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RESEARCH ARTICLE

Neurophysiological mechanisms underlying motor skill learning in young and older adults

Ronan A. Mooney[1,2] · John Cirillo[1,2] · Winston D. Byblow[1,2]

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Abstract

The ability to acquire and retain novel motor skills is preserved with advancing age. However, the neurophysiological mechanisms underlying skill acquisition in older adults have received little systematic investigation. The aim of the present study was to assess the modulation of primary motor cortex excitability and inhibition after skill acquisition in young and older adults. Sixteen young and sixteen older adults trained on a sequential visual isometric wrist extension task. Anodal or sham transcranial direct current stimulation was applied during training in a pseudorandomized crossover design. Skill was quantified before, immediately after, 24 h and 7 days post-training. Transcranial magnetic stimulation protocols were used to examine corticomotor excitability and intracortical inhibition pre- and post-training. Corticomotor excitability increased and intracortical inhibition decreased after skill acquisition in both age groups. Anodal transcranial direct current stimulation did not enhance skill acquisition or the modulation of neurophysiological variables. These findings indicate potential neurophysiological mechanisms relevant for motor learning in neurorehabilitation contexts involving older adults, such as after stroke.

Keywords Motor learning · Aging · Intracortical inhibition · Transcranial magnetic stimulation · Transcranial direct current stimulation

Introduction

Reduced motor performance typically accompanies advancing age (Seidler et al. 2010). These effects may, in part, be attributed to neurophysiological changes within primary motor cortex (M1) in older adults (Levin et al. 2014). Despite the emergence of motor deficits in older adults, the ability to acquire and retain novel motor skills may be preserved (Berghuis et al. 2016; Cirillo et al. 2011). However, the effects of healthy aging on the neurophysiological mechanisms within M1 underlying skill acquisition have received little systematic investigation. Improved understanding of these age-related effects may further elucidate the complex interaction between aging and motor skill learning (Berghuis et al. 2017).

Corticomotor excitability indexed by motor-evoked potential (MEP) amplitude from transcranial magnetic stimulation (TMS) over M1 is increased during skill acquisition in young and older adults (Berghuis et al. 2016; Cirillo et al. 2011). Animal studies indicate that these effects are attributed to long-term potentiation (LTP) of synaptic efficacy (Rioult-Pedotti et al. 1998, 2000), which requires a reduction in gamma-aminobutyric acid (GABA)-mediated inhibition (Hess et al. 1996). Paired-pulse TMS can be used to assess GABAergic neurotransmission in human M1 (Kujirai et al. 1993). Short-interval intracortical inhibition (SICI) at 1 and 3 ms ($SICI_1$ and $SICI_3$), which may reflect extrasynaptic (Stagg et al. 2011) and synaptic (Ziemann et al. 1996) $GABA_A$ receptor activity, respectively, is reduced after skill acquisition in young adults (Coxon et al. 2014). Older adults exhibit similar reductions in $SICI_3$ during skill acquisition as young adults (Cirillo et al. 2011). However, lower $SICI_1$ in older adults compared with young (Mooney et al. 2017; Peinemann et al. 2001) may preclude modulation during skill learning. Long-interval intracortical inhibition (LICI), a marker of $GABA_B$ receptor activity (McDonnell et al. 2006),

✉ Winston D. Byblow
w.byblow@auckland.ac.nz

1 Movement Neuroscience Laboratory, Department of Exercise Sciences, Centre for Brain Research, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand

2 Centre for Brain Research, The University of Auckland, Auckland, New Zealand

may also be lower in older adults (Opie and Semmler 2014), but modulation during learning has not been assessed. It remains unknown whether reduced GABA-mediated inhibition during skill acquisition is receptor specific and/or age-dependent.

Typically, GABAergic neurotransmission within M1 is examined using paired-pulse TMS that induces posterior–anterior (PA) current in the brain. However, previous studies have shown that more robust SICI and LICI is usually observed with anterior–posterior (AP) induced current than PA (Cirillo and Byblow 2016; Cirillo et al. 2018; Mooney et al. 2018; Sale et al. 2016; Zoghi et al. 2003). Therefore, the modulation of GABAergic inhibition during skill acquisition may be more evident with AP-induced current.

The concurrent application of anodal transcranial direct current stimulation (tDCS) to M1 presents a promising approach to enhance skill acquisition in young and older adults (for a review, see Buch et al. 2017). Anodal tDCS induces LTP-like plasticity within M1 by modulating *N*-methyl-D-aspartate receptor activity (Nitsche et al. 2003) and GABAergic neurotransmission (Mooney et al. 2018; Nitsche et al. 2004). Concurrent anodal tDCS may enhance skill learning by promoting disinhibition and LTP-like plasticity within M1 (Zimerman et al. 2013). However, the efficacy of concurrent anodal tDCS to enhance motor learning within a single session is inconsistent (Buch et al. 2017) and the neurophysiological effects induced in young and older adults are incompletely understood.

The primary aim of the present study was to assess the modulation of corticomotor excitability and inhibition after skill acquisition in young and older adults using TMS with PA- and AP-induced current. We hypothesized that corticomotor excitability would increase after skill acquisition in both age groups. However, reduced inhibition after skill acquisition would only be observed in young adults as older adults would exhibit overall lower inhibitory tone. The secondary aim was to determine whether concurrent anodal tDCS would enhance skill acquisition and retention and promote the modulation of neurophysiological measures.

Methods

Participants

Sixteen neurologically healthy young (mean [range] age 23 [19–34] years, 7 males) and sixteen older adults (mean [range] age 75 [67–86] years, 7 males) participated in this study. Handedness was assessed using the short version of the Edinburgh Handedness Inventory (Veale 2014) (Young: 14 right, 2 left; Older: 15 right, 1 left). Participants were screened for contraindications to TMS before participation using a safety screening questionnaire. Each participant provided written informed consent and the study was approved by the University of Auckland Human Participants Research Ethics Committee.

Experimental design

Participants completed six sessions in total, with an acquisition session and two retention sessions in each arm of the experiment (Fig. 1a). In the acquisition session, a speed–accuracy function (SAF) for a sequential isometric force task was obtained for each participant as a measure of skill. Participants were then trained (9 blocks of 12 trials) at the task, during which they received either anodal or sham tDCS in a pseudorandomized double-blinded crossover design. After training, the SAF was reassessed. Measures of corticomotor excitability and inhibition were assessed before and after the training using TMS. The SAF was reassessed 24 h and 7 days post-training to determine skill retention. All sessions were completed at the same time of day for each participant. There was at least 14 days between the day 7 retention session of the first arm and the acquisition session of the second arm.

Sequential isometric force task

Participants sat in front of a computer screen with their elbows and forearms positioned on a table directly in front of their chair. The dorsum of the nondominant hand was placed beneath a platform embedded with an MLP-100 force transducer (Transducer Techniques, Temecula, CA). The nondominant hand was used to perform the task consistent with previous studies (Coxon et al. 2014; Fujiyama et al. 2017). The height of the platform was adjusted to accommodate each participant's hand size and then fixed in place. Extending the wrist against the platform generated vertical displacement of a cursor on the screen. The goal was to produce five individual force peaks by moving the cursor to five targets on the screen in a specific colour sequence (red–blue–green–yellow–white) and returning to the home position between each colour (Coxon et al. 2014). The furthest target was set at 45% of the participant's maximum voluntary extension strength, determined from a brief maximal isometric wrist extension against the platform. Logarithmic and exponential transformations were applied to the relationship between applied force and cursor movement, in the first and second arms of the experiment, respectively, to increase task difficulty. Different colour positions were used for the logarithmic and exponential transforms (Fig. 1b), but sequence order was the same.

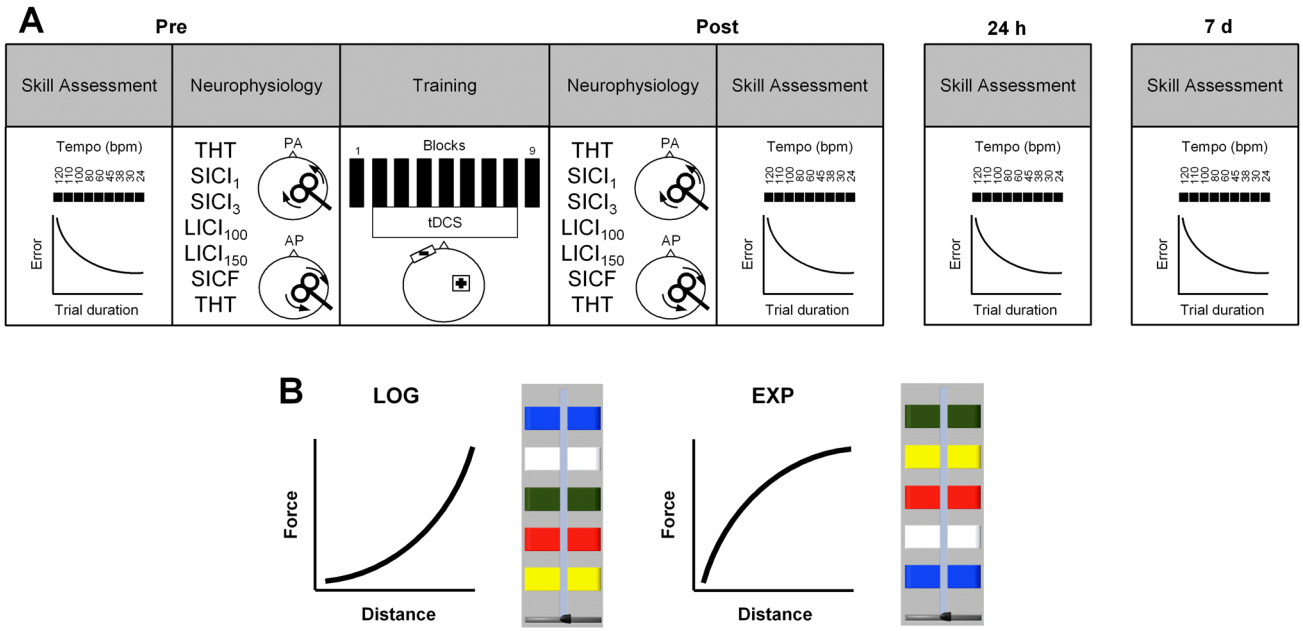

Fig. 1 Experimental design. **a** Participants completed six sessions in total, with an acquisition session and two retention sessions in each arm of the experiment. The speed–accuracy function for the force task was used to index skill by determining error at each trial duration set by an auditory metronome (indicated by tempo in beats per minute; bpm). Transcranial magnetic stimulation with posterior–anterior (PA)- and anterior–posterior (AP)-induced current was used to assess the threshold-hunting target (THT), short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI), and short-interval intracortical facilitation (SICF). Skill and neurophysiological measures were assessed pre- and post-training with additional skill retention assessments completed 24 h and 7 days later. Anodal or sham transcranial direct current stimulation (tDCS) was applied during training in a double-blinded crossover design. **b** Relationship between applied force and cursor movement and the on-screen display for the logarithmic (LOG) and exponential (EXP) transforms of the sequential isometric force task. Each trial involved navigating the cursor through the sequence red–blue–green–yellow–white by performing isometric wrist extension against a force transducer. The LOG and EXP transforms were used in the first and second arms of the experiment, respectively (for interpretation of the references to colour in the figure legend, the reader is referred to the web version of this article.)

Skill assessment

Skill was determined by measuring error at fixed execution speeds to compute the SAF (Reis et al. 2009). Participants were instructed to move the cursor to each of the targets in time with a metronome, with the aim of being at the centre of a target on the beep. The assessment comprised completing a single block of three trials at nine different tempos, 24/30/38/45/60/80/100/110/120 bpm, corresponding to approximate trial durations of 12.5/10.0/7.9/6.7/5.0/3.8/3.0/2.7/2.5 s, respectively. Blocks were completed in a random order.

Training

For the training intervention, participants completed 9 blocks of 12 trials. Participants were instructed to complete the training trials at a self-selected pace, with the aim of completing each trial as quickly and as accurately as possible (Reis et al. 2009). To prevent fatigue, participants rested for 1 min between blocks. During the rest periods, participants received visual feedback of their mean skill for the completed block along with one of the two performance-dependent messages: (1) Well done! Your skill has increased compared with the previous block; or (2) Try harder! Your skill has decreased compared with the previous block.

Recording and stimulation procedures

Surface electromyography

Surface electromyography (EMG) was recorded from the nondominant *extensor carpi radialis* (ECR) using 10 mm diameter Ag–AgCl recording electrodes (Ambu, Ballerup, Denmark), arranged in a belly–tendon montage, with a 20 mm ground electrode (3 M, Canada Health Care) positioned on the lateral epicondyle. EMG signals were amplified (1000×) and band-pass filtered (10–1000 Hz) using a CED1902 amplifier (Cambridge Electronic Design Ltd, UK), sampled at 10 kHz using a CED1401 interface and recorded with Signal Software (CED, Version 5.03).

Transcranial magnetic stimulation

Single- and paired-pulse TMS was delivered using a figure-of-eight coil (70 mm wing diameter) connected to two monophasic Magstim 200^2 magnetic stimulators via a Bistim module (Magstim, Whitland, Wales, UK). Descending volleys with an early or late onset were preferentially activated by alternating current flow through M1 (Sakai et al. 1997). PA stimulation (coil ~ 45° to the mid-sagittal line) preferentially elicits early I-waves, whereas AP (coil angle same as PA, but current reversed) preferentially elicits I waves that have a later onset latency. The optimal site to elicit consistent MEPs in the nondominant ECR with PA current was marked on the scalp. The same scalp position was used for AP-induced current and was continually monitored using visual inspection throughout the experiment. Current direction order was pseudorandomized between participants and kept constant within participants. TMS was delivered at 0.2 Hz ± 20%.

Motor thresholds

A freeware program (TMS Motor Threshold Assessment Tool; MTAT 2.0, F. Awiszus and J. Borckardt) that employs a maximum-likelihood parameter estimation by sequential testing (PEST) was used for adaptive threshold hunting. The procedure involves adjusting the stimulus intensity up or down as required based on an MEP amplitude criterion for 12 trials (approximate duration of procedure is 1 min) until the target intensity is determined. Two operators were involved in the TMS procedures. One experimenter held the coil, while the other manually entered data into PEST software and adjusted stimulator intensity according to PEST output. For rest motor threshold (RMT), a trial was deemed successful if the stimulus intensity elicited an MEP of at least 50 µV in amplitude (Rossini et al. 2015). For active motor threshold (AMT), a trial was deemed successful if the stimulus intensity elicited an MEP of at least 200 µV in amplitude, with ECR pre-activated to approximately 10% of the participant's perceived maximum voluntary contraction.

Intracortical inhibition and facilitation

Adaptive threshold-hunting paired-pulse TMS was used to quantify the extent of SICI, LICI, and short-interval intracortical facilitation (SICF) within M1 in line with previous work (Amandusson et al. 2017; Awiszus et al. 1999; Cirillo et al. 2018; Mooney et al. 2018). A non-conditioned threshold-hunting target (THT), whereby the MEP amplitude criterion for a successful trial was 200 µV (Fig. 2), was obtained at the beginning and end of the paired-pulse measures and the average value calculated. To elicit SICI, a subthreshold stimulus set to 90% AMT was delivered 1 and 3 ms prior to a test stimulus (Kujirai et al. 1993). To elicit

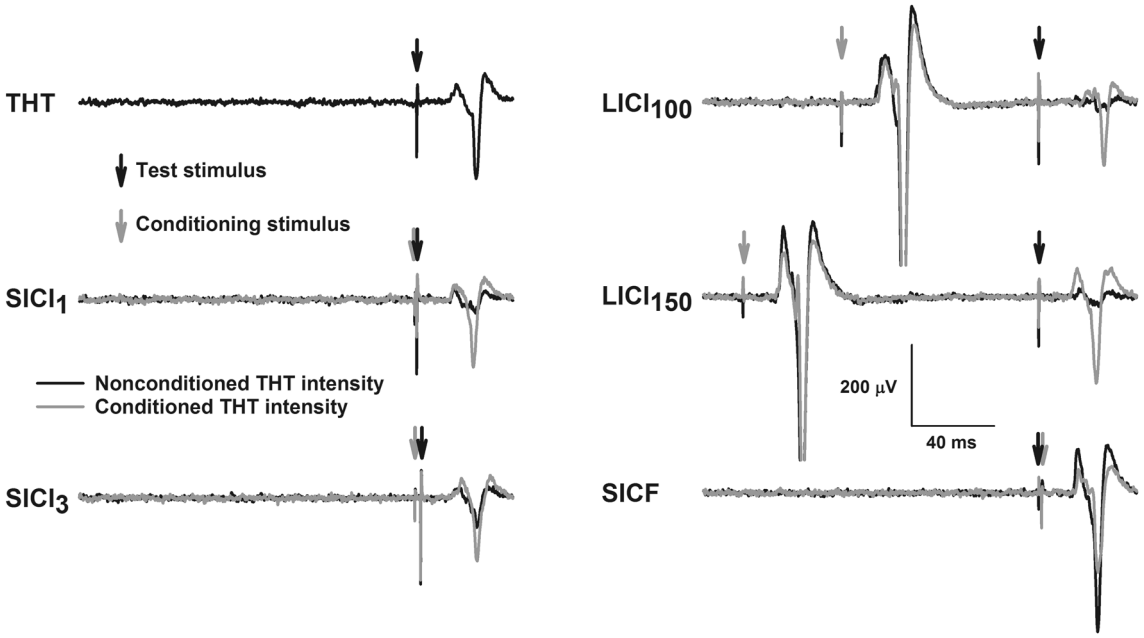

Fig. 2 Example electromyography traces depict motor-evoked potentials from the *extensor carpi radialis* muscle of an older adult. Traces depict the transcranial magnetic stimulation intensity required to elicit a fixed motor-evoked potential amplitude (200 µV) to the single-pulse test stimulus (threshold-hunting target; THT), short-interval intracortical inhibition (SICI) at 1 and 3 ms, long-interval intracortical inhibition (LICI) at 100 and 150 ms, and short-interval intracortical facilitation (SICF). Threshold-hunting requires an increase or decrease in the test stimulus intensity to evoke the target response in the presence of the conditioning stimulus (grey traces)

LICI, a suprathreshold stimulus set to 120% RMT was delivered 100 and 150 ms prior to a test stimulus (Valls-Sole et al. 1992). To elicit SICF, a subthreshold stimulus set to 90% RMT was delivered 1.5 ms after a test stimulus (Ziemann et al. 1998). For SICI, LICI, and SICF procedures, PEST was used to determine the test stimulus intensity required to achieve the THT (200 µV MEP) in the presence of the conditioning stimulus.

Transcranial direct current stimulation

A NeuroConn DC stimulator (NeuroConn, Ilmenau, Germany) was used to administer tDCS through two rubber electrodes inserted into saline-soaked sponges. The active electrode (25 cm^2) was placed over the nondominant M1 hotspot and the reference electrode (35 cm^2) was placed over the dominant supraorbital ridge. For anodal tDCS (anode over M1), the current was ramped up for 30 s and then maintained at a constant 1 mA current for 20 min. For sham tDCS, the current was ramped up to 1 mA and immediately ramped down to 0 mA within 30 s.

Data analysis

Sequential isometric force task

For each trial in the SAF assessment, an error value was calculated as the sum of differences between the centre of each target and the five respective force peaks (Coxon et al. 2014). To quantify skill for each individual participant at each time point, we used the following function (Reis et al. 2009):

$$\text{Skill} = \frac{1 - \text{error}}{\text{error}\left(\ln(\text{trial duration})^{b}\right)},$$

where error is the mean error for the respective trial duration and b is the dimension free parameter. Although Reis et al. (2009) used a constant b value of 5.42 based on results from a small control group, we calculated b values for each individual participant at each time point to account for inter-individual differences in the profile of the SAF (Fujiyama et al. 2017; Saucedo Marquez et al. 2013). The b values were calculated using the Curve Fitting Tool in MATLAB (Mathworks, MA) to optimize the fit of the skill function. The average b values for young adults were 1.08 ± 0.06 and 1.08 ± 0.10 in the anodal and sham tDCS sessions, respectively. The average b values for older adults were 1.44 ± 0.10 and 1.51 ± 0.10 in the anodal and sham tDCS sessions, respectively.

For the training trials, skill was quantified using the same equation above, where trial duration was calculated from onset of the first force peak to the last force peak and b was set to the b value calculated from the pre-training SAF for each participant. Mean block skill was presented as visual feedback during rest periods.

Neurophysiology

During threshold hunting, trials that were contaminated by pre-stimulus EMG activity (root mean squared EMG > 10 µV; 50 ms before stimulation) were rejected online and repeated immediately. The peak-to-peak amplitude of the 24 MEPs elicited by the suprathreshold stimulus (120% RMT) from the LICI protocols was used to index corticomotor excitability. Mean MEP amplitude was calculated after trimming the upper and lower 10% of trials (total trials = 20). SICI, LICI and SICF were quantified as the relative percent increase or decrease in the test stimulus intensity required to evoke the THT:

$$\text{Threshold change (\%)} = \frac{(\text{Conditioned THT} - \text{Nonconditioned THT})}{\text{Nonconditioned THT}} \times 100,$$

where larger positive values indicate more inhibition and negatives values indicate facilitation.

Statistical analysis

Normality was assessed using the Shapiro–Wilk's test and homoscedasticity of variance using the Levene's test of equality and Mauchly's test of sphericity. Non-normal data (MEP amplitude) were log transformed for statistical analysis; however, non-transformed data are reported for clarity. To test for carry-over effects, baseline skill from the first and second arms of the experiment was analyzed with a two-way repeated-measures ANOVA with factors AGE (young and older) and TRANSFORM (LOG and EXP). The complete skill data set was analyzed with a three-way repeated-measures ANOVA with factors AGE, tDCS (anodal and sham), and TIME (pre, post, 24 h, and 7 days). One-sample t tests (hypothesized mean = 0) were performed for $SICI_1$, $SICI_3$, $LICI_{100}$, $LICI_{150}$, and SICF to confirm significant inhibition/facilitation at baseline for both age groups. Pre-training neurophysiological variables (RMT, AMT, MEP amplitude, THT, $SICI_1$, $SICI_3$, $LICI_{100}$, $LICI_{150}$, and SICF) were analyzed with a three-way repeated-measures ANOVA with factors AGE, tDCS, and CURRENT DIRECTION (PA and AP). Pre- and post-training neurophysiological variables (MEP amplitude, THT, $SICI_1$, $SICI_3$, $LICI_{100}$, $LICI_{150}$, and SICF) were analyzed with a three-way repeated-measures ANOVA with factors AGE, tDCS, and TIME (pre and post) for each current direction. Pearson correlation analyses (two-tailed) were used to investigate the relationship between the magnitude of skill acquisition and the modulation of neurophysiological variables. Partial eta squared (η_p^2) values are

reported to demonstrate small (0.01), medium (0.06), and large (0.14) effect sizes (Cohen 1973). The significance level was set at $P < 0.05$. Group data are presented as mean ± SEM in the text.

Results

SAF assessment

For baseline skill, there was a main effect of AGE ($F_{1, 30} = 27.64$, $P < 0.001$, $\eta_p^2 = 0.48$) but no main effect of TRANSFORM ($F_{1, 30} = 2.12$, $P = 0.16$, $\eta_p^2 = 0.07$) and no interaction ($P = 0.54$), indicating no differences between the first (young = 3.07 ± 0.27, older = 1.60 ± 0.18) and second (young = 3.47 ± 0.34, older = 1.76 ± 0.21) arms of the experiment. For the complete skill data set, there were main effects of AGE ($F_{1, 30} = 28.64$, $P < 0.001$, $\eta_p^2 = 0.49$) and TIME ($F_{3, 90} = 46.65$, $P < 0.001$, $\eta_p^2 = 0.61$) and no main effect of tDCS ($F_{1, 30} = 0.28$, $P = 0.60$, $\eta_p^2 = 0.01$). There was a TIME × AGE interaction ($F_{3, 90} = 3.83$, $P = 0.013$, $\eta_p^2 = 0.11$), but no other interactions were present (all $P > 0.72$). Overall, skill was higher in young compared with older adults (Fig. 3e), which is likely attributed to young adults having greater accuracy at faster speeds (Fig. 3a–d). For both age groups, skill was greater post-training and at each retention time point compared with pre-training (all $P < 0.001$). There were no differences in skill at the post-training and retention time points for either group (all $P > 0.17$).

Neurophysiology

Neurophysiological variables are displayed in Table 1 and the results of the pre-training ANOVAs are displayed in Table 2. RMT, AMT, and non-conditioned THT were higher and MEP amplitude lower for AP-induced current compared with PA. MEP amplitude was lower in older adults (PA = 0.87 ± 0.13 mV, AP = 0.59 ± 0.10 mV) compared with young (PA = 1.07 ± 0.13 mV, AP = 0.74 ± 0.07 mV). One-sample *t* tests showed that inhibition/facilitation was present at baseline for all paired-pulse TMS protocols in both young (all $P < 0.009$) and older (all $P < 0.008$) adults. $SICI_3$ and $LICI_{150}$ were higher and SICF lower with AP-induced current compared with PA.

Results of the ANOVAs for each current direction are displayed in Table 3. $SICI_1$ with PA-induced current was lower in older adults (12.9 ± 2.1%) compared with young (21.0 ± 3.3%). After training, the non-conditioned THT with PA- and AP-induced current decreased in both age groups. In contrast, MEP amplitude with PA- and AP-induced current increased in both age groups (Fig. 4). $SICI_1$, $SICI_3$, and $LICI_{150}$ decreased in both age groups (Fig. 5), but this was only evident for PA-induced current. There was no modulation of $LICI_{100}$ or SICF. Pearson's correlation analyses indicated that there were no associations between the magnitude of skill acquisition and the magnitude of modulation of MEP amplitude, $SICI_1$, $SICI_3$, or $LICI_{150}$ in either session for young (all $P > 0.11$) or older adults (all $P > 0.14$).

Discussion

The present study investigated the neurophysiological mechanisms underlying motor skill learning in young and older adults. In support of our hypothesis, $GABA_A$ receptor-mediated inhibition was lower in older adults. Despite this age-related difference, both young and older adults exhibited increased corticomotor excitability and reduced $GABA_A$ and $GABA_B$ receptor-mediated inhibition after skill acquisition. The application of anodal tDCS during training had no effect on skill acquisition or the modulation of neurophysiological variables in either age group. A downregulation of $GABA_A$ and $GABA_B$ receptor-mediated inhibition may promote plasticity within M1 during skill learning, and may have relevance for neurorehabilitation of age-similar individuals after stroke.

Skill acquisition and retention in young and older adults

Older adults exhibited lower absolute skill level compared with the younger cohort, although both groups displayed successful skill acquisition and retention. Previous studies with older adults have typically quantified learning as the reduction in error or improvement in accuracy after training (Berghuis et al. 2016; Cirillo et al. 2011; Goodwill et al. 2013; Roig et al. 2014; Zimerman et al. 2013, 2014). In contrast, the present study quantified learning as an increase in skill by determining the SAF for a sequential isometric force task (Fujiyama et al. 2017; Reis et al. 2009; Saucedo Marquez et al. 2013). Because speed and accuracy are inherently linked (Fitts 1954), our approach controlled for the tendency of older adults to make slower movements compared to young to maintain a similar level of accuracy (Lamb et al. 2016). If participants had not been externally paced during the skill assessment, then older adults may have achieved a similar error to young adults simply by performing the task at a slower speed. Furthermore, because of differences in baseline skill, we compared absolute skill levels between age groups and did not make any comparisons of normalized changes as such analyses are viewed to be conceptually fraught (Hardwick et al. 2017). Our findings demonstrate that despite a lower absolute skill level, older adults maintain the ability to acquire and retain a novel motor skill.

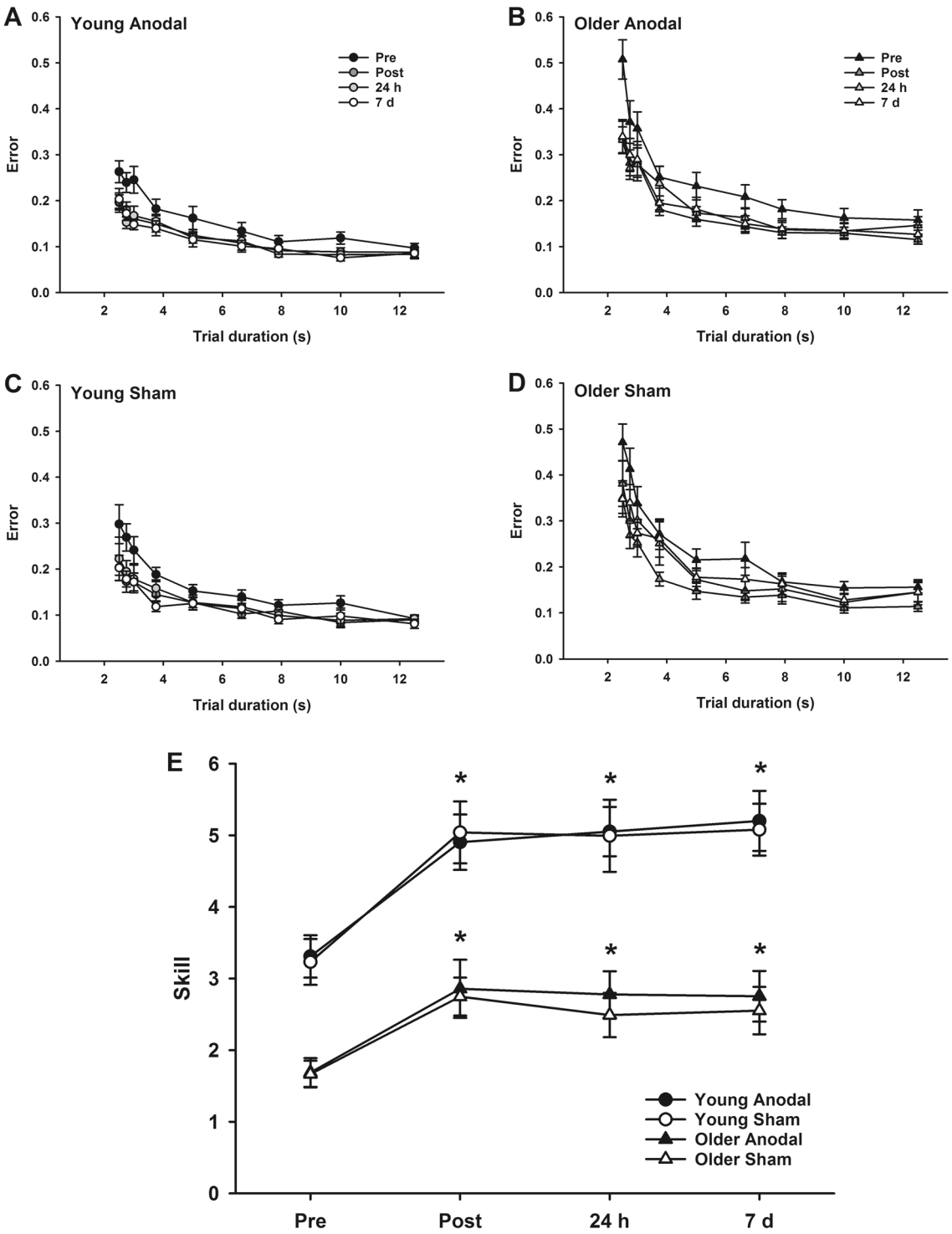

Fig. 3 Speed–accuracy function data obtained at each time point (pre, post, 24 h, and 7 days) for young (**a** and **c**) and older adults (**b** and **d**) and the corresponding skill values (**e**). Data are presented as mean ± SEM. $N = 16$ young and 16 older. $^{*}P < 0.05$ compared with pre

Modulation of corticomotor excitability

Corticomotor excitability indexed from MEP amplitude increased immediately after skill acquisition in both young and older adults. These findings coincide with previous studies (Berghuis et al. 2016; Cirillo et al. 2011) and may be attributed to LTP of synaptic inputs to corticomotor neurons (Hess and Donoghue 1994). The observed increase in

Table 1 Neurophysiology data

	Young				Older			
	Anodal		Sham		Anodal		Sham	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Posterior–anterior								
RMT (% MSO)	51.5 ± 2.1	–	50.1 ± 2.3	–	53.7 ± 2.0	–	53.3 ± 2.0	–
AMT (% MSO)	41.4 ± 2.1	–	39.6 ± 1.7	–	42.8 ± 1.9	–	43.8 ± 1.8	–
MEP amplitude (mV)	1.10 ± 0.14	1.36 ± 0.16	1.04 ± 0.13	1.24 ± 0.16	0.89 ± 0.14	1.35 ± 0.22	0.86 ± 0.16	1.03 ± 0.19
THT (% MSO)	54.0 ± 2.3	52.3 ± 2.1	52.3 ± 2.6	52.3 ± 2.2	58.1 ± 2.4	56.8 ± 2.3	58.1 ± 2.5	56.9 ± 2.6
$SICI_1$ (%)	21.9 ± 3.5	20.3 ± 4.1	23.4 ± 3.6	18.5 ± 3.5	14.2 ± 2.0	10.2 ± 3.0	15.5 ± 2.5	11.8 ± 2.2
$SICI_3$ (%)	6.4 ± 2.1	5.3 ± 2.8	5.1 ± 1.5	1.7 ± 2.5	7.3 ± 2.4	4.3 ± 2.8	8.5 ± 1.7	3.7 ± 2.0
$LICI_{100}$ (%)	17.2 ± 2.0	18.0 ± 3.0	17.4 ± 2.1	15.4 ± 2.9	22.0 ± 3.2	24.5 ± 2.4	21.1 ± 3.1	22.4 ± 4.1
$LICI_{150}$ (%)	16.8 ± 1.5	12.4 ± 3.3	15.1 ± 2.0	10.6 ± 2.5	15.5 ± 3.2	13.6 ± 2.3	14.8 ± 3.2	12.7 ± 2.5
SICF (%)	− 19.0 ± 1.7	− 21.5 ± 2.1	− 18.8 ± 1.9	− 22.7 ± 1.5	− 21.5 ± 1.3	− 21.7 ± 2.1	− 20.3 ± 2.2	− 20.3 ± 1.7
Anterior–posterior								
RMT (% MSO)	64.2 ± 2.8	–	63.3 ± 2.9	–	63.7 ± 2.4	–	63.4 ± 3.0	–
AMT (% MSO)	57.3 ± 2.7	–	54.9 ± 2.6	–	54.7 ± 2.0	–	54.2 ± 2.0	–
MEP amplitude (mV)	0.72 ± 0.07	0.86 ± 0.08	0.75 ± 0.10	0.92 ± 0.09	0.71 ± 0.15	0.99 ± 0.26	0.48 ± 0.07	0.71 ± 0.11
THT (% MSO)	68.4 ± 3.2	66.6 ± 2.9	67.8 ± 3.3	67.1 ± 3.1	69.8 ± 2.8	67.7 ± 2.7	69.1 ± 3.1	68.1 ± 3.0
$SICI_1$ (%)	19.2 ± 2.2	17.2 ± 3.1	18.0 ± 1.9	15.6 ± 1.9	20.7 ± 2.1	17.7 ± 2.5	21.0 ± 1.3	20.2 ± 3.3
$SICI_3$ (%)	19.8 ± 1.9	20.3 ± 2.2	20.7 ± 2.0	16.6 ± 2.7	20.9 ± 2.7	22.9 ± 3.5	22.3 ± 2.4	20.3 ± 3.7
$LICI_{100}$ (%)	19.3 ± 2.3	21.0 ± 2.3	19.4 ± 2.1	19.5 ± 2.9	27.5 ± 2.4	24.7 ± 4.0	25.9 ± 2.5	24.5 ± 3.7
$LICI_{150}$ (%)	17.5 ± 2.3	17.6 ± 2.8	17.4 ± 2.1	16.3 ± 3.4	22.0 ± 2.0	20.1 ± 3.3	22.7 ± 2.7	20.5 ± 3.4
SICF (%)	− 14.7 ± 1.3	− 13.8 ± 1.4	− 12.5 ± 1.4	− 16.7 ± 2.4	− 17.0 ± 1.4	− 17.8 ± 2.5	− 15.0 ± 1.4	− 16.7 ± 2.6

Values are mean ± SEM

RMT rest motor threshold, *MSO* maximum stimulator output, *AMT* active motor threshold, *MEP* motor-evoked potential, *THT* threshold-hunting target, *SICI* short-interval intracortical inhibition, *LICI* long-interval intracortical inhibition, *SICF* short-interval intracortical facilitation

MEP amplitude was present for both PA- and AP-induced currents, which are thought to activate distinct excitatory inputs to corticospinal neurons (Di Lazzaro et al. 2012). PA-induced current preferentially recruits early I-wave inputs (Di Lazzaro et al. 1998a), which likely synapse close to the soma (Di Lazzaro and Ziemann 2013). In contrast, AP-induced current preferentially recruits less synchronized I-wave inputs which have a later onset latency (Di Lazzaro et al. 2001) and may synapse with dendritic compartments (Di Lazzaro and Ziemann 2013). Therefore, LTP of early and late I-wave inputs to corticomotor neurons may contribute to increased MEP amplitude after skill acquisition in young and older adults.

Modulation of intracortical inhibition

Increased corticomotor excitability after skill acquisition was accompanied by reduced $GABA_A$ receptor-mediated SICI within M1. Reduced SICI was evident at interstimulus intervals of 1 and 3 ms in both age groups, corroborating the findings from a previous study in young adults (Coxon et al. 2014). $SICI_1$ may in part reflect extrasynaptic $GABA_A$ receptor activity (Stagg et al. 2011), which regulates cortical excitability through tonic inhibition (Belelli et al. 2009). In contrast, $SICI_3$ reflects synaptic $GABA_A$ receptor activity (Ziemann et al. 1996), which mediates phasic inhibitory currents. Despite lower $SICI_1$ in older adults compared with young, as observed previously (Mooney et al. 2017; Peinemann et al. 2001), both age groups exhibited a reduction after skill acquisition. Reducing tonic inhibition mediated by extrasynaptic $GABA_A$ receptors promotes functional recovery after experimental stroke in rodents (Clarkson et al. 2010). In humans, motor learning mechanisms are operative during motor recovery after stroke (Krakauer 2006), during which $GABA_A$ receptor activity may be lower in ipsilesional M1 (McDonnell and Stinear 2017). Reduced $GABA_A$ receptor-mediated inhibition may promote plasticity within M1 during motor learning and may have relevance for motor recovery after stroke.

Similar to SICI, LICI was also reduced after skill acquisition. Inhibitory interneurons mediating LICI primarily exert their effects via postsynaptic $GABA_B$ receptors (McDonnell et al. 2006). In the present study, two interstimulus intervals (100 and 150 ms) were used to

Table 2 Statistical results of pre-training neurophysiology ANOVAs

	Factor	*F*	*P*	η_p^2
RMT	AGE	0.14	0.71	< 0.01
	tDCS	1.50	0.23	0.05
	CURRENT DIRECTION	182.59	< 0.001[a]	0.86
	AGE × tDCS	0.30	0.59	0.01
	AGE × CURRENT DIRECTION	3.20	0.08	0.10
	tDCS × CURRENT DIRECTION	0.09	0.76	< 0.01
	AGE × tDCS × CURRENT DIRECTION	0.23	0.64	< 0.01
AMT	AGE	0.04	0.85	< 0.01
	tDCS	1.64	0.21	0.05
	CURRENT DIRECTION	187.61	< 0.001[a]	0.86
	AGE × tDCS	2.64	0.12	0.08
	AGE × CURRENT DIRECTION	5.02	0.033	0.14
	tDCS × CURRENT DIRECTION	2.16	0.15	0.07
	AGE × tDCS × CURRENT DIRECTION	0.37	0.55	0.01
MEP amplitude	AGE	4.43	0.044[c]	0.13
	tDCS	2.15	0.15	0.07
	CURRENT DIRECTION	12.37	0.001[b]	0.29
	AGE × tDCS	0.76	0.39	0.03
	AGE × CURRENT DIRECTION	< 0.01	0.96	< 0.01
	tDCS × CURRENT DIRECTION	0.07	0.80	< 0.01
	AGE × tDCS × CURRENT DIRECTION	0.19	0.67	< 0.01
THT	AGE	0.67	0.42	0.02
	tDCS	0.08	0.77	< 0.01
	CURRENT DIRECTION	134.73	< 0.001[a]	0.82
	AGE × tDCS	< 0.01	0.99	< 0.01
	AGE × CURRENT DIRECTION	2.60	0.12	0.08
	tDCS × CURRENT DIRECTION	0.20	0.66	< 0.01
	AGE × tDCS × CURRENT DIRECTION	0.02	0.88	< 0.01
$SICI_1$	AGE	1.10	0.30	0.04
	tDCS	0.01	0.92	< 0.01
	CURRENT DIRECTION	1.02	0.32	0.03
	AGE × tDCS	1.26	0.27	0.04
	AGE × CURRENT DIRECTION	4.94	0.034	0.14
	tDCS × CURRENT DIRECTION	0.03	0.86	< 0.01
	AGE × tDCS × CURRENT DIRECTION	0.01	0.92	< 0.01
$SICI_3$	AGE	0.47	0.50	0.02
	tDCS	2.68	0.11	0.08
	CURRENT DIRECTION	52.88	< 0.001[a]	0.64
	AGE × tDCS	0.41	0.53	0.01
	AGE × CURRENT DIRECTION	0.35	0.56	0.01
	tDCS × CURRENT DIRECTION	0.18	0.68	< 0.01
	AGE × tDCS × CURRENT DIRECTION	0.16	0.69	< 0.01
$LICI_{100}$	AGE	2.74	0.11	0.08
	tDCS	0.84	0.37	0.03
	CURRENT DIRECTION	1.28	0.27	0.04
	AGE × tDCS	0.07	0.80	< 0.01
	AGE × CURRENT DIRECTION	0.30	0.59	0.01
	tDCS × CURRENT DIRECTION	0.30	0.59	0.01
	AGE × tDCS × CURRENT DIRECTION	0.03	0.87	< 0.01
$LICI_{150}$	AGE	0.58	0.45	0.02
	tDCS	0.44	0.52	0.01

Table 2 (continued)

	Factor	*F*	*P*	η_p^2
	CURRENT DIRECTION	10.61	0.003[a]	0.26
	AGE × tDCS	0.24	0.63	< 0.01
	AGE × CURRENT DIRECTION	0.20	0.66	< 0.01
	tDCS × CURRENT DIRECTION	0.17	0.69	< 0.01
	AGE × tDCS × CURRENT DIRECTION	0.03	0.86	< 0.01
SICF	AGE	0.06	0.80	< 0.01
	tDCS	0.21	0.65	< 0.01
	CURRENT DIRECTION	8.18	0.008[b]	0.21
	AGE × tDCS	3.85	0.06	0.11
	AGE × CURRENT DIRECTION	0.72	0.40	0.02
	tDCS × CURRENT DIRECTION	0.22	0.64	< 0.01
	AGE × tDCS× CURRENT DIRECTION	0.08	0.78	< 0.01

RMT rest motor threshold, *tDCS* transcranial direct current stimulation, *AMT* active motor threshold, *MEP* motor-evoked potential, *THT* threshold-hunting target, *SICI* short-interval intracortical inhibition, *LICI* long-interval intracortical inhibition, *SICF* short-interval intracortical facilitation

[a]Anterior–posterior > posterior–anterior

[b]Posterior–anterior > anterior–posterior

[c]Older < young

assess LICI, which have been shown to reflect comparable underlying mechanisms (Opie et al. 2017). However, decreased LICI was observed at 150 ms but not 100 ms, which may indicate that the duration rather than the magnitude of postsynaptic $GABA_B$ receptor activity is reduced with skill learning. Downregulation of both $GABA_A$ and $GABA_B$ receptor-mediated inhibition may promote plasticity within M1 during motor learning.

Reduced SICI and LICI after skill acquisition was evident with PA but not AP-induced current. The conditioning stimulus giving rise to SICI and LICI suppresses the amplitude of late I waves, whereas early I waves are virtually unaffected (Di Lazzaro et al. 1998b; Nakamura et al. 1997). AP-induced current preferentially recruits I-wave inputs which have a later onset latency (Di Lazzaro et al. 2001), and more robust SICI and LICI are usually observed with AP compared with PA stimulation (Cirillo and Byblow 2016; Cirillo et al. 2018; Mooney et al. 2018; Sale et al. 2016; Zoghi et al. 2003). Although PA stimulation preferentially recruits early I-wave inputs, late I-wave inputs are also evoked (Di Lazzaro et al. 1998a), but are likely distinct to those evoked with AP stimulation (Di Lazzaro et al. 2012). It seems unlikely that contamination of SICI by facilitatory inputs contributed to the observed results, because the conditioning intensity for SICI was below the threshold for facilitatory contamination (Peurala et al. 2008) and SICF was not modulated after skill acquisition for either current direction. Reduced SICI and LICI after skill acquisition may be specific to inhibitory networks targeting late I-wave inputs evoked with PA-induced current.

No effect of concurrent anodal tDCS on skill acquisition or retention

The application of anodal tDCS during training had no effect on skill acquisition or retention in young or older adults. Our findings are in agreement with a recent review which found equivocal evidence of anodal tDCS to enhance skill learning (Buch et al. 2017). Previous studies have shown that the beneficial effects of concurrent anodal tDCS and motor skill learning are increasingly evident over multiple training sessions (Saucedo Marquez et al. 2013; Schambra et al. 2011), primarily through an enhancement of offline consolidation (Reis et al. 2009, 2015). However, the present study was limited to a single training session. Therefore, the effects of concurrent anodal tDCS on skill learning in young and older adults may be dependent on the duration of training and requires further investigation.

The present study has some further limitations. The physiological effects of tDCS can be relatively widespread throughout the brain (Kuo et al. 2013). Improving the focality of neuromodulation, in an attempt to enhance endogenous learning-related processes within M1, may benefit from more focal procedures such as high-definition tDCS or repetitive TMS. Also, in the present study, the effectiveness of tDCS

Table 3 Statistical results of neurophysiology ANOVAs for each current direction

	Factor	Posterior–anterior			Anterior–posterior		
		F	*P*	η_p^2	*F*	*P*	η_p^2
MEP amplitude	AGE	2.47	0.13	0.08	3.06	0.09	0.09
	tDCS	2.33	0.14	0.07	0.81	0.38	0.03
	TIME	14.92	0.001[a]	0.33	21.14	< 0.001[a]	0.41
	AGE × tDCS	0.54	0.47	0.02	0.93	0.34	0.03
	AGE × TIME	0.41	0.53	0.01	0.51	0.48	0.02
	tDCS × TIME	1.53	0.23	0.05	1.91	0.18	0.06
	AGE × tDCS × TIME	0.53	0.47	0.02	0.02	0.88	< 0.01
THT	AGE	2.18	0.15	0.07	0.08	0.78	< 0.01
	tDCS	0.25	0.62	< 0.01	0.01	0.92	< 0.01
	TIME	4.56	0.041[b]	0.13	5.38	0.027[b]	0.15
	AGE × tDCS	0.33	0.57	0.01	< 0.01	0.95	< 0.01
	AGE × TIME	0.14	0.71	< 0.01	0.06	0.81	< 0.01
	tDCS × TIME	1.32	0.26	0.04	2.20	0.15	0.07
	AGE × tDCS × TIME	0.96	0.33	0.03	< 0.01	0.98	< 0.01
$SICI_1$	AGE	4.39	0.045[c]	0.13	1.10	0.30	0.04
	tDCS	0.18	0.68	< 0.01	< 0.01	0.98	< 0.01
	TIME	10.60	0.003[b]	0.26	1.53	0.23	0.05
	AGE × tDCS	0.29	0.59	0.01	0.92	0.34	0.03
	AGE × TIME	0.07	0.79	< 0.01	< 0.01	0.93	< 0.01
	tDCS × TIME	0.47	0.50	0.02	0.16	0.69	< 0.01
	AGE × tDCS × TIME	0.73	0.40	0.02	0.39	0.54	0.01
$SICI_3$	AGE	0.23	0.64	< 0.01	0.53	0.47	0.02
	tDCS	0.94	0.34	0.03	0.66	0.42	0.02
	TIME	9.90	0.004[b]	0.25	0.40	0.53	0.01
	AGE × tDCS	2.49	0.13	0.09	0.11	0.74	< 0.01
	AGE × TIME	0.66	0.43	0.03	0.41	0.53	0.01
	tDCS × TIME	1.29	0.27	0.05	2.70	0.11	0.08
	AGE × tDCS × TIME	0.10	0.75	< 0.01	0.01	0.91	< 0.01
$LICI_{100}$	AGE	3.04	0.09	0.09	3.33	0.08	0.10
	tDCS	0.61	0.44	0.02	0.37	0.55	0.01
	TIME	0.16	0.70	< 0.01	0.12	0.73	< 0.01
	AGE × tDCS	0.01	0.92	< 0.01	< 0.01	0.94	< 0.01
	AGE × TIME	0.62	0.44	0.02	0.80	0.38	0.03
	tDCS × TIME	0.57	0.46	0.02	< 0.01	0.94	< 0.01
	AGE × tDCS × TIME	0.09	0.77	< 0.01	0.51	0.48	0.02
$LICI_{150}$	AGE	0.02	0.89	< 0.01	1.57	0.22	0.05
	tDCS	1.13	0.30	0.04	< 0.01	0.95	< 0.01
	TIME	4.77	0.037[b]	0.14	0.64	0.43	0.02
	AGE × tDCS	0.17	0.68	< 0.01	0.22	0.65	< 0.01
	AGE × TIME	0.68	0.42	0.02	0.22	0.64	< 0.01
	tDCS × TIME	< 0.01	0.94	< 0.01	0.22	0.64	< 0.01
	AGE × tDCS × TIME	< 0.01	0.97	< 0.01	0.12	0.73	< 0.01
SICF	AGE	0.05	0.83	< 0.01	1.29	0.27	0.04
	tDCS	0.18	0.68	< 0.01	0.32	0.58	0.01
	TIME	3.17	0.09	0.10	1.47	0.23	0.05
	AGE × tDCS	0.90	0.35	0.03	0.73	0.40	0.02
	AGE × TIME	2.84	0.10	0.09	0.03	0.87	< 0.01
	tDCS × TIME	0.10	0.75	< 0.01	3.29	0.08	0.10
	AGE × tDCS × TIME	0.25	0.62	< 0.01	1.52	0.23	0.05

MEP motor-evoked potential, *tDCS* transcranial direct current stimulation, *THT* threshold-hunting target, *SICI* short-interval intracortical inhibition, *LICI* long-interval intracortical inhibition, *SICF* short-interval intracortical facilitation

[a]Post > pre

Table 3 (continued)

[b]Post < pre

[c]Older < young

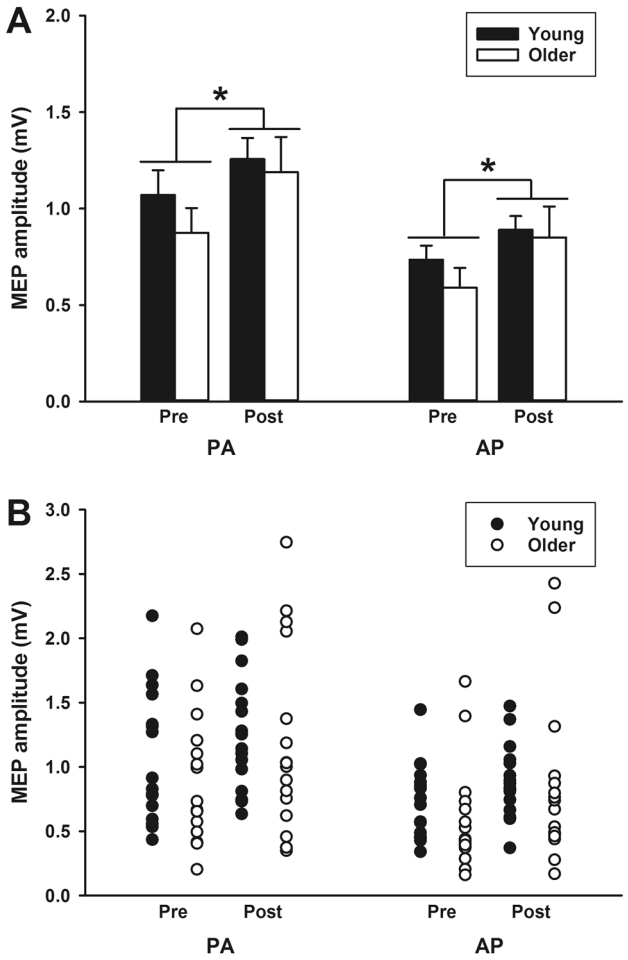

Fig. 4 Group mean (**a**) and individual (**b**) values for motor-evoked potential (MEP) amplitude with posterior–anterior (PA)- and anterior–posterior (AP)-induced current for young and older adults pre- and post-training. Data are collapsed across transcranial direct current stimulation sessions and are presented as mean + SEM. $N = 16$ young and 16 older. $^{*}P < 0.05$

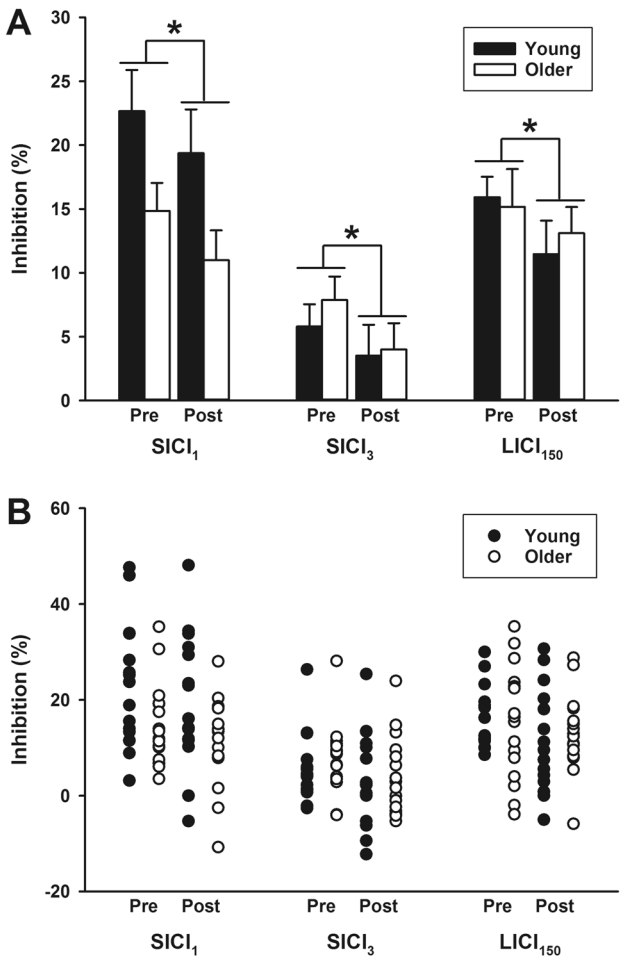

Fig. 5 Group mean (**a**) and individual (**b**) values for short-interval intracortical inhibition (SICI) with interstimulus intervals of 1 and 3 ms and long-interval intracortical inhibition (LICI) with an interstimulus interval of 150 ms assessed with posterior–anterior induced current for young and older adults pre- and post-training. Data are collapsed across transcranial direct current stimulation sessions and are presented as mean + SEM. $N = 16$ young and 16 older. $^{*}P < 0.05$

in modulating neurophysiological mechanisms with M1 may have been attenuated by the concurrent activation of the target muscle during training (Shirota et al. 2017) and the duration of stimulation (Monte-Silva et al. 2013). In addition, using a fixed duration of tDCS meant that stimulation could have ended at different stages during training for each individual, since trials were self-paced. Participants were not assessed across cognitive domains that may influence motor skill (Schaefer et al. 2015). Finally, interleaved practice structures lead to better skill retention compared to repetitive practice in young and older adults (Pauwels et al. 2018), although the latter may promote greater disinhibition within M1 during skill acquisition compared with the former (Coxon et al. 2014).

Conclusion

In summary, although older adults exhibited lower absolute skill level compared with the younger cohort, both groups displayed successful skill acquisition and retention. Corticomotor excitability increased and $GABA_A$ and $GABA_B$

receptor-mediated inhibition decreased after skill acquisition in both age groups. These effects were in part dependent on the interneuronal networks activated by TMS. Our findings indicate potential neurophysiological mechanisms relevant for motor learning in neurorehabilitation contexts that involve older adults, such as after stroke.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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