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Modulation of dorsal premotor cortex differentially influences visuomotor adaptation in young and older adults

Wei-Yeh Liao [a,*], George M. Opie [a], Ulf Ziemann [b,c], John G. Semmler [a]

[a] Discipline of Physiology, School of Biomedicine, The University of Adelaide, Adelaide, Australia
[b] Department of Neurology & Stroke, Eberhard Karls University of Tübingen, Tübingen, Germany
[c] Hertie-Institute for Clinical Brain Research, Eberhard Karls University of Tübingen, Tübingen, Germany

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ABSTRACT

The communication between dorsal premotor cortex (PMd) and primary motor cortex (M1) is important for visuomotor adaptation, but it is unclear how this relationship changes with advancing age. The present study recruited 21 young and 23 older participants for two experimental sessions during which intermittent theta burst stimulation (iTBS) or sham was applied over PMd. We assessed the effects of PMd iTBS on M1 excitability using motor evoked potentials (MEP) recorded from right first dorsal interosseous when single-pulse transcranial magnetic stimulation (TMS) was applied with posterior-anterior (PA) or anterior-posterior (AP) currents; and adaptation by quantifying error recorded during a visuomotor adaptation task (VAT). PMd iTBS potentiated PA ($P < 0.0001$) and AP ($P < 0.0001$) MEP amplitude in both young and older adults. PMd iTBS increased error in young adults during adaptation ($P = 0.026$), but had no effect in older adults ($P = 0.388$). Although PMd iTBS potentiated M1 excitability in both young and older adults, the intervention attenuated visuomotor adaptation specifically in young adults.

1. Introduction

The human neuromotor system is remarkably versatile and can quickly adapt complex visuomotor behaviour in response to the changing needs of the surrounding environment. An important region within the brain that mediates visuomotor adaption is dorsal premotor cortex (PMd), which is thought to select the appropriate action plan (Chouinard et al., 2005; Nowak et al., 2009; Parikh & Santello, 2017) before transmitting this information to primary motor cortex (M1) to form the final motor output (Koch et al., 2007). However, the capacity to adapt complex motor skills generally declines with age (Voelcker-Rehage, 2008), which can limit the ability of older adults to live independently. One possible reason for this decline is age-related changes in neuroplasticity, which refers to the ability of the brain to modify the strength of synaptic communication with long-term potentiation (LTP) and depression (LTD) (Burke & Barnes, 2006; Mahncke et al., 2006; Sanes & Donoghue, 2000). Previous studies using non-invasive brain stimulation (NIBS) have reported reduced M1 plasticity (Fathi et al., 2010; Freitas et al., 2011; Müller-Dahlhaus et al., 2008; Todd et al., 2010) and weaker PMd-M1 connectivity in older adults (Ni et al., 2015). These age-related changes within M1 likely affect PMd-M1 communication, but the mechanisms driving this decline, and how ageing modifies the influence of PMd on visuomotor adaptation, remain unclear.

Transcranial magnetic stimulation (TMS) is a type of NIBS that is useful for characterising the physiology within and between different motor networks with high temporal resolution. Application of TMS over M1 produces a complex descending volley that summates at the spinal cord, resulting in a motor evoked potential (MEP) in targeted muscles (Di Lazzaro et al., 1998; Rossini et al., 2015). The descending volley includes an early direct wave (D-wave), generated by direct activation of corticospinal neurons, followed by several indirect waves (I-waves) that are thought to stem from activation of local interneurons that are synaptically connected to corticospinal neurons (Di Lazzaro et al., 2012; Ziemann, 2020). I-waves can be further characterised as early (I_1) and late (I_2, I_3), and follow each other at a periodicity of ~1.5 ms (Di Lazzaro

Abbreviations: AP, anterior-posterior; CTBS, continuous theta burst stimulation; D-wave, direct wave; FDI, first dorsal interosseous; I-wave, indirect wave; ITBS, intermittent theta burst stimulation; M1, primary motor cortex; MEP, motor evoked potential; PA, posterior-anterior; PMd, dorsal premotor cortex; TMS, transcranial magnetic stimulation; VAT, visuomotor adaptation task.

* Correspondence to: School of Biomedicine, The University of Adelaide, Adelaide, South Australia 5005, Australia.
E-mail address: wei-yeh.liao@adelaide.edu.au (W.-Y. Liao).

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et al., 2012; Ziemann, 2020). Early and late I-waves can be selectively recruited using single-pulse TMS by changing the direction of the applied current (Di Lazzaro et al., 2001; Ni et al., 2010; Sakai et al., 1997). For example, single-pulse TMS at perithreshold currents in the brain perpendicular to the central sulcus with a posterior-anterior (PA) direction preferentially recruit early I-waves, whereas anterior-posterior (AP) currents preferentially recruit late I-waves (Di Lazzaro et al., 2001; Ni et al., 2010; Sakai et al., 1997). Using this technique, TMS research in the past decade has shown that the ability to recruit late I-waves with single-pulse TMS specifically predicts the response of M1 to plasticity-inducing NIBS (Hamada et al., 2013; Volz et al., 2019; Wiethoff et al., 2014). Late I-waves have also been associated with visuomotor behaviour and are thought to originate from the premotor areas (Aberra et al., 2020; Hamada et al., 2014; Spampinato et al., 2020; Volz et al., 2015). Importantly, it is possible to modulate visuomotor adaptation by applying TMS to PMd (Lee & van Donkelaar, 2006; Parikh & Santello, 2017; Sugiyama et al., 2022), indicating that PMd is actively involved during visuomotor adaptation (Tzvi et al., 2020). Taken together, the late I-wave circuits likely reflect PMd inputs that modulate M1 plasticity and visuomotor adaptation.

Importantly, age-related changes in I-wave activity have also been reported using the paired-pulse TMS paradigm short-interval intracortical facilitation (SICF), which is able to specifically index I-wave excitability (Opie et al., 2018). Using this paired-pulse TMS protocol, previous studies have identified reduced I-wave excitability in older adults, and specific temporal alterations to the late I-waves that influence NIBS-induced plasticity, with these changes being predictive of motor behaviour in older adults (Opie et al., 2018; Opie et al., 2020). Furthermore, PMd-M1 connectivity and the influence of PMd on I-wave activity have been reported to weaken with age (W-Y. Liao et al., 2023; Ni et al., 2015). It may therefore be possible that age-related changes in the I-wave circuits can affect PMd-M1 communication, which is important for visuomotor adaptation.

Therefore, the present study aimed to investigate the influence of PMd on M1 I-wave circuits and visuomotor adaptation in young and older adults. As previous work in young adults has shown that continuous theta burst stimulation (cTBS; LTD-like paradigm) over PMd can disrupt visuomotor performance (Huang et al., 2018; Parikh & Santello, 2017), we wished to investigate whether intermittent TBS (iTBS; LTP-like paradigm) over PMd can improve visuomotor performance. We have shown previously that PMd iTBS has a stronger potentiating effect on late I-waves (W-Y. Liao et al., 2023), whose recruitment efficiency is related to the strength of premotor-M1 functional connectivity (Volz et al., 2015). Enhancing this communication may therefore improve visuomotor performance, which would be particularly beneficial for developing interventions that improve motor function in older adults. We assessed the effects of PMd iTBS on different I-wave circuits by varying the direction of TMS current applied over M1, and on performance during a visuomotor adaptation task (VAT) that is known to specifically engage PMd (Tzvi et al., 2020). We hypothesised that the influence of PMd on M1 I-waves would be related to changes in visuomotor behaviour within older adults, and enhancing this communication with iTBS can improve visuomotor adaptation in older adults.

2. Methods

2.1. Sample size and participants

Twenty-one young (mean ± SD; 25.5 ± 5.7 years; range, 18–36 years, females = 14) and 23 older (68.8 ± 5.5 years; 60–78 years; females = 16) adults were recruited via advertisements placed on notice boards within The University of Adelaide, the wider community, and social media platforms. Suitability for TMS was assessed using a standard TMS safety screening questionnaire (Rossi et al., 2011) and exclusion criteria included a history of psychiatric or neurological disease, current use of medications that affect the central nervous system, or left handedness. The experiment was conducted in accordance with the Declaration of Helsinki and was approved by The University of Adelaide Human Research Ethics Committee (H-026–2008). Participants provided written, informed consent prior to participation.

2.2. Experimental arrangement

Participants attended a PMd iTBS and a PMd sham iTBS session (Figure 1), with a washout period of at least 1 week between sessions. The same experimental protocol was used in both sessions and the order of intervention was randomised between participants. As diurnal variations in cortisol are known to influence the neuroplastic response to TMS (Sale et al., 2008), all sessions were completed between 11 am and 5 pm at approximately the same time of day for each participant.

In each experimental session, participants were seated in a comfortable chair with their hands resting and relaxed. Surface electromyography (EMG) was recorded from first dorsal interosseous (FDI) of the right hand using two Ag-AgCl electrodes arranged in a belly-tendon montage on the skin overlying the muscle, with a third electrode attached above the styloid process of the right ulnar to ground the electrodes (Figure 1A). EMG signals were amplified (300x) and filtered (band-pass 20 Hz – 1 kHz) using a CED 1902 signal conditioner (Cambridge Electronic Design, Cambridge, UK) before being digitised at 2 kHz using a CED 1401 analogue-to-digital converter. Signal noise associated with mains power was removed using a Humbug mains noise eliminator (Quest Scientific, North Vancouver, Canada). EMG signals were stored on a PC for offline analysis. Real-time EMG signals were displayed on an oscilloscope placed in front of the participant to facilitate muscle relaxation during the experiment.

2.3. Experimental Procedures

2.3.1. Transcranial magnetic stimulation

TMS to left M1 was applied with a branding iron coil (70 mm diameter) connected to two Magstim 200^2 magnetic stimulators (Magstim, Whitland, UK) via a BiStim unit. The coil was held tangentially to the scalp above M1 at an angle of 45° to the sagittal plane, inducing a PA current relative to the central sulcus. The M1 FDI hotspot was determined as the location producing the largest and most consistent MEPs within the relaxed right FDI. This location was marked on the scalp for reference and continuously monitored throughout each experimental session. All TMS pulses were applied at a rate of 0.2 Hz, with a 10% jitter between trials to avoid anticipation of the stimulus.

Resting motor threshold (RMT, PA_{RMT}) over M1 was recorded as the lowest stimulation intensity (expressed as percentage of maximum stimulator output, % MSO) required to produce MEP amplitude $\geq$ 50 μV in 5 out of 10 consecutive trials in the relaxed FDI (Rossini et al., 2015). Following RMT, the stimulation intensities producing a standard MEP amplitude approximating 1 mV ($PA_{1\ mV}$), in addition to an MEP amplitude approximating 0.5 mV ($PA_{0.5\ mV}$), when averaged over 20 trials, were identified. The same procedure was repeated for AP TMS by rotating the coil 180° (AP_{RMT}, $AP_{1\ mV}$, $AP_{0.5\ mV}$). The same intensities for each PA and AP TMS measure were applied throughout the experimental session to assess changes in corticospinal excitability (baseline, 0 min; post-control, 40 min; post-iTBS, 70 min; post-adaptation, 110 min; post-de-adaptation, 135 min; Figure 1C).

2.3.2. Visuomotor adaptation task

Participants performed VAT in both experimental sessions, similar to previous work (Galea et al., 2011; Tzvi et al., 2020). Participants were seated in front of a 16-inch LCD monitor (IBM, Armonk, New York, US) placed 200 mm above a Wacom Intuos Pro tablet (Wacom, Kazo, Saitama, Japan) via a wooden frame, with both devices angled 10° from the horizontal plane towards the participant (Figure 1B). Participants operated the tablet using a stylus pen fixed to the right index finger and were unable to see their right hand when operating the tablet.

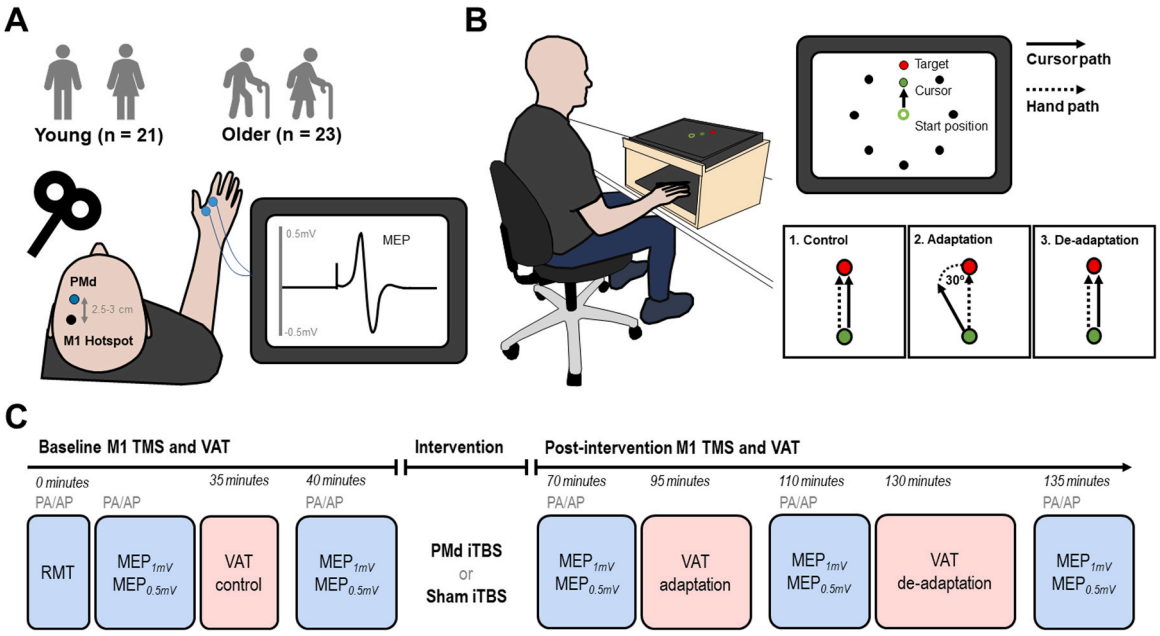

Fig. 1. Experimental setup and protocol for the study. (A) Participant recruitment and TMS setup. (B) VAT setup and protocol. (C) Experimental protocol.

The experimental stimuli for VAT were presented using Psychtoolbox-3 (Brainard, 1997) extension for MATLAB (Mathworks®, version R2017a) on the LCD monitor (resolution of 1920 x 1080 pixels; active area of 564.5 x 317.6 mm) with a refresh rate of 60 Hz. For each trial, participants were instructed to perform centre-out movements using a green cursor (3.42 mm diameter) by starting from the centre green ring (7.04 mm diameter) and 'shoot-through' one of eight randomly presented red targets (3.42 mm diameter) on an outer invisible ring (200 mm diameter, evenly spaced at 45° from 0°) as quickly and as accurately as possible. The target appeared after 1–2 s jitter and participants had a maximum movement time (MT) of 500 ms (the trial was repeated if participants exceeded this limit). Each trial took approximately 4 s and the cursor and target disappeared at the end of each trial. At baseline, a practice block of 8 trials (reaching to each of the 8 targets) followed by a control block of 48 trials were recorded. Following PMd iTBS or sham iTBS, participants performed an adaptation block of 192 trials (split into two sets of 96 trials and 1-minute break), during which cursor movement was displaced by 30° counter-clockwise relative to hand movement. Prior to adaptation, participants were explicitly informed that cursor movement had been offset, though they were not informed of the direction and extent of change. Following adaptation, a de-adaptation block of 48 trials was recorded (no rotation). Lastly, to prevent the consolidation of new motor memories ('savings') between sessions, an interference adaptation block of 192 trials (two sets of 96 trials and 1-minute break) with an opposite 30° clockwise rotation was performed at the end of each session (Krakauer et al., 2005).

2.3.3. *Intermittent theta burst stimulation*

iTBS was applied over left PMd with a figure-of-eight-coil (70 mm diameter) connected to a Magstim Super-rapid stimulator (Magstim, Whitland, UK). The coil was held tangentially to the scalp at an angle of 45° to the sagittal plane, with the handle pointing backwards and laterally, inducing a biphasic pulse with an initial PA current followed by an AP return current (Suppa et al., 2008). Consistent with previous studies, iTBS consisted of three-pulse bursts given at 50 Hz. Each triplet was repeated 10 times at 5 Hz, and this was repeated every 8 s for 20 cycles, totalling 600 pulses (Huang et al., 2018; Huang et al., 2005; Meng et al., 2020). The location of left PMd was defined as 8% of the distance between the nasion and inion anterior to the M1 hotspot (mean Euclidean distance between M1 and PMd MNI coordinates ± SD, 24.9 ± 3.9 mm; range, 18.1 – 34.9 mm), consistent with previous work (Huang et al., 2009; W-Y. Liao et al., 2023; Münchau et al., 2002; Suppa et al., 2008). Both the M1 hotspot and left PMd location were digitally recorded relative to the standard MNI-ICBM152 template using Brainsight neuronavigation (Rogue Research, Montreal, Quebec, Canada). The digital recordings were then used to guide the assessment of RMT (RMT_{Rapid}) over M1 with the Magstim Super-rapid stimulator, in addition to maintaining consistent coil positioning during the application of iTBS over left PMd. As muscle activation is known to confound the response to subsequent plasticity-inducing interventions (Goldsworthy et al., 2015; Huang et al., 2008; Thirugnanasambandam et al., 2011), we modified the conventional iTBS intensity of 80 % AMT to 70 % RMT_{Rapid}. This value approximates 80 % AMT, and has been used previously for PMd iTBS (Meng et al., 2020).

In contrast, sham iTBS was delivered using a sham figure-of-eight coil (70 mm diameter, placebo coil PN 3285–00, Magstim, Whitland, UK) to replicate the pulse noise, while a bar electrode connected to a constant current stimulator (Digitimer, Hertfordshire, UK) concurrently applied electrical stimuli (1.5 mA intensity) to the scalp to mimic the pulse sensation. Visual analogue scales (VAS) were used following each intervention to assess the degree of discomfort, FDI activation, and localisation of scalp sensation associated with iTBS.

2.4. *Data Analysis*

Visual inspection of EMG data was completed offline, and any trials with EMG activity exceeding 25 μV in the 100 ms prior to stimulus application were excluded from analysis (approximately 5.1 % MEP trials removed) (W-Y. Liao et al., 2023; Liao et al., 2022; Puri et al., 2015). The amplitude of MEPs was measured peak-to-peak and expressed in mV. MEP amplitude recorded during the post-iTBS time point were also expressed as a percentage relative to the mean MEP amplitude recorded during the post-control time point. In addition, baseline MEP onset latencies were assessed with a semi-automated process using a custom-written script via the Signal program (v 6.02, Cambridge Electronic Design) and expressed in ms (Opie et al., 2018). Onset latency for each trial was defined as the point at which the rectified EMG signal following the stimulus artefact exceeded the mean EMG amplitude + 2 SD within the 100 ms prior to the stimulus (Opie

et al., 2018).

VAT data was also inspected offline, and any trials with MT exceeding 500 ms or with the magnitude of error exceeding 60° excluded from analysis (approximately 10.1 % trials removed), similar to previous work (Tzvi et al., 2020). In addition, the practice block and interference block were excluded from analysis. MT was calculated as the time difference between the cursor velocity exceeding 5 % peak velocity and the cursor crossing the outer ring within the same trial. Each eight consecutive trials (in each direction) were epoched, totalling 36 epochs (control, epochs 1–6; adaptation, epochs 7–30; de-adaptation, epochs 31–36). In addition, previous studies have shown that rapid improvements in adaptation (Krakauer et al., 2005) and manipulation of adaptation (Galea et al., 2011) can be captured during epochs 8–17, following which performance plateaus. We therefore followed this procedure and included epochs 1–6, 8–17, and 31–36 for analysis. Performance was quantified as the angular cursor error and expressed in degrees (°), and was calculated as the difference between the endpoint angle of the cursor and the target angle within the same trial. A positive value indicated a clockwise error while a negative value indicated a counter-clockwise error. Reaction time (RT) was also included (Galea et al., 2011; Tzvi et al., 2020) as a secondary measure of performance and expressed in ms, and was calculated as the time at which the cursor left the centre ring during each trial.

2.5. Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics (IBM, version 27). Generalised linear mixed models (GLMM's) were used to analyse all TMS and VAT data (Lo & Andrews, 2015; Puri & Hinder, 2022). Each model included single trial data with repeated measures and MEP and RT data were fitted using gamma distributions with log links for positively-skewed data, whereas cursor angle error data were fitted using normal distributions with identity links. All random subject effects (intercepts and slopes) were included (Barr et al., 2013) and model fit was assessed with the Bayesian Schwartz Criterion. Two-factor GLMMs were used to investigate the effects of session (iTBS, sham) and age group (young, older) on baseline stimulation intensities and MEP amplitude for PA_{RMT}, AP_{RMT}, $PA_{1\,mV}$, $AP_{1\,mV}$, $PA_{0.5\,mV}$, and $AP_{0.5\,mV}$. A four-factor model was used to investigate the influence of session, age group, TMS intensity ($MEP_{1\,mV}$, $MEP_{0.5\,mV}$) and coil orientation (PA, AP) on baseline MEP onset latencies.

Three-factor GLMMs were used to compare the effects of session, time (baseline, post-control, post-iTBS, post-adaptation, post-de-adaptation), and age group on MEP measures of corticospinal excitability in four separate models for $PA_{1\,mV}$, $AP_{1\,mV}$, $PA_{0.5\,mV}$, and $AP_{0.5\,mV}$ throughout each experimental session. Changes in MEP measures of corticospinal excitability following PMd iTBS were investigated by comparing the effects of session and age group on normalised MEP amplitude in four separate models for $PA_{1\,mV}$, $AP_{1\,mV}$, $PA_{0.5\,mV}$, and $AP_{0.5\,mV}$. Importantly, as the variability of post-control MEP amplitude is increased relative to baseline MEP amplitude (see Figure 2), normalising post-iTBS MEP amplitude to post-control learning mean MEP amplitude could distort the effects of the intervention and produce outliers (see Figure 3). Therefore, the mean post-control MEP amplitude for each participant was included as a covariate to control for the influence of varying MEP amplitude on the normalisation procedure (Corp et al., 2020). For all models assessing MEP amplitude, participant stimulation intensities were also included as covariates to control for the influence of varying TMS intensities.

Two three-factor GLMM were used to compare the effects of session, block (control, adaptation, de-adaptation), and age group on cursor angle error and RT. As we found an differences in cursor angle error within a three-factor interaction for session, block, and age group (see Results), we included an additional three-factor GLMM assessing session, epoch (epochs 7–18) and age group on cursor angle error during adaptation. For this model, the effect of session order (session 1, session 2) on error was included in order to investigate if participants improved visuomotor adaptation during the second experimental session, and the mean cursor angle error during control was included as a covariate to account for the effects of varying baseline performance. In addition, MT

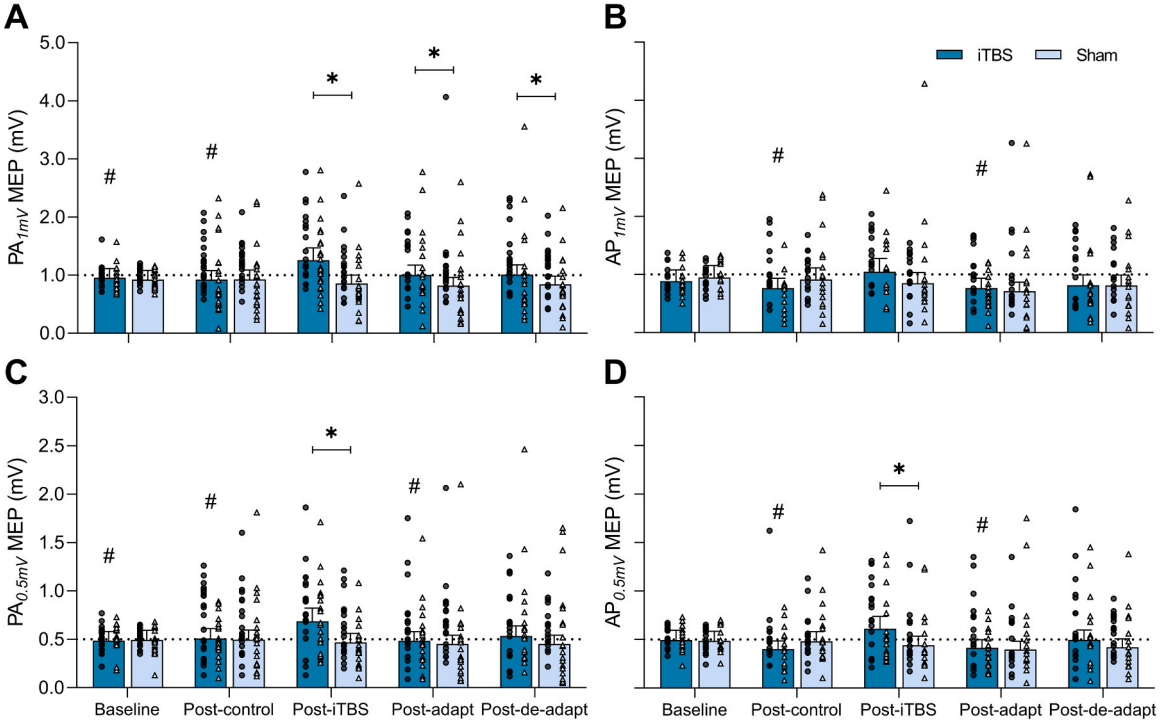

Fig. 2. TMS measures of corticospinal excitability for $PA_{1\,mV}$ (A), $AP_{1\,mV}$ (B), $PA_{0.5\,mV}$ (C), and $AP_{0.5\,mV}$ (D) in PMd iTBS (dark blue) and sham (light blue) sessions at baseline, post-control, post-iTBS, post-adaptation, and post-de-adaptation for all participants. Data are presented as EMMs [95 % CI] with individual participants means for young (black circles) and older (white triangles) adults. *$P < 0.05$. #$P < 0.05$ compared to post-iTBS.

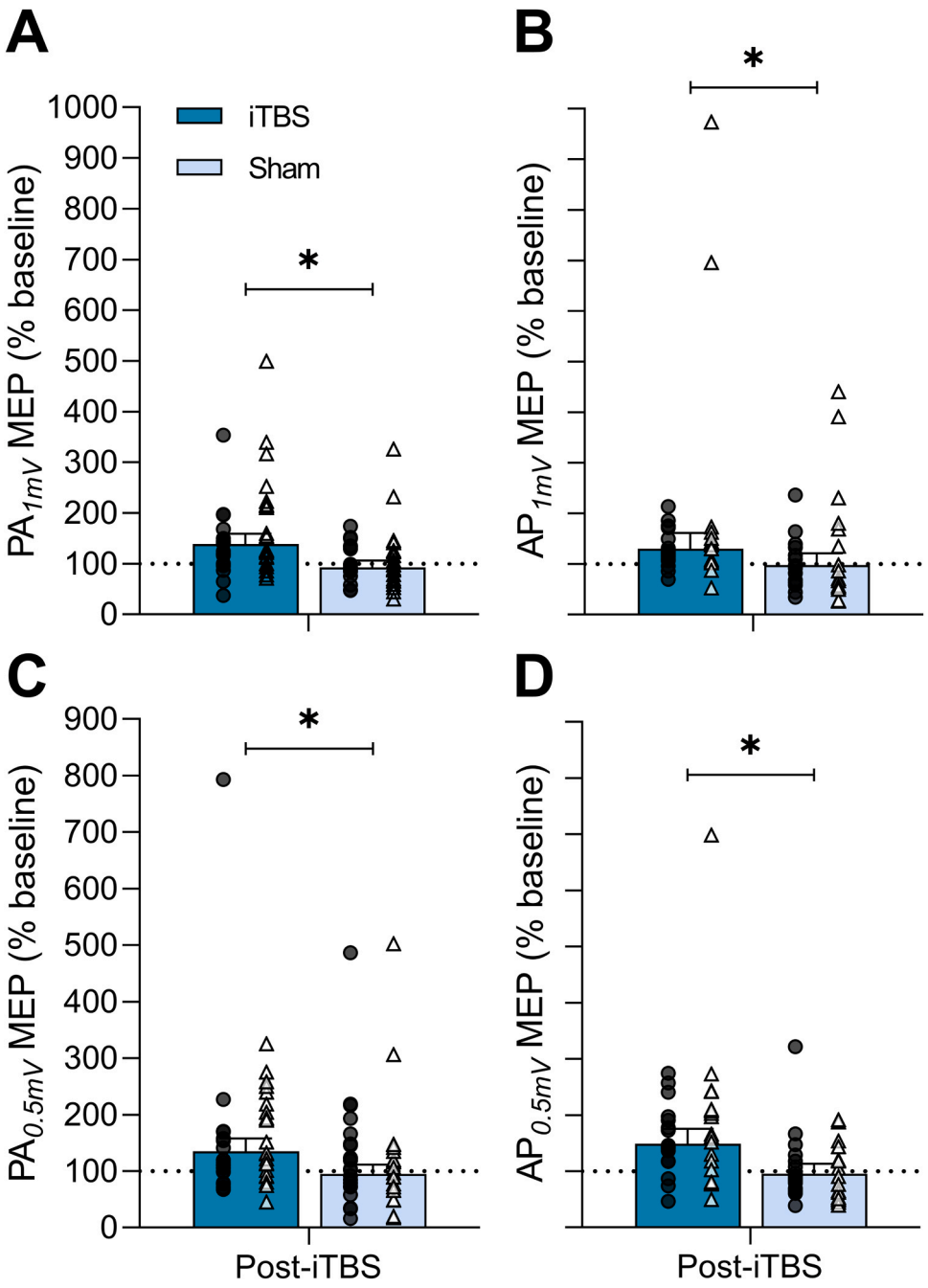

Fig. 3. Changes in TMS measures of corticospinal excitability for $PA_{1\,mV}$ (A), $AP_{1\,mV}$ (B), $PA_{0.5\,mV}$ (C), and $AP_{0.5\,mV}$ (D) following PMd iTBS (dark blue) and sham (light blue) for all participants. Data are presented as EMMs [95 % CI] with individual participants means for young (black circles) and older (white triangles) adults. $^{*}P < 0.05$.

was included as a covariate for all VAT models to adjust for the effects of varying MT on performance. *Post-hoc* comparisons were investigated for all significant effects, with Bonferroni correction applied for each investigation. All data are presented as estimated marginal means (EMM) with 95 % confidence intervals (95 % CI) and all contrasts are presented as estimated mean difference (EMD) with 95 % CI.

As MEP amplitude ($PA_{1\,mV}$, $AP_{1\,mV}$, $PA_{0.5\,mV}$, $AP_{0.5\,mV}$) and adaptation error (in young) were modulated following PMd iTBS (see Results), we used Spearman's rank correlation analysis to assess the relationship between post-iTBS MEP amplitude and mean adaptation error. In addition, we also investigated the relationship between baseline MEP onset latencies ($PA_{1\,mV}$, $AP_{1\,mV}$, $PA_{0.5\,mV}$, $AP_{0.5\,mV}$) and mean error and mean RT during adaptation of the sham session in order to assess the relationship between I-wave recruitment and visuomotor performance. Correlations are presented as Spearman's ρ with 95 % CI, with significance adjusted using Bonferroni correction. Lastly, differences in the perception of iTBS and sham iTBS were investigated by comparing VAS responses using paired t-tests with Bonferroni correction. For all statistical analyses, $P < 0.05$ is considered significant.

3. Results

Forty-two participants (21 older) completed both experimental sessions without adverse effects. One older male participant withdrew from the study after experiencing mild headache, neck pain, and mental confusion within 24 h following PMd iTBS session. Another older male

participant was excluded from receiving TMS (due to metal wiring within jaw), but completed VAT in the sham session. We were unable to record $PA_{1\ mV}$ in one young female participant (mean PA_{RMT} = 86.5 % MSO), $AP_{1\ mV}$ in 12 participants (6 young, 5 females; 6 older, 5 females), and $AP_{0.5\ mV}$ in 8 participants (4 young, 3 females; 4 older females) due to high thresholds of TMS activation (mean AP_{RMT} = 87.0 % MSO). Due to artefact contamination, we were also unable to assess MEP onset latencies for $PA_{1\ mV}$ in 7 participants (5 young, 4 females; 2 older females), $AP_{1\ mV}$ in 6 participants (4 young females; 2 older females), $PA_{0.5\ mV}$ in 5 participants (4 young, 3 females; 1 older female), and $AP_{0.5\ mV}$ in 5 participants (4 young females; 1 older female). Baseline TMS intensities, MEP amplitude, and MEP latency are presented in Table 1. MEP latencies varied between coil orientations ($F_{1,3985}$ = 111.58, $P < 0.0001$), with longer AP latencies compared to PA (EMD = 2.07 ms [1.68, 2.46], $P < 0.0001$). MEP latencies also differed between age groups ($F_{1,3985}$ = 18.04, $P < 0.0001$), with longer MEP latencies in older adults compared to young (EMD = 1.12 ms [0.61, 1.64], $P < 0.0001$). There was also an interaction between stimulation intensity and coil orientation ($F_{1,3985}$ = 5.60, P = 0.018). In particular, AP latencies were longer than PA latencies for both $MEP_{1\ mV}$ (EMD = 1.82 ms [1.37, 2.27], $P < 0.0001$) and $MEP_{0.5\ mV}$ (EMD =2.23 ms [1.89, 2.76], $P < 0.0001$), but $AP_{1\ mV}$ latencies were shorter than $AP_{0.5\ mV}$ latencies (EMD = 0.45 ms [0.03, 0.88], P = 0.035). There were no other main effects or interactions for MEP latency (all $P > 0.05$) and no main effects or interactions between session and age group for all baseline TMS intensities and MEP amplitude (all $P > 0.05$).

Table 1
Baseline TMS intensities, MEP amplitude and latency between sessions for young and older adults.

Measure	Young		Older	
	PMd iTBS	PMd sham	PMd iTBS	PMd sham
TMS intensity				
PA_{RMT} (%MSO)	55.4 [51.1, 60.1]	53.9 [49.7, 58.5]	51.3 [47.3, 55.5]	50.9 [47.0, 55.1]
$PA_{1\ mV}$ (%MSO)	65.2 [61.7, 68.9]	63.9 [60.6, 67.5]	65.3 [62.0, 68.8]	65.4 [62.0, 68.9]
$PA_{0.5\ mV}$ (%MSO)	60.1 [57.8, 62.5]	60.2 [57.9, 62.6]	61.2 [58.9, 63.5]	61.6 [59.3, 64.0]
AP_{RMT} (%MSO)	69.7 [64.0, 76.0]	68.8 [63.2, 75.0]	65.5 [60.2, 71.3]	65.3 [60.1, 71.1]
$AP_{1\ mV}$ (%MSO)	75.0 [71.3, 78.8]	73.8 [70.3, 77.5]	74.0 [70.6, 77.7]	75.5 [71.9, 79.2]
$AP_{0.5\ mV}$ (%MSO)	71.1 [68.4, 73.8]	70.8 [68.2, 73.5]	71.4 [68.9, 74.1]	72.7 [70.1, 75.5]
$Rapid_{RMT}$ (% MSO)	64.5 [59.2, 70.2]	63.7 [58.5, 69.3]	60.5 [55.6, 65.7]	59.4 [54.7, 64.6]
MEP amplitude				
$PA_{1\ mV}$ (mV)	0.98 [0.91, 1.07]	0.93 [0.86, 1.00]	0.98 [0.90, 1.06]	0.89 [0.83, 0.97]
$PA_{0.5\ mV}$ (mV)	0.49 [0.45, 0.55]	0.51 [0.46, 0.57]	0.53 [0.48, 0.59]	0.48 [0.43, 0.53]
$AP_{1\ mV}$ (mV)	0.91 [0.80, 1.02]	0.89 [0.79, 1.00]	0.92 [0.82, 1.04]	0.98 [0.87, 1.10]
$AP_{0.5\ mV}$ (mV)	0.51 [0.45, 0.57]	0.50 [0.44, 0.56]	0.49 [0.44, 0.56]	0.50 [0.44, 0.56]
MEP latency				
$PA_{1\ mV}$ latency (ms)	22.7 [22.2, 23.2]	22.2 [21.7, 22.7]	23.5 [23.0, 24.1][c]	23.8 [23.3, 24.3][c]
$PA_{0.5\ mV}$ latency (ms)	22.4 [21.9, 22.9]	22.5 [22.0, 23.0]	23.4 [22.9, 23.9][c]	23.7 [23.2, 24.3][c]
$AP_{1\ mV}$ latency (ms)[a]	24.3 [23.6, 25.0]	23.9 [23.2, 24.6]	25.6 [24.9, 26.3][c]	25.7 [24.9, 26.4][c]
$AP_{0.5\ mV}$ latency (ms)[a,b]	24.8 [24.2, 25.5]	24.5 [23.9, 25.1]	26.0 [25.3, 26.7][c]	25.9 [25.3, 26.6][c]

Data presented as EMM and 95% CI [lower, upper]. [a]$P < 0.05$ compared to PA. [b]$P < 0.05$ compared to $AP_{1\ mV}$. [c]$P < 0.05$ compared to young.

3.1. Corticospinal excitability

The participants' perception of PMd iTBS and sham are presented in Table 2. Although there were no differences in the extent of FDI activation ($t_{40} < 0.0001$, P = 0.999) or localisation of stimulation sensation (t_{40} = 2.31, P = 0.079), participants perceived the sensation of PMd iTBS as more uncomfortable (t_{40} = 2.81, P = 0.023) relative to sham.

MEP measures of corticospinal excitability are shown in Figure 2. $PA_{1\ mV}$ MEP amplitude did not differ between time points ($F_{4,7898}$ = 1.16, P = 0.327), but varied between sessions ($F_{1,7898}$ = 6.63, P = 0.01), with *post-hoc* analysis revealing increased MEP amplitude during PMd iTBS session relative to sham (EMD = 0.15 mV [0.04, 0.26], P = 0.011). $PA_{1\ mV}$ MEP amplitude also varied between age groups ($F_{1,7898}$ = 7.73, P = 0.005), with increased MEP amplitude for young adults compared to older adults (EMD = 0.27 mV [0.08, 0.47], P = 0.007). In addition, there was a session by time interaction ($F_{4,7898}$ = 5.75, $P < 0.0001$; Figure 2A). *Post-hoc* comparisons show increased MEP amplitude post-iTBS (EMD = 0.40 mV [0.22, 0.59], $P < 0.0001$), post-adaptation (EMD = 0.18 mV [0.03, 0.34], P = 0.019), and post-de-adaptation (EMD = 0.17 mV [0.01, 0.32], P = 0.035) during PMd iTBS session compared to sham. MEP amplitude during PMd iTBS session was also increased post-iTBS compared to baseline (EMD = 0.31 mV [0.04, 0.57], P = 0.012) and post-control (EMD = 0.34 mV [0.07, 0.60], P = 0.004). There were no other interactions between variables (all $P > 0.05$). Similarly, while $AP_{1\ mV}$ MEP amplitude did not vary between sessions ($F_{1,5773}$ = 0.01, P = 0.914), time points ($F_{4,5773}$ = 2.37, P = 0.05), and age groups ($F_{1,5773}$ = 2.62, P = 0.105), there was an interaction between session and time ($F_{4,5773}$ = 3.11, P = 0.015; Figure 2B). In particular, *post-hoc* comparisons reveal increased MEP amplitude during PMd iTBS session post-iTBS compared to post-control (EMD = 0.28 mV [0.00, 0.56], P = 0.046) and post-adaptation (EMD = 0.28 mV [0.00, 0.56], P = 0.046). There were no other interactions between variables (all $P > 0.05$).

$PA_{0.5\ mV}$ MEP amplitude did not differ between sessions ($F_{1,8016}$ = 3.18, P = 0.075) or time points ($F_{4,8016}$ = 1.57, P = 0.178), but varied between age groups ($F_{1,8016}$ = 4.81, P = 0.028), with *post-hoc* analysis showing increased MEP amplitude for young adults compared to older adults (EMD = 0.13 mV [0.01, 0.25], P = 0.031). Furthermore, there was an interaction between session and time ($F_{4,8016}$ = 4.20, P = 0.002; Figure 2C). *Post-hoc* comparisons demonstrated increased MEP amplitude post-iTBS during PMd iTBS session relative to sham (EMD = 0.22 mV [0.10, 0.33], $P < 0.0001$). MEP amplitude post-iTBS was also increased compared to baseline (EMD = 0.20 mV [0.04, 0.37], P = 0.007), post-control (EMD = 0.18 mV [0.01, 0.34], P = 0.025), and post-adaptation (EMD = 0.20 mV [0.04, 0.37], P = 0.006) during PMd iTBS session. There were no other interactions between variables (all $P > 0.05$). In contrast, $AP_{0.5\ mV}$ MEP amplitude did not vary between sessions ($F_{1,6508}$ = 1.06, P = 0.303) or age groups ($F_{1,6508}$ = 2.56, P = 0.11), but differed between time points ($F_{4,6508}$ = 2.49, P = 0.041), with *post-hoc* comparisons showing increased MEP amplitude post-iTBS relative to post-adaptation (EMD = 0.11 mV [0.00, 0.23], P = 0.049). Similarly, there was also an interaction between session and time ($F_{4,6508}$ = 4.97, P = 0.001; Figure 2D). *Post-hoc* analysis revealed increased MEP amplitude post-iTBS during PMd iTBS session compared to sham (EMD = 0.17 mV [0.06, 0.28], P = 0.003). MEP amplitude during PMd iTBS

Table 2
Comparison of VAS responses (mean ± STD) between sessions.

Question	PMd iTBS	PMd sham
How uncomfortable were the TMS pulses (0, not uncomfortable at all; 10, highly uncomfortable)?	2.54 ± 2.78	1.37 ± 1.89[a]
If there were any twitches in the right hand, how strong were they (0, no twitches; 10, very strong cramp)?	0.95 ± 1.56	0.95 ± 1.67
How localised were the sensations from TMS pulses (0, highly localised; 10, widespread)?	2.32 ± 2.47	1.32 ± 2.62

[a] $P < 0.05$ compared to iTBS.

session was also increased post-iTBS relative to post-control (EMD = 0.21 mV [0.05, 0.36], $P = 0.002$) and post-adaptation (EMD = 0.20 mV [0.04, 0.35], $P = 0.003$). There were no other interactions between variables (all $P > 0.05$).

Normalised MEP measures of corticospinal excitability are presented in Figure 3, which expresses post-iTBS MEP amplitude as a percentage of post-control mean MEP amplitude for each participant. Changes in $PA_{1\,mV}$ MEP amplitude did not vary between age groups ($F_{1,1582} = 0.01$, $P = 0.916$), but differed between sessions ($F_{1,1582} = 29.15$, $P < 0.0001$; Figure 3A), with *post-hoc* comparisons revealing increased MEP amplitude following PMd iTBS relative to sham (EMD = 46.2 % [28.4, 63.9], $P < 0.0001$). There was no interaction between factors ($F_{1,1582} = 1.83$, $P = 0.177$). Similarly, changes in $AP_{1\,mV}$ MEP amplitude did not differ between age groups ($F_{1,1132} = 0.03$, $P = 0.872$), but varied between sessions ($F_{1,1132} = 5.99$, $P = 0.015$; Figure 3B), with *post-hoc* analysis showing increased MEP amplitude following PMd iTBS compared to sham (EMD = 32.4 % [5.6, 59.1], $P = 0.018$). There was no interaction between factors ($F_{1,1132} = 0.277$, $P = 0.599$).

In addition, changes in $PA_{0.5\,mV}$ amplitude did not vary between age groups ($F_{1,1588} = 1.74$, $P = 0.187$), but differed between sessions ($F_{1,1588} = 14.83$, $P < 0.0001$; Figure 3C), with *post-hoc* comparisons showing increased MEP amplitude following PMd iTBS relative to sham (EMD = 39.7 % [18.7, 60.7], $P < 0.0001$). There was no interaction between factors ($F_{1,1588} = 0.55$, $P = 0.46$). Lastly, changes in $AP_{0.5\,mV}$ MEP amplitude also did not vary between age groups ($F_{1,1263} = 0.45$, $P = 0.504$), but differed between sessions ($F_{1,1263} = 19.68$, $P < 0.0001$; Figure 3D), with *post-hoc* analysis revealing increased MEP amplitude following PMd iTBS compared to sham (EMD = 53.2 % [28.3, 78.1], $P < 0.0001$). There was no interaction between factors ($F_{1,1263} = 0.38$, $P = 0.537$).

3.2. Visuomotor adaptation

Control VAT cursor angle error and RT are presented in Table 3, and cursor angle error for young and older adults throughout each session are presented in Fig. 4A. Cursor angle error did not vary between sessions ($F_{1,14914} = 0.15$, $P = 0.695$), but differed between blocks ($F_{2,14914} = 1783.10$, $P < 0.0001$), with *post-hoc* comparisons showing an estimated small control counter-clockwise error (-2.50° [-3.79, -1.21]), a large adaptation counter-clockwise error (-16.80° [-18.01, -15.58]), and a de-adaptation medium clockwise error (6.83° [5.53, 8.12]), with error varying between all blocks (all $P < 0.0001$), as expected. Error also differed between age groups ($F_{1,14914} = 9.18$, $P = 0.002$), with increased error in older compared to young adults (EMD = 3.62° [1.28, 5.97], $P = 0.002$). There was a two-factor interaction between block and age group ($F_{2,14914} = 11.32$, $P < 0.0001$). There was also a three-factor interaction between session, block, and age group ($F_{2,14914} = 4.82$, $P = 0.008$), with *post-hoc* comparisons showing that adaptation error was increased in young adults following iTBS compared to sham (EMD = 2.33° [0.00, 4.66], $P = 0.049$). Error was also increased in older adults during adaptation in both sessions (both $P < 0.05$) and during de-adaptation in the sham session (EMD =3.54° [0.41, 6.67], $P = 0.026$). For both age groups in both sessions, error varied between each block (all $P < 0.05$).

Table 3
Control VAT cursor angle error and RT between sessions for young and older adults.

Measure	Young		Older	
	PMd iTBS	PMd sham	PMd iTBS	PMd sham
Error (°)	-1.55 [-3.77, 0.66]	-1.50 [-3.76, -0.77]	-3.39 [-5.55, -1.23]	-3.58 [-5.74, -1.42]
RT (ms)	213.3 [205.2, 221.8]	211.1 [202.9, 219.7]	227.0 [218.6, 235.8][a]	227.2 [218.7, 236.0][a]

Data presented as EMM and 95% CI [lower, upper]. [a]$P < 0.05$ compared to young.

There were no other interactions (all $P > 0.05$).

Within the adaptation block, error did not vary between sessions ($F_{1,6702} = 1.13$, $P = 0.287$), but differed between adaptation epochs ($F_{9,6702} = 23.49$, $P < 0.0001$), with *post-hoc* tests revealing a progressive reduction in error from epoch 8 to epoch 17 ($P < 0.05$ for significant comparisons). Error also varied between age groups ($F_{1,6702} = 13.87$, $P < 0.0001$), with increased error in older relative to young adults (EMD = 4.19° [1.98, 6.40], $P < 0.0001$). There was also an interaction between session and age group ($F_{1,6702} = 4.69$, $P = 0.030$; Fig. 4B). While error was increased in both sessions for older compared to young adults (both $P < 0.05$), error was specifically increased in young adults following iTBS (EMD = 2.15° [0.26, 4.04], $P = 0.026$). Finally, error scores did not vary between session 1 and session 2 ($F_{1,6702} = 1.86$, $P = 0.173$). There were no other interactions (all $P > 0.05$).

RT did not vary between sessions ($F_{1,14914} = 0.75$, $P = 0.388$), but differed between blocks ($F_{2,14914} = 3.68$, $P = 0.025$), with *post-hoc* analysis revealing shorter RT during baseline compared to control (EMD = 5.0 ms [0.6, 9.5], $P = 0.022$). RT also varied between age groups ($F_{1,14914} = 27.43$, $P < 0.0001$), with shorter RT in young compared to older adults (EMD = 23.5 ms [14.7, 32.3], $P < 0.0001$). There was also an interaction between block and age group ($F_{2,14914} = 9.04$, $P < 0.0001$), but no other interactions (all $P > 0.05$).

3.3. Correlation between corticospinal excitability and visuomotor adaptation

MEP amplitude ($PA_{1\,mV}$, $AP_{1\,mV}$, $PA_{0.5\,mV}$, $AP_{0.5\,mV}$) following PMd iTBS was not related to cursor angle error during adaptation (all $P > 0.05$). Similarly, MEP onset latencies ($PA_{1\,mV}$, $AP_{1\,mV}$ shown in Fig. 4C, $PA_{0.5\,mV}$, $AP_{0.5\,mV}$) during the sham session were not related to cursor angle error (all $P > 0.05$). In contrast, $AP_{1\,mV}$ onset latencies were related to adaptation RT ($\rho = 0.55$ [0.18, 0.78], $P = 0.037$; Fig. 4D), whereas $PA_{1\,mV}$, $PA_{0.5\,mV}$, and $AP_{0.5\,mV}$ responses were not related to RT (all $P > 0.05$).

4. Discussion

In the present study, we investigated the influence of PMd on M1 excitability and visuomotor adaptation in young and older adults. This was achieved by modulating PMd with iTBS and assessing M1 excitability using single-pulse TMS ($PA_{1\,mV}$, $AP_{1\,mV}$, $PA_{0.5\,mV}$, $AP_{0.5\,mV}$) and visuomotor behaviour using VAT. We found that PMd iTBS potentiated both PA and AP TMS measures of M1 excitability in young and older adults. Importantly, we show new evidence that PMd iTBS specifically attenuates visuomotor adaptation in young but not older adults.

4.1. PMd influence on corticospinal excitability in young and older adults

We found that PA ($PA_{1\,mV}$, $PA_{0.5\,mV}$) and AP ($AP_{1\,mV}$, $AP_{0.5\,mV}$) measures of M1 excitability increased following PMd iTBS in young adults, consistent with previous work (W-Y. Liao et al., 2023; Meng et al., 2020). Application of iTBS over PMd is thought to induce LTP-like effects, which increases the excitability of circuits projecting to M1 (Meng et al., 2020). These effects may involve Ca^{2+} influx into the post-synaptic neuron that triggers LTP events due to the specific timing of the stimulus train (Suppa et al., 2016). Given the proximity of M1 and PMd, it could be suggested that PMd iTBS could also directly activate M1. However, previous work by Huang et al. (2009) suggests this is unlikely, as this study estimated the TMS intensity that spreads to M1 when applied over PMd, and showed that it had no effect on corticospinal excitability when applied directly to M1 (Huang et al., 2009). Given that PMd location was assessed using similar methods to those described previously (Huang et al., 2018; Huang et al., 2009; Meng et al., 2020), it is also unlikely that PMd iTBS directly activated M1 in the present study.

Lowering the stimulation intensity to produce ~0.5 mV MEP

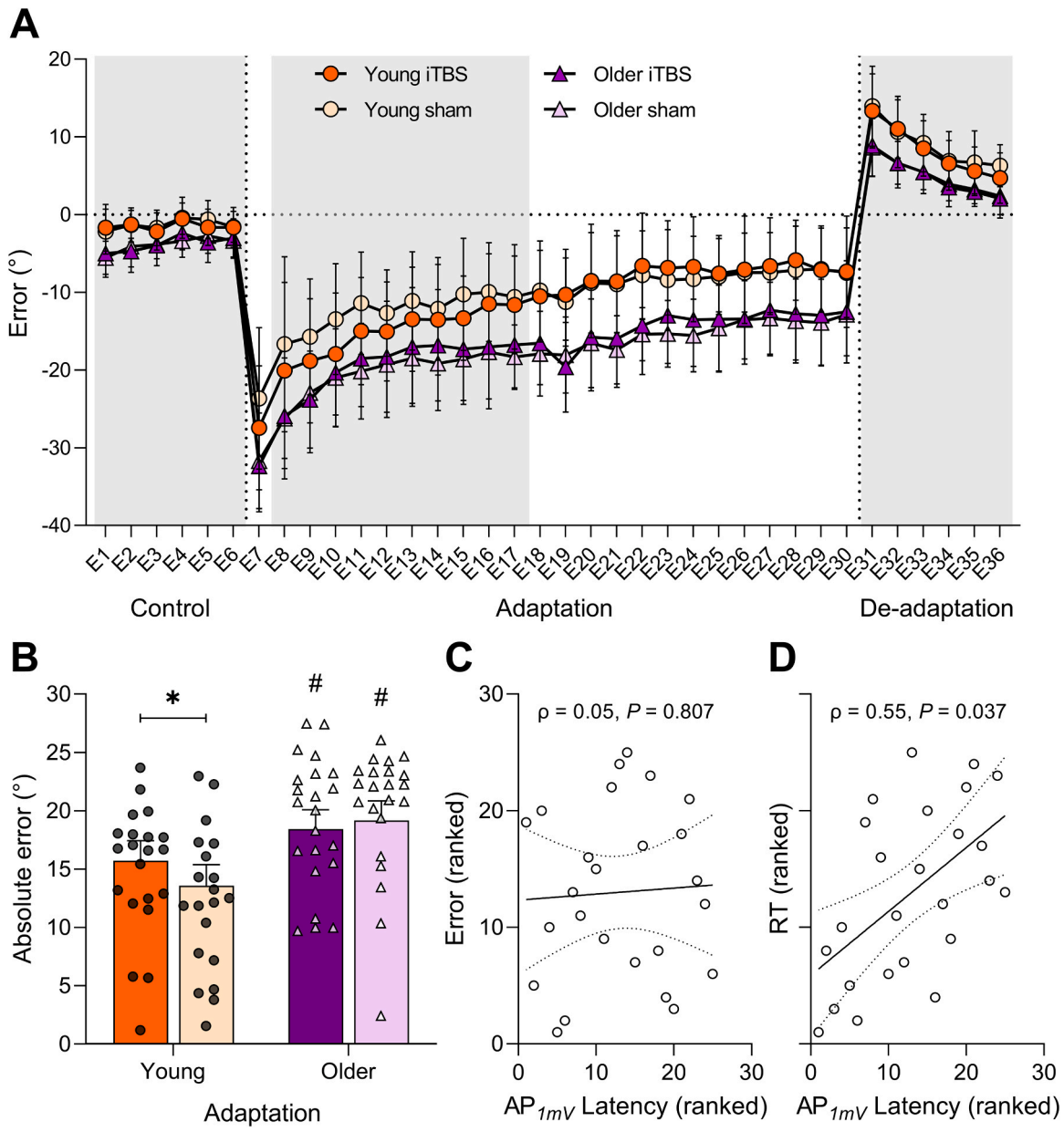

Fig. 4. (A) Cursor angle error during PMd iTBS (darker hue) and sham (lighter hue) sessions at control, adaptation, and de-adaptation for young (orange circles) and older (purple triangles) adults. Grey region denotes analysed data. (B) Cursor angle error during adaptation (epochs 8–17) following PMd iTBS and sham sessions for young and older adults. Ranked baseline $AP_{1\ mV}$ latencies and ranked error (C) and RT (D) during adaptation. Data are presented as (A) mean ± SD or (B) EMMs [95 % CI] with individual participants means for young (black circles) and older (white triangles) adults. *$P < 0.05$. #$P < 0.05$ compared to young.

amplitude (compared to 1 mV) has been shown to produce shorter latencies for $PA_{0.5\ mV}$ compared to $AP_{0.5\ mV}$ (Liao et al., 2022), consistent with the view that PA TMS preferentially recruits early I-waves, whereas AP TMS preferentially recruits late I-waves (Di Lazzaro et al., 2001; Hamada et al., 2013; Ni et al., 2010; Sakai et al., 1997). We also found shorter PA latencies compared to AP latencies in the present study, which suggests that the potentiation of PA and AP MEPs following PMd iTBS reflect a general influence of PMd on M1 I-wave circuits (W-Y. Liao et al., 2023). In addition, $AP_{1\ mV}$ showed shorter latencies compared to $AP_{0.5\ mV}$, suggesting that increasing the stimulation intensities for AP TMS may recruit early I-waves, as previously reported (Di Lazzaro et al., 2001). While this difference was not observed for $PA_{1\ mV}$ and $PA_{0.5\ mV}$, which we have found previously (Liao et al., 2022), these findings support the view that lowering stimulation intensities when assessing corticospinal excitability can improve preferential recruitment of different I-waves, particularly for late I-waves.

Although the present findings suggest that PMd iTBS can increase M1 excitability, there are some inconsistencies compared to previous work. For example, we have shown previously that changes in M1 excitability can persist from 5 to 40 min post-intervention (W-Y. Liao et al., 2023), whereas the increase in M1 excitability for $AP_{1\ mV}$, $PA_{0.5\ mV}$, and $AP_{0.5\ mV}$ within the present study was limited to 5-minutes post-intervention. These discrepancies may be related to the influence of VAT on MEP facilitation, as muscle activation is known to alter M1 neuroplasticity (Goldsworthy et al., 2015; Huang et al., 2008; Thirugnanasambandam et al., 2011). In addition, previous work has shown peak facilitation of $PA_{1\ mV}$ 15 min following PMd iTBS (Meng et al., 2020), whereas the present findings show persistent facilitation up to 65 min following the intervention. This effect may have been driven by the non-significant reduction in $PA_{1\ mV}$ following sham, as post-PMd iTBS MEP amplitude (during post-adaptation and post-de-adaptation) were not different compared to pre-intervention responses. Alternatively, brain-derived

neurotrophic factor (BDNF) polymorphisms have been reported to influence the time course of M1 continuous TBS (cTBS) aftereffects (Jannati et al., 2017). These differences in genetics may also influence PMd iTBS aftereffects, but this will need be investigated in future studies.

Furthermore, we have previously reported age-related differences in MEP facilitation following PMd iTBS (W-Y. Liao et al., 2023). Specifically, there was a time course delay in $AP_{1\,mV}$ facilitation and no $PA_{0.5\,mV}$ facilitation in older adults, which was speculated to reflect indirect and direct age-related changes in the early I-waves circuits that could be recruited by PA and AP TMS (W-Y. Liao et al., 2023; Opie & Semmler, 2021). However, these results were not replicated in the present study, which suggests that the response to PMd iTBS varies among the older population. Unfortunately, the present experimental protocol assessed M1 excitability at only one post-iTBS time point before visuomotor adaptation. While this was a deliberate decision to capture the effects of PMd iTBS on performance within a timely manner, we were unable to comprehensively assess the time course of M1 excitability, which may have limited the age-related effects that were reported previously (W-Y. Liao et al., 2023). Alternatively, we also cannot exclude the potential effects of participant factors (Semmler et al., 2021) such as genetics, pharmacology, aerobic exercise, mental alertness, and diet that are known to influence cortical plasticity (Phillips, 2017; Ridding & Ziemann, 2010). As these factors were not investigated in the present study, it will be important to characterise their involvement in future studies. Despite this, the present findings demonstrate that PMd iTBS potentiates M1 excitability assessed with both PA and AP TMS in young and older adults.

4.2. PMd influence on visuomotor adaptation in young and older adults

The present study provides new evidence that applying iTBS over PMd attenuates visuomotor adaptation in young adults. While we initially expected PMd iTBS to enhance visuomotor behaviour, this finding largely complements previous TMS studies assessing the functional role of PMd. For example, application of single-pulse TMS over PMd modulates online visuomotor adaptation, suggesting that PMd is involved in the correction of visuomotor control (Lee & van Donkelaar, 2006; Sugiyama et al., 2022). Application of cTBS over PMd has also been shown to disrupt visually-guided motor training, which suggests an integrative role of PMd for visual and motor information (Nowak et al., 2009; Parikh & Santello, 2017; Platz et al., 2012). In particular, while PMd cTBS and iTBS are expected to have opposite effects on M1 excitability, PMd is known to have both excitatory and inhibitory projections (Koch et al., 2007) whose activity are sensitive during movement preparation and execution (Beck et al., 2009; Koch et al., 2006). Therefore, disruption of this excitatory/inhibitory balance via cTBS or iTBS may produce the same attenuating effect. It is also possible that PMd function is optimal for young adults, which may have resulted in performance ceiling effects that could not be boosted by iTBS.

The present behavioural findings in young adults are also complemented by previous functional magnetic resonance imaging (fMRI) studies. For example, a previous fMRI study has estimated the directional selectivity of PMd and found that activation of PMd in a specific direction matches the actual movement direction (as opposed to cursor movement) during visuomotor adaptation, suggesting that PMd encodes the intended movement (i.e., the movement plan) (Haar et al., 2015). Taken together, these lines of TMS and functional imaging evidence suggest that iTBS may have disrupted the ability of PMd to correct the intended movement of the hand during early visuomotor adaptation in young adults. Importantly, the present findings are unlikely to be confounded by performance improvement during the second experimental session, as we randomised the intervention order and included an interference block (with opposite 30° clockwise rotation) at the end of each session. This latter approach has been shown to disrupt motor memory consolidation (Krakauer et al., 2005), and is supported by our findings showing no difference in error between the first and second session.

Although PMd iTBS attenuated early visuomotor adaptation in young adults, the mechanisms underpinning this effect are unclear. Previous fMRI studies have revealed that PMd is active during early adaptation, a process that was correlated with changes in cerebellar (CB) activity (Tzvi et al., 2020). It was thought that weakened inhibitory output from CB Purkinje cells led to increased activation of PMd during early adaptation (Tzvi et al., 2020). Indeed, the role of CB during adaptive visuomotor behaviour is well-documented within NIBS literature (Hamada et al., 2014; Jayaram et al., 2011; Schlerf et al., 2012), and recent TMS studies also support that CB may communicate with PMd (and M1 I-wave circuits) to modulate visuomotor behaviour (Spampinato et al., 2020). However, CB is also known to facilitate implicit learning processes, which can occur when the cursor perturbation occurs gradually or is small (Tzvi et al., 2022). In contrast, the present study used abrupt changes in adaptation and participants were informed of the shift in cursor movement beforehand, which likely created explicit awareness that is thought to specifically involve PMd (Kantak et al., 2012; Tzvi et al., 2022) and other prefrontal regions (Song et al., 2020). It is therefore possible that PMd iTBS disrupted the ability to implement explicit learning strategies during the early stages of visuomotor adaptation. We may further speculate a possible mechanism that involves homeostatic metaplasticity within M1 (Murakami et al., 2012). For example, the LTP-like effects produced by PMd iTBS (Meng et al., 2020) may have raised the threshold for subsequent neuroplastic changes within M1, which we have shown previously by priming M1 iTBS with PMd iTBS (Wei-Yeh Liao et al., 2024). It is possible that this effect attenuated the early stages of adaptation, but this will need to be verified in future studies.

While both age groups showed comparable performance at the end of adaptation, young adults reduced error scores faster than older adults, which is consistent with previous work (Buch et al., 2003; Fernández-Ruiz et al., 2000; Vachon et al., 2020). Importantly, PMd iTBS did not modulate visuomotor adaptation in older adults. This suggests that the influence of PMd during adaptation is weaker in older adults, which we initially thought may involve age-related differences in the late I-wave circuits (Opie et al., 2018; Opie et al., 2020). We therefore tested the relationship between PA and AP responses following PMd iTBS and error during adaptation, but found no correlation. Instead, there was a baseline age difference in MEP onset latency, but this likely reflects the slowing of nerve conduction velocity in older adults (Taylor, 1984). Interestingly, while MEP latencies were not related to adaptation error, there was a specific positive relationship between $AP_{1\,mV}$ latency and adaptation RT. As $AP_{1\,mV}$ produced shorter latencies compared to $AP_{0.5\,mV}$, this suggests that the additional recruitment of early I-waves may be related to RT, and appears to complement the previous finding that shorter AP latencies predict stronger premotor-M1 functional connectivity (Volz et al., 2015). In addition, a relationship between $AP_{1\,mV}$ latency and RT (but not error) suggests that these measures of performance may involve different processes. For example, explicit learning processes that improve error scores may reflect more cognitive processes (Fine & Hayden, 2022), whereas adaptation RT may involve specific contributions from M1 AP circuits. While this relationship will need to be verified in future research, we provide preliminary evidence that early I-waves recruited by AP TMS may be important for visuomotor adaptation.

Alternatively, the different age-related effects of PMd iTBS on visuomotor adaptation may stem from other sources. For example, it is well-documented that older adults tend to activate larger brain areas during task performance, which has been hypothesised to reflect a compensatory recruitment of resources to maintain function and counteract age-related deficits (Cabeza, 2002), which has been observed during visuomotor adaptation in older adults compared to young adults (Langan & Seidler, 2011). It is therefore possible that increased recruitment of different cortical regions in older adults during adaptation resulted in redundancies in brain activation that were able to limit

the effects of iTBS on a weaker contribution of left PMd to visuomotor adaptation. Furthermore, we cannot exclude the possibility of a floor effect of iTBS in older adults, in whom there is a decline in explicit learning (Heuer & Hegele, 2008; Vandevoorde & Orban de Xivry, 2019). Finally, it is also possible that visuomotor adaptation is influenced by other nodes of the motor network that are independent of PMd and may be different in young and older adults. For example, plasticity inducing NIBS over CB or M1 in older adults has been shown to enhance visuomotor adaptation to similar extents as young adults (Hardwick & Celnik, 2014; Panouillères et al., 2015), and it is known that CB-M1 connections can be independent of the premotor areas (Opie et al., 2022; Spampinato et al., 2020). Therefore, it will be important in future studies to characterise these complex interactions and explore alternative methods that enhance PMd activity to improve functional outcomes in older adults, which may include cortico-cortical paired associative stimulation (ccPAS) (Turrini et al., 2023) or modifying the intensity or frequency of iTBS (Goldsworthy et al., 2012).

In conclusion, the present findings provide insight into how PMd physiologically coordinates complex pathways within the motor system, and how these processes are modified with ageing. We found that PMd iTBS attenuated visuomotor adaptation specifically in young, but not older adults, which suggests an age-related change in the role of PMd on visuomotor adaptation. PMd iTBS also potentiated M1 excitability in young and older adults, with late I-waves related to aspects of visuomotor adaptation. These findings may be useful in clinical settings such as stroke, where there is substantial PMd reorganisation to support weakened motor function (Bestmann et al., 2010), and enhancement of PMd activity can improve functional outcomes in severely affected patients (Sankarasubramanian et al., 2017). It will therefore be useful in future studies to further characterise the connectivity within the broader motor system that underpins visuomotor adaptation and develop therapeutic interventions that can enhance visuomotor function in older and clinical populations.

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CRediT authorship contribution statement

John G. Semmler: Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Ulf Ziemann:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **George M. Opie:** Writing – review & editing, Supervision, Software, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Wei-Yeh Liao:** Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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.

Data Availability

Data from this study will be made available to qualified investigators upon reasonable request to the corresponding author.

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Verification

Data from this study has not been published elsewhere, and this paper is not under consideration for publication elsewhere. The publication has been approved by all authors.

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