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RESEARCH REPORT

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The effects of intermittent theta burst stimulation over dorsal premotor cortex on primary motor cortex plasticity in young and older adults

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Abstract

Previous transcranial magnetic stimulation (TMS) research suggests that the dorsal premotor cortex (PMd) influences neuroplasticity within the primary motor cortex (M1) through indirect (I) wave interneuronal circuits. However, it is unclear how the influence of PMd on the plasticity of M1 I-waves changes with advancing age. This study therefore investigated the neuroplastic effects of intermittent theta burst stimulation (iTBS) to M1 early and late I-wave circuits when preceded by iTBS (PMd iTBS-M1 iTBS) or sham stimulation (PMd sham-M1 iTBS) to PMd in 15 young and 16 older adults. M1 excitability was assessed with motor evoked potentials (MEP) recorded from the right first dorsal interosseous using posterior–anterior (PA) and anterior–posterior (AP) current TMS at standard stimulation intensities (PA_{1mV}, AP_{1mV}) and reduced stimulation intensities ($PA_{0.5mV}$, early I-waves; $AP_{0.5mV}$, late I-waves). PMd iTBS-M1 iTBS lowered the expected facilitation of $PA_{0.5mV}$ (to M1 iTBS) in young and older adults ($P = 0.009$), whereas the intervention had no effect on $AP_{0.5mV}$ facilitation in either group ($P = 0.305$). The modulation of $PA_{0.5mV}$ following PMd iTBS-M1 iTBS may reflect a specific influence of PMd on different I-wave circuits that are involved in M1 plasticity within young and older adults.

KEYWORDS
ageing, dorsal premotor cortex, neuroplasticity, transcranial magnetic stimulation

1 | INTRODUCTION

One of the universal effects of ageing is widespread deficits in motor function. Although these deficits occur at all levels of the motor system, the structural, functional and biochemical changes within the brain are important (Seidler et al., 2010). In particular, alterations to the ability of the brain's motor system to continuously modify its

Abbreviations: AMT, active motor threshold; AP, anterior–posterior; cTBS, continuous theta burst stimulation; D-wave, direct wave; FDI, first dorsal interosseous; iTBS, intermittent theta burst stimulation; I-wave, indirect wave; LM, lateral-medial; M1, primary motor cortex; MEP, motor evoked potential; PA, posterior–anterior; PMd, dorsal premotor cortex; RMT, resting motor threshold; TMS, transcranial magnetic stimulation.

structure and function are a critical factor. Termed neuroplasticity, this process is initially mediated by changes in the strength of synaptic communication with long-term potentiation (LTP) and depression (LTD) and underpins the ability to learn new motor skills (Buonomano & Merzenich, 1998; Sanes & Donoghue, 2000). While the capacity for neuroplastic change is present across the lifespan, some studies using non-invasive brain stimulation (NIBS) show reduced plasticity in older adults (Fathi et al., 2010; Freitas et al., 2011; Müller-Dahlhaus et al., 2008; Todd et al., 2010). This reduced plasticity may contribute to the motor deficits that limit the ability of older adults to learn or modify motor skills that may be essential for daily life. However, the neurophysiological mechanisms underpinning these changes with advancing age remain unclear.

Transcranial magnetic stimulation (TMS) is a type of NIBS that allows the investigation of specific neuronal networks within the motor system with high temporal resolution. Application of TMS over the primary motor cortex (M1) produces a complex series of descending volleys within corticospinal neurons that summate at the spinal cord, resulting in a motor-evoked potential (MEP) in targeted muscles (Di Lazzaro et al., 1998; Rossini et al., 2015). The first of these waves likely represents the direct activation of corticospinal neurons, whereas subsequent waves are thought to reflect the indirect activation of interneuronal inputs to the corticospinal neurons (Di Lazzaro et al., 2012; Ziemann, 2020). These responses are referred to as indirect (I) waves and are named early (I_1) or late (I_2, I_3) based on the order of their appearance, which occurs with a periodicity of ~1.5 ms (Di Lazzaro et al., 2012; Ziemann, 2020). Early and late I-waves can be preferentially recruited by applying low-intensity single-pulse TMS with different current directions (Di Lazzaro et al., 2001; Ni et al., 2010; Sakai et al., 1997). For example, a posterior–anterior (PA) current (relative to the central sulcus) preferentially recruits early I-waves, whereas an anterior–posterior (AP) current preferentially recruits late I-waves (Di Lazzaro et al., 2001; Ni et al., 2010; Sakai et al., 1997). Using these measures, previous work has shown that the ability to recruit late I-waves predicts the response to plasticity-inducing TMS paradigms over M1 (Hamada et al., 2013; Wiethoff et al., 2014) and that the late I-waves are behaviourally relevant to the acquisition of fine motor skills (Hamada et al., 2014).

I-wave circuits are also involved in mediating the communication between other motor nodes and M1 (Casarotto et al., 2023; Groppa et al., 2012; Opie et al., 2022; Spampinato et al., 2020; Volz et al., 2015), which form a wider network that influences M1 plasticity and learning (Huang et al., 2018; Liao et al., 2022). In particular, the dorsal premotor cortex (PMd) facilitates the planning, prediction and correction of movements during motor learning by updating the activity of M1 (Chouinard et al., 2005; Nowak et al., 2009; Parikh & Santello, 2017). Previous studies have demonstrated that the application of repetitive TMS (rTMS) techniques (such as theta burst stimulation; TBS) over PMd has been reported to modify M1 excitability, plasticity and motor skill acquisition (Huang et al., 2018; Meng et al., 2020). Furthermore, while PMd influences both early and late I-wave excitability (Liao et al., 2023), there is a stronger effect of premotor areas on late I-waves (Aberra et al., 2020; Volz et al., 2015). Taken together, it is likely that the influence of late I-waves on M1 plasticity reflects inputs from PMd.

Given the role of late I-wave circuits in mediating PMd-M1 communication, changes in late I-wave activity may affect the influence of PMd on M1 plasticity. In particular, late I-wave activity is known to be altered with advancing age (Opie et al., 2018). Age-related changes in I-wave excitability have been investigated using the paired-pulse TMS protocol short intracortical facilitation (SICF) (Opie et al., 2018), which revealed reduced I-wave excitability and a specific delay in the temporal characteristics of the late I-waves in older adults (Opie et al., 2018). Importantly, this delay influences NIBS-induced plasticity and is associated with specific aspects of motor behaviour in older adults (Opie et al., 2018, 2020). In addition, it is also known that PMd-M1 effective connectivity (Ni et al., 2015) and direct PMd modulation of early I-waves within M1 is reduced in older adults (Liao et al., 2023). Consequently, it is possible that the influence of PMd on M1 plasticity is altered with advancing age, but this remains to be tested.

The purpose of the present study was, therefore, to investigate the influence of PMd on the plasticity of early and late I-wave circuits in M1 of young and older adults. Given that previous work has used TBS to modulate M1 plasticity in young adults (Huang et al., 2018), we applied intermittent TBS (iTBS) over PMd in young and older participants and assessed how this influenced the neuroplastic response of M1 to iTBS. Different I-wave circuits were assessed by varying the direction of current used to apply TMS over M1. In particular, we applied PA and AP TMS at two stimulation intensities: the standard intensity that is known to result in mixed recruitment of early and late I-waves, and a relatively lower intensity that is more selective to early (PA) or late (AP) I-waves (Di Lazzaro et al., 2001; Liao et al., 2022). Although we expected iTBS over PMd to selectively modulate the plasticity of late I-wave circuits, we hypothesised that the effect of PMd on M1 plasticity would be weaker in older adults, given the likely alterations in late I-wave activity and PMd-M1 connectivity with advancing age.

2 | MATERIALS AND METHODS

2.1 | Sample size and participants

Sample size for the present study was determined using simulation-based power estimations on Rstudio (version 2023.12.1 + 402) (Team, 2015) using 'lme4' (Bates et al., 2015) and 'simr' (Green & MacLeod, 2016) packages. Our previous work assessing the effects of PMd iTBS on M1 excitability in young and older adults (Liao et al., 2023) revealed a fixed effects coefficient of −0.349 for the intervention that was used as an unstandardised measure of effect size (Green & MacLeod, 2016). This value was lowered by 15% (−0.297) to account for biases in power calculations derived from experimental data (Green & MacLeod, 2016) and revealed a required sample size of 25 total participants to observe a small to moderate effect of PMd iTBS on M1 excitability, given $\alpha = 0.05$ and $1 - \beta = 0.9$. We increased this to 30 total participants to account for dropouts.

Fifteen young (mean ± standard deviation, 24.7 ± 5.0 years, 12 females; range, 19–36 years) and 16 older adults (67.0 ± 5.3 years; 61–78 years, 10 females) were recruited for the study via advertisements placed on notice boards within The University of Adelaide and the wider community, in addition to social media platforms. Applicants for the study were excluded if they had a history of psychiatric or neurological disease, current use of medication that affects the central nervous system, pregnancy, metal implants or left-handedness, as assessed by a standard TMS screening questionnaire (Rossi et al., 2011). 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). Subjects provided written, informed consent prior to participation.

2.2 | Experimental arrangement

All participants attended two experimental sessions where iTBS or sham iTBS was applied to PMd, followed 30 minutes later by plasticity induction within M1 via iTBS (PMd iTBS-M1 iTBS, PMd sham-M1 iTBS), totalling a ∼ 3-hour experimental period each session in a single-blind study design. This follows a previously reported protocol that investigated the modulatory effects of PMd continuous TBS (cTBS) on M1 iTBS and cTBS aftereffects (Huang et al., 2018). The same experimental protocol was used in both sessions (Figure 1), with the order of intervention randomised between participants, and a washout period of at least 1 week between sessions. As the time of day is known to predict iTBS-induced plasticity (Corp et al., 2020), likely due to diurnal variations in cortisol (Sale et al., 2008), all sessions were completed between 11 am and 5 pm at approximately the same time of day for each participant. All de-identified data and used scripts are openly available via the repository Figshare (https://doi.org/10.25909/25241791).

During each experimental session, participants were seated in a comfortable chair with their hands resting and relaxed. Surface electromyography (EMG) was recorded from the first dorsal interosseous (FDI) of the right hand using two Ag-AgCl electrodes arranged in a belly-tendon montage on the skin above the muscle, with a third electrode attached above the styloid process of the right ulnar used to ground the electrodes. Electrode placement over FDI was assessed via EMG signals on an oscilloscope. 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)

A branding iron coil connected to two Magstim 200^2 magnetic stimulators (Magstim, Whitland, UK) via a BiStim unit was used to apply TMS to the left M1. The coil was held tangentially to the scalp at an angle of 45° to the sagittal plane, inducing a PA current relative to the central sulcus. We identified the M1 hotspot by applying TMS at suprathreshold intensities to observe the location that produced the largest and most consistent MEPs within the relaxed FDI muscle of the right hand (Rossini et al., 2015), in addition to a visible twitch of the right FDI. This location was marked on the scalp for reference and continuously monitored throughout each experimental session. All baseline, post-PMd iTBS and post-M1 iTBS (5 minutes, 30 minutes) TMS was applied at a rate of 0.2 Hz, with a 10% jitter between trials to avoid anticipation of the stimulus.

Resting motor threshold (RMT) was recorded as the lowest stimulus intensity producing an MEP amplitude ≥ 50 μV in at least 5 out of 10 trials during relaxation of the right FDI. RMT was assessed at the beginning of each

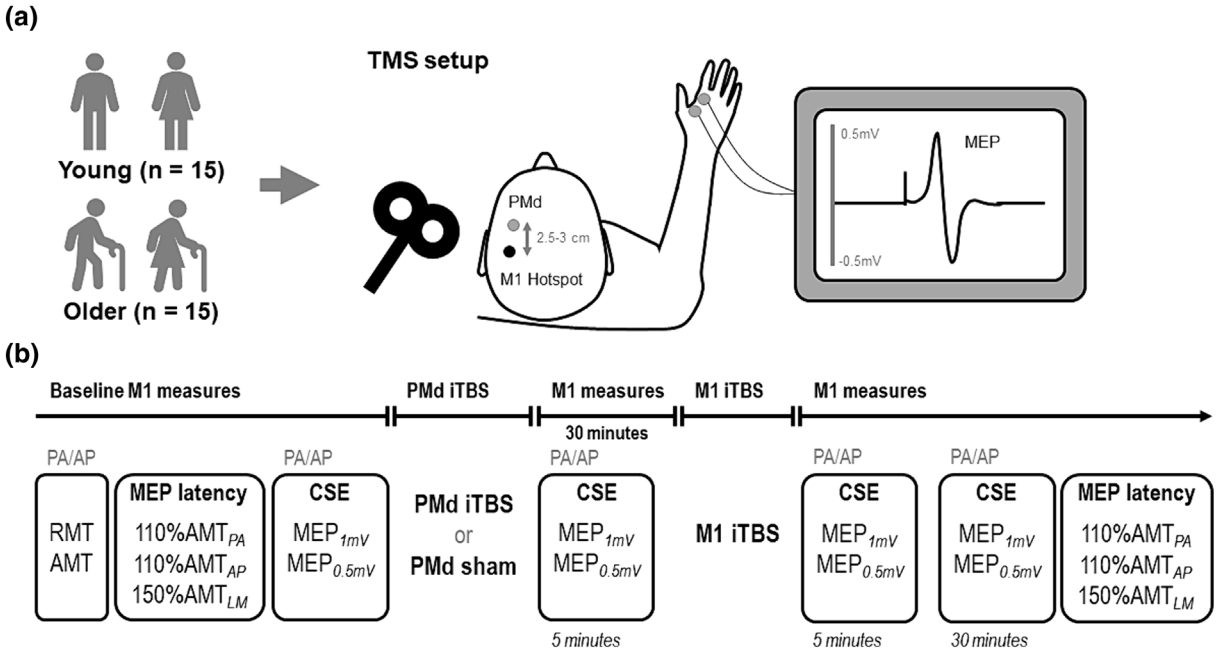

FIGURE 1 (a) Subject sample and experimental setup. (b) Experimental procedure. PA, posterior-to-anterior; AP, anterior-to-posterior; LM, lateral-to-medial; RMT, resting motor threshold; AMT, active motor threshold; MEP_{1mV}, standard MEP of ~ 1 mV at baseline; $MEP_{0.5mV}$, MEP of ~ 0.5 mV at baseline; PMd, dorsal premotor cortex; iTBS, intermittent theta burst stimulation; CSE, corticospinal excitability.

experimental session and expressed as a percentage of maximum stimulator output (% MSO) (Rossini et al., 2015). Active motor threshold (AMT) was then assessed, defined as the lowest % MSO producing an MEP amplitude ≥ 200 μV in at least 5 out of 10 trials during concurrent low-level activation (~10% voluntary activation) of the right FDI (Hamada et al., 2013). These measures were then repeated using the AP current by rotating the coil 180°. Then, the stimulus intensities producing a standard MEP amplitude approximating 1 mV (MEP_{1mV}) recorded using PA (PA_{1mV}) and AP (AP_{1mV}) TMS currents, in addition to an MEP amplitude approximating 0.5 mV ($MEP_{0.5mV}$) record using PA ($PA_{0.5mV}$) and AP ($AP_{0.5mV}$) currents, when averaged over 20 trials, were identified. The same intensities (PA_{1mV}; AP_{1mV}, $PA_{0.5mV}$, $AP_{0.5mV}$) were then applied following PMd iTBS and following M1 iTBS to assess changes in corticospinal excitability.

2.3.2 | I-wave recruitment

To investigate the ability to recruit I-waves, the onset latencies of PA (early) and AP (late) MEPs were assessed relative to the MEP onset generated by direct activation of corticospinal neurons using a lateral-to-medial (LM) current (Hamada et al., 2013). A block of 15 MEP trials in the active FDI was recorded for 110% of PA and AP AMT (PA_{AMT}, AP_{AMT}), in addition to 150% LM AMT (LM_{AMT}) (Hamada et al., 2013). If 150% LM_{AMT} exceeded 100% MSO, 100% MSO was used, or if 150% LM_{AMT} was below 50% MSO, 50% MSO was used (Hamada et al., 2013) (see Results, Table 1). The difference in onset latencies between PA and LM (PA-LM) and AP and LM (AP-LM) were calculated as measures of early and late I-wave recruitment efficiency, respectively, in line with previous work (Hamada et al., 2013). In an attempt to reduce the confounding influence of muscle contraction on neuroplasticity induction (Goldsworthy et al., 2015; Huang et al., 2008; Thirugnanasambandam et al., 2011), these measures were recorded at the start and at the end of the experimental session, at least 45 minutes apart from the plasticity induction of PMd and M1.

2.3.3 | Theta burst stimulation (TBS)

Intermittent theta burst stimulation (iTBS) was delivered over left PMd and left M1 using a Magstim Super-rapid stimulator (Magstim, Whitland, UK), connected to an air-cooled figure-of-eight coil. 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). In accordance with existing literature, iTBS consisted of bursts of

TABLE 1 Baseline TMS intensities between sessions for young and older adults.

	Young		Older	
Measure	**PMd iTBS-M1 iTBS**	**PMd sham-M1 iTBS**	**PMd iTBS-M1 iTBS**	**PMd sham-M1 iTBS**
Resting				
PA_{RMT} (% MSO) ($n = 31$)	47.3 [42.4, 52.2]	47.8 [42.9, 52.7]	50.3 [45.6, 55.1]	51.3 [46.5, 56.1]
AP_{RMT} (% MSO) ($n = 30$)	60.4 [55.1, 66.1]	61.2 [55.9, 67.1]	65.3 [59.6, 71.6]	64.0 [58.4, 70.2]
$Rapid_{RMT}$ (% MSO) ($n = 31$)	55.0 [50.5, 59.9]	56.9 [52.3, 62.0]	56.8 [52.3, 61.7]	57.2 [52.6, 62.1]
PA_{1mV} (% MSO) ($n = 30$)	58.4 [56.5, 60.2]	57.8 [56.0, 60.0]	61.2 [59.3, 63.2]	59.1 [57.2, 61.0]
AP_{1mV} (% MSO) ($n = 26$)	75.3 [73.3, 77.3]	74.3 [72.4, 76.4]	76.4 [74.2, 78.7]	76.9 [74.6, 79.2]
$PA_{0.5mV}$ (% MSO) ($n = 31$)	54.3 [51.4, 57.4]	54.0 [51.1, 57.0]	58.5 [55.5, 61.7]	57.0 [54.0, 60.2]
$AP_{0.5mV}$ (% MSO) ($n = 29$)	71.7 [68.5, 75.1]	70.5 [67.3, 73.8]	75.8 [72.3, 79.5]	74.2 [70.7, 77.9]
Active				
PA_{AMT} (% MSO) ($n = 31$)	39.4 [35.9, 43.3]	38.9 [35.4, 42.7]	42.0 [38.3, 46.0]	42.4 [38.7, 46.5]
AP_{AMT} (% MSO) ($n = 31$)	53.4 [48.8, 58.5]	53.3 [48.6, 58.4]	58.2 [53.3, 63.5]	56.1 [51.3, 61.3]
LM_{AMT} (% MSO) ($n = 31$)	44.6 [40.3, 49.4]	44.6 [40.3, 49.3]	49.6 [45.0, 54.7]	48.1 [43.5, 53.2]

Note: Data show EMM [95% CI; lower, upper].

three pulses given at a frequency of 50 Hz. Each burst was repeated at 5 Hz for 2 s, and repeated every 8 s for 20 cycles, totalling 600 pulses (Huang et al., 2005). The location of left PMd was defined as 8% of the distance between the nasion and inion (approximately 2.5–3 cm) anterior to the M1 hotspot, consistent with previous work (Huang et al., 2018; Koch et al., 2007; Meng et al., 2020; Münchau et al., 2002). The location of both the M1 hotspot and left PMd site was logged relative to the MNI-ICBM152 template using Brainsight neuronavigation (Rogue Research, Montreal, Quebec, Canada). These locations were then used to guide the assessment of RMT ($Rapid_{RMT}$) over M1 with the Magstim Super-rapid stimulator, in addition to the application of iTBS over left PMd and M1 at 70% $Rapid_{RMT}$.

Sham iTBS to left PMd was delivered using a sham figure-of-eight coil to replicate the TMS click (70 mm diameter, placebo coil PN 3285–00, Magstim, Whitland, UK), with a bar electrode connected to a constant current stimulator (Digitimer, Hertfordshire, UK) placed underneath the coil delivering electrical stimulation (1.5 mA) to the scalp in order to mimic the pulse sensation. Following either intervention, participants provided answers to a visual analogue scale (VAS) questionnaire indexing the degree of discomfort, muscle activation and localisation of scalp sensation during PMd iTBS for the assessment of participant blinding.

2.4 | Data analysis

Visual inspection of EMG data was completed offline, with any trials obtained from the resting muscle having EMG activity exceeding 25 μV in the 100 ms prior to stimulus application excluded from analysis (6.8% removed). The amplitude of MEPs obtained from resting muscle recordings was measured peak-to-peak and expressed in mV. Individual MEP trials throughout each experimental session were separated into blocks at baseline, post-PMd iTBS and post-M1 iTBS. In particular, we grouped MEP trials recorded 5 and 30 minutes following M1 iTBS into a single post-intervention time point, as MEP amplitude during these blocks did not vary (see Results). The MEP onset latencies obtained from active and resting muscle recordings were assessed with a semi-automated process using a custom script within the

Signal program (v 6.02, Cambridge Electronic Design) and expressed in ms. Trials unable to be assessed by the custom script due to artefact contamination were removed (17.0% removed). MEP latency was recorded as the period from stimulus application to the start of the MEP response. This was defined as the point at which post-stimulus EMG amplitude exceeded the mean EMG amplitude recorded within the 100 ms pre-stimulus, plus 2 standard deviations (Opie et al., 2018). The latencies obtained from active muscle recordings with PA or AP TMS were subtracted from the mean LM latency at the same time point to determine PA-LM and AP-LM MEP latency differences (ms) at baseline and post-intervention.

2.5 | Statistical analysis

All statistical analyses of present data were performed using IBM SPSS Statistics (IBM, version 29). Visual inspection and Kolmogorov–Smirnov tests of the data residuals revealed non-normal, positively skewed distributions for all TMS data. Consequently, all TMS data was analysed using generalised linear mixed models (GLMM) fitted using gamma distributions with log links (Lo & Andrews, 2015). Each model included single trial data and random participant effects (intercepts and slopes) (Barr et al., 2013), and model fit was assessed using the Bayesian Schwartz Criterion (BIC). Two-factor GLMMs were used to investigate the effects of session (PMd iTBS-M1 iTBS, PMd sham-M1 iTBS) and age group (young, older) on stimulation intensities for PA and AP coil orientations during assessment of RMT, AMT, MEP_{1mV} and $MEP_{0.5mV}$; LM coil orientations for AMT; and assessment of RMT_{Rapid}.

In addition, two-factor GLMMs were used to investigate the effects of session and age group on baseline MEP amplitude for PA_{1mV}, AP_{1mV}, $PA_{0.5mV}$ and $AP_{0.5mV}$, with TMS intensities used for each measure within each participant included as a covariate to control for inter-individual variations in stimulation intensity. A three-factor model was used to compare the effects of the session, age group and coil orientation (PA, AP) on baseline PA-LM and AP-LM latency differences. A four-factor model was used to compare the effects of session, age group, coil orientation and state (AMT, MEP_{1mV}, $MEP_{0.5mV}$) on baseline MEP latencies. The effects of the intervention on PA_{1mV}, AP_{1mV}, $PA_{0.5mV}$ and $AP_{0.5mV}$ were investigated using three-factor models comparing the effects of the session, age group and time point (baseline, post-PMd iTBS, post-M1 iTBS), with stimulation intensities used for each measure within each participant included as a covariate. In addition, as baseline MEP amplitude is known to influence post-iTBS MEP amplitude (Corp et al., 2020), the mean baseline MEP amplitude for each participant was included as a covariate.

The effects of PMd iTBS-M1 iTBS and PMd sham-M1 iTBS on PA-LM and AP-LM latency differences were investigated using a four-factor model comparing the effects of session, age group, time point (baseline, post-intervention) and coil orientation, with mean baseline PA-LM and AP-LM latency differences include as a covariate. For all models, *post-hoc* assessments of significant main effects and interactions were performed using custom contrasts with Bonferroni correction. Data for all models are presented as estimated marginal means (EMMs) and 95% confidence intervals (95% CI), whereas pairwise comparisons are presented as the estimated mean difference (EMD) and 95% CI for the estimate for an unstandardised measure of effect size. Differences in the perception of iTBS and sham iTBS were investigated by comparing VAS responses using paired t-tests with Bonferroni correction.

Finally, we used linear correlation analyses to assess the relationship between MEP latency differences and statistically significant changes in MEP amplitude that were observed following PMd iTBS or M1 iTBS (in isolation). In particular, we assessed whether the increase in $PA_{0.5mV}$ MEP amplitude following PMd iTBS (see Results, Figure 2c) was related to baseline PA-LM and AP-LM latency differences. In addition, as $PA_{0.5mV}$ and $AP_{0.5mV}$ increased following M1 iTBS (during PMd sham-M1 iTBS sessions; see Results, Figure 2c,d), we took the average MEP amplitude of $PA_{0.5mV}$ and $AP_{0.5mV}$ to reduce the number of comparisons and assessed whether this was related to baseline PA-LM and AP-LM latency differences, as undertaken previously (Hamada et al., 2013). For these models, young and older adults were included as a single group, given that no age-related differences were observed (see Results). Correlations are presented as Pearson's correlation coefficient (r). For all models, $P < 0.05$ was considered significant.

3 | RESULTS

Thirty participants completed both experimental sessions without adverse reactions. We were unable to record PA_{1mV} MEP amplitude in one older male participant, $AP_{0.5mV}$ MEP amplitude in two older participants (1 female, 1 male) and AP_{1mV} MEP amplitude in five participants (1 young female; 3 older females, 1 older male) due to high thresholds of activation (mean $PA_{RMT} = 80.0\%$ MSO, mean $AP_{RMT} = 73.0\%$ MSO). One older female participant withdrew after one session (PMd iTBS-M1 iTBS) due to personal reasons (not related to the study). We recorded 150% LM AMT stimulation

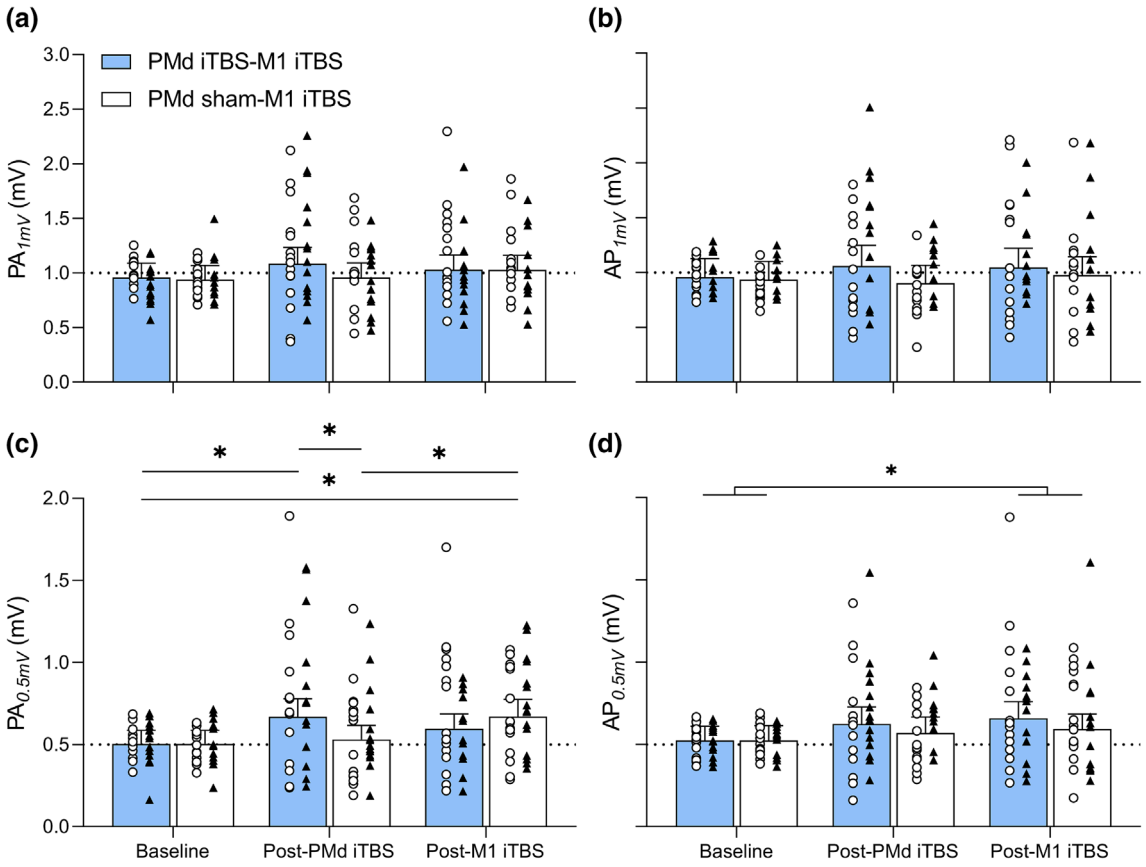

FIGURE 2 MEP amplitude (a, PA_{1mV}; b, AP_{1mV}; c, $PA_{0.5mV}$; d, $AP_{0.5mV}$) during PMd iTBS-M1 iTBS (blue) and PMd sham-M1 iTBS (white) sessions for all participants at baseline, post-PMd iTBS and post-M1 iTBS (collapsed 5- and 30-minutes post-intervention). Data are presented as EMM [95% CI] with individual participant means (young, white circles; older, black triangles). *$P < 0.05$.

intensities below 50% in one young male participant during the PMd iTBS-M1 iTBS session and above 100% in one older male participant during PMd sham-M1 iTBS session. We were unable to record PA_{1mV} and AP_{1mV} latencies in one older female, $PA_{0.5mV}$ latencies in two older participants (1 female) and $AP_{0.5mV}$ latencies in two participants (1 older female, 1 young female) due to stimulation artefacts.

Baseline stimulation intensities are presented in Table 1. There were no significant main effects or interactions for all stimulation intensities ($P > 0.05$). The baseline MEP amplitude for corticospinal excitability and MEP latencies are shown in Table 2. MEP latency differences varied between coil orientations ($F_{1,1529} = 134.51$, $P < 0.0001$), with *post-hoc* analysis revealing longer AP-LM latency differences relative to PA-LM latencies (EMD = 1.96 ms [1.54, 2.37], $P < 0.0001$), as expected. MEP latency differences also varied between age groups ($F_{1,1529} = 5.14$, $P = 0.024$), with older participants showing longer MEP latency differences compared to young (EMD = 0.63 ms [0.08, 1.18], $P = 0.025$). There was also an interaction between coil orientation and age group ($F_{1,1529} = 5.52$, $P = 0.019$) that revealed longer MEP PA-LM latency differences in older compared to young adults (EMD = 0.69 ms [0.24, 1.13], $P = 0.002$). AP-LM latency differences were consistently longer than PA-LM latencies in both young (EMD = 2.09 ms [1.52, 2.65], $P < 0.0001$) and older adults (EMD = 1.76 ms [1.15, 2.37], $P < 0.0001$).

In contrast, active and resting MEP latencies varied between states ($F_{2,4556} = 3.78$, $P = 0.023$), with shorter MEP_{1mV} latencies compared to $MEP_{0.5mV}$ (EMD = 0.33 ms [0.01, 0.65], $P = 0.043$) and AMT (EMD = 0.31 ms [0.01, 0.62], $P = 0.043$). MEP latencies also differed between age groups ($F_{1,4556} = 9.73$, $P = 0.002$), with longer latencies in older compared to young adults (EMD = 0.69 ms [0.26, 1.13], $P = 0.002$). In addition, MEP latencies varied between coil orientations ($F_{1,4556} = 202.11$, $P < 0.0001$), with longer AP latencies compared to PA (EMD = 1.72 ms [1.48, 1.96], $P < 0.0001$), as expected. There was also an interaction between state and coil orientation ($F_{2,4556} = 4.23$, $P = 0.015$), which revealed longer AP latencies compared to PA across all states (all $P < 0.0001$), and shorter AP_{1mV} latencies compared to $AP_{0.5mV}$ (EMD = 0.48 ms [0.12, 0.84], $P = 0.006$) and AP_{AMT} (EMD = 0.54 ms [0.17, 0.92], $P = 0.002$). There were no other significant main

TABLE 2 Baseline MEP amplitude and MEP latency differences between sessions for young and older adults.

	Young		Older	
Measure	**PMd iTBS-M1 iTBS**	**PMd sham-M1 iTBS**	**PMd iTBS-M1 iTBS**	**PMd sham-M1 iTBS**
MEP amplitude				
PA_{1mV} (mV) ($n = 30$)	1.02 [0.94, 1.11]	0.92 [0.85, 1.00]	0.91 [0.83, 0.99]	0.97 [0.89, 1.06]
AP_{1mV} (mV) ($n = 26$)	0.96 [0.87, 1.06]	0.87 [0.79, 0.96]	1.02 [0.91, 1.13]	0.99 [0.89, 1.11]
$PA_{0.5mV}$ (mV) ($n = 31$)	0.52 [0.45, 0.59]	0.48 [0.43, 0.55]	0.51 [0.45, 0.58]	0.53 [0.47 0.60]
$AP_{0.5mV}$ (mV) ($n = 29$)	0.53 [0.48, 0.59]	0.54 [0.48, 0.60]	0.52 [0.47, 0.59]	0.53 [0.47, 0.59]
MEP latency				
PA-LM latency (ms) ($n = 31$)	1.25 [1.01, 1.56]	1.35 [1.08, 1.68]	1.98 [1.60, 2.45][a]	1.99 [1.60, 2.47][a]
AP-LM latency (ms)[b] ($n = 31$)	3.32 [2.66, 4.13]	3.46 [2.78, 4.31]	3.60 [2.91, 4.46]	3.90 [3.13, 4.85]
PA_{AMT} (ms) ($n = 31$)	21.9 [21.6, 22.2]	22.1 [21.9, 22.3]	23.8 [23.5, 24.1][a]	24.5 [24.1, 24.8][a]
AP_{AMT} (ms)[b,c] ($n = 31$)	24.0 [23.7, 24.3]	24.1 [23.9, 24.4]	25.7 [25.4, 26.0][a]	26.4 [26.1, 26.8][a]
PA_{1mV} (ms) ($n = 28$)	21.9 [21.6, 22.1]	21.9 [21.7, 22.0]	23.9 [23.5, 24.2][a]	24.6 [24.2, 25.0][a]
AP_{1mV} (ms)[b] ($n = 25$)	23.2 [23.0, 23.5]	23.7 [23.4, 23.9]	25.1 [24.7, 25.6][a]	25.8 [25.2, 26.4][a]
$PA_{0.5mV}$ (ms) ($n = 30$)	22.0 [21.8, 22.2]	22.2 [22.0, 22.4]	24.0 [23.8, 24.3][a]	24.3 [23.9, 24.6][a]
$AP_{0.5mV}$ (ms)[b,c] ($n = 27$)	23.8 [23.5, 24.1]	24.0 [23.7, 24.2]	25.0 [24.6, 25.4][a]	26.5 [26.0, 27.0][a]

Note: Data show EMM [95% CI; lower, upper].
[a]$P < 0.05$ compared to young adults.
[b]$P < 0.05$ compared to the same PA latency measure.
[c]$P < 0.05$ compared to AP_{1mV} latency.

effects or interactions for baseline MEP amplitude and MEP latencies (all $P > 0.05$). Lastly, while MEP amplitude varied by time point throughout each experimental session ($F_{3,17,582} = 6.86$, $P < 0.0001$), *post-hoc* comparisons revealed that there were no differences between 5- and 30-minutes post-intervention (EMD = 0.05 mV [−0.05, 0.15], $P = 0.627$).

3.1 | Corticospinal excitability during PMd iTBS-M1 iTBS and PMd sham-M1 iTBS sessions

The participants' perceptions of PMd iTBS and PMd sham are shown in Table 3. While there were no differences between sessions in the extent of discomfort ($t_{29} = 0.25$, $P = 0.804$) or FDI activation ($t_{29} = 0.10$, $P = 0.918$) experienced by the participants, the locality of stimulation differed ($t_{29} = 3.98$, $P = 0.012$), with the sensation of iTBS perceived as more widespread relative to electrical scalp stimulation in sham. MEP amplitude during PMd iTBS-M1 iTBS and PMd sham-M1 iTBS sessions are presented in Figure 2, whereas baseline-normalised MEP amplitude is presented in Figure 3. PA_{1mV} MEP amplitude (Figure 2a) did not differ between sessions ($F_{1,4546} = 0.85$, $P = 0.356$), age groups ($F_{1,4546} = 0.85$, $P = 0.356$), or time points ($F_{2,4546} = 1.19$, $P = 0.305$), and there were no interactions between factors (all $P > 0.05$). Similarly, AP_{1mV} MEP amplitude (Figure 2b) did not vary between sessions ($F_{1,3928} = 1.46$, $P = 0.227$), age groups ($F_{1,3928} = 0.292$, $P = 0.589$) or time points ($F_{2,3928} = 0.43$, $P = 0.653$), and there were no interactions between factors (all $P > 0.05$).

In contrast, while $PA_{0.5mV}$ MEP amplitude did not differ between sessions ($F_{1,4700} = 0.41$, $P = 0.523$) or age

groups ($F_{1,4700} = 0.00$, $P = 0.971$), responses varied between time points ($F_{2,4700} = 6.11$, $P = 0.002$). *Post-hoc* comparisons revealed increased MEP amplitude following PMd iTBS (EMD = 0.09 mV [0.01, 0.18], $P = 0.033$) and M1 iTBS (EMD = 0.13 mV [0.04, 0.22], $P = 0.002$) relative to baseline. There was also an interaction between session and time point ($F_{2,4700} = 7.27$, $P = 0.001$), with *post-hoc* tests showing increased MEP amplitude following PMd iTBS compared to sham iTBS (EMD = 0.14 mV [0.04, 0.24], $P = 0.007$) and baseline (EMD = 0.17 mV [0.04, 0.29], $P = 0.003$). MEP amplitude during PMd sham-M1 iTBS session also increased following M1 iTBS compared to baseline (EMD = 0.17 mV [0.05, 0.28], $P = 0.002$) and PMd sham (EMD = 0.14 mV [0.03, 0.25], $P = 0.009$). There were no other interactions (all $P > 0.05$). Similarly, $AP_{0.5mV}$ MEP amplitude did not vary between sessions ($F_{1,4356} = 1.05$, $P = 0.305$) or age groups ($F_{1,4356} = 0.42$, $P = 0.518$), but differed between time points ($F_{2,4356} = 3.44$, $P = 0.032$), with increased MEP amplitude following M1 iTBS compared to baseline (EMD = 0.10 mV [0.01, 0.19], $P = 0.006$). There were no interactions between factors (all $P > 0.05$).

TABLE 3 Comparison of VAS responses (mean ± STD) between sessions.

Question	PMd iTBS-M1 iTBS	PMd sham-M1 iTBS
How uncomfortable were the TMS pulses (0, not uncomfortable at all; 10, highly uncomfortable)?	2.67 ± 2.60	2.5 ± 2.79
If there were any twitches in the right hand, how strong were they (0, no twitches; 10, very strong cramp)?	0.63 ± 1.40	0.60 ± 1.13
How localised were the sensations from TMS pulses (0, highly localised; 10, widespread)?	2.03 ± 2.47	0.50 ± 1.04*

Note: Data show mean ± standard deviation.
*$P < 0.05$ compared to iTBS.

3.2 | I-wave recruitment during PMd iTBS-M1 iTBS and PMd sham-M1 iTBS sessions

MEP latency differences did not differ between sessions ($F_{1,3063} = 0.00$, $P = 0.995$), age groups ($F_{1,3063} = 1.53$, $P = 0.216$) or time points ($F_{1,3063} = 0.01$, $P = 0.932$), but varied between coil orientations ($F_{1,3063} = 14.68$,

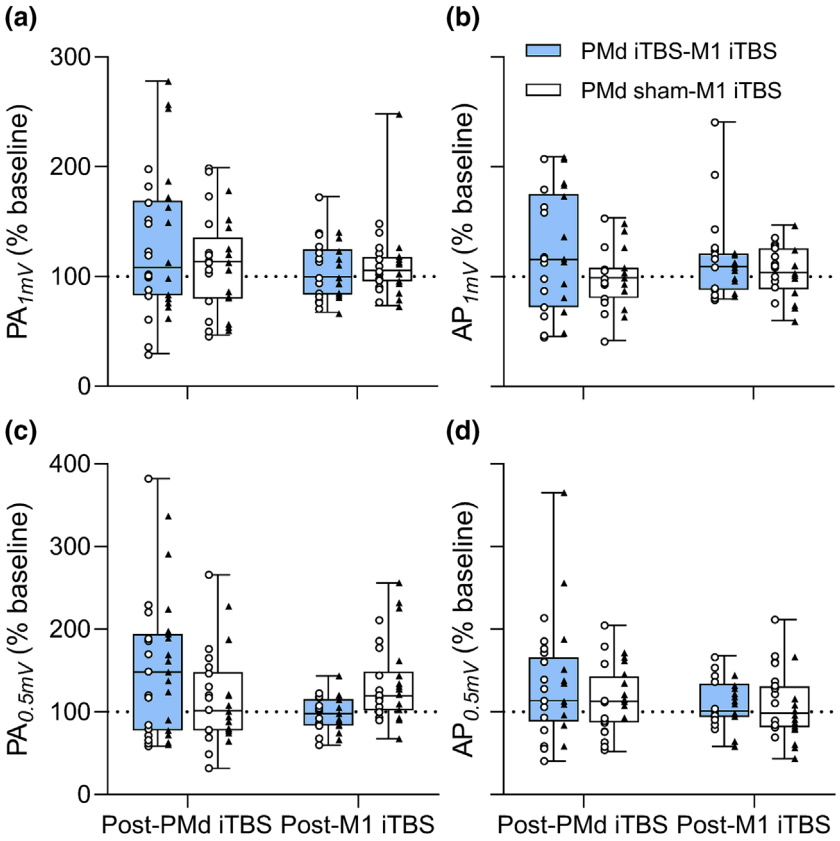

FIGURE 3 Baseline-normalised MEP amplitude (a, PA_{1mV}; b, AP_{1mV}; c, $PA_{0.5mV}$; d, $AP_{0.5mV}$) during PMd iTBS-M1 iTBS (blue) and PMd sham-M1 iTBS (white) sessions for all participants post-PMd iTBS and post-M1 iTBS (collapsed 5- and 30-minutes post-intervention). Data are presented as median [min, 25th percentile, 75th percentile, max] with individual participant means (young, white circles; older, black triangles).

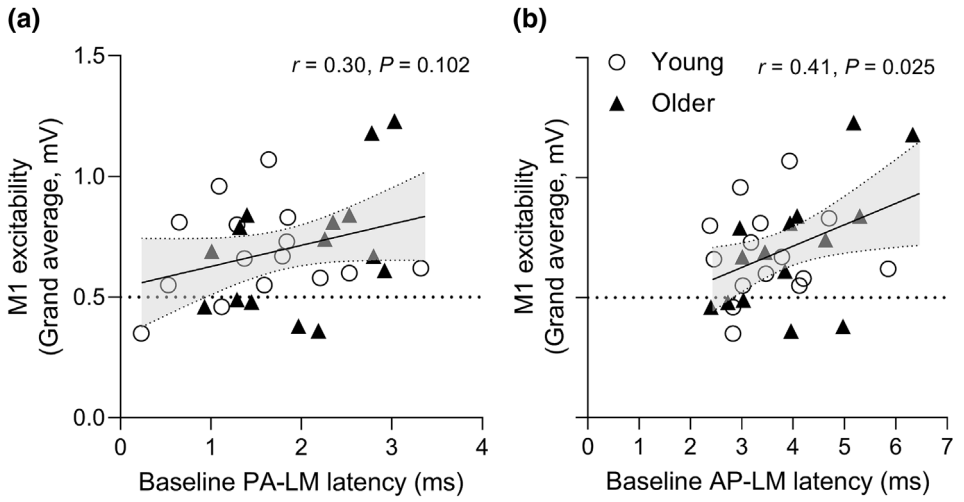

FIGURE 4 Correlation between baseline PA-LM latency difference (a) and AP-LM latency difference (b) and M1 excitability (grand average of $PA_{0.5mV}$ and $AP_{0.5mV}$) following M1 iTBS (PMd sham-M1 iTBS) in all participants (young, white circles; older, black triangles). Correlation presented as Pearson's correlation coefficient [95% CI].

$P < 0.0001$), with longer AP-LM latencies compared to PA-LM latencies (EMD = 0.64 ms [0.31, 0.97], $P < 0.0001$), as expected. There were no interactions between factors (all $P > 0.05$). Furthermore, baseline PA-LM ($r = 0.07$, $P = 0.730$) and AP-LM ($r = -0.05$, $P = 0.785$) latency differences were not related to $PA_{0.5mV}$ following PMd iTBS. In contrast, while PA-LM latencies were not related to M1 excitability ($r = 0.30$, $P = 0.102$; Figure 4a), longer AP-LM latencies were correlated with increased M1 excitability following M1 iTBS ($r = 0.41$, $P = 0.025$; Figure 4b).

4 | DISCUSSION

In the present study, we investigated whether the influence of PMd on the plasticity of M1 I-waves is different in young and older adults. This was achieved by applying PMd iTBS as a priming intervention to modify the neuroplastic response of M1 to subsequent iTBS (PMd iTBS-M1 iTBS, PMd sham-M1 iTBS). We measured changes in corticospinal excitability (PA_{1mV}, AP_{1mV}, $PA_{0.5mV}$, $AP_{0.5mV}$) and I-wave recruitment (PA-LM latency, AP-LM latency) following the intervention. The findings demonstrated that PMd iTBS lowered the response of $PA_{0.5mV}$ to M1 iTBS, whereas $AP_{0.5mV}$ was potentiated following M1 iTBS in both sessions. Importantly, these findings were not different between young and older adults.

4.1 | PMd iTBS and M1 excitability

Previous work from our group (Liao et al., 2023) and others (Meng et al., 2020) have reported that the application of iTBS to PMd broadly increases M1 excitability in young adults. This effect is thought to stem from the induction of LTP-like effects within PMd (Meng et al., 2020), resulting in increased excitability within M1 when assessed with PA and AP single-pulse TMS (PA_{1mV}, AP_{1mV}, $PA_{0.5mV}$, $AP_{0.5mV}$) (Liao et al., 2023). In particular, we show that resting and active PA MEPs produce shorter latencies compared to AP MEPs, 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). In addition, while PA_{AMT}, PA_{1mV} and $PA_{0.5mV}$ latencies did not vary (Liao et al., 2022), AP_{1mV} latencies were shorter than AP_{AMT} and $AP_{0.5mV}$, suggesting early I-wave recruitment via AP TMS at higher intensities. These findings suggest that lowering the stimulation intensity can increase the selective recruitment of different I-waves, particularly for AP TMS. Therefore, the potentiation of both $PA_{0.5mV}$ and $AP_{0.5mV}$ reported previously suggests that PMd broadly influences both early and late I-wave circuits within M1 (Liao et al., 2023). The present finding demonstrating specific potentiation of $PA_{0.5mV}$ following PMd iTBS is thus inconsistent with previous work and highlights the known inter- and intra-individual variability of TBS protocols. Given that the present study controlled for factors that are strongly related to iTBS-induced plasticity (baseline MEP amplitude, time of day and target muscle) (Corp et al., 2020), a possible explanation may be contributions from variations in participant factors such as genetics, pharmacology, aerobic exercise and diet (Phillips, 2017; Ridding & Ziemann, 2010). In addition, while our power analysis determined a study sample size of at least 25 total participants to observe an effect of PMd iTBS on M1 excitability, we cannot exclude the possibility that our analysis was underpowered to detect small effect sizes.

Furthermore, the findings show that $PA_{0.5mV}$ was potentiated 5 minutes following PMd iTBS and this effect was not different between young and older adults, in contrast to our previous work (Liao et al., 2023). However, one difference between the present and previous study is that

stronger baseline stimulation intensities for $PA_{0.5mV}$ were recorded in older adults (~64% MSO) compared to young (~54% MSO) previously (Liao et al., 2023), whereas there were no age-related differences in baseline stimulation intensity presently (both groups ~56% MSO). Previous work has demonstrated using MEP input–output curves that iTBS over M1 modulates MEP amplitude at lower intensities (near 110–120% RMT) (Goldsworthy et al., 2016), and we may speculate a similar effect for iTBS over PMd. Therefore, the present findings may complement our previous work. For example, increasing stimulation intensities over M1 are known to result in overlapping recruitment of early and late I-waves (Di Lazzaro et al., 2001). Age-related differences in $PA_{0.5mV}$ potentiation (Liao et al., 2023) may therefore stem from the additional recruitment of age-altered late I-waves with increasing stimulation intensities (Opie et al., 2018, 2020).

Another important consideration regarding the source of variability between these findings is that there are many anatomical changes in the brain with advancing age. In particular, cortical thinning can increase the coil-to-cortex distance (Freitas et al., 2011), which is known to influence the TMS intensity that is required to activate the cortex (Stokes et al., 2007). While previous work suggests that age-related cortical atrophy does not affect the induction of M1 plasticity following (M1) iTBS (Freitas et al., 2011), we cannot exclude the possibility that age-related anatomical changes within PMd influenced the effects of iTBS in older adults. For example, previous work has shown that increased coil-to-cortex distance due to frontal lobe atrophy is related to the efficacy of rTMS protocols for treating depression in older adults (Manes et al., 2001; Mosimann et al., 2002). This is particularly critical as the extent of frontal lobe atrophy is variable within older adults (Peters, 2006), which may directly influence the efficacy of PMd iTBS and contribute to the variability within our findings. Therefore, despite the assessment of PMd location following previously reported protocols (Huang et al., 2018; Koch et al., 2007; Meng et al., 2020; Münchau et al., 2002), the absence of individualised MRI-based neuronavigation is a limitation in the present study, and its inclusion will be useful in future work to control for age-related anatomical changes in the brain.

4.2 | PMd iTBS and iTBS-induced M1 plasticity

Following the application of priming iTBS over PMd, the facilitatory effects of M1 iTBS (applied in isolation) on $PA_{0.5mV}$ were disrupted. This finding is similar to previous work in young participants who reported a disruption of M1 iTBS and cTBS aftereffects following PMd cTBS (Huang et al., 2018). This demonstrated that LTP- and LTD-like effects within M1 can be modulated by PMd cTBS, possibly via heterosynaptic metaplastic effects. Within this construct, the TBS-dependent modulation of local synaptic plasticity within PMd affected subsequent changes in remote synapses (that were not initially activated) within M1 (Huang et al., 2018). However, given that iTBS is more likely to produce LTP-like effects while cTBS is more likely to produce LTD-like effects (Corp et al., 2020; Huang et al., 2005), this disruption of $PA_{0.5mV}$ facilitation may stem from a different mechanism more consistent with homeostatic metaplasticity (Müller et al., 2007; Murakami et al., 2012; Todd et al., 2009). In particular, the LTP-like effects of PMd iTBS may have raised the threshold for the subsequent induction of LTP-like effects following M1 iTBS (Ziemann & Siebner, 2008). Importantly, this response did not differ between young and older adults, suggesting that the influence of PMd on the circuits recruited by $PA_{0.5mV}$ is maintained with age.

In contrast, while $AP_{0.5mV}$ was not modulated by PMd iTBS, responses potentiated following M1 iTBS in both sessions. There are at least two possible interpretations for this finding. Firstly, it is possible PMd iTBS had no effect on $AP_{0.5mV}$ and was instead potentiated by M1 iTBS, but this appears unlikely as our previous work reported strong potentiation of $AP_{0.5mV}$ 5 minutes following PMd iTBS (Liao et al., 2023). Alternatively, PMd iTBS had a weak (modulatory) effect on $AP_{0.5mV}$ that was boosted by M1 iTBS. For example, it has been shown that PMd iTBS first reduces M1 intracortical inhibition (assessed with short-interval intracortical inhibition, SICI) and is then followed by an increase in M1 facilitation (assessed with intracortical facilitation, ICF) (Meng et al., 2020). It is possible that $AP_{0.5mV}$ potentiation following M1 iTBS reflects a gating mechanism (Ziemann & Siebner, 2008) where PMd iTBS initially reduced the activity of M1 inhibitory circuits, which are known to preferentially modulate the late I-wave circuits (Wagle-Shukla et al., 2009). However, this interpretation is highly speculative and requires a specific assessment of M1 inhibitory circuits, and further investigation in larger sample sizes that can account for the level of attrition that is often experienced with AP TMS (Opie et al., 2020, 2021). We also cannot exclude the possibility that the present findings are shaped by inputs from other motor nodes that target I-wave circuits (e.g., cerebellum, somatosensory cortex) (Ziemann, 2020). Despite this, the present study provides preliminary evidence that PMd iTBS specifically modulates the response of $PA_{0.5mV}$ circuits to M1 iTBS in young and older adults, demonstrating that this effect may be preserved with ageing.

Interestingly, the potentiation of $PA_{0.5mV}$ and $AP_{0.5mV}$ following M1 iTBS was not different between young and

older adults, consistent with current literature on the age-related effects of M1 iTBS (Di Lazzaro et al., 2008; Dickins et al., 2015; Opie et al., 2017; Young-Bernier et al., 2014). Importantly, the ability to recruit late I-waves non-invasively using AP TMS has been shown to be an important determinant for the induction of M1 plasticity (Hamada et al., 2013; Hordacre et al., 2017; Huang & Mouraux, 2015; Volz et al., 2019; Wiethoff et al., 2014). This is assessed by comparing PA and AP MEP onset latencies relative to LM latencies (PA-LM, early; AP-LM, late), which reveal prototypical values that index I-wave recruitment (Hamada et al., 2013). In particular, PA-LM latencies (~1.5 ms) are shorter compared to AP-LM latencies (~3 ms), with high retest reliability (Hamada et al., 2013). The present findings replicated this relationship and demonstrated that longer AP-LM latencies are related to M1 excitability following M1 iTBS, but not PMd iTBS. Importantly, given that this finding included young and older adults, this suggests that the relationship between late I-wave recruitment and M1 plasticity is preserved with ageing.

However, there are some inconsistencies between the present I-wave recruitment findings and previous work. For example, we were unable to shorten AP-LM latencies following M1 iTBS (Volz et al., 2019). A possible reason for this difference is that we recorded MEP latencies 45-minutes following M1 iTBS in order to avoid complications involving the effects of muscle activation on neuroplasticity (Goldsworthy et al., 2015; Huang et al., 2008; Thirugnanasambandam et al., 2011), but this delay allowed the effects of iTBS to return to baseline. Furthermore, although we have also previously reported no relationship between AP-LM latencies and M1 excitability following PMd iTBS (Liao et al., 2023), this appears inconsistent with the understanding that AP inputs likely originate from premotor areas (Aberra et al., 2020; Volz et al., 2015). It is possible that this relationship is difficult to quantify using MEP latency differences and measures of corticospinal excitability, as the projections from PMd to M1 are inherently complex and involve both facilitatory and inhibitory connections (Koch et al., 2007). Therefore, TMS measures that can more accurately quantify the relationship between PMd and M1, such as dual-site TMS that can assess (Ni et al., 2015) or even modulate the effective connectivity between two motor nodes (Casarotto et al., 2023, 2023) will be useful in future studies.

5 | CONCLUSION

In conclusion, the application of iTBS over PMd lowered the facilitatory response of $PA_{0.5mV}$ to M1 iTBS in young and older adults. This preliminary finding may represent a specific influence of PMd on early I-wave circuits that are involved in M1 plasticity. Importantly, this effect did not vary between young and older adults, suggesting that it may be possible for the influence of PMd on M1 early I-waves to be preserved with ageing. It will therefore be necessary in future studies to validate the present findings and investigate how the influence of PMd on M1 plasticity modifies model-based motor learning in young and older adults.

AUTHOR CONTRIBUTIONS

Wei-Yeh Liao: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; validation; visualization; writing—original draft. **George M Opie:** Conceptualization; formal analysis; funding acquisition; methodology; project administration; resources; supervision; validation; writing—review and editing. **Ulf Ziemann:** Conceptualization; funding acquisition; methodology; project administration; resources; supervision; writing—review and editing. **John G Semmler:** Conceptualization; data curation; funding acquisition; methodology; project administration; resources; supervision; validation; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in the repository Figshare (https://doi.org/10.25909/25241791).

ETHICS APPROVAL STATEMENT

This research was approved by The University of Adelaide Human research Ethics Committee (H-026-2008).

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