

University of Groningen

Age-dependent modulation of motor network connectivity for skill acquisition, consolidation and interlimb transfer after motor practice

Veldman, M. P.; Maurits, N. M.; Mantini, D.; Hortobagyi, T.

Published in:
Clinical Neurophysiology

DOI:
[10.1016/j.clinph.2021.03.051](https://doi.org/10.1016/j.clinph.2021.03.051)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Veldman, M. P., Maurits, N. M., Mantini, D., & Hortobagyi, T. (2021). Age-dependent modulation of motor network connectivity for skill acquisition, consolidation and interlimb transfer after motor practice. *Clinical Neurophysiology*, 132(8), 1790-1801. <https://doi.org/10.1016/j.clinph.2021.03.051>

Copyright

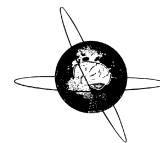
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



Age-dependent modulation of motor network connectivity for skill acquisition, consolidation and interlimb transfer after motor practice



M.P. Veldman^{a,b,c,*}, N.M. Maurits^d, D. Mantini^{a,e}, T. Hortobágyi^{b,f,g}

^a KU Leuven, Department of Movement Sciences, Movement Control and Neuroplasticity Research Group, Leuven, Belgium

^b University of Groningen, University Medical Center Groningen, Center for Human Movement Sciences, Groningen, the Netherlands

^c KU Leuven, Leuven Brain Institute (LBI), Leuven, Belgium

^d University of Groningen, University Medical Center Groningen, Department of Neurology, Groningen, the Netherlands

^e Brain Imaging and Neural Dynamics Research Group, IRCCS San Camillo Hospital, Venice, Italy

^f Institute of Sport Sciences and Physical Education, Faculty of Sciences, University of Pécs, Pécs, Hungary

^g Somogy County Kaposi Mór Teaching Hospital, Kaposvár, Hungary

ARTICLE INFO

Article history:

Accepted 22 March 2021

Available online 8 May 2021

Keywords:

Aging

Dynamic imaging of coherent sources

Electroencephalography

Motor learning

HIGHLIGHTS

- Skill acquisition and consolidation, but not interlimb transfer, are intact in older adults.
- Unilateral practice increases ipsilateral primary motor cortex (M1)-related coherence in older adults.
- Motor practice modulates the relationship between M1-related coherence and learning in older adults.

ABSTRACT

Objective: Age-related differences in neural strategies for motor learning are not fully understood. We determined the effects of age on the relationship between motor network connectivity and motor skill acquisition, consolidation, and interlimb transfer using dynamic imaging of coherent sources.

Methods: Healthy younger ($n = 24$, 18–24 y) and older ($n = 24$, 65–87 y) adults unilaterally practiced a visuomotor task and resting-state electroencephalographic data was acquired before and after practice as well as at retention.

Results: The results showed that right-hand skill acquisition and consolidation did not differ between age groups. However, age affected the ability to transfer the newly acquired motor skill to the non-practiced limb. Moreover, strengthened left- and right-primary motor cortex-related beta connectivity was negatively and positively associated with right-hand skill acquisition and left-hand skill consolidation in older adults, respectively.

Conclusion: Age-dependent modulations of bilateral resting-state motor network connectivity indicate age-specific strategies for the acquisition, consolidation, and interlimb transfer of novel motor tasks.

Significance: The present results provide insights into the mechanisms underlying motor learning that are important for the development of interventions for patients with unilateral injuries.

© 2021 International Federation of Clinical Neurophysiology. Published by Elsevier B.V. All rights reserved.

Abbreviations: ANOVA, Analysis of Variance; DICS, Dynamic Imaging of Coherent Sources; EEG, Electroencephalography; FDR, false discovery rate; HAROLD, Hemispheric Asymmetry Reduction in Older Adults; M1, Primary motor cortex; MMSE, mini mental state examination; PSQI, Pittsburgh sleep quality inventory.

* Corresponding author at: Motor Control and Neuroplasticity Research Group, Department of Movement Sciences, Tervuursevest, 101 Box 1501, 3001 Leuven, Belgium.

E-mail address: menno.veldman@kuleuven.be (M.P. Veldman).

<https://doi.org/10.1016/j.clinph.2021.03.051>

1388–2457/© 2021 International Federation of Clinical Neurophysiology. Published by Elsevier B.V. All rights reserved.

1. Introduction

The decline in motor performance during physiological aging (Berghuis et al., 2016; Brown et al., 2009; Mary et al., 2017a) is accompanied by structural, functional, and neurochemical changes in the brain (Seidler et al., 2010). Yet, the capacity to acquire unfamiliar motor skills is not necessarily compromised. Indeed, it has been shown that compared to young adults, older individuals have

lower (Anguera et al., 2010; Bo et al., 2011; Coats et al., 2014; Raz et al., 2000; Rueda-Delgado et al., 2019; Swinnen et al., 1998; Zimerman et al., 2013), similar (Berghuis et al., 2016, 2019; Cirillo et al., 2011), or even higher (Anshel, 1978; Brown et al., 2009) learning rates. Following skill acquisition, fragile memory traces become more stable motor memories, evidenced on the behavioral level through performance stabilization or enhancement (Robertson et al., 2004). While such motor memory consolidation processes are generally observed in young adults (Brown et al., 2009; Nemeth and Janacek, 2010), evidence in older adults is more ambiguous showing both decreased (Fogel et al., 2014) and stabilized (Berghuis et al., 2016) performance after the offline, i.e., no-practice, period [see (King et al., 2017) for a review].

Whereas healthy aging not necessarily affects the magnitude of skill acquisition and consolidation, imaging data suggest that the use-dependent neuronal plasticity underlying motor learning is age-specific (Berghuis et al., 2016, 2019; Mary et al., 2017b, 2017a; Rueda-Delgado et al., 2019). Age-related adaptations often include greater and bilateral cortical recruitment during the execution and acquisition of unilateral motor skills [e.g. (Berghuis et al., 2019; Ward et al., 2008)]. These data tend to favor the Hemispheric Asymmetry Reduction in Older Adults (HAROLD) model (Carbeza, 2002), which suggests that the age-dependent reorganization in brain activation is compensatory in order to minimize motor deficits and preserve motor flexibility. At the network level, white matter integrity between bilateral primary and secondary motor areas decreases with age (Schulz et al., 2014). Moreover, decreases in structural connectivity are related to increased functional connectivity that may be maladaptive, as the latter increases connectivity but can also be associated with poorer motor performance, skill acquisition, and skill consolidation at a 30-min retention interval (Babaeeghazvini et al., 2019; Mary et al., 2017b, 2017a). However, because brain activation patterns change beyond this 30-min interval following skill acquisition (Shadmehr, 1997), there is a need to extend these data and relate the age-related changes in motor network connectivity to motor memory consolidation measured at longer retention intervals.

In addition to the practice effects in the trained limb, the transfer of the acquired skill to the non-practice limb also provides insights into motor flexibility, as it reflects the spatial specificity of plasticity. The magnitude of interlimb transfer varies with age evidenced by reduced (Krishnan et al., 2018), similar (Dickins et al., 2015; Hester et al., 2019b) or even greater interlimb transfer (Graziadio et al., 2015) in older compared to younger adults. In young adults, magnetic stimulation studies attributed interlimb transfer to synaptic adaptations in the primary motor cortex (M1) ipsilateral to the practiced limb (Hortobágyi et al., 2011; Lee and Carroll, 2007; Nojima et al., 2012; Perez et al., 2007a; Veldman et al., 2015). Yet, while conceptually and clinically relevant for older adults who suffered a stroke or orthopedic injury (DeLuca et al., 2017; Dragert and Zehr, 2013; Ehrensberger et al., 2016; Kim et al., 2015; Liao et al., 2019; Manca et al., 2017, 2016; Sun et al., 2018; Urbin et al., 2015; Zult et al., 2016), the neural underpinnings of interlimb transfer at the network level have not been examined in the context of aging.

Therefore, the aim of the present study was to determine for the first time the effects of age on motor skill acquisition, consolidation, and interlimb transfer in relation to the changes in resting-state motor network connectivity that occur during in the motor learning process. To that end, we examined bilateral motor performance and resting-state motor network connectivity using a dynamic imaging of coherent sources (DICS) beamformer analysis approach before, after, and at 24-hour retention following unilateral motor practice. We focused our analyses on the beta rhythm that has been associated with motor learning processes in young and older adults (Mary et al., 2017b; Pollok et al., 2014; Sugata

et al., 2020; Wu et al., 2014), although its role in consolidation processes is still under debate (Espenhahn et al., 2019). This approach allowed us to determine the relationship between motor learning and cortical networks connected with the regions of interest [i.e., the primary motor cortex (M1)] for skill acquisition, consolidation, and interlimb transfer. The absence of age-related declines in learning rates (Anshel, 1978; Berghuis et al., 2016, 2019; Brown et al., 2009; Cirillo et al., 2011), notwithstanding the age-typical decreases in white matter integrity and structural connectivity [e.g., (Schulz et al., 2014)] and changes in brain activity (Berghuis et al., 2019), collectively suggest the operation of compensatory mechanisms to counteract age-related structural declines. Therefore, we surmise that older adults use different neural strategies to achieve young-like motor learning. Specifically, we hypothesized that (1) the acquisition, consolidation, and interlimb transfer of a novel motor skill would be characterized by age-specific higher connectivity of bilateral motor networks and (2) that the modulation of motor network-related connectivity would be related to the changes in performance observed after the practice and consolidation interval.

2. Methods

2.1. Participants

The 48 young ($n = 24$, 10 males, 18–24 y) and older ($n = 24$, 11 males, 65–87 y) participants were healthy and right-handed (Oldfield, 1971; Rossi et al., 2009), had no history of neurological or psychological conditions nor took medication that affected the functioning of the nervous system. Intact global cognitive function of the older adults was verified with the mini mental state examination [MMSE (Folstein et al., 1975); individuals with a score lower than 26 were excluded]. The Medical Ethical Committee of the University Medical Center Groningen approved the study protocol, which was conducted according to the declaration of Helsinki (2013) and registered in the Dutch trial register (NL5484). Data from the young participants were used in a previous study (Veldman et al., 2018). They were re-analyzed and compared with new data collected in older adults. All participants provided written informed consent before participation in the study protocol. Table 1 provides an overview of the participant characteristics.

2.2. Experimental design

Participants were randomly assigned to one of two experimental groups either performing a 15-min motor practice intervention (motor practice group (MPG); $n = 12$ for each age group) or resting for 15 min (Control group (COG); $n = 12$ for each age group). The control group was included to isolate the effects of the 15-min practice intervention irrespective of the behavioral testing. On the first of two visits on consecutive days (starting between 9AM and 3PM), electroencephalography (EEG) baseline measures were obtained and participants were familiarized with and tested on the visuomotor task executed with each hand, separately. Immediately (between 11AM and 5PM; Day 1) and 24 hours (± 1 hour of baseline testing; Day 2) after the intervention, the baseline measures were repeated to determine the immediate and delayed effects of visuomotor practice on motor performance and neuronal plasticity in all participants. Because sleep influences motor memory consolidation [for a review, see (King et al. 2017)], we measured the quality and quantity of sleep of the night in between the two sessions using an adapted version of the Pittsburgh Sleep Inventory (PSQI) on Day 2 (Buysse et al., 1989). Fig. 1A provides a schematic overview of the experimental design.

Table 1
Participant characteristics.

	Older		Young	
	MPG	COG	MPG	COG
Age (y)	70.1 (2.1)	72.3 (1.3)	21.0 (0.5)	20.7 (0.4)
Gender (M/F)	5/7	6/6	5/7	5/7
BMI	27.0 (1.6)	26.0 (0.9)	21.8 (0.5)	24.1 (1.3)
MMSE	28.6 (1.1)	29.5 (1.0)		
PSQI	6.4 (4.5)	4.3 (3.2)	3.7 (1.4)	4.3 (2.6)

Values are mean (\pm standard deviation). BMI, body mass index; COG, control group; MPG, motor practice group; MMSE, mini mental state examination; PSQI, Pittsburgh Sleep Quality Index.

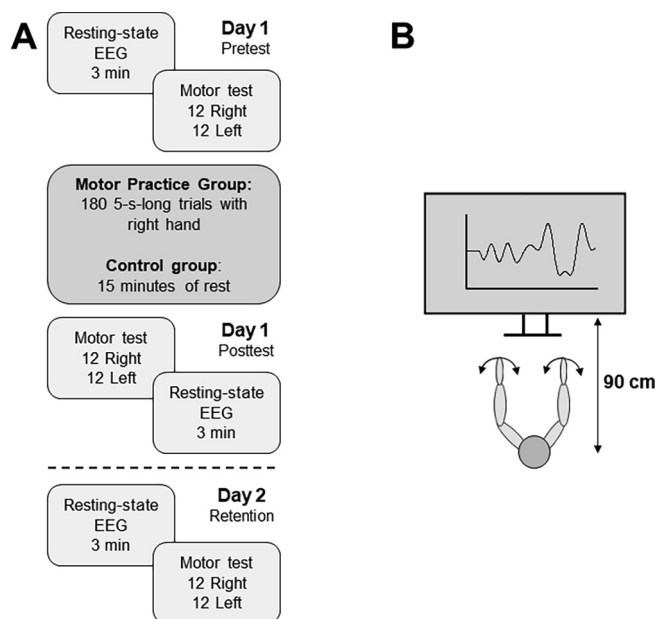


Fig. 1. Experimental design. Schematic overview of the experimental design (A) and visuomotor task (B). Resting-state electroencephalography (EEG) was acquired before and after (Day 1) as well as 24 hours after (Day 2) practicing a visuomotor task. The visuomotor task consisted of following a template using right- and left-wrist flexion and extension movements.

2.3. Visuomotor skill testing

Participants sat 0.9 m in front of a computer monitor with the hand performing the task comfortably fixed in a foam-padded manipulandum so that only the wrist could move. The resting hand was placed on the ipsilateral knee and both knees were flexed 90°. To determine visuomotor performance, participants performed the task using 12 templates with both the right and left hand that consisted of complex sinusoid waveforms. The testing of visuomotor performance in the right and left hand occurred in a blocked fashion and the participants were verbally instructed which hand to use. Before the start of the experiment, a pool of 32 templates was created in which each of the 32 templates consisted of the sum of 10 sine waves with pseudorandom amplitude and frequency resulting in a set of 32 unique templates. Twelve of these templates were used for performance testing and the other 20 templates were used for the practice intervention. As such, participants were not tested on the templates that they practiced and thus not tested on the extent to which they were able to acquire new motor memory traces but rather on the ability to track sinusoid templates. The templates progressed on the monitor from left to right at a fixed speed, ranging from 3.3 to 4.0 cm/s with an

average duration of five seconds. The templates were displayed in white over a sharp blue background. Participants were instructed to track these templates as accurately as possible by flexing and extending the wrist in the transverse plane in order to move the cursor downward and upward, respectively. We opted to use movements in the transversal plane to move the cursor in the sagittal plane to increase the difficulty of the task and thereby increase the room for improvement on task performance. The templates were scaled to the participants' range of motion. Importantly, both young and older adults used the exact same templates for performance testing and motor practice. The position data were sampled at 100 Hz. Fig. 1B provides a schematic overview of the task setup.

2.4. Motor practice and control intervention

The motor practice intervention was designed to improve participants' ability to accurately track the sinusoid templates. Participants performed three blocks of 60 trials (every trial was started manually to make sure the participant was in the starting position, but there were no more than 2 s between trials) with the right hand only with 2 min of rest between blocks. The test templates were different from the training templates. In each block, 20 unique templates were repeated three times and consistent with the contextual interference hypothesis (Shea and Morgan, 1979), the order and template duration were randomized. The 15-min duration of the motor practice intervention allowed us to examine the initial phase of skill acquisition and interlimb transfer and avoid ceiling effects or early consolidation effects in the posttest on Day 1.

The control intervention was identical to the motor practice intervention except that the participants in COG did not move their wrist and practiced the tracking skill for 15 min. The comparison between the motor practice and control intervention therefore allowed us to examine the effect of practicing a visuomotor skill.

2.5. EEG recording

Resting-state EEG data were recorded in a shielded room using a 64-channel ANT waveguard EEG cap placed on the scalp according to the international 10–10 system (ANT Neuro, Enschede, The Netherlands). Data were recorded at 2048 Hz with an average reference. In addition, we recorded horizontal and vertical electro-oculogram and bilateral mastoid activity for offline eye-movement artifact rejection and re-referencing, respectively. The impedance was kept below 10 k Ω for all electrodes throughout the experiment. EEG data were acquired for three minutes while the participants sat with the hands resting on the anterior thighs and gazed slightly downward at a fixation cross, and to avoid blinking, chewing, and swallowing.

2.6. Data analysis

2.6.1. Analysis of motor performance

Behavioral data in three older participants (one in MPG, two in COG) were compromised and excluded from the analyses. Motor performance for both hands was quantified as the mean absolute deviation between the target template and participants' cursor in the vertical direction. This procedure was repeated for the twelve trials in each hand and the average of twelve trials for the pre, post, and retention tests was used as a measure of motor performance. Difference scores between pre- and post-test and between post- and retention-test were computed as a measure of skill acquisition and consolidation, respectively, for the right- and left hand, separately.

2.6.2. Analysis of EEG data

EEG were exported from the acquisition software (Eemagine Medical Imaging solutions GmbH, Berlin, Germany) to a custom Matlab code for analysis (The Mathworks, Natick, Massachusetts, USA, version 2017b). The preprocessing and analysis of EEG data was performed using the open-source FieldTrip toolbox (Oostenveld et al., 2011) and in accordance with recent guidelines (Pernet et al., 2020). Continuous resting-state EEG data were cleaned from line noise, detrended, low-pass filtered (6th order Butterworth; 70 Hz, 36 dB/octave), and segmented into non-overlapping 1-s-epochs before the application of independent component analysis (Delorme et al., 2007). The components were visually inspected regarding their amplitude topography and time series, and those containing eye, muscle, or cardiac artifacts, or artifacts that occurred in only one channel, were projected out of the EEG data. To perform a quality check, we transformed the pre-processed data to the frequency domain using the multitaper Fast Fourier Transformation with a 10% Hanning window, resulting in a 1 Hz frequency resolution. We focused on frequencies from 8 to 30 Hz (i.e., covering the alpha and beta frequency ranges). In this manner, we were able to examine whether effects of age generally observed in EEG power [e.g., (Sally et al., 2018; Voytek et al., 2015)] were present in our data. For the DICS analysis, artifact-free data were filtered in the beta frequency range (13–30 Hz). We limited the analyses to neural oscillations in the beta frequency range, as they are known to be involved in sensorimotor processing and motor learning (Bhatt et al., 2016; Pfurtscheller and Lopes, 1999; Pollok et al., 2014; Rossiter et al., 2014; Sugata et al., 2020; Veldman et al., 2018; Wu et al., 2014). For the definition of the source space, we used a generic magnetic resonance imaging template available in Fieldtrip with a 5 mm voxel size, which was segmented and resliced using SPM12 (Wellcome Centre for Human Neuroimaging, London, UK). A headmodel consisting of three layers (brain, skull, and scalp) was constructed to serve as a grid for the leadfield matrix during subsequent source localization. We used standard conductivity values for the three layers included in the headmodel: 0.33 S/m for the brain and scalp, and 0.0042 S/m for the skull. Because the primary aim of this study was to identify the role of connectivity in the acquisition, consolidation, and interlimb transfer of a visuomotor skill, we performed DICS beamformer analysis on the resting-state data in the beta frequency range, which is instrumental in visuomotor learning (Gross et al., 2001; Veldman et al., 2018; Wu et al., 2014). The DICS method uses adaptive spatial filters to relate the electrical activity measured at the scalp to the underlying neural activity with a high spatial resolution (Greenblatt et al., 2005; Sekihara et al., 2005). Because connectivity within the motor network correlates with skill acquisition and consolidation following unilateral motor practice (Sugata et al., 2020; Veldman et al., 2018; Wu et al., 2014), we designed our analysis to compute whole-brain connectivity with a priori specified regions of interest (left M1 and right M1) that were

used as seeds for the connectivity analysis via a two-step process. In step 1, we reconstructed the power distribution across the brain using DICS and extracted participant-specific coordinates of maximal power in the regions of interest that were anatomically defined according to the Automated Anatomical Labeling atlas available in Fieldtrip similar to a previous report (Sugata et al., 2020). In step 2, these coordinates were used as the locations for the reference dipole (i.e., seed) for the calculation of the sources of coherence with the regions of interest across the brain (i.e., between all other voxels and the reference voxel), again performed with DICS. In both steps, we used a 1% regularization factor on the pre-produced grid that was aligned to a structural image. To differentiate between the within-session skill acquisition phase and the between-session consolidation phase of motor learning (Robertson et al., 2004) and examine the changes in coherence during these phases, the reconstructed coherence was contrasted between Pre and Post [(Post – Pre) / Pre] and between Post and Retention [(Retention – Post) / Post] for each seed-voxel pair, respectively. Subsequently, the contrasted coherence was averaged across participants within age- and intervention-groups after Z-transformation (i.e., Z-transformation was performed within-subject). This approach allowed us to derive bilateral M1-related connectivity from data recorded with high temporal resolution in order to obtain novel and complementary insights as compared to those provided by transcranial magnetic stimulation and functional magnetic resonance imaging studies (Hortobágyi et al., 2011; Nojima et al., 2012; Perez et al., 2007b). As readouts of plasticity in the left and right M1 following unimanual motor practice, we examined whether these regions became connected with an increasing number of regions (i.e., voxels; total coherence computed as the sum of the extracted coherence values), whether the average strength of new and existing connections increased (average coherence, computed as the total coherence divided by the number of coherence values), whether the maximal coherence increased, or a combination of these measures. These measures were extracted from pre, post, and retention tests as well as from the contrasted and transformed source coherence before proceeding to the statistical analyses.

2.7. Statistical analysis

Statistical analyses were performed in SPSS version 25.0. First, normality of the data was checked by using the Shapiro-Wilk test and non-parametric equivalents of parametric tests were used if the assumption of normality was violated.

Independent sample *t*-tests were used to examine there were differences between age and intervention groups in terms of demographic variables, baseline motor performance, and baseline coherence. On raw behavioral data (i.e., error) as well as the average and total left- and right M1 -related coherence, we performed repeated measures ANOVA with repeated measures on Time (pre Day 1, post Day 1, Day 2). Age (Young vs. Old) and Intervention (MPG vs. COG) were included as between-subject factors. Greenhouse-Geisser correction was applied when the assumption of sphericity was violated and partial eta-squared (η_p^2) was used as a measure of effect size, where 0.01 is considered small, 0.06 medium, and >0.14 as large. Given the evidence that the acquisition and consolidation of motor skills are supported by separate processes (Floyer-Lea and Matthews, 2005), we ran separate repeated measures ANOVA's for pre-post and post-retention time points. Because the distributions of average and maximal connectivity (see Section 2.6) did not meet the assumption of normality for parametric tests, we performed non-parametric Independent Samples Mann-Whitney U tests to examine whether the change in coherence (Z-transformed, see Section 2.6) differed between Age and Intervention groups. Finally, we performed Spearman

correlation analysis to examine the relationship between behavioral and neurophysiological data. The false discovery rate (FDR) (Benjamini and Hochberg, 1995) was adopted to control for multiple comparisons. To reduce the number of comparisons, the correlation analyses were driven by the results of the ANOVAs. As such, the number of comparisons for each family of hypothesis was (1) four comparisons to test the relationship between skill acquisition and consolidation in the right and left hand for the MPG and COG, (2) four comparisons for the relationship between maximal left-M1-related coherence and right-hand skill acquisition and (3) four comparisons to test the relationship between average right-M1-related coherence and left-hand skill acquisition and consolidation. Finally, Fischer's r to z transformation was used to compare correlation coefficients between intervention and control groups. All data are reported as means \pm standard deviations and significance level was set at $\alpha = 0.05$ (two-sided).

3. Results

Within age groups, there were no differences between MPG and COG in terms of age (Older adults: $t_{(21)} = -0.944$, $p = 0.356$; young adults: $t_{(22)} = 0.528$, $p = 0.603$) and MMSE scores (Older adults: $t_{(21)} = -1.954$, $p = 0.064$). Older and young adults reported similar quality of sleep as assessed by the PSQI questionnaire ($\chi^2_{(1)} = 0.582$, $p = 0.446$). Older adults' motor performance at baseline was similar to young adults' motor performance in the dominant right hand (20.5 vs. 19.3; $t_{(46)} = 1.2$, $p = 0.251$) but motor performance was worse in the non-dominant left hand (22.6 vs. 20.6; $t_{(46)} = 2.1$, $p = 0.037$). There were no differences at baseline between the MPG and COG within and across age groups (all $p > 0.05$).

3.1. Behavioral data

3.1.1. Right-hand skill acquisition and consolidation

To examine right-hand skill acquisition and consolidation in young and older adults after a right-handed practice intervention, we performed a 3 (Time: pre vs. post vs. retention) by 2 (Intervention: MPG vs. COG) by 2 (Young vs. Old) repeated measures ANOVA on dominant right-hand motor performance. The results showed that right-hand motor performance increased across age and intervention groups over the three time points (Time: $F_{(2, 86)} = 46.2$, $\eta^2_p = 0.518$, $p < 0.001$; Fig. 2A). Post-hoc analyses revealed that motor performance increased from pre to post ($t_{46} = 9.308$, $p < 0.001$) and decreased from post to retention ($t_{46} = -3.258$, $p = 0.002$). Moreover, performance was superior for younger vs. older adults (Age: $F_{(1, 43)} = 7.1$, $\eta^2_p = 0.141$, $p = 0.011$) and performance across the three time points was better in MPG as compared to COG (Group: $F_{(1, 43)} = 5.2$, $\eta^2_p = 0.108$, $p = 0.027$). In addition to these main effects, we observed a significant Intervention by Time interaction ($F_{(2, 86)} = 3.3$, $\eta^2_p = 0.092$, $p = 0.016$). Follow-up two (Time: pre vs. post and post vs. retention) by two (Intervention: MPG vs. COG) repeated measures ANOVAs revealed that the MPG group improved more from pre to post as compared to COG (4.7 vs. 2.5%; $F_{(1, 45)} = 10.3$, $\eta^2_p = 0.187$, $p = 0.002$) but that there were no differences from post to retention between the two intervention groups ($F_{(1, 45)} = 0.3$, $\eta^2_p = 0.028$, $p = 0.262$). There were no Age by Time ($F_{(2, 86)} = 2.8$, $\eta^2_p = 0.062$, $p = 0.064$), Age by Intervention ($F_{(1, 43)} = 0.9$, $\eta^2_p = 0.020$, $p = 0.358$) or Intervention by Age by Time interactions ($F_{(2, 86)} = 1.8$, $\eta^2_p = 0.039$, $p = 0.179$). Follow-up multivariate tests on change scores confirmed the analyses above and revealed that the Intervention by Time interaction was predominantly driven by differences in skill improvements between MPG and COG on Day 1 ($F_{(1, 43)} = 10.2$, $\eta^2_p = 0.192$, $p = 0.003$) but not Day 2 ($F_{(1, 43)} = 1.4$, $\eta^2_p = 0.032$, $p = 0.241$). Together, these results suggest that motor practice improved right-hand motor performance in the

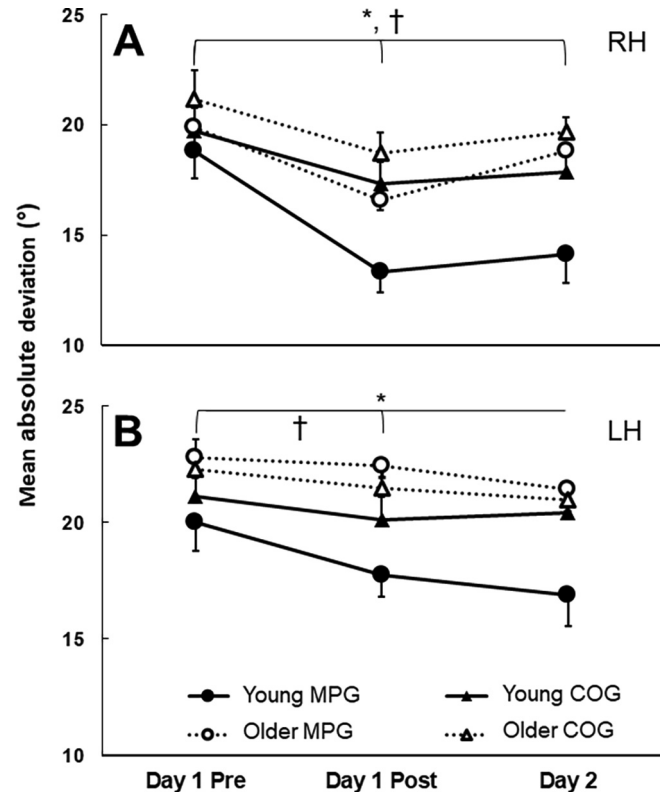


Fig. 2. Motor learning. Motor performance before (Day 1 pre), after (Day 1 post), and 24 hours after (Day 2) motor practice (motor practice group, MPG) in a visuomotor task or resting for an equivalent amount of time (control group, COG) in the right hand (RH; panel A) and left hand (LH; panel B). Motor performance, quantified as the mean absolute deviation from the preprogrammed template, improved in both hands (*, Time main effect, $p < 0.05$). Right-hand motor performance improved more in MPG compared to COG in the right hand (†, Group by Time interaction, $p < 0.05$). Left hand motor performance improved more in young vs. older adults and more in MPG group compared to COG (†, Group by Age interaction, $p < 0.05$). Error bars denote ± 1 SEM.

trained right hand measured on the same day as compared to a control intervention.

3.1.2. Interlimb transfer

To examine whether a right-handed practice intervention caused interlimb transfer to the non-trained left hand, we performed a similar statistical model as in the right hand to left-hand motor performance. Similar to the right-dominant practice hand, non-dominant left-hand motor performance in young and older adults improved by over time across age and intervention groups as indicated by a main effect of Time ($F_{(2, 86)} = 13.5$, $\eta^2_p = 0.238$, $p < 0.001$; Fig. 2B). Post-hoc analyses revealed that left-hand motor performance increased from pre to post ($t_{46} = 4.1$, $p < 0.001$) and remained stable from post to retention ($t_{46} = 1.5$, $p = 0.144$). Across intervention groups and time points, young adults showed superior non-dominant left hand motor performance as indicated by a main effect of Age ($F_{(1, 43)} = 9.6$, $\eta^2_p = 0.074$, $p = 0.003$). There were no Time by Intervention ($F_{(2, 86)} = 2.1$, $\eta^2_p = 0.046$, $p = 0.130$), Time by Age ($F_{(2, 86)} = 0.8$, $\eta^2_p = 0.018$, $p = 0.434$), or Time by Intervention by Age interactions ($F_{(2, 86)} = 1.2$, $\eta^2_p = 0.026$, $p = 0.317$). However, there was an Intervention by Age interaction ($F_{(1, 43)} = 3.5$, $\eta^2_p = 0.074$, $p = 0.035$). Post-hoc paired t -tests revealed that young adults in the MPG showed interlimb transfer from pre to post ($t_{(11)} = 5.4$, $p < 0.001$) but that there was no significant interlimb transfer from pre to post in the young COG ($t_{(11)} = 2.1$, $p = 0.064$), old MPG ($t_{(11)} = 1.0$,

$p = 0.345$) or old COG ($t_{(11)} = 1.3, p = 0.228$). Left-hand performance did not change in any of the groups from post to retention. Collectively, the behavioral data suggest that right-hand motor practice results in performance improvements in both hands in young and older adults but that motor performance was worse in older as compared to young adults. Furthermore, while there were no significant differences between the improvements as a result of motor practice between age groups in the trained right hand, interlimb transfer to the untrained left hand after motor practice was larger in young vs. older adults. The behavioral data are summarized in Table 2.

3.2. Connectivity data

As mentioned before (Section 2.6.2: analysis of EEG data), we performed an initial quality check of the baseline resting-state EEG data in the two age groups to examine whether our data reveal effects of age generally observed in EEG power spectra [e.g., (Scally et al., 2018; Voytek et al., 2015)]. Indeed, the present data confirm lower alpha (8–12 Hz) peak frequencies and higher beta (13–30 Hz) power in older vs. young adults. Specifically, the peak alpha frequency in young vs. older adults, averaged over MPG and COG groups within each age group, was 9.67 vs. 9.26 Hz, respectively. Moreover, beta power was higher in older as compared to young adults (0.556 vs. 0.324 μV^2 , respectively).

3.2.1. Baseline coherence

First, we checked whether total baseline coherence was similar between intervention and age groups. A multivariate ANOVA revealed that within age groups, MPG and COG had similar left-M1-related coherence ($F_{(1, 44)} = 0.1, \eta_p^2 = 0.002, p = 0.753$) and right-M1-related coherence ($F_{(1, 44)} = 1.0, \eta_p^2 = 0.023, p = 0.316$). When comparing baseline coherence between age groups, results revealed that left-M1-related baseline coherence was higher in younger compared to older adults ($F_{(1, 44)} = 4.5, \eta_p^2 = 0.093, p = 0.040$), but there was no age effect on non-dominant right-M1-related coherence ($F_{(1, 44)} = 1.3, \eta_p^2 = 0.029, p = 0.257$; Fig. 3-A-B).

3.2.2. Left-M1-related coherence

To examine the effects of right-hand motor practice on left-M1-related coherence over the skill acquisition interval, we performed a 2 (Time: pre Day 1 vs. post Day 1) by 2 (Intervention: MPG vs. COG) by 2 (Age: Young vs. Old) repeated measures ANOVA. Results revealed that left-M1-related coherence decreased over time ($F_{(1, 42)} = 5.3, \eta_p^2 = 0.111, p = 0.027$; Fig. 3A) and that left-M1-related coherence was lower in older adults ($F_{(1,42)} = 4.4, \eta_p^2 = 0.095, p = 0.042$). There were no Time by Intervention ($F_{(1, 42)} = 1.7, \eta_p^2 = 0.038, p = 0.206$), Time by Age interactions ($F_{(1,42)} = 1.6, \eta_p^2 = 0.036, p = 0.214$) or Intervention by Age interaction ($F_{(1, 42)} = 0.016, \eta_p^2 = 0.0, p = 0.901$), suggesting that changes in left-M1-related coherence were independent of Age or Intervention. However, there was an interaction between Time, Intervention

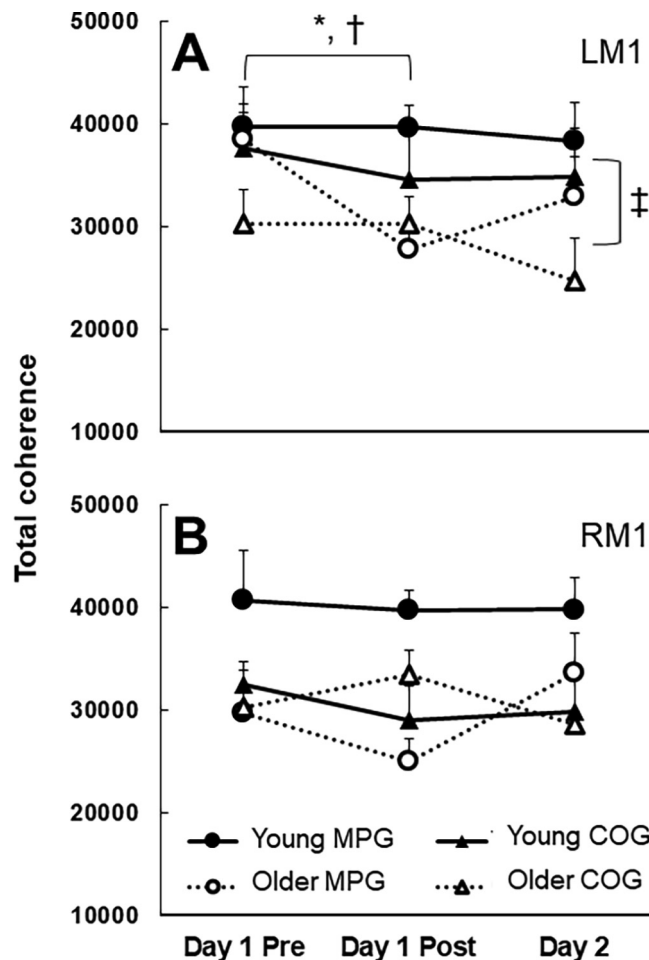


Fig. 3. Time-courses of coherence. Total coherence with the left primary motor cortex (LM1; panel A) and right primary motor cortex (RM1, panel B) before (Day 1 pre), after (Day 1 post), and 24 hours after (Day 2) motor practice (motor practice group, MPG) in a visuomotor task or resting for an equivalent amount of time (control group, COG) in the right (A) and left hemisphere (B). There was an effect of Time (*, $p < 0.05$), Age (‡, $p < 0.05$), and Group by Time interaction (†, $p < 0.05$). Error bars denote + 1 SEM.

and Age ($F_{(1, 42)} = 5.1, \eta_p^2 = 0.109, p = 0.028$; Fig. 3A). Follow-up paired t -tests within age and intervention groups revealed that the decrease in left-M1-related coherence was significant in the old MPG ($t_{11} = 3.4, p = 0.006$) but not in the old COG ($t_9 = 0.001, p = 0.999$), young MPG ($t_{11} = 0.024, p = 0.982$) or young COG ($t_{11} = 1.1, p = 0.294$).

Because the neural signatures of motor memory consolidation are different from skill acquisition, we performed a separate 2 (Time: post Day 1 vs. Day 2) by 2 (Intervention: MPG vs. COG) by 2 (Age: Young vs. Old) repeated measures ANOVA. The results

Table 2
Behavioral data.

		Older		Young	
		MPG	COG	MPG	COG
Right hand	Pre Day 1	19.9 (3.0)	21.2 (4.5)	18.8 (4.3)	19.8 (3.2)
	Post Day 1	16.6 (1.6)	18.7 (3.3)	13.3 (3.3)	17.3 (3.1)
	Retention Day 2	19.8 (3.4)	19.7 (2.3)	14.2 (4.7)	17.9 (3.1)
Left hand	Pre Day 1	22.8 (3.0)	22.3 (3.5)	20.0 (4.3)	21.1 (1.7)
	Post Day 1	22.4 (2.4)	21.5 (2.5)	17.7 (4.2)	20.1 (2.5)
	Retention Day 2	21.4 (2.8)	21.0 (3.2)	16.9 (3.4)	20.4 (3.4)

Values are ° of errors from the preprogrammed template and presented as mean (\pm standard deviation). MPG, motor practice group; COG, control group.

indicated that there was no further increase in left-M1-related coherence in the consolidation phase ($F_{(1, 42)} = 0.03$, $\eta_p^2 = 0.001$, $p = 0.855$). We did also not observe an effect of Intervention ($F_{(1, 42)} = 1.319$, $\eta_p^2 = 0.030$, $p = 0.257$), but there was an effect of Age ($F_{(1, 42)} = 6.7$, $\eta_p^2 = 0.138$, $p = 0.013$) again indicating that, across intervention groups, left-M1-related coherence was lower in older adults as compared to young adults. None of the interactions significant ($F < 2.426$, $p > 0.127$). Subsequent independent samples Mann-Whitney U tests on contrasted coherence (see Section 2.6.2) revealed that the increases in left-M1-related maximal coherence after motor practice were observed in young ($U = 35.5$, $p = 0.030$) but not in older adults ($U = 58.0$, $p = 0.325$) on Day 1 (Fig. 4A).

3.2.3. Right-M1-related coherence

To examine changes in right-M1-related coherence, a similar statistical model as for left-M1-related coherence was performed. The results revealed that over the skill acquisition period, there were no effects of Time ($F_{(1, 42)} = 1.119$, $\eta_p^2 = 0.026$, $p = 0.296$) and Intervention ($F_{(1, 42)} = 0.891$, $\eta_p^2 = 0.021$, $p = 0.351$), but there was an effect of Age ($F_{(1, 42)} = 4.895$, $\eta_p^2 = 0.104$, $p = 0.032$): right-M1-related coherence was lower in older vs. young adults. There were no Time by Intervention, Time by Age, or Time by Intervention by Age interactions ($F < 3.406$, $p > 0.072$), but there was an Intervention by Age interaction ($F_{(1, 42)} = 6.990$, $\eta_p^2 = 0.143$, $p = 0.011$) driven by reduced right-M1-related coherence in the older MPG.

The repeated measures ANOVA over the consolidation interval revealed no main effects of Time ($F_{(1, 42)} = 0.3$, $\eta_p^2 = 0.006$, $p = 0.613$), Intervention ($F_{(1, 42)} = 2.996$, $\eta_p^2 = 0.067$, $p = 0.091$) or Age ($F_{(1, 42)} = 3.3$, $\eta_p^2 = 0.072$, $p = 0.077$; Fig. 3B). However, there was an Age by Intervention interaction ($F_{(1, 42)} = 5.881$, $\eta_p^2 = 0.123$, $p = 0.020$), driven by decreases and increases in

right-M1-related coherence in MPG and COG in older adults while coherence in young adults remained stable. None of the other interaction effects reached significance ($F < 2.003$, $p > 0.164$). In addition, independent samples Mann-Whitney U tests on the contrasted coherence revealed that, in contrast to the statistical analysis on contrasted coherence in the left hemisphere, motor practice increased maximal and average right-M1-related coherence in older but not in young adults on Day 1 ($U = 22.0$, $p = 0.011$ vs. $U = 90.0$, $p = 0.319$) and between Days 1 and 2 ($U = 13.0$, $p = 0.001$ vs. $U = 83.5$, $p = 0.514$; Fig. 4C-D).

Collectively, the present results suggest that age mediates the influence of motor practice on the coherence observed in both hemispheres. Specifically, maximal and average left-M1-related coherence increased more in young as compared to older adults on Days 1 and 2, respectively. In contrast, in the untrained right hemisphere, right-M1-related coherence average and maximal increased after motor practice in older adults.

3.3. Correlation analysis

Within and across age and intervention groups, skill acquisition in the left and right hand were uncorrelated (all $p > 0.05$). However, in MPG ($\rho = 0.547$, $p_{\text{FDRcor}} = 0.028$), but not in COG ($\rho = -0.258$, $p_{\text{FDRcor}} = 0.223$; $Z = 2.85$; $p = 0.004$), changes in performance for the right- and left hand on Day 2 were correlated.

3.3.1. Correlations with right-hand motor performance

In older adults, correlation analysis showed that after FDR correction, increases in right-hand motor performance in MPG were correlated with reductions in maximal coherence with the left M1 ($\rho = -0.825$, $p_{\text{FDRcor}} = 0.008$), but not in COG ($\rho = 0.534$, $p_{\text{FDRcor}} = 0.074$; $Z = 3.75$, $p = 0.002$; Fig. 5A). This relationship was

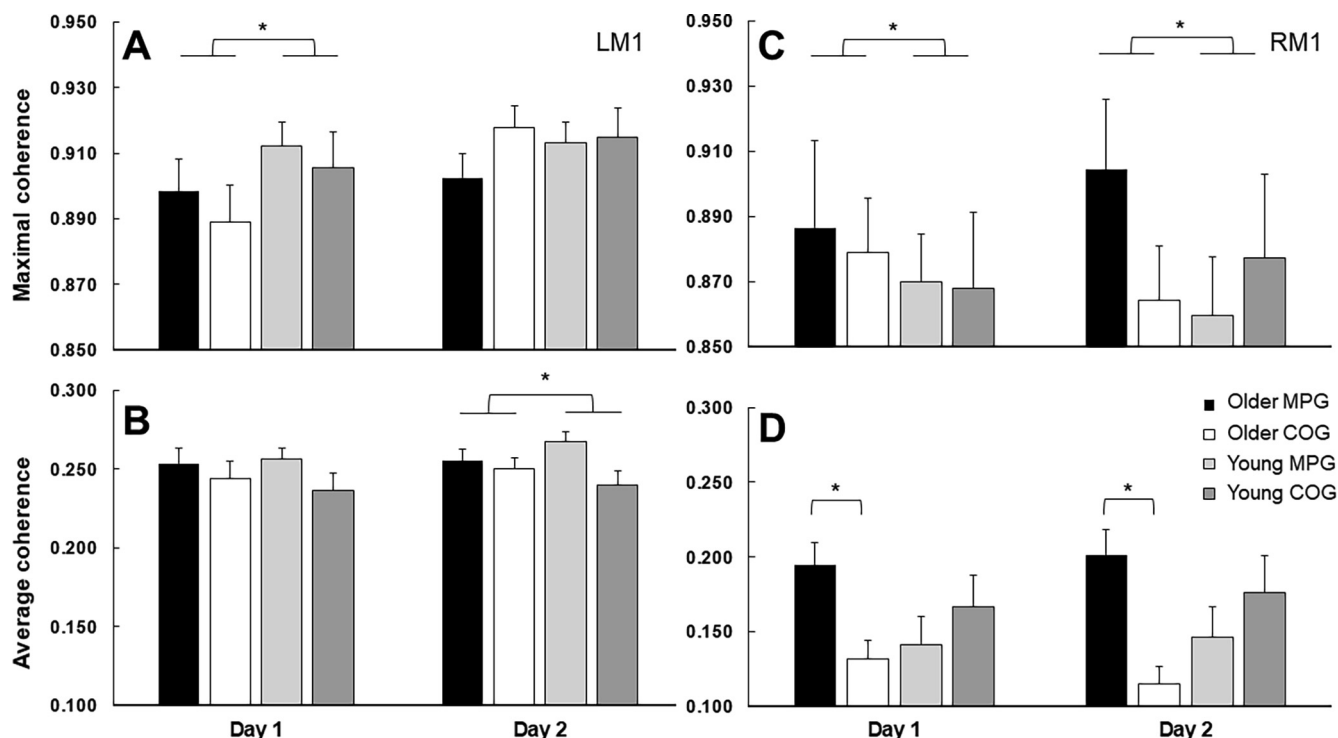


Fig. 4. Changes in coherence. Contrasted source-reconstructed coherence in the older and young motor practice group (MPG) and in the older and young control group (COG) showed an effect of Intervention on Days 1 and 2 for maximal (A) and average (B) coherence with the left primary motor cortex (LM1) (*, $p < 0.05$). Furthermore, there was an effect of Age on coherence with the right primary motor cortex (RM1) on Days 1 and 2 (C, $p < 0.05$) driven by increases in coherence in older adults (D, effect of Age on maximal coherence, $p < 0.05$). Error bars denote + 1 SEM.

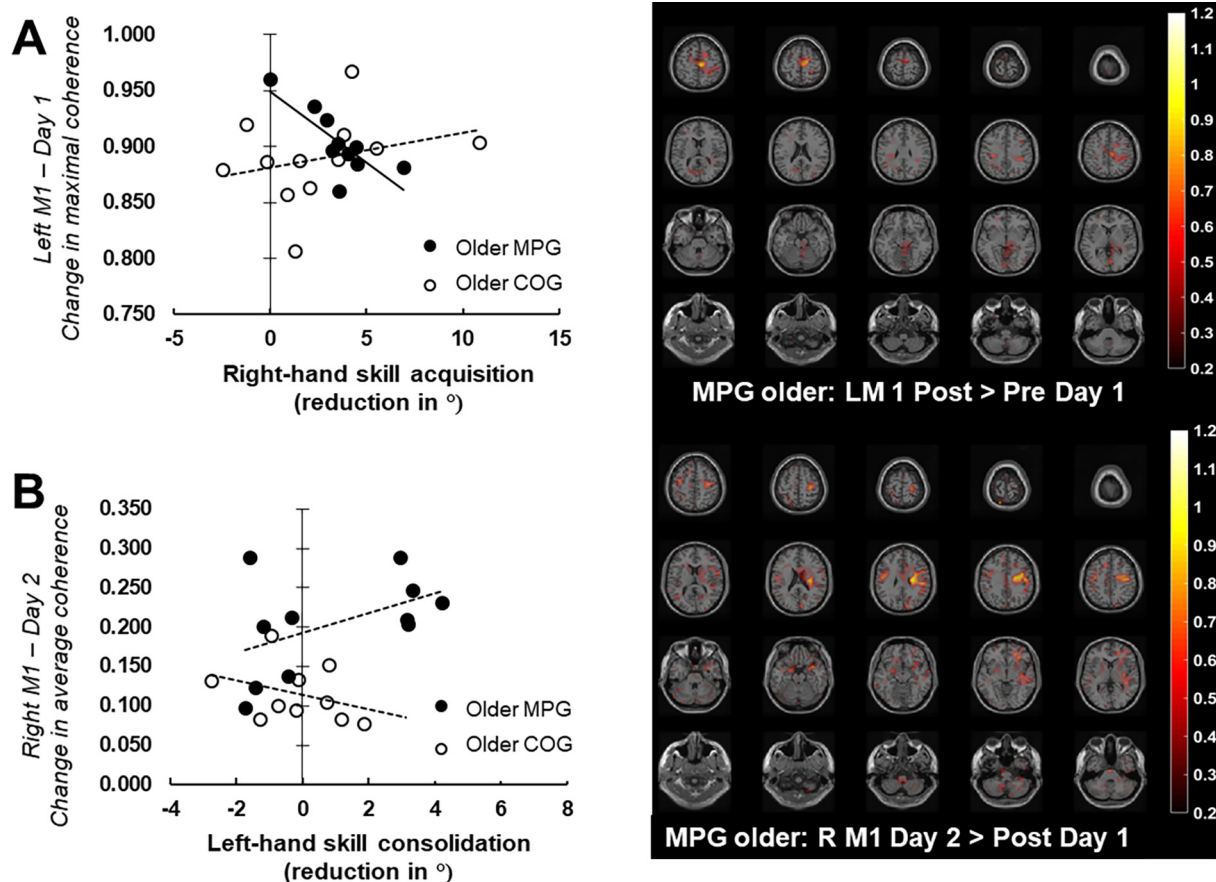


Fig. 5. Correlation between coherence and motor learning. The scatterplots on the left side of panels A–B show the relationships between right-hand skill acquisition (panel A) and left-hand skill consolidation (panel B) and changes in coherence with the seed structure (left primary motor cortex (L M1, panel A) and right primary motor cortex (R M1, panel B)). Continuous lines reflect significant correlations after correction for multiple comparisons ($p_{\text{FDRcor}} < 0.05$) whereas dashed lines reflect non-significant correlations between coherence and motor learning. Positive scores on the x-axes reflect improvements in performance in the motor practice group (MPG) and control group (COG). The figures on the right sides of in panels A–B show the reconstructed source coherence in a representative participant from the motor practice group. Warmer colors reflect greater strengthening of coherence ranging from 0.2 to 1.2.

specific to older adults, as these correlations were absent in young adults (MPG: $\rho = 0.018$, $p_{\text{FDRcor}} = 0.478$; COG: $\rho = 0.074$, $p_{\text{FDRcor}} = 0.553$). Skill consolidation in the right hand on Day 2 in young adults was positively correlated with the increases in average left-M1-related coherence in MPG ($\rho_{\text{unc}} = 0.653$, $p = 0.044$), but not in COG ($\rho_{\text{unc}} = 0.415$, $p = 0.102$), on Day 2 ($Z = -2.44$, $p = 0.007$; Fig. 5B).

3.3.2. Correlations with left-hand motor performance

We hypothesized that increased motor network connectivity would support the interlimb transfer of motor skills to the non-dominant left hand after right-hand motor practice. Therefore, we tested whether there were relationships between behavioral improvements in non-dominant left-hand performance and left-M1-related coherence (i.e., involved in MP), as well as right-M1-related coherence. In contrast to the hypothesis, none of the correlation coefficients for interlimb transfer on Day 1 survived correction for multiple comparisons. However, changes in left-hand motor performance on Day 2 in older adults were differently correlated with increases in average right-M1-related coherence in MPG ($\rho = 0.556$, $p_{\text{FDRcor}} = 0.152$) compared to COG ($\rho = -0.292$, $p_{\text{FDRcor}} = 0.276$; $Z = 1.79$, $p = 0.037$; Fig. 5B). Please note that the correlations coefficients alone did not survive FDR correction. In young adults, there were no correlations between interlimb transfer on Days 1 and 2 and the EEG-derived measures of connectivity assessed here.

4. Discussion

We determined for the first time the effects of age on motor skill acquisition and consolidation in combination with the effects on interlimb transfer in relation to the changes in resting-state motor network connectivity during motor learning. We found that visuomotor performance in the trained right hand improved independent of age, but the magnitude of interlimb skill transfer to the left hand decreased with age. These motor practice-related changes were accompanied by increases in left- and right-M1-related connectivity in young and older adults, respectively. Moreover, changes in left- and right-M1-related connectivity were negatively and positively correlated to right-hand skill acquisition and left-hand skill consolidation in older adults, respectively. Altogether, the current data suggest an age-dependent modulation of bilateral motor network connectivity for the acquisition, consolidation, and interlimb transfer of unimanual visuomotor skills.

4.1. Skill acquisition and consolidation but not interlimb transfer are intact in older adults

4.1.1. Right-hand motor performance

Motor practice produced similar learning rates in young (5.5 vs. 2.4% or 5.5 vs. 2.5° reduction in error) and older adults (3.8 vs. 2.5% or 3.3 vs. 2.5° reduction in error). These data agree with data from several studies also using a unilateral visuomotor tracking

paradigm [e.g., (Berghuis et al., 2016, 2019; Cirillo et al., 2011)]. However, this relative preservation of the ability to acquire new skills in older vs. young adults seems task-dependent because the present results contrast with findings in sequence learning and coordination tasks (Brown et al., 2009; Coats et al., 2014; Rueda-Delgado et al., 2019). Similarly, in agreement with previous studies (Berghuis et al., 2016; Brown et al., 2009), the consolidation of the acquired skills was similar in young (-0.8 vs. -0.5% or -0.9° vs. -0.6° reduction in error) and older adults (0.9 vs. 0.5% or 1.0° vs. 0.5° reduction in error). Because the quality of sleep assessed by the PSQI in the two age groups, these observations may be mediated by the full night of sleep in between the two sessions (Korman et al., 2015). That is, while procedural memory consolidation during the day may be affected in older vs. young adults, post-learning sleep has been shown to counteract such age-related effects and consequently may have resulted in the statistically similar performance levels in older vs. young adults on Day 2. Since baseline motor performance in the right hand was similar in the two age groups, the present results provide reliable evidence that older adults have a preserved ability to acquire and retain visuo-motor tracking skills, albeit the neural strategies to achieve similar learning rates appear to be age-specific.

4.1.2. Interlimb transfer

Interlimb transfer in young adults has been shown in a variety of tasks including voluntary force (Zhou, 2000), ballistic (Lee et al., 2010), and visuomotor tracking skills (Veldman et al., 2018, 2015). In contrast, data on interlimb transfer in older adults are scant. Here, we show that in contrast with the practiced right hand, interlimb transfer to the non-practiced left hand after motor practice was greater in young (2.3% or 2.3° reduction in error) compared to older adults (0.7% or 0.7° reduction in error). These data agree with some (Krishnan et al., 2018) but contrast with other studies using different tasks (Dickins et al., 2015; Graziadio et al., 2015; Hester et al., 2019a; Hinder et al., 2011). A lack of interlimb transfer in older adults is somewhat surprising considering previous data showing increased bilateral cortical activation according to the HAROLD model as well as the greater mirror activity, i.e., muscle activity in the limb presumably at rest, in older compared to young adults (Berghuis et al., 2019; Hinder et al., 2011; Ward et al., 2008). These data suggest that bilateral cortical and muscle activity do not directly support the interlimb transfer of skills. Hence, different mechanisms at the spinal and supraspinal level must contribute to the acquisition of skills in the practiced vs. the non-practiced side as well as in older vs. young adults. At the behavioral level, such predictions are at least partly supported by the lack of correlations between increases in right- and left-hand motor performance in the present and previous studies (Nojima et al., 2012; Veldman et al., 2018, 2015). At the neural level, the present data add to the increasing body of literature providing evidence that bilateral activity and connectivity in the sensorimotor network contribute to interlimb transfer of motor skills in older adults (see Section 4.2.2). In total, the ability to acquire and consolidate a visuomotor skill after unimanual visuomotor practice, but not the ability to transfer the skill to the non-practiced side, is retained at older age.

4.2. Age-dependent changes in motor network connectivity contribute to motor learning

Behavioral, neurophysiological, and neuroimaging data suggest that the neuronal mechanisms for the acquisition, consolidation, and interlimb transfer of motor skills are age-dependent. The present study confirms previous reports and highlights the importance of both the left and right M1 in motor learning following motor practice in an aging context (Cirillo et al., 2011;

Hortobágyi et al., 2011; Muellbacher et al., 2002; Nojima et al., 2012; Perez et al., 2007; Ruddy et al., 2017; Veldman et al., 2018, 2015; Ziemann et al., 2001). In this section, we will discuss our results in more detail concerning the role of the left- and right-M1 in right hand motor learning (Section 4.2.1) and left-hand motor learning (Section 4.2.2.) following right-hand motor practice.

4.2.1. Neural correlates of right-hand skill acquisition and consolidation

The unique role of M1 in motor learning for the execution, acquisition, and consolidation of skilled right-hand movements is well established (Muellbacher et al., 2002; Ziemann et al., 2001). The present data confirm previous findings that suggest the importance of motor network connectivity for the acquisition and consolidation of more complex skills (Mehrkanoon et al., 2016; Veldman et al., 2018; Wu et al., 2014). Moreover, the age-dependent modulation of the strength of motor network connectivity in the beta frequency range on Days 1 and 2 (Fig. 4A-B) align with electrophysiological and imaging data showing lower beta power and greater activation in sensorimotor regions in older vs. young adults (Berghuis et al., 2019; Rossiter et al., 2014; Rueda-Delgado et al., 2019). These data, together with imaging data and the observation that young and older adults show similar learning rates, favor the interpretation of age-related compensatory mechanisms that include decreased default mode network, striatal and sensorimotor activity (Ward 2006; Ward et al. 2008; Berghuis et al. 2019). Here, in addition to altered changes in activity patterns relative to younger adults after motor practice, we observed that older adults are also less able to strengthen left-M1-related connectivity over the course of right-hand skill acquisition and consolidation. In fact, improved right-hand motor performance after motor practice in older adults negatively correlated with increases in maximal coherence with the left M1 (Fig. 5A). Such relationships may be task-dependent because a previous study found a positive correlation between sensorimotor connectivity and motor learning in older adults after practicing a serial reaction time task (Mary et al., 2017a). In total, the reduced modulation of motor-learning-related beta frequencies in the sensorimotor network in older compared to young adults may indicate that other regions are also involved in right-hand skill acquisition and consolidation in older adults. Although the present measures of plasticity do not provide direct evidence, one could speculate that our data provide further support for the HAROLD model as the age-related modulation of right-M1-related connectivity may reflect increased involvement of the right M1 in older vs. young adults which could constitute a compensatory mechanism for right-hand skill acquisition and consolidation in older adults.

4.2.2. Neural correlates of interlimb transfer

Interlimb transfer of motor performance following unilateral motor practice is commonly attributed to synaptic plasticity at the supraspinal level through 'cross-activation' or 'bilateral access' (Ruddy and Carson, 2013). Within this view, a series of studies focused on excitability changes in bilateral M1 (Hinder et al., 2011; Hortobágyi et al., 2011; Lee et al., 2010; Nojima et al., 2012; Veldman et al., 2015). However, magnetic stimulation data showed age-dependent effects on motor cortical excitability after ballistic motor practice (Hinder et al., 2011). Moreover, imaging studies revealed that bilateral activation during unilateral movements is not limited to M1 but includes the supplementary motor cortex, primary sensory cortex, cerebellum, parietal cortex, and cingulate cortex (for a review, see Ruddy and Carson 2013). Based on these data, Ruddy and colleagues hypothesized that connectivity in the wider motor network must be involved in the interlimb transfer of motor skills. Their recent results showing increased

connectivity between left and right SMA following training in a ballistic wrist flexion task (Ruddy et al., 2017) further supported the hypothesis. Here, we extend these findings and show that unilateral motor practice not only increased connectivity with the practiced left M1, but also with the transfer-receiving right M1, a finding that may reflect increased interhemispheric connectivity following unilateral motor practice. Interestingly, right-M1-related connectivity increased more in older adults compared to young adults (Fig. 4C–D) in agreement with recent electrophysiological data showing strengthened connectivity between ipsilateral and contralateral motor cortices during unimanual movements (Larivière et al., 2019). Yet, while the magnitude of interlimb transfer in older adults did not reach significance on the group level, increases in right-M1-related connectivity positively correlated with changes in motor performance on Day 2 (Fig. 5B), suggesting that right hemisphere motor network connectivity is related to right-to-left interlimb transfer in older adults.

Based on the present results suggesting that motor learning in young and older adults depends on activity in the motor networks in the left and right hemisphere, respectively, one may argue that cortical activity is a prerequisite for changes in connectivity that are of direct relevance for increases in motor performance. We speculate that the present data can be explained as first evidence for the hypothesis that interlimb transfer in young and older adults is achieved through different strategies derived from the extant hypotheses for interlimb transfer. Specifically, our data could imply that young adults use the ‘bilateral access strategy’, where unilateral activation can be accessed by bilateral effectors (i.e., left and right hand) while older adults use the ‘cross-activation strategy’ where unilateral practice leads to bilateral motor network activity to enhance performance. Further research is required to verify these speculations. For example, the present analysis could not determine the pathways that contributed to the increased ipsilateral connectivity. The absence of correlations between interlimb transfer and EEG connectivity in young adults further complicate the suggestion of an age-specific strategy of interlimb transfer. However, the lower variability in the young data makes it difficult to observe significant relationships. Altogether, the current data show age-dependent modulation of bilateral motor network connectivity for the acquisition, consolidation, and interlimb transfer of a unimanual visuomotor skill.

5. Limitations

The main aim of this study was to examine age-related modulations in motor network connectivity associated with motor learning after a motor practice in an aging context. Such a between-subject design reduced the statistical power but was needed to appropriately address the current research question. In line with this, although sleep has a known effect on motor memory consolidation [for a review see (King et al., 2017)], we did not formally assess sleep or the presence of sleep disorders for feasibility reasons. Consequently, age-related differences in sleep characteristics [e.g., (Fogel et al., 2017)] may have contributed to the results of this study. Moreover, our experimental design did not allow us to exclude the possibility that merely movements during the motor practice intervention (i.e., as opposed to no movements in COG) already resulted in increased performance. With respect to the EEG outcome measures, the DICS method was initially developed for magnetoencephalography data (Gross et al., 2001). However, evidence indicates that DICS analysis on data obtained from a 64-channel EEG system as used in the present study yields comparable results compared to a 275-sensor magnetoencephalography system when it comes to resting-state data (Muthuraman et al., 2015). Moreover, we are aware that coherence as a measure of

connectivity is prone to sources of noise such as volume conduction. While the noise bias is removed by contrasting two intervals (e.g., Pre and Post), it assumes that the noise bias is similar in the two intervals, which may not have been the case. However, a findings of a recent study suggest that test–retest reliability of source-localized functional connectivity in older adults is good (Vecchio et al., 2020), indicating that modulations observed in MPG may be interpreted as resulting from the intervention. Next, although functional connectivity in resting-state data has been shown to have predictive value for the magnitude of motor learning (Wu et al., 2014), the DICS method may not have provided the dipole with peak power that was active during task practice. As such, the changes in coherence may have been underestimated. A future study using EEG data obtained during task practice may provide further insight into connectivity changes during task practice. Lastly, because we focused our analysis on the motor network we might have missed connectivity in structures less accessible by EEG source localization such as subcortical structures that have previously been shown to be involved in sleep-dependent motor memory consolidation [for a review, see (King et al., 2017)] and interlimb transfer (Perez et al., 2007) or parieto-frontal networks known to be associated with motor learning in an aging context (Lin et al., 2012).

Summary and conclusions

To the best of our knowledge, this is the first study that determined the effects of age on the relationship between brain network connectivity and motor skill acquisition, consolidation, and interlimb transfer with changes in the underlying motor network connectivity based on source-reconstructed high-density EEG data. At the behavioral level, our findings show that skill acquisition and consolidation but not interlimb transfer can be age-resistant processes. At the neural level, the results revealed that unilateral motor practice results in age-dependent modulation of cortical motor network connectivity in the practiced as well as in the non-practiced hemisphere. We suggest that the dependence on left- and right-hemisphere motor network connectivity in young and older adults, respectively, indicates the use of different strategies to achieve behavioral improvements in right- and left-hand motor performance following unilateral practice. In conclusion, the present data show age-dependent modulation of bilateral motor network connectivity for the acquisition, consolidation, and interlimb transfer of unimanual visuomotor skills.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors thank dr. Chris Mizelle for his comments on the study design. In addition, we thank Nine Wolters and Merle Nijland for their efforts during data collection. The study was partially supported by the Research Foundation Flanders (grants G0F76.16N, G0936.16N and EOS.30446199) and the KU Leuven Research Fund (grant C16/15/070).

References

- Anguera JA, Reuter-lorenz PA, Willingham DT, Seidler RD. Failure to engage spatial working memory contributes to age-related declines in visuomotor learning. *J Cogn* 2010;23:11–25.
- Anshel MH. Effect of aging on acquisition and short-term retention of a motor skill. *Percept Mot Skills* 1978;47:993–4.
- Babaeeghazvini P, Rueda-delgado LM, Adab HZ, Gooijers J, Swinnen SP, Daffertshofer A. A combined diffusion-weighted and electroencephalography

- study on age-related differences in connectivity in the motor network during bimanual performance. *Hum Brain Mapp* 2019;40:1799–813.
- Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc B* 1995;57:289–300.
- Berghuis K, De Rond V, Zijdwind I, Koch G, Veldman M, Hortobágyi T. Neuronal mechanisms of motor learning are age dependent. *Neurobiol Aging* 2016;46:149–59.
- Berghuis KMM, Fagioli S, Maurits NM, Zijdwind I, Marsman JBC, Hortobágyi T, et al. Age-related changes in brain deactivation but not in activation after motor learning. *Neuroimage* 2019;186:358–68.
- Bhatt MB, Bowen S, Rossiter HE, Dupont-Hadwen J, Moran RJ, Friston KJ, et al. Computational modelling of movement-related beta-oscillatory dynamics in human motor cortex. *Neuroimage* 2016;133:224–32.
- Bo J, Peltier SJ, Noll DC, Seidler RD. Age differences in symbolic representations of motor sequence learning. *Neurosci Lett* 2011;504:68–72.
- Brown RM, Robertson EM, Press DZ. Sequence skill acquisition and off-line learning in normal aging. *PLoS One* 2009;4:e6683.
- Buyssse DJ, Reynolds III CF, Monk TH, Berman SR, Kupfer DJ. The pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
- Carbeza R. Hemispheric asymmetry reduction in older adults: The HAROLD model. *Psychol Aging* 2002;17:85–100.
- Cirillo J, Todd G, Semmler JG. Corticomotor excitability and plasticity following complex visuomotor training in young and old adults. *Eur J Neurosci* 2011;34:1847–56.
- Coats RO, Wilson AD, Snapp-childs W, Fath AJ, Bingham GP. The 50s cliff: perceptuo-motor learning rates across the lifespan. *PLoS One* 2014;9:e85758.
- Delorme A, Sejnowski T, Makeig S. Enhanced detection of artifacts in EEG data using higher-order statistics and independent component analysis. *Neuroimage* 2007;34:1443–9.
- DeLuca A, Giannoni P, Vernetti H, Capra C, Siva RR, Lentino C, et al. Training the unimpaired arm improves the motion of the impaired arm and the sitting balance in chronic stroke survivors. *IEEE Trans Neural Syst Rehabil Eng* 2017;25:873–82.
- Dickins DSE, Sale MV, Kamke MR. Intermanual transfer and bilateral cortical plasticity is maintained in older adults after skilled motor training with simple and complex tasks. *Front Aging Neurosci* 2015;7:1–12.
- Dragert K, Zehr EP. High-intensity unilateral dorsiflexor resistance training results in bilateral neuromuscular plasticity after stroke. *Exp Brain Res* 2013;225:93–104.
- Ehrensberger M, Simpson D, Broderick P, Ehrensberger M, Simpson D, Broderick P. Cross-education of strength has a positive impact on post-stroke rehabilitation: a systematic literature review. *Top Stroke Rehabil* 2016;23:126–35.
- Espenhahn S, van Wijk BCM, Rossiter HE, de Berker AO, Redman ND, Rondina J, et al. Cortical beta oscillations are associated with motor performance following visuomotor learning. *Neuroimage* 2019;195:340–53.
- Floyer-Lea A, Matthews PM. Distinguishable brain activation networks for short- and long-term motor skill learning. *J Neurophysiol* 2005;94:512–8.
- Fogel S, Vien C, Karni A, Benali H, Carrier J, Doyon J. Sleep spindles: a physiological marker of age-related changes in gray matter in brain regions supporting motor skill memory consolidation. *Neurobiol Aging* 2017;49:154–64.
- Fogel SM, Albouy G, Vien C, Popovici R, King BR, Hoge R, et al. fMRI and sleep correlates of the age-related impairment in motor memory consolidation. *Hum Brain Mapp* 2014;35:3625–45.
- Folstein M, Folstein S, McHugh P. “Mini-mental state”: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–98.
- Graziadio S, Nazarpour K, Gretenkord S, Jackson A, Eyre JA. Greater intermanual transfer in the elderly suggests age-related. *J Mot Behav* 2015;47:47–55.
- Greenblatt RE, Ossadtchi A, Pflieger ME. Local linear estimators for the bioelectromagnetic inverse problem. *IEEE Trans SIGNAL Process* 2005;53:3403–12.
- Gross J, Kujala J, Hamalainen M, Timmermann L, Schnitzler A, Salmelin R. Dynamic imaging of coherent sources: studying neural interactions in the human brain. *Proc Natl Acad Sci* 2001;98:694–9.
- Hester GM, Magrini MA, Colquhoun RJ, Barrera A, Carlos C, Olmos AA, et al. Cross-education: effects of age on rapid and maximal voluntary contractile characteristics in males. *Eur J Appl Physiol* 2019a;119:1313–22.
- Hester GM, Pope ZK, Magrini MA, Colquhoun RJ, Barrera-curiel A, Estrada CA, et al. In the ipsilateral and contralateral limbs during unilateral resistance training. *J Aging Phys Act* 2019b;27:1–8.
- Hinder MR, Schmidt MW, Garry MI, Carroll TJ, Summers JJ. Absence of cross-limb transfer of performance gains following ballistic motor practice in older adults. *J Appl Physiol* 2011;110:166–75.
- Hortobágyi T, Richardson SP, Lomarev M, Shamim E, Meunier S, Russman H, et al. Interhemispheric plasticity in humans. *Med Sci Sports Exerc* 2011;43:1188–99.
- Kim C-Y, Lee J, Kim H-D, Kim J. The effect of progressive task-oriented training on a supplementary tilt table on lower extremity muscle strength and gait recovery in patients with hemiplegic stroke. *Gait Posture* 2015;41:425–30.
- King BR, Hoedlmoser K, Hirschauer F, Dolfen N, Albouy G. Sleeping on the motor engram: the multifaceted nature of sleep-related motor memory consolidation. *Neurosci Biobehav Rev* 2017;80:1–22.
- Korman M, Dagan Y, Karni A. Nap it or leave it in the elderly: a nap after practice relaxes age-related limitations in procedural memory consolidation. *Neurosci Lett* 2015;606:173–6.
- Krishnan C, Washabaugh EP, Reid CE, Althoen MM, Ranganathan R. Learning new gait patterns: age-related differences in skill acquisition and interlimb transfer. *Exp Gerontol* 2018;111:45–52.
- Larivière S, Xifra-Porxas A, Kassinosopoulos M, Niso G, Baillet S, Mitsis GD, et al. Functional and effective reorganization of the aging brain during unimanual and bimanual hand movements. *Hum Brain Mapp* 2019;40:3027–40.
- Lee M, Carroll TJ. Cross education: possible mechanisms for the contralateral effects of unilateral resistance training. *Sports Med* 2007;37:1–14.
- Lee M, Hinder MR, Gandevia SC, Carroll TJ. The ipsilateral motor cortex contributes to cross-limb transfer of performance gains after ballistic motor practice. *J Physiol* 2010;588:201–12.
- Liao W, Whittall J, Wittenberg GF, Barton JE, Mccombe S. Not all brain regions are created equal for improving bimanual coordination in individuals with chronic stroke. *Clin Neurophysiol* 2019;130:1218–30.
- Lin C-H-J, Chiang M-C, Wu AD, Iacoboni M, Udompholkul P, Yazdanshenas O, et al. Enhanced motor learning in older adults is accompanied by increased bilateral frontal and fronto-parietal connectivity. *Brain Connect* 2012;2:56–68.
- Manca A, Cabboi MP, Ortu E, Ginatempo F, Dragone D, Zarbo IR, et al. Effect of contralateral strength training on muscle weakness in people with multiple sclerosis: proof-of-concept case series. *Phys Ther* 2016;96:828–38.
- Manca A, Cabboi P, Dragone D, Ginatempo F, Ortu E, De NER, et al. Resistance training for muscle weakness in multiple sclerosis: direct versus contralateral approach in individuals with ankle dorsiflexors' disparity in strength. *Arch Phys Med Rehabil* 2017;98:1348–56.
- Mary A, Wens V, Op de Beeck M, Leproult R, De Tiège X, Peigneux P. Resting-state functional connectivity is an age-dependent predictor of motor learning abilities. *Cereb Cortex* 2017a;27:4923–32.
- Mary A, Wens V, Op de Beeck M, Leproult R, De Tiège X, Peigneux P. Age-related differences in practice-dependent resting-state functional connectivity related to motor sequence learning. *Hum Brain Mapp* 2017b;38:923–37.
- Mehrkanoon S, Boonstra TW, Breakspear M, Hinder M, Summers JJ. Upregulation of cortico-cerebellar functional connectivity after motor learning. *Neuroimage* 2016;128:252–63.
- Muellbacher W, Ziemann U, Wissel J, Dang N, Kofler M, Facchini S, et al. Early consolidation in human primary motor cortex. *Nature* 2002;415:640–4.
- Muthuraman M, Moliadze V, Mideksa KG, Siniatchkin M. EEG-MEG integration enhances the characterization of functional and effective connectivity in the resting state network. *PLoS One* 2015;10:e0140832.
- Nemeth D, Janacsek K. The dynamics of implicit skill consolidation in young and elderly adults. *J Gerontol* 2010;66B:15–22.
- Nojima I, Mima T, Koganemaru S, Thabit MN, Fukuyama H, Kawamata T. Human motor plasticity induced by mirror visual feedback. *J Neurosci* 2012;32:1293–300.
- Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971;9:97–113.
- Oostenveld R, Fries P, Maris E, Schoffelen JM. FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Comput Intell Neurosci* 2011;2011:1–9.
- Perez M, Tanaka S, Wise S, Sadato N, Tanabe H, Willingham D, et al. Neural substrates of intermanual transfer of a newly acquired motor skill. *Curr Biol* 2007a;17:1896–902.
- Perez MA, Wise SP, Willingham DT, Cohen LG. Neurophysiological mechanisms involved in transfer of procedural knowledge. *J Neurosci* 2007b;27:1045–53.
- Pernet C, Garrido MI, Gramfort A, Maurits N, Michel CM, Pang E, et al. Issues and recommendations from the OHBM COBIDAS MEEG committee for reproducible EEG and MEG research. *Nat Neurosci* 2020;23:1473–83.
- Pfurtscheller G, Lopes FH. Event-related EEG / MEG synchronization and desynchronization: basic principles. *Clin Neurophysiol* 1999;110:1842–57.
- Pollok B, Latz D, Krause V, Butz M, Schnitzler A. Changes of motor-cortical oscillations associated with motor learning. *Neuroscience* 2014;275:47–53.
- Raz N, Williamson A, Gunning-dixon F, Head D, Acker JD. Neuroanatomical and cognitive correlates of adult age differences in acquisition of a perceptual-motor skill. *Microsc Res Tech* 2000;51:85–93.
- Robertson EM, Pascual-leone A, Miall RC. Current concepts in procedural consolidation. *Nat Rev Neurosci* 2004;5:1–7.
- Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009;120:2008–39.
- Rossiter HE, Davis EM, Clark EV, Boudrias MH, Ward NS. Beta oscillations reflect changes in motor cortex inhibition in healthy ageing. *Neuroimage* 2014;91:360–5.
- Ruddy KL, Carson RG. Neural pathways mediating cross education of motor function. *Front Hum Neurosci* 2013;7:397.
- Ruddy KL, Leemans A, Woolley DG, Wenderoth N, Carson RG. Structural and functional cortical connectivity mediating cross education of motor function. *J Neurosci* 2017;37:2555–64.
- Rueda-Delgado L, Heise K, Daffertshofer A, Mantini D, Swinnen S. Age-related differences in neural spectral power during motor learning. *Neurobiol Aging* 2019;77:44–57.
- Scally B, Burke MR, Bunce D, Delvenne J-F. Resting-state EEG power and connectivity are associated with alpha peak frequency slowing in healthy aging. *Neurobiol Aging* 2018;71:149–55.
- Schulz R, Zimmerman M, Timmermann JE, Wessel MJ, Gerloff C, Hummel FC. White matter integrity of motor connections related to training gains in healthy aging. *Neurobiol Aging* 2014;35:1404–11.

- Seidler RD, Bernard JA, Burutolu TB, Fling BW, Gordon MT, Gwin JT, et al. Motor control and Aging: Links to age-related brain structural, functional and biomechanical effects. *Neurosci Biobehav Rev* 2010;34:721–33.
- Sekihara K, Sahani M, Nagarajan SS. Localization bias and spatial resolution of adaptive and non-adaptive spatial filters for MEG source reconstruction 2005;25:1056–67.
- Shadmehr R. Neural correlates of motor memory consolidation. *Science* 1997;277:821–5.
- Shea J, Morgan R. Contextual interference effects on the acquisition, retention, and transfer of a motor skill. *Hum Learn Mem* 1979;15:179–87.
- Sugata H, Yagi K, Yazawa S, Nagase Y, Tsuruta K, Ikeda T, et al. Role of beta-band resting-state functional connectivity as a predictor of motor learning ability. *Neuroimage* 2020;210 116562.
- Sun Y, Ledwell NMH, Boyd LA, Zehr EP. Unilateral wrist extension training after stroke improves strength and neural plasticity in both arms. *Exp Brain Res* 2018;236:2009–21.
- Swinnen SP, Verschueren SMP, Bogaerts H, Dounskaia N, Lee TD, Stelmach GE, et al. Age-related deficits in motor learning and differences in feedback processing during the production of a bimanual coordination pattern. *Cogn Neuropsychol* 1998;15:439–66.
- Urbin MA, Harris-love ML, Carter AR, Lang CE. High-intensity, unilateral resistance training of a non-paretic muscle group increases active range of motion in a severely paretic upper extremity muscle group after stroke. *Front Neurol* 2015;6.
- Vecchio F, Miraglia F, Judica E, Cotelli M, Alù F, Rossini PM. Human brain networks: a graph theoretical analysis of cortical connectivity normative database from EEG data in healthy elderly subjects. *GeroScience* 2020;42:575–84.
- Veldman M, Maurits N, Nijland MM, Wolters N, Mizelle J, Hortobágyi T. Spectral and temporal electroencephalography measures reveal distinct neural networks for the acquisition, consolidation, and interlimb transfer of motor skills in healthy young adults. *Clin Neurophysiol* 2018;129:419–30.
- Veldman MP, Zijdewind I, Solnik S, Maffioletti NA, Berghuis KMM, Javet M, et al. Direct and crossed effects of somatosensory electrical stimulation on motor learning and neuronal plasticity in humans. *Eur J Appl Physiol* 2015;115:2505–19.
- Voytek B, Kramer MA, Case J, Lepage KQ, Tempesta ZR, Knight RT, et al. Age-related changes in 1/f neural electrophysiological noise. *J Neurosci* 2015;35:13257–65.
- Ward NS, Swayne OBC, Newton JM. Age-dependent changes in the neural correlates of force modulation: an fMRI study. *Neurobiol Aging* 2008;29:1434–46.
- Wu J, Srinivasan R, Kaur A, Cramer SC. Resting-state cortical connectivity predicts motor skill acquisition. *Neuroimage* 2014;91:84–90.
- Zhou S. Chronic neural adaptations to unilateral exercise; mechanisms of cross-education. *Exerc Sport Sci Rev* 2000;28:177–84.
- Ziemann U, Muellbacher W, Hallett M, Cohen LG. Modulation of practice-dependent plasticity in human motor cortex. *Brain* 2001;124:1171–81.
- Zimmerman M, Nitsch M, Giroux P, Gerloff C, Cohen LG, Hummel FC. Neuroenhancement of the aging brain: restoring skill acquisition in old subjects. *Ann Neurol* 2013;73:10–5.
- Zult T, Goodall S, Thomas K, Solnik S, Hortobágyi T, Howatson G. Mirror training augments the cross-education of strength and affects inhibitory paths. *Med Sci Sports Exerc* 2016;48:1001–13.