path as quickly as possible, touching each circle and trying to stay within the dotted lines (Figure 2D). The execution time for each trial was measured using the same custom Matlab script described for the 9HPT. This version of the trail-making test minimized cognitive involvement and relied on visuomotor abilities (visuospatial ability, attention, speed, and motor coordination). The mean execution time of all 10 trails was calculated for analysis, as the trails were all different.

Manual Strength Tests. These tests assessed force and pinch grip strength. A digital hand dynamometer (Vernier mod. HD-BTA, Vernier, USA) was used to measure participants' peak strength. Whole hand power grip strength, termed power grip strength (Figure 2E), and thumb-index finger precision grip, termed pinch grip strength (Figure 2F), were tested. Participants were asked to press the strain gauge as hard as possible for approximately 3-5 s. The trimmed means of the five power and pinch grip strength trials were calculated for analysis (56).

TMS and EMG

TMS was delivered using two monophasic waveform stimulators (Magstim 200^2, Magstim, UK) connected to figure-of-eight focal coils with an outer wing diameter of 50 mm. A high-precision trigger station (BrainTrends s.r.l., Italy), controlled by a custom-made Matlab script, was used to trigger the stimulators during the experiment. To obtain a comprehensive assessment of the hand representation in the left M1, we measured the EMG activity of two key intrinsic hand muscles of the participants' right hand, namely the first dorsal interosseus (FDI) and the abductor digiti minimi (ADM) muscles in the participants' right hand. Three Ag/AgCl surface electrodes were placed on each muscle using a tendon-belly montage. The EMG signal was acquired and band-pass filtered (30-500 Hz) at a sampling rate of 5 kHz using a Biopac MP-35 system (Biopac System Inc., USA).

For stimulation of the left M1, the coil was positioned over the hotspot where MEPs of maximal amplitude were obtained from the right FDI muscle. The coil was held tangentially to the scalp at a 45° angle from the midline to induce a posterior-to-anterior current in the brain (59,60). The rMT was determined as the minimum TMS intensity required to generate five out of 10 consecutive MEPs larger than 50 μV in the relaxed FDI (61). The stimulation intensity for M1 (TS) was set to create an FDI MEP of ∼1 mV in amplitude (SI_{1mV}). This intensity was also sufficient to elicit stable MEPs in the ADM muscle, which has a nearby cortical representation in M1.

For IFG and preSMA stimulation, the coil was placed over the scalp sites identified using neuronavigation. For IFG stimulation, the coil was rotated to induce a current flow in the neural tissue pointing toward the M1 site (24,52). For preSMA stimulation, the coil was rotated to induce an antero-medial to postero-lateral current in the brain, directed toward the M1 site (24). The CS intensity for both IFG and preSMA was set at 90% of the individual rMT (62–66), based on previous studies in young participants that reported the facilitatory influence of premotor conditioning on M1 excitability at an early time (65).

Neuronavigation

The M1 stimulation site was functionally localized as the FDI motor hotspot, while the IFG and preSMA sites were identified using the SofTaxic neuronavigation system (EMS, Electromedical systems, Bologna, Italy). The localization procedure involved digitizing four skull landmarks (nasion, inion, and two preauricular points) and approximately 80 points on the scalp to create a uniform representation. We employed a 3D warping procedure to obtain an individual estimated magnetic resonance image (MRI) for each participant. This procedure involved fitting a high-resolution MRI template to the participant's scalp model and craniometric points. Previous research has demonstrated that this procedure ensures a global localization accuracy of approximately 5 mm (67).

We targeted the left IFG posteriorly at the border of the precentral gyrus (ventral premotor cortex), using the Talairach target coordinates x = -54 y = 10, z = 24. These coordinates have been used in previous dsTMS studies (24,52,65) and correspond to a ventral frontal location involved in the planning, execution, and perception of hand actions (37,68–72). For the preSMA, we first placed the coil at Talairach coordinates x = 0, y = 10 (24,25); we then checked that this site was at least 4 cm rostral from the vertex on the sagittal midline, otherwise, we moved the coil rostrally (73). Stimulation sites were marked with a pen on the tight-fitting cap worn by participants. Neuronavigation software was used to estimate Talairach coordinates corresponding to the projection of the scalp target site positions onto the brain surface in both groups (Figure 3).

Data Analysis

To compare the two groups, we conducted a series of preliminary tests using parametric (t-test) or non-parametric

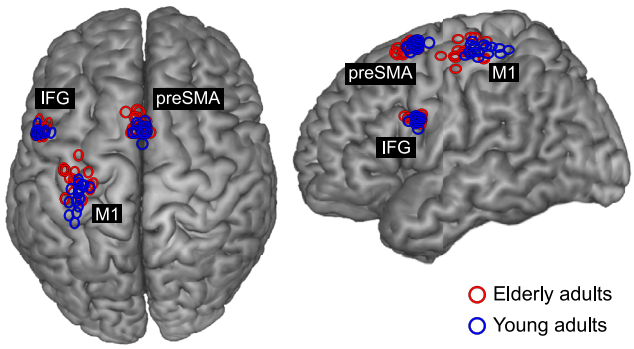

Figure 3. Map of stimulated sites of both groups generated with MRIcron software (www.nitrc.org) after conversion to the MNI coordinate system using the Brett method with GingerALE (http://brainmap.org/ale) for illustrative purposes. Mean (± SD) coordinates for the target sites are reported in Talairach space: M1: younger group: -39.9 ± 2.9, -23.1 ± 6.4, +59.3 ± 2.3; elderly group: -35.6 ± 5.4, -14.8 ± 6.4, +58.2 ± 4.2. IFG: younger group: -54.0 ± 2.3, +8.4 ± 1.2, +23.5 ± 1.6; elderly group: -51.1 ± 4.7, +9.2 ± 3.9, +23.8 ± 1.2. preSMA: younger group: -0.61 ± 2.4, +11.4 ± 2.2, +60.5 ± 2.0; elderly group: -2.0 ± 3.5, +14.9 ± 4.7, +58.2 ± 2.8. The M1 hand representation was found to be more anterior in older participants compared to younger ones (two-sample *t*-tests comparing Talairach coordinate y: $t_{32} = 3.7$, $p = 0.001$; x, z: $t_{32} \geq 1.1$, $p \geq 0.28$).

(Mann-Whitney *U* test; χ^2 test) methods. These tests examined age, years of education, gender balance, TMS intensity (rMT and SI_{1mV}), the principal component coefficients indexing motor performance, and the performance on the six motor tasks (9HPT, FT, VMT, 4-CRT, power grip strength, and pinch grip strength; reported in the Supplementary Material). To address skewness, motor performance data were log-transformed. Additionally, to reduce dimensionality, we performed an exploratory factor analysis using principal component analysis as the extraction method for the six motor performance variables. The analysis was based on the Spearman correlation matrix of the raw variables. We set the criterion for extracting components at eigenvalue >1 and applied a varimax rotation.

MEP amplitudes were measured by calculating the peak-to-peak EMG amplitude (in mV) over a 45-ms time window, starting 15 ms after the TMS pulse. Trials with background EMG activity exceeding two SD of the individual block average, 100 ms before the TMS pulse, were excluded from the analysis (approximately 5% on average). The mean MEP amplitude of each dsTMS trial was expressed as a ratio to the mean of the five nearest spTMS trials. This method was adopted to mitigate the influence of slow, naturally occurring amplitude fluctuations that can affect the size of MEPs (74–77). Assuming that these temporal fluctuations are consistent across both spTMS and dsTMS trials, comparing dsTMS trials to their nearest spTMS counterparts offers the most effective way to address these fluctuations (78–81).

MEP ratios were log-transformed using the formula *ln(value+1)* to address data skewness. A mixed-factor ANOVA was conducted, with Age (two levels: young, elderly) as the between-subjects factor, and Site (two levels: IFG, preSMA), Muscle (two levels: FDI, ADM) and ISI (seven levels: 4, 6, 8, 10, 12, 16, 20 ms) as the within-subject factors. The ANOVA showed a significant three-way interaction of Age x Site x ISI, which was further analyzed through Fisher's least significant difference post-hoc tests.

To investigate the highest order interaction revealed by the main ANOVA, MEP ratios were averaged across muscles, as the factor Muscle was not involved in the interaction. We employed one-sample *t*-tests to compare MEP ratios at each ISI against the null value of 0.69 (i.e., the log transformation of value 1, such as $\ln[1 + 1] = 0.69$), to detect significant conditioning effects induced by dsTMS. We did not correct the one-sample *t*-tests to maximize statistical sensitivity, thereby facilitating the identification of intervals of interest, i.e., singular or adjacent ISIs at which the modulatory effects of premotor conditioning were significantly different from null or diverged between young and elderly adults. These specific intervals were then used for subsequent analyses that shifted the focus from connectivity to the relationship between connectivity and behavior.

Analyses of MEP ratios revealed four intervals of interest (two per conditioning site) showing differences in the strength of connectivity between young and elderly adults (IFG 8 ms, IFG 10-16 ms, preSMA 10-12 ms, and preSMA 20 ms). For intervals of interest spanning multiple ISIs (i.e., IFG 10-16 ms and preSMA 10-12 ms), MEP ratios were averaged across ISIs to obtain a single value. These effective connectivity metrics were then used as predictors in general linear models to examine their relationship with motor performance in both age groups. The dependent variables in the models were the two components extracted from the factorial analysis of the motor performance data (PC1-Dext and PC2-Strength), while the connectivity indices served as continuous predictors and the age group (two levels: young, and elderly) as categorical predictors. The model considered the main effects and two-way interactions between age and neurophysiological indices. To in-

Table 1. Demographic, neurocognitive profile, TMS parameters, and motor performance data (mean ± standard deviation, or numerosity of cases) in the two groups

	Young adults	Elderly adults	Statistical comparison
Age (years)	23.0 ± 2.3 (range: 20–27)	70.1 ± 6.1 (range: 61–83)	$Z = 4.96$, $p < 0.001$
Education (years)	16.4 ± 1.3	13.5 ± 4.5	$Z = 1.58$, $p = 0.11$
Sex balance (F/M)	8/9	9/8	$\chi^2 = 0.12$, $p = 0.73$
MMSE (scores)	26.4 ± 0.9	26.7 ± 1.2	$Z = 1.17$, $p = 0.24$
RCPM (scores)	34.6 ± 1.3	33.5 ± 2.2	$Z = 1.59$, $p = 0.11$
rMT intensity (% MSO)	43.4 ± 7.3	49.1 ± 6.1	$t_{32} = 2.46$, $p = 0.019$
SI_{1mV} (% MSO) IFG block	60.3 ± 11.3	72.5± 12.9	$t_{32} = 2.94$, $p = 0.006$
SI_{1mV} (% MSO) preSMA block	58.6 ± 10.8	68.4 ± 12.3	$t_{32} = 2.47$, $p = 0.019$
PC1-Dext	–0.88 ± 0.3	0.88 ± 0.5	$t_{32} = 12.49$, $p < 0.001$
PC2-Strength	0.11 ± 0.8	–0.11 ± 1.2	$t_{32} = 0.62$, $p = 0.54$

The stimulation intensity necessary to obtain 1 mV MEPs (SI_{1mV}) was assessed in each of the two blocks (IFG and preSMA conditioning).

vestigate the specific relationship between markers of brain connectivity and motor performance in the two groups, in further analyses we included in the models the rMT, MMSE, and RCPM scores in the models as covariates of no interest, even though MMSE and RCPM did not differ between groups (Table 1). This allowed us to test the unique contribution of markers of IFG-M1 and preSMA-M1 connectivity in predicting different aspects of motor performance in young and older participants. All statistical analyses were conducted using SPSS v 28.0.1.1. Unless otherwise stated, values reported in the text are expressed as mean ± standard deviation. The significance level for statistical analyses was set at $p < 0.05$. Effect size measures, such as partial η^2 ($\eta_p{}^2$) and adjusted R^2 ($R^2{}_{adj}$), were calculated for significant main effects/interactions and the general linear models, respectively. For one-sample *t*-tests, between-group and within-group post hoc comparisons, we calculated the respective effect size indices: Cohen's d_z, Cohen's d_s, and Cohen's d_{rm}, following the recommendations of Lakens (82).

Results

Preliminary Analyses: Group Comparisons

To explore differences between young and older participants, we conducted between-group comparisons (Table 1). Age groups did not differ concerning education or sex (all $p \geq 0.11$). Notably, elderly participants were cognitively healthy, as shown by their MMSE and RCPM scores, which were comparable to those of younger adults (all $p \geq 0.11$). Confirming previous literature (83), older participants had a more anterior M1 hand representation (two-sample t-tests comparing Talairach coordinates y: $p = 0.001$; x and z: $p \geq 0.28$), equivalent to a mean distance of 8.4 mm in Euclidean space (Figure 3). Older participants also showed lower overall motor excitability compared to their younger counterparts, as indexed by higher rMT and SI_{1mV} values (all $p \leq 0.019$). Thus, because CS and TS intensities were adjusted based on rMT and SI_{1mV} values, they were on average higher in the elderly compared to the young group. Furthermore, older participants exhibited lower motor performance in tasks requiring manual dexterity and speed (all $p < 0.001$), and in power grip strength ($p = 0.01$). See Supplementary Table 1 in the Supplementary Material for more details on motor tasks.

Table 2. Factor loadings matrix following varimax rotation

	PC1-Dext	PC2-Strength
9HPT	**0.89**	0.10
FT	**–0.83**	0.28
vmTMT	**0.93**	–0.11
4CRT	**0.90**	–0.29
Power grip strength	–0.28	**0.90**
Pinch grip strength	0.01	**0.93**

The highest factor loading is in bold for each of the original variables. The two PCs were interpreted and labeled PC1-Dext and PC2-Strength, based on factor loadings.

Preliminary Analyses: Data Reduction

We conducted an exploratory factor analysis to reduce the dimensionality of the performance data gathered from the six motor tasks. This analysis revealed two components: PC1-Dext, which reflects performance on the dexterity test, and PC2-Strength, which reflects manual strength. The 2-PCs solution explained 85.3% of the variance and was also considered acceptable based on the slope changes in the scree plot of the eigenvalues (Supplementary Figure 1). The other four components had eigenvalues <0.40 and together explained the remaining 14.7% of the variance. We used varimax rotation to obtain a simple structure, and based on the factor loadings, we interpreted and assigned labels to the two PCs (Table 2).

The first PC captured the performance on four motor tasks emphasizing dexterity and motor speed (9HPT, FT, 4CRT, vmTMT), while the second PC represented the scores related to strength tests (power and pinch grip). As a result, we designed these PCs as PC1-Dext and PC2-Strength, respectively. The two groups differed in PC1-Dext ($p < 0.001$), but not on PC2-Strength ($p = 0.54$; Table 1; Supplementary Table 1 for further details).

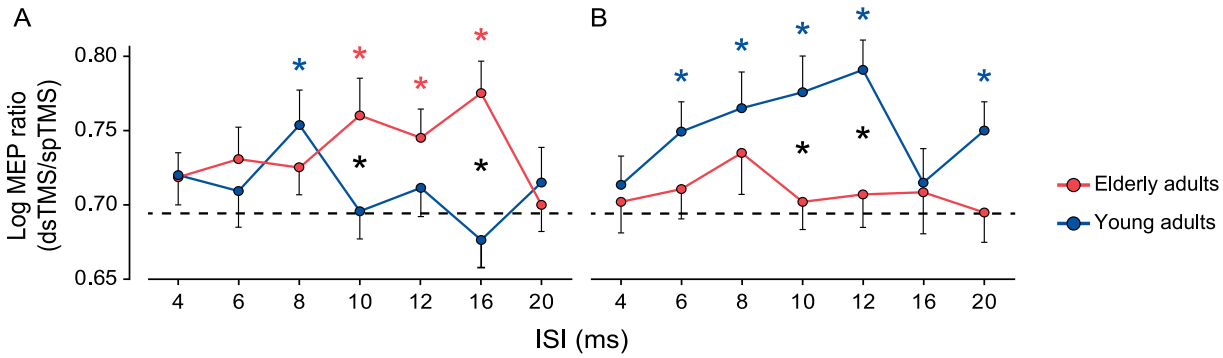

Figure 4. Log-transformed MEP ratios (dsTMS relative to spTMS) showing a Site x Age x ISI interaction. A, IFG site conditioning; B, preSMA conditioning. Red and blue asterisks indicate significant one-sample *t*-tests in the two corresponding groups. Black asterisks indicate significant comparisons between groups. The dashed gray line represents the natural logarithm value of 0.69, indicating the point at which the MEPs recorded by dsTMS correspond to those recorded by spTMS (natural log of dsTMS/spTMS = 100%).

Preliminary Analyses: Single Pulse TMS

We conducted a preliminary Age x Site x Muscle ANOVA on the log-transformed spTMS data. The results showed no significant main effect of age or any interactions involving this factor (all $F \leq 1.66$, $p \geq 0.21$), suggesting that the selected SI_{1mV} intensity elicited similar baseline MEP amplitudes across the two groups. The main effect of the muscle factor approached significance ($F_{1,32} = 3.72$, $p = 0.063$, $\eta_p^2 = 0.10$), with non-significant higher amplitudes in the FDI (0.64 ± 0.18, non-log transformed value: 0.93 mV ± 0.39) compared to the ADM (0.53 ± 0.29, non-log transformed value: 0.79 mV ± 0.64). No other effects were significant (all $F \leq 3.4$, all $p \geq 0.074$).

Neurophysiological Markers of Premotor-motor connectivity in Young and Older Individuals

Results of the Age x Site x Muscle x ISI ANOVA on MEP ratios (dsTMS trials versus spTMS trials) revealed significant interactions. Specifically, a Site x Muscle interaction was found ($F_{1,32} = 6.73$, $p = 0.014$, $\eta_p^2 = 0.17$), indicating larger MEP ratios for ADM compared to FDI in the preSMA session (ADM: 0.74 ± 0.11; FDI: 0.71 ± 0.10; $p = 0.003$, $d_{rm} = 0.43$) but MEP ratios did not differ in the IFG session (ADM: 0.72 ± 0.11; FDI: 0.73 ± 0.09; $p = 0.63$). An Age x Site interaction ($F_{1,32} = 8.45$, $p = 0.007$, $\eta_p^2 = 0.21$) and an Age x ISI interaction ($F_{6,192} = 2.31$, $p = 0.035$, $\eta_p^2 = 0.07$) were also observed. Importantly, these interactions were further qualified by a significant three-way Age x Site x ISI interaction ($F_{6,192} = 2.51$, $p = 0.023$, $\eta_p^2 = 0.07$). None of the other main effects or interactions reached significance (all $p > 0.11$). The three-way interaction was analyzed through post-hoc tests and showed that in the IFG-M1 block, older participants had larger MEP ratios compared to younger participants at both the 10 ms ISI (old: 0.76 ± 0.10; young: 0.7 ± 0.08; $p = 0.046$, $d_s = 0.70$) and the 16 ms ISI (old: 0.77 ± 0.09; young: 0.68 ± 0.08; $p = 0.003$, $d_s = 1.16$; Figure 4A). In the preSMA-M1 block, the analysis showed that MEPs were smaller in older participants compared to younger participants at the 10 ms ISI (old: 0.70 ± 0.08; young: 0.77 ± 0.10; $p = 0.022$, $d_s = 0.82$) and 12 ms ISI (old: 0.71 ± 0.09; young: 0.79 ± 0.08; $p = 0.010$, $d_s = 0.97$; Figure 4B).

Additionally, to assess whether IFG/preSMA conditioning had a net modulatory influence on the M1 response, a series of one-sample t-tests were performed to determine the ISI at which the conditioned MEPs (dsTMS) were significantly different from the unconditioned MEPs (spTMS). After IFG conditioning, the younger group showed excitatory M1 effects at an ISI of 8 ms (0.75 ± 0.10; $p = 0.023$, $d_z = 0.62$), while the older group showed a delayed and more extended window of excitatory effects at ISIs of 10 ms (0.76 ± 0.10; $p = 0.025$, $d_z = 0.64$), 12 ms (0.74 ± 0.08; $p = 0.019$, $d_z = 0.64$), and 16 ms (0.77 ± 0.09; $p = 0.022$, $d_z = 0.89$; Figure 4A). In contrast, preSMA conditioning exerted a general excitatory effect in the younger group, as evidenced by larger dsTMS MEPs compared with spTMS MEPs at ISIs of 6 ms (0.75 ± 0.08; $p = 0.014$, $d_z = 0.67$), 8 ms (0.76 ± 0.10; $p = 0.011$, $d_z = 0.70$), 10 ms (0.77 ± 0.10; $p = 0.004$, $d_z = 0.81$), 12 ms (0.79 ± 0.08; $p < 0.001$, $d_z = 1.17$) and 20 ms (0.75 ± 0.08; $p = 0.011$, $d_z = 0.70$). Such an effect was not observed in the older group, where no comparisons reached significance (all $p \geq 0.17$; Figure 4B).

These results suggest that the effects of the two conditioning areas on M1 excitability vary with age and specific ISIs. The facilitatory effect of the IFG over M1 observed in the young group was early and limited to a narrow time window, whereas it was delayed and more prolonged in older participants. On the other hand, preSMA conditioning, which facilitates the M1 response in younger participants, was completely absent in the elderly. Thus, we identified four intervals of interest: i) IFG at 8 ms ISI (IFG8) showed excitatory effects exclusively in younger participants; ii) IFG at 10-16 ms ISI (IFG10-16) showed

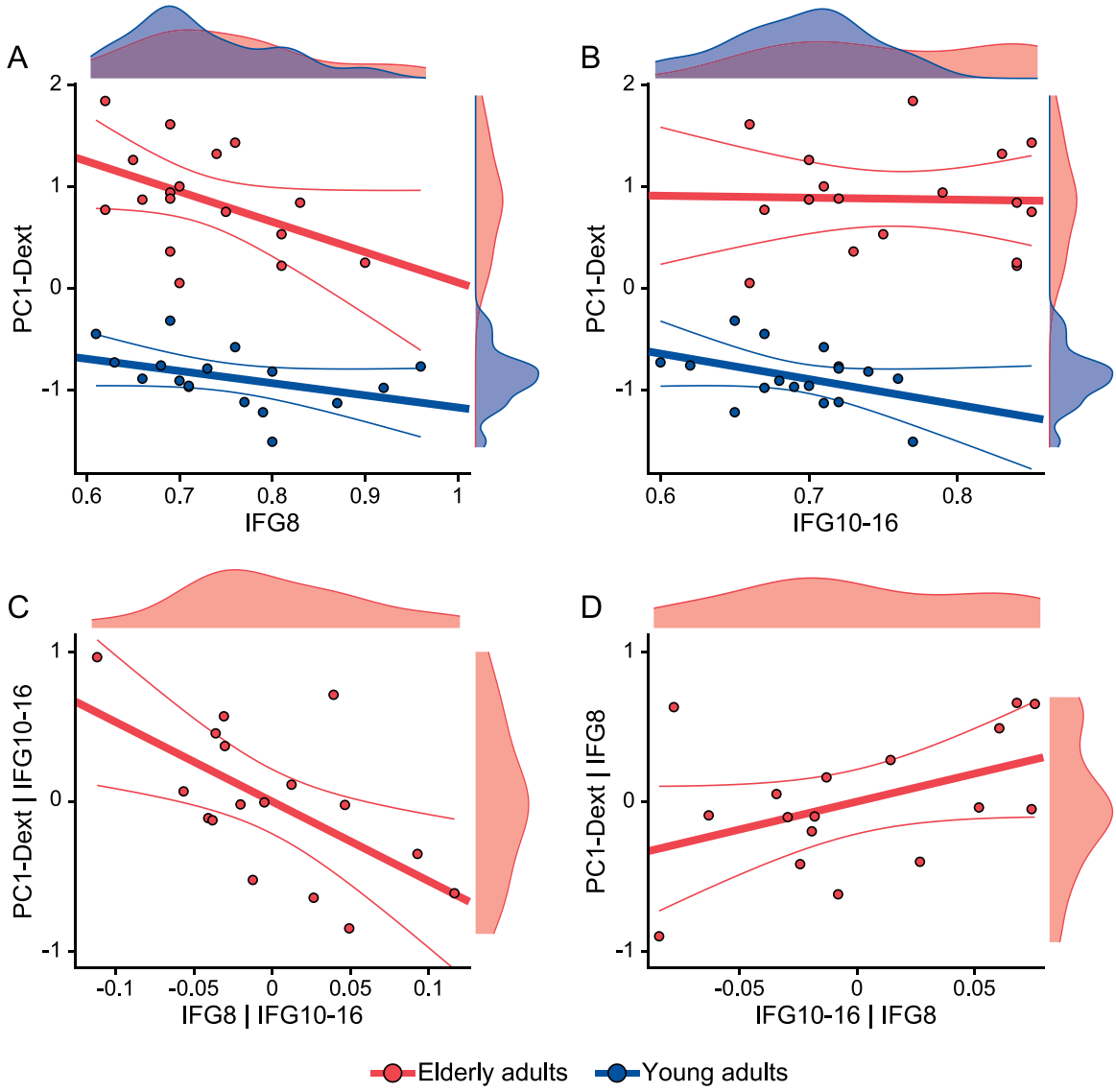

Figure 5. Relationship between neurophysiological markers of IFG-M1 connectivity and behavioral measures of dexterity/speed (PC1-Dext) as a function of age. A, AGE x IFG8 interaction and B, AGE x IFG10-16 interaction. Partial regression plots show the relationship between C, PC1-Dext and IFG8 while controlling for IFG10-16 and between D, PC1-Dext and IFG10-16 while controlling for IFG8 in the elderly group.

excitatory effects just in older participants; iii) preSMA at 10-12 ms ISI (pSMA10-12) showed excitatory effects only in younger participants; iv) preSMA at 20 ms ISI (preSMA20) showed excitatory effects exclusively in younger participants.

Neurophysiological Markers of Premotor-motor Connectivity Predict Behavioral Performance

We conducted four general linear models to examine whether age and effective connectivity at the four identified intervals of interest predicted behavioral performance.

In the first analysis, we included manual dexterity (PC1-Dext) as the dependent variable and age as a categorical predictor; the MEP ratios during the IFG block at the two intervals of interest (IFG8 and IFG10-16, see previous paragraph) were included as continuous predictors. We also tested for potential interactions between age and the two MEP ratios. The model yielded significant results (R^2_{adj} = 0.87, $F_{5,28}$ = 43.72, p <0.001, η_p^2 = 0.89). Specifically, we found that IFG8 emerged as a significant predictor of PC1-Dext ($F_{1,28}$ = 11.20, p = 0.002, η_p^2 = 0.29). Furthermore, the factor age interacted with both IFG8 ($F_{1,28}$ = 5.70, p = 0.024, η_p^2 = 0.17; Figure 5A) and IFG10-16 ($F_{1,28}$ = 4.38, p = 0.046, η_p^2 = 0.14; Figure 5B), while other effects were not statistically significant (all p ≥0.63).

Analyzing the parameter estimates, we found that in the elderly group, IFG8 negatively predicted PC1-Dext (B = −5.31, t = −3.38, p = 0.002, η_p^2 = 0.29;

Figure 5C); this indicates that higher IFG-M1 facilitation at 8 ms ISI was associated with better performance in manual speed and dexterity tasks. On the other hand, IFG10-16 positively predicted PC1-Dext in the elderly group ($B = 3.72$, $t = 2.18$, $p = 0.037$, $\eta_p^2 = 0.15$; Figure 5D), indicating that the worst performance was associated with the magnitude of such later facilitation, which was specific to the elderly group and not observed in the young group. No significant parameter estimates were observed in the young group (all $p \geq 0.37$).

In the group of elderly individuals, the parameter estimates for IFG8 and IFG10-16 consistently remained significant predictors of PC1-Dext, even when adding the covariate of no interest, rMT, was added either as a main effect or in interaction with the factor age (all $|B| \geq 3.79$, $|t| \geq 2.19$, $p \leq 0.037$, $\eta_p^2 \geq 0.15$). Moreover, the predictive power of the IFG8 and IFG10-16 parameter estimates for PC1-Dext remained even when additional covariates of no interest, such as MMSE and RCPM scores were introduced (all $|B| \geq 4.39$, $|t| \geq 2.46$, $p \leq 0.022$, $\eta_p^2 \geq 0.20$).

In summary, better performance on manual speed and dexterity tasks in older participants was predicted by a greater similarity to younger participants in terms of IFG-M1 connectivity metrics. Specifically, it was predicted by two neurophysiological markers: i) greater IFG-M1 facilitation at 8 ms ISI, and ii) absent/reduced facilitation at 10-16 ms ISI. The unique relationships between dexterity and these markers of early IFG-M1 connectivity remained significant even after partial removal of all shared variance with covariates of no interest, such as global indices of motor excitability and cognitive profile (rMT, MMSE, RCPM).

The second analysis replicated the first, with the only difference being the inclusion of MEP ratios from the preSMA block at the two intervals of interest (pSMA10-12 and pSMA20) as predictors. The model yielded significant results ($R^2_{adj} = 0.85$, $F_{5,28} = 39.72$, $p < 0.001$). The interaction between age and pSMA10-12 showed a marginally significant effect ($p = 0.058$, $\eta_p^2 = 0.12$); however, the pSMA10-12 did not significantly predict PC1-Dext for either the younger ($B = -1.53$, $p = 0.28$) or the older ($B = 2.62$, $p = 0.11$) group. None of the other main effects or interactions of the predictors were significant (all $p \geq 0.13$).

In the third general linear model, we examined the relationship between manual strength (PC2-Strength) as the dependent variable, age as a categorical predictor, and IFG8 and IFG10-16 as continuous predictors. The results were not significant ($R^2_{adj} = -0.11$, $F_{5,28} = 0.37$, $p = 0.87$).

Finally, the last general linear model, which examined the relationship between the dependent variable manual strength (PC2-Strength), the categorical predictor age, and the continuous predictors pSMA10-12 and pSMA20, was not significant although it approached the significance threshold ($R^2_{adj} = 0.18$, $F_{5,28} = 2.49$, $p = 0.055$).

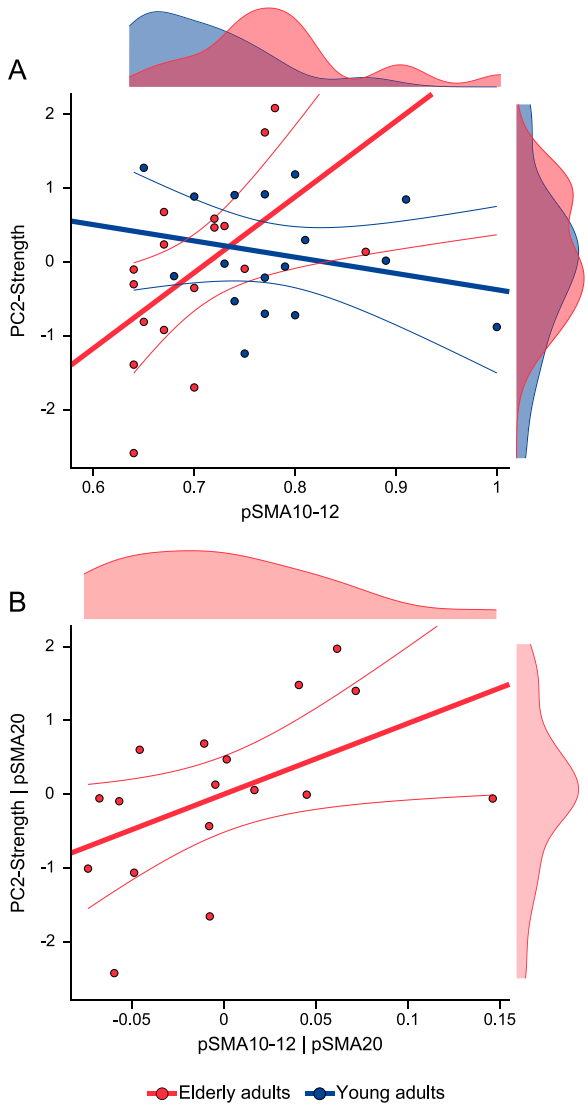

Figure 6. Relationship between neurophysiological measures of preSMA-M1 (pSMA10-12) connectivity and behavioral measures of manual strength (PC2-Strength) as a function of age. A, AGE x pSMA10-12 interaction. B, Partial regression plot showing the relationship between PC2-Strength and pSMA10-12 while controlling for pSMA20 in the elderly group.

Age emerged as a significant predictor of PC2-Strength ($p = 0.034$, $\eta_p^2 = 0.15$) and showed an interaction with the predictor pSMA10-12 ($p = 0.006$, $\eta_p^2 = 0.24$), while no other significant effects were observed (all $p \geq 0.13$; Figure 6A). Parameter estimates revealed that pSMA10-12 positively predicted strength values in the elderly group ($B = 9.6$, $t = 2.55$, $p = 0.017$, $\eta_p^2 = 0.19$) but not in the young group ($B = -5.48$, $t = -1.66$, $p = 0.11$; Figure 6B). In the older group, the parameter estimates for pSMA10-12 remained a significant predictor of PC2-Strength even when the covariate of no interest, rMT, was added, either as a main effect or in interaction with the factor age (all $|B| \geq 7.90$, $|t| \geq 2.10$, $p \leq 0.045$, η_p^2

≥0.15). The predictive power of this parameter estimate remained significant also when adding MMSE and RCPM scores as additional covariates of no interest ($B = 7.39$, $t = 2.21$, $p = 0.036$, $\eta_p^2 = 0.16$). The results from the fourth general linear model, while speculative, are consistent with those obtained from the first model analyzing the dexterity/speed data. These findings suggest that greater preSMA-M1 connectivity in the elderly group, similar to that of their younger counterparts, is associated with preserved manual strength performance. Again, the unique relationship between manual strength and markers of early preSMA-M1 connectivity remained significant when rMT, MMSE, and RCPM scores were removed.

Discussion

Aging can significantly affect motor behavior, negatively impacting daily activities and autonomy. These effects may be multifactorial, including peripheral changes; however, it is increasingly recognized that changes in the central nervous system may play a role (9–11,84). Here, we focused on age-related changes in cortico-cortical connectivity and the associated impairment in network efficiency. We used spTMS to assess M1 excitability and dsTMS to examine IFG-M1 and preSMA-M1 connectivity about motor performance in young and older adults. Confirming previous work, we observed a consistent reduction in motor excitability (85) and a more anterior location of the M1 hand representation in the elderly (83), which is also consistent with the notion of functional reorganization in the aging M1 (86–88). Moreover, we observed reduced performance on tasks involving dexterity/speed and strength (85). Crucially, our study significantly extends previous studies by providing unprecedented neurophysiological evidence of time-dependent changes in communication between IFG/preSMA sites and M1 in the elderly and by demonstrating that these connectivity changes predict age-related interindividual variability in motor performance.

Remarkably, our results suggest a functional dissociation between the two rostral premotor-motor circuits and motor behavior in older participants. Specifically, interindividual variability in early IFG-M1 interactions at 8 and 10-16 ms (represented by the IFG8 and IFG10-16 markers, respectively) predicted differences in dexterity/speed performance, while variability in preSMA-M1 interactions at 10-12 ms (indexed by the preSMA10-12 marker) predicted differences in manual strength. Control analyses verified the robustness of these relationships, considering the different levels of motor excitability between the two groups (rMT) and other potential variables such as individual cognitive profiles (MMSE, RCPM). These analyses revealed a unique relationship between time-specific markers of premotor-motor connectivity and motor performance. This reinforces our hypothesis that the observed changes in motor behavior reflect specific changes in brain connectivity. Across both circuits, our results suggest that maintaining a connectivity profile similar to that of young adults is associated with preserved behavioral performance in older individuals.

IFG-M1 Neurophysiological Connectivity Predicts Manual Dexterity

Using dsTMS, we showed distinct effects of IFG and preSMA subthreshold conditioning on M1 excitability in young and older participants, providing novel insights into the neural mechanisms underlying age-related changes in motor control. In young individuals, IFG conditioning produced an early and precisely timed facilitation of M1 excitability at an 8-ms ISI.

At this ISI, previous dsTMS studies investigating IFG/ventral premotor-M1 interactions in young adults consistently showed early excitatory and inhibitory modulations depending on stimulation parameters (52,63–66,89). Specifically, the IFG8 early marker is consistent with previous studies using the same dsTMS parameters as the present study, which reported similar early facilitatory IFG-M1 interactions in young individuals (65) or used these interactions to induce long-term potentiation-like effects (63–65,90–93). Moreover, this excitatory effect is consistent with monkey evidence suggesting that premotor projections to M1 primarily involve glutamatergic synapses (94,95). However, we observed excitatory interactions in a delayed and prolonged window, occurring between 10 and 16 ms (i.e., the IFG10-16 marker). Our findings significantly extend previous work on premotor-motor connectivity, by demonstrating age-related neurophysiological changes in IFG-M1 neural interactions. Indeed, we demonstrated a shift in the excitatory effects of an 8 ms ISI detected in young individuals (IFG8), to later timings in older adults (IFG10-16). This shift likely reflects a slowing of cortico-cortical IFG-M1 interactions, consistent with diffusion tensor imaging (DTI) evidence of age-related attenuation of white matter tracts (9,11,13,96,97). Beyond a mere slowing of cortico-cortical connectivity in the elderly, our results may also reflect differences in the organization of motor networks between young and older adults, as the 8-16 ms time window may involve different pathways, including primarily direct cortico-cortical projections at early timings (8 ms) and more extended cortico-subcortical circuits at later timings (>12 ms) (15).

The crucial finding of this study is that age-related changes in brain connectivity are predictive of different aspects of motor performance. Specifically, the two intervals of interest that characterized participants' neurophysiological IFG-M1 connectivity profile (i.e., the IFG8 and IFG10-16 markers) predicted older adults' performance on tasks that tapped into speed and visuomotor dexterity skills. In particular, older adults who had greater MEP facilitation in IFG-M1 at 8 ms ISI (IFG8 marker) and less MEP fa-

cilitation in IFG-M1 at 10-16 ms ISI (IFG10-16 marker) – that is a connectivity pattern similar to that of the young group – had better performance on speed/dexterity tasks.

Proficient execution of speed/dexterity tasks relies on the integration of visual and somatosensory information for fast, appropriate manual responses. Sensorimotor transformations occur within a fronto-parietal network that encodes the spatial location and physical properties (e.g., mass, shape, size) of objects and guides action selection (34,98). Within this network, the premotor cortices play a critical role in selecting the appropriate motor representation and transmitting it to M1 for execution (39,99–102). In addition to receiving parietal inputs, the premotor cortex, especially its ventral subdivision adjacent to the IFG, receives projections from structures involved in action guidance and performance monitoring, including the prefrontal cortices, the supplementary eye field, and the basal ganglia (103,104). This underscores the critical role of IFG-M1 connectivity in proficient motor control during externally sensory-guided manual tasks such as those loaded on the PC1-Dext. The 9HPT involves motor skills such as spatial localization of small pegs, fine grasping, manipulation, and precise placement. It relies on the fronto-parietal grasping network, particularly on ventral premotor-motor connections, in young adults (52). The cRT performance correlates with the integrity of white matter connecting frontoparietal areas involved in visuomotor transformations, including the tracts connecting IFG and M1 (49). Monkey studies highlight the importance of the IFG in cRT tasks, representing the associative rule, selecting the correct response, and organizing the action (51). Regarding the FT task, this task involves cortical and subcortical sensorimotor regions, with older adults showing overactivation of sensorimotor and premotor cortices (105). The vmTMT couples vision with action and relies on the control of hand and forearm movements. Although there is limited evidence on the neural correlates of tracking tasks in older adults, existing research suggests that visuomotor control of target-directed hand movements engages parietal-frontal networks including intraparietal cortex, premotor cortices, and M1 (106,107). Taken together, this evidence supports the central role of the IFG and its connection to M1 in completing the tasks gathered in the PC1-Dext index.

Interestingly, our study also sheds light on previous research using cortico-cortical paired associative stimulation (ccPAS) to manipulate connectivity between the same IFG/premotor and M1 sites targeted in this study (108). In particular, Fiori F, et al. (52) and Turrini S, et al. (63,64) demonstrated that ccPAS targeting early IFG-M1 interactions (i.e., using an 8 ms ISI) improves hand motor excitability and manual dexterity in young adults, but has limited efficacy in older adults. In light of the present data, it could be suggested that effective ccPAS targeting of IFG-M1 areas should be tailored to the specific timing of cortico-cortical communication, which, as we show here, may be significantly delayed in older individuals. Our findings are consistent with existing evidence indicating that the reduced efficacy of IFG-M1 ccPAS to increase motor excitability predicts poor baseline hand motor performance across young and older individuals (63). Expanding on this prior knowledge, our study reveals that slower IFG-M1 communication in older individuals uniquely predicts and accounts for age-related differences in hand dexterity/speed. As a result, our findings provide insight into understanding the mechanism behind previous ccPAS outcomes and also guide the future application of ccPAS over IFG-M1 areas in young and older individuals (89).

PreSMA-M1 Neurophysiological Connectivity Predicts Manual Strength

Our study also revealed that preSMA-M1 connectivity exhibited broad facilitatory interactions at latencies ranging from 6–12 ms and at a 20-ms ISI, in young participants.

These findings are consistent with previous reports documenting facilitatory interactions at specific ISIs such as 6, 8, and 12 ms (15,31–33). Furthermore, by examining a wider range of ISIs we were able to demonstrate that preSMA-M1 communication also occurs at different time scales in young individuals. These preSMA-M1 interactions are distinct from those observed within the IFG-M1 network in the same group of participants, supporting the notion that cortico-cortical dynamics may be specific and even unique to each network (62,91,93). However, when examining this network in older adults, significant age-related asymmetries emerged. Indeed, the facilitatory effects observed in young adults were absent in older adults.

These results are consistent with those of Green and colleagues (31), who demonstrated age-related differences in SMA-M1 interactions using conditioning delivered over a medial site (4 cm anterior to the vertex), close to our stimulation site (4.6 cm anterior to the vertex, on average). Their study showed MEP facilitation at a 6 ms ISI in young but not older adults, even with conditioning TMS delivered at intensities higher than those used in the present work (∼120-130% of the rMT) (31). The results of our study support and expand these observations, reporting age-related differences in the timing of the preSMA-M1 interaction not only at short but also at longer ISIs (>8 ms). Overall, the lack of a conditioning effect of preSMA over M1 in older adults, as well as the previously described results regarding the IFG-M1 pathway, are consistent with evidence for age-related changes in structural and functional connectivity within the frontal lobe (30,109). However, by using dsTMS we have provided a novel critical piece of information that is difficult to extract from imaging studies. Our findings reveal the temporal dynamics of premotor-motor interactions and their changes in the elderly population. Furthermore, they

highlight the nature of these changes in terms of time-specific strength attenuation or delayed communication.

Importantly, connectivity changes in the preSMA-M1 circuit were found to predict manual strength (PC2-Strength) in the elderly. Older adults with greater preSMA-M1 facilitation (i.e., similar to the young group) exhibited greater strength than those with reduced facilitation. Graded force generation during grasping tasks recruits both ventral and dorsal components of the premotor cortices and the SMA complex (47,48,110–112). These cortices regulate M1 cortico-spinal projections in real time to match the motor output required by the task, especially during pinch grip (110,113), and studies suggest that this regulation may occur directly through cortico-spinal projections originating from the SMA (114).

There is general agreement that increased force production is associated with M1 activation in both young and older adults (45,46,48,115), along with enhanced activation of the basal ganglia, specifically the subthalamic nucleus (STN) and the internal part of the globus pallidus (116,117). However, the cortical correlates of force production in older adults differ from those of young adults in their greater recruitment of M1, preSMA, and other sensorimotor areas, including the basal ganglia (45,46,118). For instance, older adults performing upper limb movements extensively activate a large medial region that includes preSMA and SMA, likely reflecting a compensatory mechanism in which the supplementary motor complex is recruited to achieve a strong grip, and the more effective the region is in modulating motor output, the better the performance (119). Because the basal ganglia are physiologically connected to preSMA (120–129), and the preSMA-STN-M1 pathway has connectivity timings around 12 ms (15), which closely resembles the ISI driving our findings, our results complement and tie together previous evidence. Based on our novel finding that interindividual variability in preSMA-M1 connectivity at the 10-12 ms ISI predicts differences in grip strength, it can be argued that the facilitatory physiological inputs from preSMA to M1, possibly involving the basal ganglia, may contribute to the generation of high levels of strength in older adults, while their absence may partially account for the observed loss of strength.

Conclusions

Our study provides unprecedented evidence that specific alterations in the early dynamics of IFG-M1 and preSMA-M1 connectivity contribute to different aspects of motor performance decline in aging. Our results have significant implications for non-invasive brain stimulation techniques, as they suggest that strengthening cortico-cortical pathways may be an effective strategy to improve specific functional abilities in the elderly.

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Conflict of Interest

The authors declare that they have no competing interests.

Availability of Data and Material

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.arcmed.2024.103031. All tables, figures, and references cited in the supplementary material are correctly included in the main text of the article.

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