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Functional role of left PMd and left M1 during preparation and execution of left hand movements in older adults

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Fujiyama H, Hinder MR, Summers JJ. Functional role of left PMd and left M1 during preparation and execution of left hand movements in older adults. *J Neurophysiol* 110: 1062–1069, 2013. First published June 12, 2013; doi:10.1152/jn.00075.2013.—A disruptive transcranial magnetic stimulation (TMS) approach was used to determine whether the increased frontal activation and reduced hemispheric laterality brain activation patterns observed in older adults during motor tasks play a functional role. Young and older adults abducted their left index finger as soon as possible after a visual imperative signal presented 500 ms after a warning signal. TMS was applied to the dorsal premotor (PMd) or primary motor (M1) cortex in the left or right hemisphere at seven times during response preparation and execution. Both groups exhibited faster reaction times in their left hand after stimulation of the left PMd (i.e., ipsilateral to the responding hand) relative to trials with no TMS, indicating a functional role of the left PMd in the regulation of impulse control. This result also suggests that the function of the left PMd appears to be unaffected by the healthy aging process. Right M1 TMS resulted in a response time delay in both groups. Only for older adults did left M1 stimulation delay responses, suggesting the involvement of ipsilateral motor pathways in the preparation of motor actions in older adults.

aging; motor cortex; response time; transcranial magnetic stimulation

ONE OF THE MOST APPARENT behavioral changes accompanying advancing age is progressive slowing of volitional motor actions (i.e., reaction times) after extrinsic cues that require a rapid motor response (see, e.g., Hunter et al. 2001; Morgan et al. 1994; Salthouse 1991, 1996). Response delays in older adults have been associated with declined efficiency in movement preparation (foreperiod) processes (Hillman et al. 2002), which are likely to optimize relevant systems to generate speeded responses. Specifically, in reaction time (RT) tasks older adults show compromised physiological activity related to preparation in the interval between a warning signal (WS) and an imperative signal (IS) (see, e.g., Bherer and Belleville 2004). During movement preparation, Cohen and colleagues (Cohen et al. 2010) suggested that two functionally distinct processes operate: suppression of cortical excitability and release of intracortical inhibition (ICI). The first of these processes, suppression of corticospinal excitability (prior to the motor action), is believed to circumvent premature responses, i.e., impulse control (Davranche et al. 2007; Duque and Ivry 2009; Touge et al. 1998), and has been shown to be less pronounced, or absent, in older adults (Fujiyama et al. 2011, 2012b) compared with young adults (Cuypers et al. 2012). It is proposed that this mechanism is mediated via projections from secondary motor areas including dorsal premotor cortex (PMd) to primary motor cortex (M1) and spinal cord (Cohen et al. 2010). This proposition is supported by recent evidence from Duque and colleagues (Duque et al. 2012), who demonstrated increased excitability of a left hand muscle shortly after 10-Hz repetitive transcranial magnetic stimulation (rTMS) was applied to the left PMd (disrupting impulse control) during movement preparation in healthy young adults. A significant behavioral effect has also been observed after disruption of the left PMd by way of rTMS (Davare et al. 2006). In this study, conducted in young adults, left PMd stimulation selectively disrupted the timing of the lifting phase of a grasp and lift task conducted with the right hand. In a recent study (Hinder et al. 2012), we observed greater task-related facilitatory changes in the connections between left PMd and right M1 for older compared with young adults during preparation of a speeded left hand response. Furthermore, for older adults the extent of this neurophysiological change was associated with faster responses, suggesting an important role for left PMd in planning left hand responses; however, the causality of this relationship is yet to be determined.

The second distinct process, a simultaneous release of ICI, is hypothesized to drive fast responses (Sinclair and Hammond 2008, 2009). For example, in a previous study we observed in young adults a significant reduction of ICI relative to resting state during movement preparation in a Go/NoGo RT task. Similar reductions in ICI during movement preparation have been reported in a number of studies (e.g., Fujiyama et al. 2011, 2012b; Tandonnet et al. 2010).

Another feature of motor function in aging is decreased hemispheric laterality during the performance of motor tasks. Several recent fMRI and TMS studies have demonstrated that the extent of bilateral activation in motor cortices is greater in older compared with young adults during the performance of unilateral movements (e.g., Fujiyama et al. 2012a; Ward and Frackowiak 2003). Currently, two opposing views are put forward to explain this observation: the compensation hypothesis and the dedifferentiation hypothesis. The compensation hypothesis suggests that the involvement of additional brain areas counteracts age-related decline of brain function (see, e.g., Cabeza et al. 2002). Specifically, the hemispheric asymmetry reduction in older adults (HAROLD) (Cabeza et al. 2002) model proposes that the increased bilateral brain activation is likely to be compensatory, enabling the maintenance of motor performance in old age (Heuninckx et al. 2008). This compensation may reflect the plasticity of the aging brain to counteract other central and peripheral changes that would otherwise result in poorer motor or cognitive abilities (Swinnen et al. 2011).

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In contrast, the dedifferentiation hypothesis argues that the additional activation in some older adults represents difficulty in specifically recruiting the neural mechanisms specialized for the required task (Seidler et al. 2010). Consistent with this hypothesis, there is evidence that some inhibitory interactions between brain areas break down with age (Talelli et al. 2008), such that additional activation may reflect the nonselective recruitment of disinhibited regions (Logan et al. 2002). Accordingly, the functional significance of the increased bilateral activation is still unclear.

The present experiment was designed to determine causal associations between task performance and neural activity originating in PMd and M1 with a double-pulse disruptive TMS protocol (van den Berg et al. 2010). The transient disruption approach has the advantage of dissociating effects originating from different cortical areas at different times (Schluter et al. 1998). We systematically tested the involvement of PMd and M1 in both the ipsilateral (*experiment 1*) and contralateral (*experiment 2*) hemispheres during the preparatory period of a simple visuomotor RT task undertaken with the left index finger. The transient disruption of PMd (by way of double-pulse disruptive TMS) was aimed at elucidating the specific involvement of PMd in motor preparation and how this varies as a result of healthy aging. We hypothesized that the extent to which response times were facilitated (i.e., shortened) after the left PMd stimulation would be greater in older than in young adults. This is postulated on the basis of the observation of greater functional connectivity from the left PMd during the preparation and execution of left hand motor responses in older compared with younger adults (Hinder et al. 2012). In contrast, stimulation of ipsilateral M1 (i.e., left) was aimed at determining the significance of the increased bilateral M1 activation with advancing age. If any observed response time modulation that occurs after stimulation of the ipsilateral M1 (during the preparation period) mirrors any response time modulation following contralateral M1 stimulation, we would argue that the age-related increase in bilateral M1 activation observed in previous research is likely a manifestation of compensatory mechanisms. In contrast, the absence of response time modulations by ipsilateral (left) M1 stimulation would suggest that ipsilateral M1 is not functionally involved in the task, providing support for the dedifferentiation hypothesis. The investigation of both left and right hemispheres thus enables us to determine hemisphere-specific function during preparation and execution of a motor action.

METHODS

Participants

Forty-eight right-handed volunteers were recruited from the community and from students at the University of Tasmania, consisting of 26 young (*experiment 1*: $n = 14$, 3 men, 11 women, $M_{age} = 21.6$, $SD_{age} = 2.9$ yr; *experiment 2*: $n = 12$, 3 men, 9 women, $M_{age} = 24.4$, $SD_{age} = 4.8$ yr) and 26 older (*experiment 1*: $n = 14$, 3 men, 11 women, $M_{age} = 70.6$, $SD_{age} = 6.4$ yr; *experiment 2*: $n = 12$, 3 men, 9 women, $M_{age} = 69.4$, $SD_{age} = 6.9$ yr) participants. The Mini-Mental State examination (Dick et al. 1984) was used to screen for cognitive deficits in the sample of older adults. All participants scored within the normal range (score ≥ 26) and were free of any neurological or symptomatic cardiovascular disease, diabetes, or hypertension. Ethics approval for the study was obtained from the Human Research Ethics (Tasmania) Network, and written informed consent was obtained from each participant prior to his/her participation.

Warned Simple Reaction Time Task

The experiments were designed to evaluate the role of the left and right PMd and left and right M1 in the preparation period of a simple RT (SRT) task. Participants were comfortably seated on a chair with their forearms placed on a horizontal board on a table situated in front of them. Both palms faced down, with the elbows slightly bent (100–120°). Vertical wooden pegs designed to restrict movements to the second metacarpophalangeal joint (Carroll et al. 2008; Lee et al. 2010) inserted into the board helped participants to maintain a consistent posture with hand and forearm muscle relaxed throughout the experiment (Hinder et al. 2011). About 80 cm in front of participants at eye level, two light-emitting diodes (LEDs) were vertically arranged on a black panel 3 cm apart. The upper orange LED served as a warning signal (WS), while the lower green LED designated the imperative signal (IS) to indicate "Go" responses. Each trial began with presentation of the WS for 500 ms, followed immediately by the IS for 500 ms. The intertrial interval was varied between 5 and 7 s (Fig. 1).

Participants were instructed to prepare during the WS interval (500 ms) to abduct the left index finger as quickly as possible on presentation of the "Go" green LED signal.

Procedure

In both experiments participants first performed two baseline blocks of 22 trials in the absence of TMS. WS were presented in one of the blocks, and a comparison between RTs in the blocks with and without WS indicated whether participants used the WS, when available, to prepare the upcoming response. The order of these blocks was counterbalanced across participants. Two trials in each of these blocks were "catch" trials, in which the IS did not appear. Since participants were instructed to respond to Go signals, in the catch trials participants needed to withhold their response. Catch trials were included to reduce the incidence of premature responses being triggered by the WS (Hinder et al. 2012).

The main part of the experiments consisted of 12 experimental blocks of 31 trials (28 warned Go trials, 3 catch trials) in which TMS was administered to disrupt processing in the left (*experiment 1*) and right (*experiment 2*) PMd and M1. Cz (vertex) stimulation was used

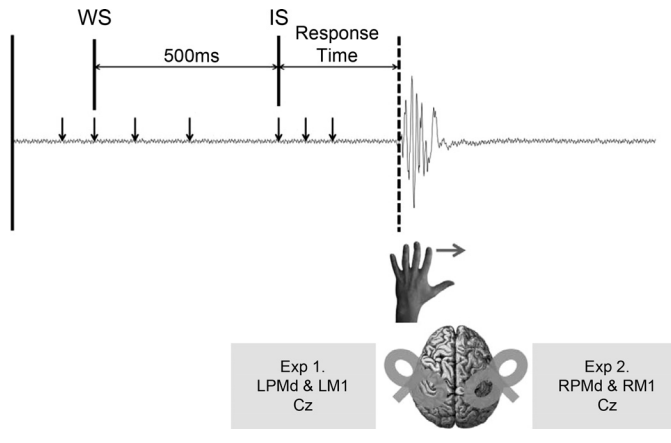

Fig. 1. Schematic illustrating the time course of the visual warning signal (WS), followed by the imperative signal (IS), response-related EMG activity (RT), and transcranial magnetic stimulation (TMS) delivery. TMS pulses are indicated with downward facing arrows. Participants were required to abduct the left index finger as fast as possible in response to the IS. The left (*experiment 1*) and right (*experiment 2*) PMd and M1 were stimulated, with Cz as a control site for both experiments.

as a control for each experiment. For each cortical region 4 blocks of trials were administered: in 14 of the 28 warned Go trials in each block TMS was administered at various time points between the WS and IS and between the IS and the onset of the volitional muscle activity (see *TMS Procedure and EMG Recording*).

TMS Procedure and EMG Recording

Electrodes (Ag/AgCl) were used to measure surface EMG in the first dorsal interosseous (FDI) in both hands in a belly-tendon montage. Signals were amplified with a gain of 1,000, band-pass filtered (10–500 Hz), and sampled at 2,000 Hz with a 16-bit AD system (CED 1902, Cambridge, UK) before being fed to disk for off-line analysis. TMS was applied with a single figure-of-eight coil (7-cm diameter of each wing) connected to two Magstim 200^2 stimulators via a BiStim unit (Magstim, Whitland, UK). The individual resting motor threshold (rMT) for each cortex was determined as the lowest stimulus intensity that produced motor evoked potentials (MEPs) in FDI of >50 μV in at least three of five consecutive trials with the coil placed tangentially over the optimal scalp location to induce MEPs with posterior-anterior current flow. During the experimental blocks, double-pulse TMS was then applied at 110% rMT at 10-ms interstimulus intervals (van den Berg et al. 2010) at these predetermined hot spots (i.e., left and right M1), at 8% of nasion-inion distance (Kroeger et al. 2010) anterior to these locations (left and right PMd), or at the vertex (Cz). The pulses were delivered at one of seven different time points in 50% of Go trials (see Fig. 1) in both experiments. Four of these time points were related to the WS interval: 100 ms prior to the WS (WS − 100 ms), coincident with the onset of the WS (WS), and 100 ms (WS + 100 ms) and 250 ms (WS + 250 ms) after the WS. The remaining three TMS delivery times were related to the response time interval: coincident with the onset of IS (IS) and 50 ms (IS + 50 ms) and 100 ms (IS + 100 ms) after the onset of the IS.

Data Processing and Analysis

Data are expressed as means ± 95% confidence intervals. Response time was defined as the time between the onset of the Go IS and the onset of muscle activity in the left FDI, determined as the time at which root mean square (rms) EMG first increased above a threshold level equivalent to four times the background EMG evident 100 ms prior to the onset of the WS (Hinder et al. 2012). EMG onset was inspected visually in each trial to ensure the detection of true voluntary EMG responses rather than a return of prestimulus EMG levels following TMS-evoked silent periods. The time window allowed for a response made between 80 ms and 750 ms after the onset of the Go signal to be included in data analysis. Incorrect responses including premature responses and responses to catch trials were not analyzed, as the number of errors made by participants was small (all M $<$ 5.8%, mode = 0 for all stimulation times/locations in both experiments). Response times during the TMS trials were normalized to the mean response time obtained from the no-TMS trials for each individual. Thus a normalized response time value $>$ 1 reflects delayed response time, whereas a value $<$ 1 indicates speeded response time.

To initially determine whether participants utilized the WS to prepare their response in the absence of the (disruptive) effects of TMS, we compared response times in the baseline trial blocks with and without WS, using a 2 [GROUP: Young, Older] × 2 [WS: WS, noWS] repeated-measures ANOVA. The effect of TMS during the experimental blocks was addressed by analyzing normalized response time data with a 2 [GROUP: Young, Older] × 3 [SITE: PMd, M1, Cz] × 7 [TIME (of TMS delivery): WS − 100 ms, WS, WS + 100 ms, WS + 250 ms, IS, IS + 50 ms, IS + 100 ms] repeated-measures ANOVA. If the sphericity assumption was violated ($\varepsilon < 0.7$), Greenhouse-Geisser's degrees of freedom adjustment was applied to the critical P values (Quinn and Keough 2002). Tukey honestly significant difference (HSD) post hoc procedure was used to explore significant main effects and interactions.

Furthermore, paired-sample t-tests were used to investigate whether response times following TMS of each site at each time point during preparation/execution were modulated relative to trials in the absence of TMS using nonnormalized response times. A significant difference in response time with and without TMS suggests functional involvement of the stimulated site at the time point. The critical P value was set at 0.05. Cohen's d and partial η^2 (η_p^2) values were provided as a measure of effect size with cutoffs ≥0.2 small, ≥0.5 medium, and ≥0.8 large for Cohen's d and ≥0.01 small, ≥0.06 medium, and ≥0.14 large for η_p^2 (Sink and Stroh 2006).

RESULTS

Experiment 1: Ipsilateral (Left) Hemisphere Stimulation

Stimulation intensities. rMT (as % of maximum stimulator output, MSO) was not significantly different between young (M = 48.64 ± 4.99%) and older (M = 44.86 ± 2.89%) adults [$t(26) = 1.41$, $P = 0.168$, $d = 0.54$].

Comparison between WS trials and noWS trials (both without TMS) in baseline blocks. Response time (averaged over both WS and noWS trials) was slower for older (M = 213.20 ± 13.67 ms) than for young (M = 190.54 ± 16.58 ms) adults [$F(1,26) = 5.19$, $P = 0.031$, $\eta_p^2 = 0.17$]. A significant main effect of WS [$F(1,26) = 23.95$, $P < 0.001$, $\eta_p^2 = 0.48$] and a nonsignificant interaction between GROUP and WS [$F(1,26) = 0.005$, $P = 0.942$, $\eta_p^2 = 0.0002$] suggest that both groups of participants utilized the WS to prepare their responses (Young: M_{WS} = 174.31 ± 9.66 ms, M_{noWS} = 206.76 ± 26.44 ms; Older: M_{WS} = 196.47 ± 17.04 ms; M_{noWS} = 229.92 ± 16.25 ms).

Effect of ipsilateral (left) hemisphere TMS on response times. To determine whether response times differed as a function of stimulated site and time, an ANOVA was performed on the normalized response times using GROUP, SITE, and TIME as factors, with repeated measures on the latter two of these factors. There were significant main effects of SITE [$F(2,52) = 11.14$, $P < 0.001$, $\eta_p^2 = 0.30$] and TIME [$F(6,156) = 6.42$, $P < 0.001$, $\eta_p^2 = 0.20$]. Importantly, the three-way interaction between GROUP, SITE, and TIME was significant [$F(12,312) = 1.98$, $P = 0.025$, $\eta_p^2 = 0.07$]. To further address this interaction, we conducted a separate two-way ANOVA using GROUP and TIME (repeated measures) as factors for each stimulation site (PMd, M1, Cz).

For PMd, the effect of TMS on response time was not uniform across time of stimulation [$F(6,156) = 3.58$, $P = 0.002$, $\eta_p^2 = 0.12$]. Post hoc Tukey analysis revealed that TMS at the onset of WS and WS + 100 ms produced significantly faster response times than TMS delivered at WS + 250 ms (both $P < 0.029$) (Fig. 2*A*). TMS at the onset of WS also resulted in significantly faster response times than at IS + 100 ms ($P = 0.027$). The main effect of GROUP and the GROUP × TIME interaction were not significant (both $F < 0.60$, $P > 0.446$, $\eta_p^2 > 0.02$).

For M1 stimulation, response time modulation also varied as a function of TIME [$F(6,156) = 8.05$, $P < 0.001$, $\eta_p^2 = 0.24$]. While the main effect of GROUP was not significant [$F(1,26) = 2.22$, $P = 0.148$, $\eta_p^2 = 0.08$], importantly, the interaction of GROUP × TIME was significant [$F(6,156) = 4.89$, $P < 0.001$, $\eta_p^2 = 0.19$]. As illustrated in Fig. 2*B*, for older adults M1 stimulation at WS + 250 ms resulted in a significantly slower response time than other time points (all $P < 0.0143$), except WS + 100

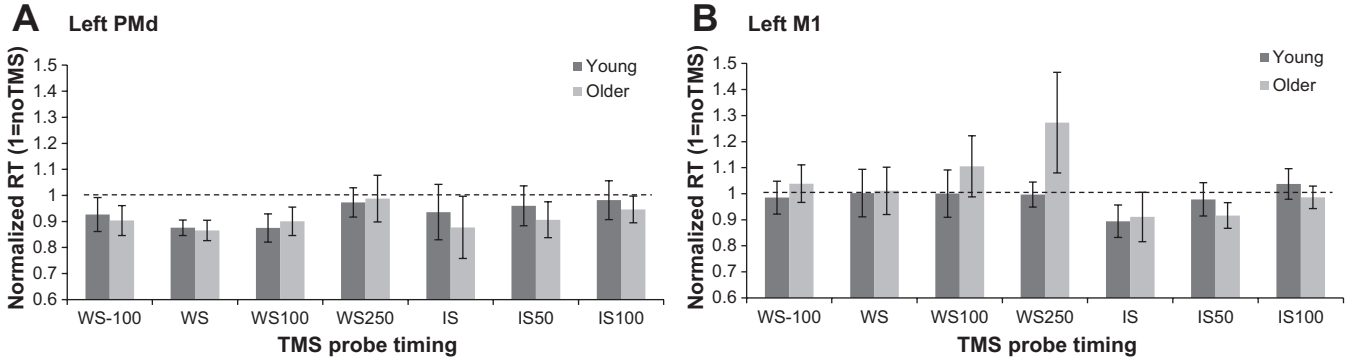

Fig. 2. Normalized mean response time for young and older adults resulting from disruption of left PMd (*A*) and left M1 (*B*) at various time points. Values > 1 (horizontal dashed line) reflect delayed response time, whereas values < 1 indicate speeded response time. Error bars show 95% CI. For PMd, the main effect of TIME and subsequent post hoc comparisons revealed that TMS at the onset of WS and WS + 100 ms produced significantly faster response times than TMS delivered at WS + 250 ms (both $P < 0.029$). TMS at the onset of WS also resulted in significantly faster response times than at IS + 100 ms ($P = 0.027$). M1 TMS at WS + 250 ms in older adults significantly delayed response time relative to other time points (all $P < 0.014$), except WS + 100 ms ($P = 0.076$).

ms ($P = 0.076$), while in young adults response times at all time points did not significantly differ from each other (all $P > 0.254$).

For Cz stimulation, there were no significant main effects or interactions (all $F < 1.30$, $P > 0.260$, $\eta_p^2 < 0.05$). Accordingly, the time-specific effects observed after M1 and PMd stimulation (see above) can be interpreted as site-specific neurophysiological effects rather than general effects due to TMS stimulation (e.g., intersensory facilitation or attentional changes).

To investigate whether response time was modulated by TMS delivery, response times in the 50% of trials with TMS were compared with response times in the 50% of trials without TMS (see METHODS) by paired-sample *t*-tests, for each stimulation site and each age group separately. As shown in Table 1, for PMd stimulation, during the preparatory period response times were quickened by TMS for both young and older adults at WS − 100 ms, WS, and WS + 100 ms. Older adults also showed a response time shortening due to PMd stimulation at the onset of the IS and IS + 50 ms. With respect to M1 stimulation, TMS quickened response times at IS for both young and older adults and at IS + 50 ms for older adults. A slowing of response times was also observed in older adults when TMS was delivered at WS + 250 ms. Cz stimulation resulted in shortening of response times only in older adults at the onset of the IS and IS + 50 ms.

Experiment 2: Contralateral (Right) Hemisphere Stimulation

Stimulation intensities. In contrast to *experiment 1*, mean rMT was significantly higher in older (M = 48.92 ± 2.92%) than in young (M = 41.42 ± 5.83%) adults [$t(22) = 2.53$, $P = 0.019$, $d = 1.03$].

Evidence of preparation: comparison between WS trials and noWS trials (both without TMS) in baseline blocks. Replicating the results of *experiment 1*, we observed that response times were slower in older adults than in young adults [$F(1,22) = 10.58$, $P = 0.003$, $\eta_p^2 = 0.32$] and response times in warned trials were faster than in noWS trials [$F(1,22) = 15.86$, $P <$

Table 1. *Mean response times and statistical values for experiment 1*

	PMd (left)				M1 (left)				Cz			
	M	95% CI	*P* value	*d*	M	95% CI	*P* value	*d*	M	95% CI	*P* value	*d*
Young												
noTMS	171.25	14.02			169.00	14.13			168.38	14.17		
WS − 100 ms	**157.88**	**18.31**	**0.03**	**0.65**	164.04	18.17	0.60	0.14	166.08	22.12	0.64	0.13
WS	**150.54**	**13.71**	**0.00**	**2.44**	170.50	27.84	0.91	0.03	165.17	20.50	0.31	0.28
WS + 100 ms	**149.83**	**17.68**	**0.00**	**1.24**	169.75	26.38	0.95	0.02	166.46	16.68	0.38	0.24
WS + 250 ms	164.42	15.37	0.30	0.29	170.38	17.18	0.88	0.04	161.42	16.60	0.69	0.11
IS	162.29	31.62	0.27	0.31	**151.04**	**22.15**	**0.00**	**0.92**	169.92	29.83	0.86	0.05
IS + 50 ms	165.79	26.72	0.38	0.24	166.21	17.81	0.44	0.21	160.83	22.63	0.13	0.43
IS + 100 ms	170.25	22.90	0.63	0.13	177.46	18.30	0.22	0.34	167.67	21.54	0.88	0.04
Older												
noTMS	206.09	18.02			198.05	16.94			198.32	17.03		
WS − 100 ms	**186.59**	**21.52**	**0.00**	**0.92**	203.73	18.13	0.33	0.27	189.64	20.98	0.28	0.30
WS	**175.73**	**15.44**	**0.00**	**1.85**	193.73	20.78	0.89	0.04	202.36	23.88	0.96	0.01
WS + 100 ms	**192.14**	**23.22**	**0.00**	**1.01**	217.50	29.04	0.10	0.48	186.95	15.06	0.24	0.33
WS + 250 ms	204.73	32.45	0.78	0.08	**234.09**	**26.58**	**0.01**	**0.83**	202.95	9.63	0.60	0.14
IS	**183.59**	**30.46**	**0.03**	**0.67**	**176.82**	**26.53**	**0.04**	**0.57**	**180.68**	**24.96**	**0.01**	**0.89**
IS + 50 ms	**183.91**	**28.65**	**0.02**	**0.73**	**181.27**	**25.40**	**0.00**	**0.95**	**182.77**	**22.61**	**0.00**	**0.92**
IS + 100 ms	199.32	25.63	0.06	0.55	194.77	25.27	0.60	0.14	193.18	22.69	0.54	0.17

TMS, transcranial magnetic stimulation; WS, warning signal; IS, imperative signal. Values in bold indicate that the response time in the condition was significantly modulated (tested by paired-sample *t*-tests) relative to noTMS condition

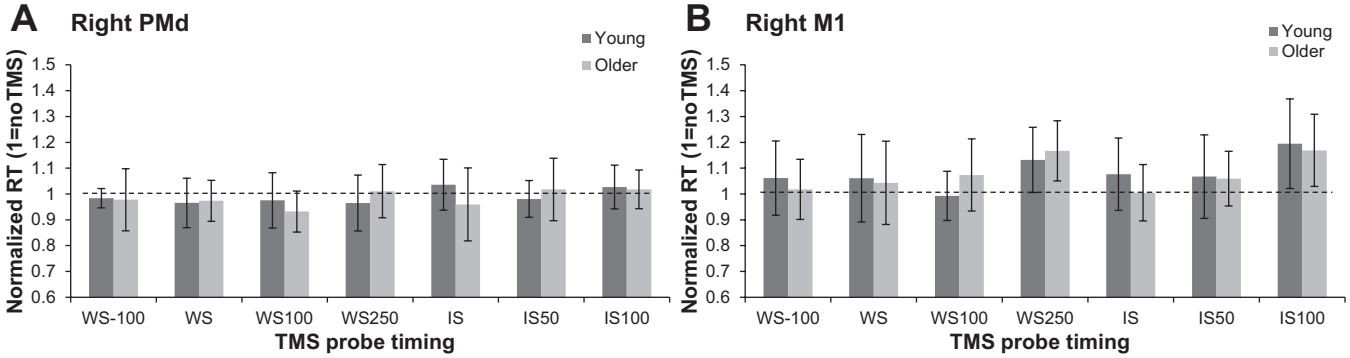

Fig. 3. Normalized mean response time for young and older adults during the disruption of right PMd (*A*) and right M1 (*B*) at various time points. Values > 1 (horizontal dashed line) reflect delayed response time, whereas values < 1 indicate speeded response time. Error bars show 95% CI.

0.001, $\eta_p^2 = 0.42$]. Moreover, the nonsignificant interaction of GROUP × WS [$F(1,22) = 0.06$, $P = 0.805$, $\eta_p^2 = 0.002$] indicates that both young ($M_{WS} = 181.55 \pm 20.69$ ms; $M_{noWS} = 200.05 \pm 14.94$ ms) and older ($M_{WS} = 208.96 \pm 9.45$ ms; $M_{noWS} = 229.48 \pm 16.23$ ms) adults utilized the WS to prepare their responses.

Effect of contralateral (right) hemisphere TMS on response times. To investigate the effect of TMS for each site, a 2 GROUP × 3 SITE × 7 TIME ANOVA was conducted. Response times differed significantly as a function of site of stimulation [$F(2,44) = 15.74$, $P < 0.001$, $\eta_p^2 = 0.42$]. Specifically, M1 stimulation resulted in slower response times (M = 1.08 ± 0.03) than both Cz (M = 0.97 ± 0.02) and PMd (M = 0.97 ± 0.02) stimulation (both $P < 0.001$). Furthermore, the effect of stimulation TIME [$F(6,132) = 3.33$, $P = 0.004$, $\eta_p^2 = 0.13$] was also significant. Response times were slower when TMS was delivered 100 ms after the onset of IS (M = 1.07 ± 0.04) relative to the response times obtained by stimulation prior to WS + 100 ms (all M < 0.99, $P < 0.031$). The main effect of GROUP and all interactions were not significant (all $F < 1.45$, $P > 0.144$, $\eta_p^2 > 0.05$). Figure 3 illustrates the time course of response time modulations for right PMd (Fig. 3*A*) and right M1 (Fig. 3*B*) stimulation in young and older adults.

To investigate whether TMS modulated response time, the response times during trials with and without TMS were compared by paired-sample *t*-tests for young and older adults separately (Table 2). PMd stimulation did not modulate response times relative to the trials without TMS. M1 stimulation showed that, for both groups of participants, contralateral M1 TMS slowed response times when applied at WS + 250 ms and shortly before the response (IS + 100 ms). For Cz, response time shortening by TMS was limited to older adults at the onset of IS.

DISCUSSION

The present study used a disruptive TMS approach to elucidate the roles of distinct motor regions during motor preparation. Consistent with previous research (e.g., Leocani et al. 2000), suprathreshold stimulation of the contralateral motor cortex immediately prior to response onset (*experiment 2*) resulted in response time delays. This confirms that the double-pulse TMS stimulation (see for review Chouinard and Paus

Table 2. *Mean response times and statistical values for experiment 2*

	PMd (right)				M1 (right)				Cz			
	M	95% CI	*P* value	*d*	M	95% CI	*P* value	*d*	M	95% CI	*P* value	*d*
Young												
noTMS	187.75	21.25			173.47	20.55			183.44	23.69		
WS − 100 ms	176.95	20.94	0.24	0.36	183.71	24.58	0.21	0.38	173.16	19.04	0.10	0.51
WS	173.35	13.82	0.31	0.31	181.98	22.22	0.42	0.24	174.04	19.35	0.23	0.36
WS + 100 ms	167.25	13.74	0.66	0.13	171.74	20.69	0.74	0.10	173.28	28.01	0.16	0.43
WS + 250 ms	178.02	26.65	0.40	0.25	**194.83**	**19.36**	**0.01**	**0.87**	184.12	18.01	0.90	0.04
IS	189.79	21.31	0.34	0.29	187.71	31.69	0.10	0.51	186.44	33.79	0.75	0.10
IS + 50 ms	181.33	24.90	0.63	0.14	184.98	30.52	0.25	0.35	176.03	29.32	0.12	0.48
IS + 100 ms	189.39	23.95	0.34	0.29	**207.74**	**34.26**	**0.01**	**0.89**	183.13	30.31	0.95	0.02
Older												
noTMS	207.66	14.66			206.89	11.13			207.60	9.34		
WS − 100 ms	203.88	11.37	0.45	0.23	207.49	27.26	0.66	0.13	199.74	18.91	0.23	0.37
WS	204.63	19.25	0.35	0.28	220.12	35.98	0.50	0.20	199.86	19.91	0.24	0.36
WS + 100 ms	195.67	16.10	0.10	0.53	222.44	25.73	0.21	0.38	204.66	15.01	0.16	0.44
WS + 250 ms	207.72	14.05	0.91	0.04	**242.55**	**27.60**	**0.01**	**0.99**	196.25	18.90	0.39	0.26
IS	197.39	28.83	0.45	0.23	203.13	18.68	0.94	0.02	**190.38**	**14.18**	**0.02**	**0.76**
IS + 50 ms	210.12	32.46	0.61	0.15	218.14	25.79	0.17	0.42	197.25	22.12	0.36	0.28
IS + 100 ms	212.64	25.68	0.48	0.21	**241.26**	**24.39**	**0.01**	**0.99**	205.66	18.22	0.77	0.09

Values in bold indicate that the response time in the condition was significantly modulated (tested by paired-sample *t*-tests) relative to noTMS condition

2010) successfully disrupted cortical processing associated with response generation. It can therefore be assumed that the application of TMS to other brain regions (e.g., left M1, left and right PMd) had a similar disruptive effect on cortical processing. Depending on the role of these distinct regions during motor preparation, we postulated that modulation of the behavioral response may or may not be observed. We observed that left PMd disruption (but not right PMd) led to decreased reaction times in both young and older adults, suggesting that the left PMd is specifically involved in inhibitory processing related to impulse control. In contrast, stimulation of the left (ipsilateral) M1 only resulted in a modulation of behavior (response time increases) in older adults during movement preparation. The latter result suggests that the reported bilateral activation of motor cortices in older adults during motor preparation represents functional cortical activity. Furthermore, these results together with the observed response time delay induced by TMS applied to the right M1 close to response onset are consistent with a view that the left PMd is involved in the preparation of movements of either hand and the contralateral M1 plays a crucial role in movement execution (Hinder et al. 2012).

Response Time Facilitation Induced by Ipsilateral (Left) PMd TMS

Disruption of the left PMd (*experiment 1*), but not the right PMd (*experiment 2*), during the early preparatory period facilitated performance (i.e., speeding response time) of the SRT task undertaken with the left finger in both young and older adults. We suggest that this improved performance occurred as a result of TMS to the left PMd disrupting inhibitory function associated with impulse control, for which the left PMd has been identified as a key brain region (Duque et al. 2012) for both left and right hands (Cisek et al. 2003). As such, it is possible to expect similar shortening of response times in the right hand after left PMd stimulation. Further work to investigate the extent to which right hand responses are modulated by left PMd stimulation is warranted to provide a behavioral test of this hypothesis. The present findings are consistent with a recent study in healthy young adults by Kroeger and colleagues (Kroeger et al. 2010) showing greater interhemispheric inhibition (IHI) between left PMd and right M1 after a "stop" cue that required the withholding of a planned action (with the left hand). Similarly, Duque and colleagues found that the application of rTMS (5 pulses at 10 Hz) to the ipsilateral left PMd produced increased MEP amplitude in the left FDI muscle during the preparatory period, indicating that attenuating the inhibitory influence from the left PMd enhanced the corticospinal excitability of the right M1 (Duque et al. 2012).

It is possible that the observed facilitation of responses was due to nonspecific intersensory facilitation caused by TMS (see, e.g., Burle et al. 2002; Terao et al. 1997), rather than being a consequence of disrupting left PMd function. Intersensory facilitation can be observed in a situation where a cue signal is paired with a second stimulus in a different modality (see for review Nickerson 1973) with no or little temporal delay (Sawaki et al. 1999) as we observed in PMd, M1, and Cz stimulation close to the onset of IS in both *experiment 1* and *experiment 2* (see Tables 1 and 2). However, because TMS-induced response time facilitation in the present study was observed early during the preparation period (i.e., when the TMS was not temporally coupled to the imperative signal), it seems likely that the effect was a result of disruption of inhibitory function associated with impulse control.

We observed that left PMd TMS affected response times similarly for both groups of participants, suggesting that the degree of left PMd involvement in impulse control was similar for young and older adults. Although there is some evidence that the cortico-striatum network, which is involved in the disinhibition of impulse control, is degraded in older adults because of the degeneration of white matter connections between cortex and striatum (Forstmann et al. 2011), the present study suggests that, at least, in this group of older adults the left PMd was as involved in impulse control as it is in younger adults. This finding is consistent with our previous study (Hinder et al. 2012), where a facilitation of left PMd-right M1 interactions early in the preparation period was associated with faster responses in older adults in a similar SRT task. Accordingly, in tasks that are relatively predictable [i.e., SRT as opposed to choice RT (CRT)], older adults maintain the ability for impulse control. Indeed, there is evidence that older adults showed less pronounced MEP suppression in the preparatory period during a CRT task relative to young adults, suggesting declined preparatory function with advancing age (Cuypers et al. 2012). More work is warranted to investigate whether response tasks requiring within- or between-hand choice result in age-related degradation of impulse control. Specifically, the use of an informative cue in a between-hand CRT task may shed a light on effector-specific preparatory effects.

Response Time Delay Induced by M1 TMS

In contrast to left PMd stimulation, only for older adults did ipsilateral (left) M1 stimulation during the preparatory period result in response time delay. This delay (which was most prominent at WS + 250 ms) suggests that ipsilateral M1, as well as contralateral M1, plays a functional role during movement preparation in older adults. A number of studies have reported increased bilateral activation in older adults relative to younger adults during the performance of unilateral movements (e.g., Fujiyama et al. 2012a; Hinder et al. 2011; Riecker et al. 2006; Ward and Frackowiak 2003). Although one view is that the recruitment of bilateral motor cortices in older adults is due to nonselective recruitment (e.g., Langan et al. 2010), the present results suggest that the activation of the ipsilateral M1 plays a functional role, lending support to the HAROLD model (Cabeza et al. 2002), which postulates that reduced asymmetry of motor cortical activation in the aging brain is beneficial for the maintenance of motor performance (Heuninckx et al. 2008). It is conceivable that left M1 stimulation resulted in different effects on response time for the two groups because of age-related differences in interhemispheric connectivity, i.e., left M1 stimulation affected the right (responding) M1 differently in the two groups, resulting in different behavioral effects. However, in a recent study (Hinder et al. 2012) we showed that task-related modulation of M1-M1 interactions was similar for both young and older groups during the preparation period of a fast-as-possible (reaction time) task similar to the task employed in the present study. As such, we feel the explanation of involvement of ipsilateral pathways from left M1 to the responding left hand (in older adults) is the

most parsimonious explanation of the present findings. Thus we suggest that the symmetric impact on response time by stimulation of either M1 during the response preparation observed in older adults is the manifestation of increased functional bilateral M1 activation with advancing age. In contrast, response time reductions by stimulation of ipsilateral left M1 during the response generation stage in both young and older adults are likely due to nonspecific intersensory facilitation caused by TMS. While reduced asymmetric activation of the motor cortices may be beneficial for the task used in the present study, i.e., SRT, it is not necessarily the case that such activation patterns would assist performance in tasks that require selective activation of one or the other hand on the basis of external cues. Indeed, Tandonnet et al. (2011) showed that in a CRT task it is necessary to selectively inhibit the nonresponding hand—possibly via IHI mechanisms (Talelli et al. 2008)—while simultaneously facilitating the responding hand. Because greater activation of ipsilateral M1 during unimanual movement is associated with a release of IHI (i.e., a facilitatory change) from the contralateral to ipsilateral cortex (Talelli et al. 2008), bilateral activation in older adults may therefore counteract the necessary inhibition onto the nonresponding hand if the task requires accurate and rapid selection of the appropriate effector, i.e., a CRT task, thus negatively impacting on accurate and rapid selection of the appropriate effector.

In summary, the findings from the present study indicate that M1 and PMd have distinct roles in the preparation of fast responses, which are characterized as facilitation and inhibition of corticospinal pathways, respectively. In line with previous research (Duque et al. 2012), the left PMd appears to play an important role in inhibitory function associated with impulse control. The present results extend our current understanding of the role of the left PMd during the preparation of responses by suggesting a causal relationship between task performance and left PMd neuronal activity that, at least in this simple motor task, was unaffected by advancing age. Specifically, we demonstrated a temporally specific functional role of the left PMd in regulating inhibitory function related to impulse control in the early preparatory period. A second main finding was that, particularly for older adults, M1 ipsilateral to the responding hand assumed a functional role during movement preparation. Transient disruption of its function resulted in delayed response time, consistent with the view that the bilateral activation of M1 in older adults during unimanual actions is functional and may help to compensate for motor slowing that occurs with advancing age.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: H.F., M.R.H., and J.J.S. conception and design of research; H.F. and M.R.H. performed experiments; H.F. analyzed data; H.F., M.R.H., and J.J.S. interpreted results of experiments; H.F. prepared figures; H.F. drafted manuscript; H.F., M.R.H., and J.J.S. edited and revised manuscript; H.F., M.R.H., and J.J.S. approved final version of manuscript.

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