

Age-related Differences in Corticomotor Excitability and Inhibitory Processes during a Visuomotor RT Task

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Abstract

■ This study tested the postulation that change in the ability to modulate corticospinal excitability and inhibitory processes underlie age-related differences in response preparation and generation during tasks requiring either rapid execution of a motor action or actively withholding that same action. Younger ($n = 13$, mean age = 26.0 years) and older adults ($n = 13$, mean age = 65.5 years) performed an RT task in which a warning signal (WS) was followed by an imperative signal (IS) to which participants were required to respond with a rapid flexion of the right thumb (go condition) or withhold their response (no-go condition). We explored the neural correlates of response preparation, generation, and inhibition using single- and paired-pulse TMS, which was administered at various times between WS and IS (response preparation phase) and between IS and onset of

response-related muscle activity in the right thumb (response generation phase). Both groups exhibited increases in motor-evoked potential amplitudes (relative to WS onset) during response generation; however, this increase began earlier and was more pronounced for the younger adults in the go condition. Moreover, younger adults showed a general decrease in short-interval intracortical inhibition during response preparation in both the go and no-go conditions, which was not observed in older adults. Importantly, correlation analysis suggested that for older adults the task-related increases of corticospinal excitability and intracortical inhibition were associated with faster RT. We propose that the declined ability to functionally modulate corticospinal activity with advancing age may underlie response slowing in older adults. ■

INTRODUCTION

The ability to quickly respond (or withhold a planned response) on the basis of an external cue is one of the crucial aspects of cognitive and motor control that allows individuals to appropriately adapt to changes in the environment. There is, however, a large volume of literature documenting progressive slowing of RTs as we age (e.g., Hunter, Thompson, & Roger, 2001; Salthouse, 1991, 1996; Morgan et al., 1994), which may affect an individual's quality of life by compromising work productivity, mobility, and independence. Because RT is a good indicator of the functional integrity of the CNS, RT slowing has been associated with age-related decline in central information processing including sensorimotor integration and motor generation (Yordanova, Kolev, Hohnsbein, & Falkenstein, 2004). A number of recent studies have suggested that the major source of slowing with age may be the degradation of motor response generation processes, rather than delays in stimulus processing or response selection (Roggeveen, Prime, & Ward, 2007; Falkenstein, Yordanova, & Kolev, 2006; Yordanova et al., 2004). In these studies motor-related potentials of EEG indicated that the RT delay in

older adults was associated with mechanisms relating to the activation of contralateral motor areas responsible for triggering the responding effector (Kolev, Falkenstein, & Yordanova, 2006; Yordanova et al., 2004). The deficient motor activation in older adults may reflect reduced excitability of corticospinal motor neurons with age that has been reported in studies using TMS (Peinemann, Lehner, Conrad, & Siebner, 2001; Rossini, Desiato, & Caramia, 1992).

TMS provides the means to assess cortical excitability in a noninvasive manner (Rossini, Rossini, & Ferreri, 2010; Hallett, 2000; Rothwell, 1997) and provides accurate temporal information about the regulation of neural processes. The technique involves producing a magnetic field through a coil held over the scalp that induces rapid changes in the magnetic field that consequently delivers brief electrical currents in the brain. The physiological effect of TMS over the motor cortex (M1) can be quantified by measuring the motor-evoked potential (MEP) with surface EMG techniques. The MEP elicited by single-pulse TMS is a compound measure that may reflect both cortical and spinal excitability (Hallett, 2000). In the paired-pulse TMS paradigm, however, two separate pulses with a short ISI (3 msec) are delivered to the motor cortex through the same TMS coil to provide a measure of the involvement

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of GABA_A-ergic short-interval intracortical inhibition (SICI; Kujirai et al., 1993).

Using TMS, a number of studies have investigated the activity of excitatory and inhibitory interneurons during response preparation (Tandonnet, Garry, & Summers, 2010; Davranche et al., 2007; Hasbroucq, Mouret, Seal, & Akamatsu, 1995), selection (Leocani, Cohen, Wassermann, Ikoma, & Hallett, 2000; Chen, Yaseen, Cohen, & Hallett, 1998), and execution (Tandonnet, Garry, & Summers, 2011; Yamanaka et al., 2002; Chen et al., 1998) in healthy younger adults. Increases in corticospinal excitability in the responding hand, beginning around 120 msec following the IS have been observed in a variety of RT paradigms including go/no-go RT (Yamanaka et al., 2002; Leocani et al., 2000; Hoshiyama et al., 1996, 1997), simple RT (Chen et al., 1998; Rossini, Zarola, Stalberg, & Caramia, 1988), and choice RT tasks (Tandonnet et al., 2011; Leocani et al., 2000). Only a few studies (Fujiyama, Tandonnet, & Summers, 2011; Levin et al., 2011), however, have investigated age-related changes in the time course of corticospinal excitability and inhibitory processes during an RT task. To examine the effects of aging on preparatory and motor generation stages, Fujiyama et al. (2011) applied TMS at three time points during a go/no-go RT task: onset of warning and imperative signals and onset of response-related EMG activity. Older adults showed slower RT to go signals than younger adults with TMS measures revealing age-related differences only at the time of EMG onset, when selective facilitation was required. By contrast, younger adults demonstrated a greater increase of corticospinal excitability than older adults. The observed age differences immediately before the EMG activity is consistent with the EEG studies, suggesting the motor generation stage as the source of RT delay in older adults (Falkenstein et al., 2006; Kolev et al., 2006; Yordanova et al., 2004). In contrast, Levin and colleagues (2011) reported that during a simple RT task older adults exhibited changes in corticospinal excitability that were larger and occurred earlier with respect to the onset of the go response than a group of younger adults. The authors suggested that this earlier “facilitation” of the corticospinal pathways was a manifestation of an optimized preparatory strategy that may be beneficial for compensating for motor slowing in older adults. However, correlations between these neurophysiological changes and performance (RT speed) were not assessed. Accordingly, the relationship between the dynamics of response generation at the level of the primary motor cortex (M1) in older adults and age-related changes in RT, particularly in the situation where the required response is uncertain, remains unclear.

To elucidate the role of M1 in response preparation and generation processes in older adults, in this study, we applied single- and paired-pulse TMS protocols during a visual go/no-go RT task requiring participants to execute a speeded manual response to go signals and to withhold any overt response to no-go signals. Thus, correct performance requires the suppression of the motor response in

a no-go trial (van den Wildenberg et al., 2010). The go/no-go task is particularly attractive in this context, because it reflects an important characteristic of motor behavior, which is the ability to selectively execute or withhold voluntary movements to accommodate environmental demands. Additionally, our previous study (Fujiyama et al., 2011) used the go/no-go paradigm and revealed slower RT in older adults relative to younger adults; this enables us to examine the age-related changes in the dynamics of motor generation processes in the corticospinal pathway in a task where RT delays in older adults are to be expected.

Previous studies using the go/no-go task in conjunction with single-pulse TMS have reported increased corticospinal excitability 120–300 msec after go signals and decreased excitability 160–200 msec after the no-go signal presentation (Yamanaka et al., 2002). The reduction of MEP amplitude after a no-go signal has been hypothesized to reflect the operation of an inhibitory function related to withholding a response (Leocani et al., 2000; Hoshiyama et al., 1996, 1997). Thus, TMS has proven to be a useful technique in revealing the interplay between excitatory and inhibitory neural mechanisms in the go/no-go decision-making process in younger healthy adults.

In the current study, we used a go/no-go RT task (Fujiyama et al., 2011) in which each trial began with a warning signal (WS), followed after a short fixed foreperiod (500 msec) by the IS. Our previous study (Fujiyama et al., 2011) focused on age-related differences in the response generation stage (immediately before the EMG onset) of sensorimotor information processing with equal probability of go and no-go signals. However, the specific time course of corticospinal excitability and inhibitory function during motor preparation (i.e., before the response stage) in young and older adults has not been examined. Previous studies have suggested that presenting go and no-go signals with equal probability may not be optimal for inducing preparation of the go response (Nakata et al., 2005; Casey et al., 2001). Therefore, in this study, we aimed to encourage preparatory responses by employing a higher probability for go trials (i.e., 70% go, 30% no-go) and examined the modulation of corticospinal excitability and inhibition at five different time points between the onset of a WS and onset of the voluntary EMG activity. As the increased go probability in the current study was likely lead to increased response preparation, we hypothesized that changes in cortical excitability relating to this preparation, as well as evidence for active inhibition of the prepared response (to prevent early release on go trials or to prevent release on no-go trials), would be observed (e.g., Tandonnet et al., 2010; Sinclair & Hammond, 2008; Davranche et al., 2007; for a review, see Cohen, Sherman, Zinger, Perlmutter, & Prut, 2010). To our knowledge, this study is the first to track the corticospinal excitability and inhibitory circuits over multiple time points in older adults during the performance of a task involving execution or inhibition.

METHODS

Participants

There were 26 right-handed healthy volunteers consisting 13 older adults recruited from the community (3 men, 10 women; mean age = 65.5 years, $SD = 6.5$ years) and 13 younger adults recruited from the students of the University of Tasmania (3 men, 10 women; mean age = 26.0 years, $SD = 6.4$ years). Within the older group, participants had similar socioeconomic status and were involved in active social activities and/or paid employment. All participants completed at least high school education. 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, symptomatic, and 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 before participation in the study.

Go/No-go Task

Participants were comfortably seated on a chair with their right arm placed on a table situated in front of them. The right hand was held in a neutral position with the thumb resting on a button mounted on the top of a vertical cylinder fixed to the table approximately 30 cm in front of participants. At about 50 cm in front of participants at eye level, two light-emitting diodes (LEDs) were vertically arranged on a black panel 3.0 cm apart. The higher orange LED served as a WS, whereas the lower LED was illuminated either green or red (IS) to indicate go or no-go responses, respectively. Each trial began with presentation of the WS for 500 msec, followed immediately by the IS for 500 msec. The intertrial interval was 5 sec. The green and red LEDs were illuminated in a pseudorandom order (see Procedure).

Participants were instructed to prepare during the WS interval (500 msec) to either press the button as quickly as possible with their right thumb upon presentation of the go green LED signal or not to press the button upon presentation of the no-go red LED signal. Participants were also informed that the go signal would occur more frequently than the no-go signal.

Procedure

Participants first performed two blocks of the go/no-go task (WS + IS) without TMS delivery (no-TMS with WS). In each block, there were 20 trials of which 70% were go trials and 30% were no-go trials. The onset of muscle responses to go signals in the second of these blocks were marked (visual inspection) and the average latency between the go signal and the onset of muscle activity for each participant was established and referred to as base-

line premotor time (pre-MT) in the absence of TMS. This value was subsequently used to specify the timing of TMS delivery. After the no-TMS with WS blocks, an additional no-TMS block of 20 trials was conducted without a WS (no-TMS without WS) to evaluate the influence of a WS on motor preparation and RTs. Five experimental blocks, each consisting 122 trials, were then performed with 3–5 min of rest between blocks. The probability of go signals was set at 70%. Of the 122 trials in each block, there were 100 WS trials (70 go trials, 30 no-go trials), with half of the WS trials involving single-pulse TMS and half involving paired-pulse TMS (see TMS Procedure and EMG Recording for more details). In the same 122 trial blocks, 10 WS trials (seven go trials, three no-go trials) were presented without TMS to track participants' RT throughout the experiment in the absence of TMS. The remaining 12 trials were "catch" trials, in which the WS was presented but no IS followed. The purpose of catch trials was to discourage premature responses before the IS. These catch trials involved six single-pulse and six paired-pulse TMS.

In go, no-go, and catch trials, single- and paired-pulse TMS was delivered at five time points to track the time course of excitability and inhibition (see Figure 1). The first two TMS delivery times were within the foreperiod: coincident with the onset of the WS and at 250 msec after the WS. The remaining three TMS delivery times were between the onset of the IS and the average predetermined pre-MT for each individual. Specifically, TMS was delivered at $1/4$, $1/2$, and $3/4$ of the average pre-MT (previously determined for each participant from the no-TMS block performed earlier) following the IS. For catch trials, TMS was only delivered at the three time points during the pre-MT period. The mean pre-MTs were 229.92 msec ($SD = 36.78$ msec, range = 165–276 msec) for younger adults and 296.95 msec ($SD = 54.84$ msec, range = 242–373 msec) for older adults. Accordingly, mean TMS delivery times at $1/4$, $1/2$, and $3/4$ MT were 57, 115, and 172 msec, respectively, for younger adults and 74, 48, and 222 msec, respectively, for older adults.

TMS Procedure and EMG Recording

TMS was applied to the left motor cortex using a standard figure-of-eight coil (7 cm diameter of each wing) connected

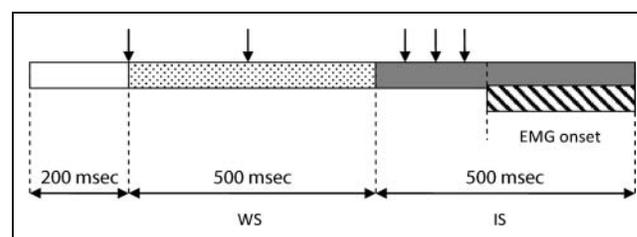


Figure 1. Schematic illustrating the time course of the visual warning (dotted), IS (filled), response-related EMG activity (shaded), and TMS delivery. TMS pulses are indicated with downward-facing arrows.

to a Magstim BiStim unit (Magstim Company, Dyfed, UK). The coil was tangentially placed over the optimal position of the head to induce a posterior–anterior current flow and to elicit MEPs in the right flexor pollicis brevis (FPB) muscle. EMG surface electrodes (Ag–AgCl) were placed over the FPB in a belly-tendon montage and signals were amplified with a gain of 1000, band pass filtered (10–500 Hz), and sampled at 2000 Hz using a 16-bit AD system (CED 1902, Cambridge, UK). EMG data were fed to disk for off-line analysis. The individual resting motor threshold (rMT) was determined as the lowest stimulus intensity that produced MEPs of greater than 50 μ V in at least three of five consecutive trials. To assess SICI, the two Magstim units were configured to deliver paired-pulse stimulation with an ISI of 3 msec (Kujirai et al., 1993). The intensity of the test TMS pulse was set at 120% of rMT. The intensity of the conditioning stimulus was initially set at 70% of rMT and adjusted upward or downward until the MEP was suppressed by at least 50%, although still present on all trials in the rest condition. This intensity was then maintained throughout the experiment. On the basis of a recent demonstration that SICI is systematically affected by test stimulus intensity independent of corticospinal excitability (and therefore MEP size; Garry & Thomson, 2009), we opted to maintain a constant test TMS intensity throughout the experiment. To establish baseline measures of corticospinal excitability and SICI, 15 single-pulse and 15 paired-pulse TMS were delivered in a random order while the participant remained at rest. As previously described, in both go and no-go trials, TMS was delivered at one of five different time points during each trial (see Figure 1). The first two TMS delivery times were within the foreperiod, and the remaining three TMS delivery times were between onset of IS and the average pre-MT for each individual.

Data Processing and Analysis

In presenting the results, the data are expressed as mean \pm 95% confidence intervals. RTs were calculated from the second no-TMS block of trials performed at the beginning of the testing session. RT was defined as the time between the onset of the go signal and the time of the button press. The time window allowed for a response was 1000 msec after the onset of the go signal. RT was further divided into pre-MT and MT (Botwinick & Thompson, 1966). Pre-MT was defined as stated above, whereas MT was the time interval between the onset of movement-related EMG activity in the FPB of the right hand and the time of the button press (Hasbroucq et al., 1995). Pre-MT is generally considered to reflect the duration of central processes including central motor processes, whereas MT provides an index of the duration of peripheral motor execution processes (e.g., Tandonnet, Burle, Vidal, & Hasbroucq, 2003). MEP size was measured by calculating the maximum absolute value from 20 to 100 msec post-TMS and averaged across all trials in each condition for each participant. Trials in which RMS EMG exceeded 12.5 μ V (Carson et al., 2004) during the

40 msec immediately preceding the TMS pulse were discarded. The mean MEP amplitude at each time point was then normalized for each participant as a percentage of the mean MEP amplitude obtained at the onset of WS for that participant. Similarly, SICI ratio (conditioned MEP/nonconditioned MEP) was normalized for each participant to the mean SICI values obtained at the onset of WS. Thus, a normalized SICI ratio larger than 1 reflects release of inhibition, whereas a value lower than 1 indicates increased inhibition, relative to the onset of WS.

RT, pre-MT, and MT data were analyzed using independent sample *t* tests to compare participant groups. The effect of a WS was examined using paired sample *t* tests to compare RTs in the second no-TMS trial block with WSs and the no-TMS block without WSs. To investigate whether MEP amplitudes and SICIs were modulated during the task relative to baseline (rest), non-normalized MEP amplitudes and SICI values at each time point were compared with the baseline condition using pairwise comparisons for each group. Normalized MEP data were analyzed by a 2 (Group: younger, older) \times 2 (Response Type: go, no-go) \times 4 [Timing of TMS Delivery: 250 msec after the WS (WS 250 msec), 1/4 pre-MT, 1/2 pre-MT, 3/4 pre-MT] repeated measures ANOVA. If the sphericity assumption was violated, Greenhouse–Geisser's degrees of freedom adjustment was applied to the critical *p* values. Tukey's HSD post hoc procedure was used to explore significant main and interaction effects. The critical *p* value was set at .05. Cohen's *d* and partial eta squared (η^2) values were provided as measure of effect size with cut-offs of ≥ 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^2 (Sink & Stroh, 2006). The relationship between TMS measures and pre-MT was examined by calculating Spearman's rank correlation coefficients between normalized MEP amplitude and SICI (relative to the onset of WS) in go trials and pre-MT obtained from non-TMS trials in the experimental TMS blocks for each group.

RESULTS

As age differences were of primary interest in this study, only main effects and interactions involving group as a factor will be described in detail, whereas some nonsignificant results will also be reported if theoretically relevant.

Behavioral Measures: No-TMS Trials

Younger adults exhibited significantly faster RT when responding to go signals than older adults, which was fully accounted for by the age-related difference in pre-MT, as peripheral neuromuscular processes (MT) did not differ between age groups (Table 1). Because response accuracy data were proportions, arcsine-root transformations were applied (Howell, 2009). For clarity, nontransformed data are reported in the text. Response accuracy was not

Table 1. Mean (*SD*) of RT, Pre-MT, and MT in Milliseconds for Younger and Older Adults in WS Trials and Statistical Values

	<i>RT</i>	<i>Pre-MT</i>	<i>MT</i>
Younger group	332.97 (46.09)	229.92 (36.78)	111.23 (69.69)
Older group	406.98 (79.40)	295.95 (54.84)	111.02 (76.81)
Statistical values	$t(24) = 2.91, p = .007$	$t(24) = 3.61, p = .001$	$t(24) = 0.01, p = ns$
Effect size	$d = 1.14$	$d = 1.41$	$d = 0.003$

significantly different between younger ($M = 98.39\% \pm 1.92\%$) and older adults ($M = 98.98\% \pm 1.11\%$), $t(24) = 0.88, p = .393, d = 0.34$, suggesting that there was no speed-accuracy trade-off in older adults. The younger group utilized the WS, as indicated by faster RT in WS trials ($M = 332.97 \pm 46.09$ msec) compared with trials without WS ($M = 366.50 \pm 58.15$ msec), $t(12) = 3.33, p = .006, d = 0.93$. In contrast, for older adults, the WS did not significantly reduce RT (WS, $M = 406.13 \pm 79.40$ msec; no-WS, $M = 426.13 \pm 97.04$ msec), $t(12) = 1.38, p = .193, d = 0.38$.

TMS Measures

On average, the final conditioning stimulus intensities were 33.85% ($SD = 5.30\%$) of the maximum stimulator output for younger adults and 33.54% ($SD = 7.62\%$) of the maximum stimulator output for older adults. These intensities correspond to 73.06% ($SD = 10.18\%$) of rMT

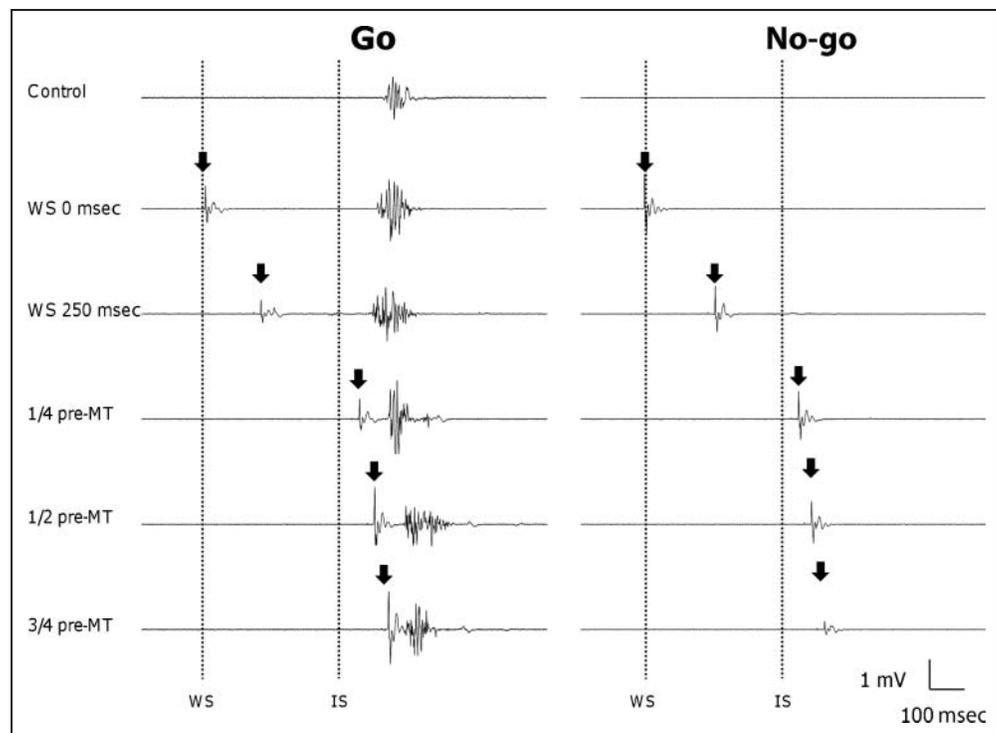
for younger adults and 72.60% ($SD = 9.80\%$) of rMT for older adults.

There was no significant difference between rMTs of younger ($M = 46.77\% \pm 7.08\%$) and older adults ($M = 45.85\% \pm 7.03\%$), $t(24) = 0.33, p = .741, d = 0.13$. Figure 2 illustrates typical EMG recordings during TMS experimental trials. The rejection rate (%) to which arcsine-root transformations were applied, based on EMG before TMS delivery (see Methods), did not statistically differ between younger ($M = 3.45\% \pm 4.02\%$) and older adults ($M = 6.59\% \pm 9.83\%$), $t(24) = 1.16, p = .258, d = 0.45$.

MEP Amplitude

There were no significant differences between younger ($M = 0.50 \pm 0.35$ mV) and older adults ($M = 0.54 \pm 0.34$ mV) in baseline (rest) MEP amplitudes, $t(24) = 0.29, p = .772, d = 0.12$.

Figure 2. Representative FPB EMG traces from a typical younger participant during the go/no-go task in the go (left) and no-go (right) conditions. Vertical dotted lines indicate the onsets of the WS and IS. Time of stimulation is shown on the left. Arrows on the EMG traces indicate stimulus artifact from the TMS pulses, followed by MEP and voluntary EMG (pre-MT = the latency between the onset of the IS and the first occurrence of the onset of response-related EMG activity).



General Changes in Corticospinal Excitability (Comparison with Baseline Resting Condition)

During the RT task, younger adults exhibited a generalized increase in MEP amplitude (across all time points) relative to the baseline (rest) condition ($ps < .04$, $d > 0.63$) irrespective of whether the IS indicated a go or no-go response. However, for the older adults, MEP amplitudes were significantly larger than baseline only at the 3/4 pre-MT time point in go trials, $t(12) = 3.02$, $p = .011$, $d = 0.83$.

Time Course of Corticospinal Excitability

Analysis of normalized MEP amplitude (relative to WS onset) revealed significant main effects of Response Type, $F(1, 24) = 11.54$, $p = .002$, $\epsilon = 1.00$, $\eta^2 = 0.32$, timing, $F(3, 72) = 19.79$, $p < .001$, $\epsilon = 0.53$, $\eta^2 = 0.45$, and significant interactions of Group \times Timing, $F(3, 72) = 6.14$, $p < .001$, $\epsilon = 0.53$, $\eta^2 = 0.20$, and Response Type \times Timing, $F(3, 72) = 17.64$, $p < .001$, $\epsilon = 0.77$, $\eta^2 = 0.42$. These main effects and interactions were best interpreted in a significant three-way interaction of Group \times Timing \times Response Type, $F(3, 72) = 3.37$, $p = .023$, $\epsilon = 0.77$, $\eta^2 = 0.12$. As can be seen in Figure 3A and B, both younger and older adults showed increased MEP amplitude at 3/4 pre-MT in go trials compared with the other time points (younger, $ps < .001$; older, $ps < .041$), but the increase was larger in younger adults than older adults ($p < .001$). In younger adults, the two response types started to show divergent trajectories at 1/2 pre-MT with MEP amplitudes at 1/2 ($p = .023$) and 3/4 pre-MT ($p < .001$) being significantly higher during go trials than no-go trials (Figure 3A). In contrast, differences in MEP amplitude between two response types was only evident at 3/4 pre-MT ($p = .002$) in older adults (Figure 3B). There was also evidence of MEP suppression at 1/4 pre-MT for both re-

sponse types in young adults with MEP amplitudes being significantly lower at other time points ($ps < .044$). To investigate whether the suppression at 1/4 pre-MT was evident when no IS was presented, the “catch” trials were analyzed using a 2 (Group) \times 4 (Timing of TMS Delivery) repeated measures ANOVA. The catch trial analysis revealed a significant interaction of Group \times Timing, $F(3, 72) = 5.30$, $p = .002$, $\epsilon = 1.00$, $\eta^2 = 0.18$. Post-hoc analyses indicated that in young adults MEP amplitude at the time point equivalent to 1/4 pre-MT during normal trials was significantly smaller ($M = 0.43 \pm 0.09$) than at other stimulation time points (>0.76 , $ps < .009$), except 3/4 pre-MT ($M = 0.62 \pm 0.12$; $p = .061$). In contrast to younger adults, older adults did not show modulation of MEP amplitudes across time points in either normal or catch trials ($p > .215$).

SICI

There were no statistically significant differences in baseline (rest) SICI values between younger ($M = 0.47 \pm 0.15$) and older adults ($M = 0.57 \pm 0.15$), $t(24) = 1.71$, $p = .100$, $d = 0.67$.

General Changes in Intracortical Inhibition (Comparison with Baseline Resting Condition)

For young adults, SICI was significantly reduced at 250 msec, 1/2, and 3/4 pre-MT relative to baseline ($ps < .040$, $d > 0.64$) regardless of the nature of the IS (i.e., go or no-go). For older adults, SICI at 3/4 pre-MT in go trials was significantly reduced relative to baseline, $t(12) = 4.20$, $p = .001$, $d = 1.17$. At all other TMS stimulation time points, the older group SICI did not differ significantly from baseline ($ps > .089$, $ds < 0.527$).

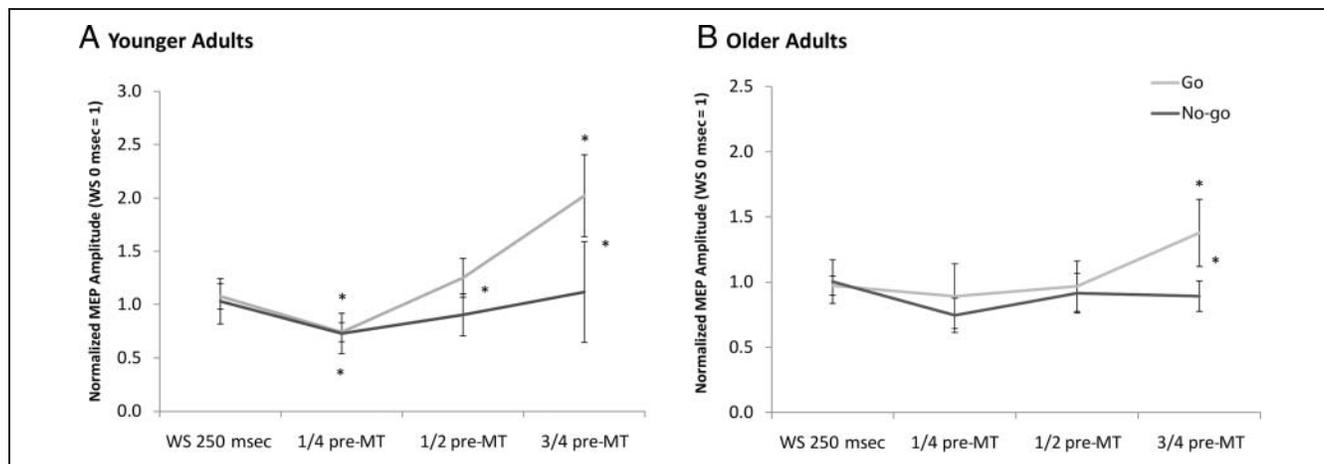


Figure 3. Mean normalized MEP amplitude for younger (A) and older (B) adults across conditions (WS = onset of WS; pre-MT = the latency between the onset of the IS and the first occurrence of the motor response) in go and no-go trials. Asterisks above data points indicate statistically significant differences relative to other TMS time points, whereas asterisks between data points reflect significant differences between response types ($p < .05$). Error bars indicate 95% confidence interval.

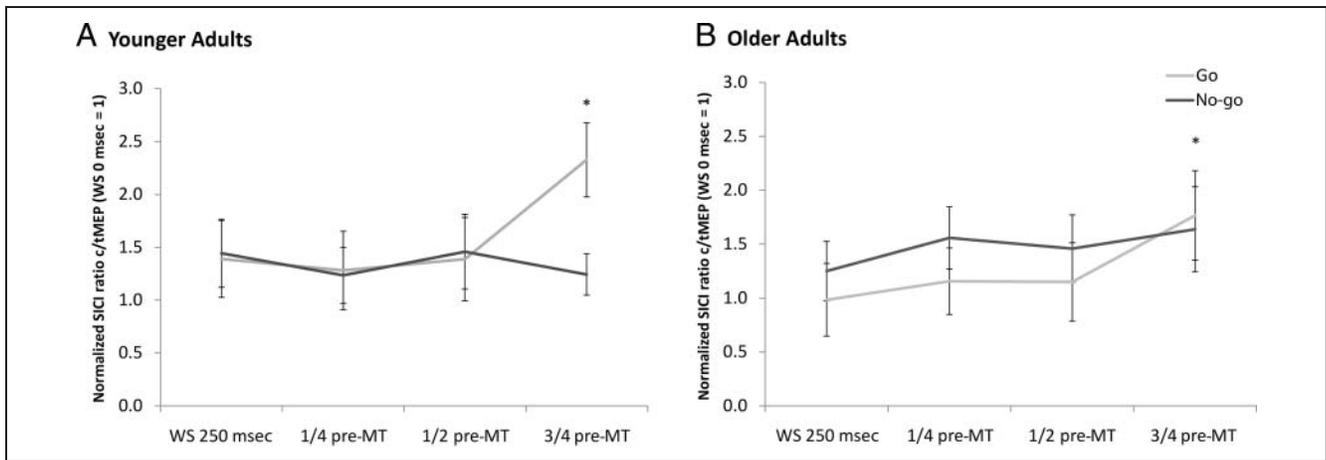


Figure 4. Mean normalized SICI in younger (A) and older (B) adults across conditions (WS = onset of WS; pre-MT = the latency between the onset of the IS and the first occurrence of the motor response) in go and no-go trials. Asterisks indicate statistically significant differences relative to other TMS time points ($p < .05$). Error bars indicate 95% confidence interval.

Time Course of Intracortical Inhibition

For normalized SICI, there was a significant main effect of Timing, $F(3, 72) = 6.96, p < .001, \epsilon = 0.99, \eta^2 = 0.22$ and an interaction of Response Type \times Timing, $F(3, 72) = 5.18, p = .002, \epsilon = 0.59, \eta^2 = 0.18$. Minimal changes in SICI were observed for either group across early time intervals; however, a significant reduction in inhibition (higher SICI value) was observed at 3/4 pre-MT when a go response was signaled relative to all other time points ($ps < .002$; see Figure 4A and B). The main effect of group and all interactions including group as a factor were not significant ($ps > .277$).

Correlation between TMS Variables and RT Measures

The relationship between TMS variables and pre-MT obtained from the non-TMS trials during the experimental blocks was investigated using Spearman's rank correlation coefficients. In younger adults, no significant relationships between TMS measures and pre-MT were observed. In contrast, in older adults normalized MEP amplitude (relative to WS onset) showed small to large negative correlations with pre-MT across TMS time points (Table 2). In particular, MEP amplitudes at WS 250 msec (Figure 5A) and 3/4 pre-MT (Figure 5B) were significantly correlated to pre-MT, suggesting that older individuals who showed MEP facilitation in these time points had a faster pre-MT. Furthermore, SICI value at WS 250 msec in older adults was positively correlated to pre-MT, suggesting that increased intracortical inhibition in the preparation period resulted in faster pre-MT.

DISCUSSION

In this experiment, we investigated, for the first time, the time course of corticospinal excitability and inhibitory

processes in younger and older adults in a visuomotor RT task. At the behavioral level, age-related increases in RT were evident when the IS required a volitional (go) response. Consistent with previous studies (Fujiyama et al., 2011; Clarkson, 1978; Botwinick & Thompson, 1966; Weiss, 1965), when total RT was decomposed into pre-MT and MT, the source of the slowing in the older adults was predominantly the premotor component, that is, the delay between IS and onset of muscle activity in the responding hand. No age-related difference was observed in MT, that is, the time from EMG onset until force production reached the threshold level required to register a button press response. On the basis of our previous work (Fujiyama et al., 2011), we hypothesized that increases in corticospinal excitability would be observed for both groups, but these increases would be more pronounced and occur earlier in the younger adults. As predicted, we found greater excitability changes just before the volitional EMG burst (3/4 pre-MT) in young adults than older adults. The present data expand on our previous study by showing that younger adults also increased

Table 2. Correlation Coefficients between Normalized MEP Amplitude and SICI (Relative to the Onset of WS) and Pre-MT for Younger and Older Adults

TMS Time	MEP Amplitude		SICI	
	Younger	Older	Younger	Older
WS 250 msec	-.124	-.791**	-.033	.676*
1/4 pre-MT	.151	-.242	.118	.258
1/2 pre-MT	-.146	-.495	.110	.429
3/4 pre-MT	-.226	-.571*	.110	.110

* $p < .05$.

** $p < .01$.

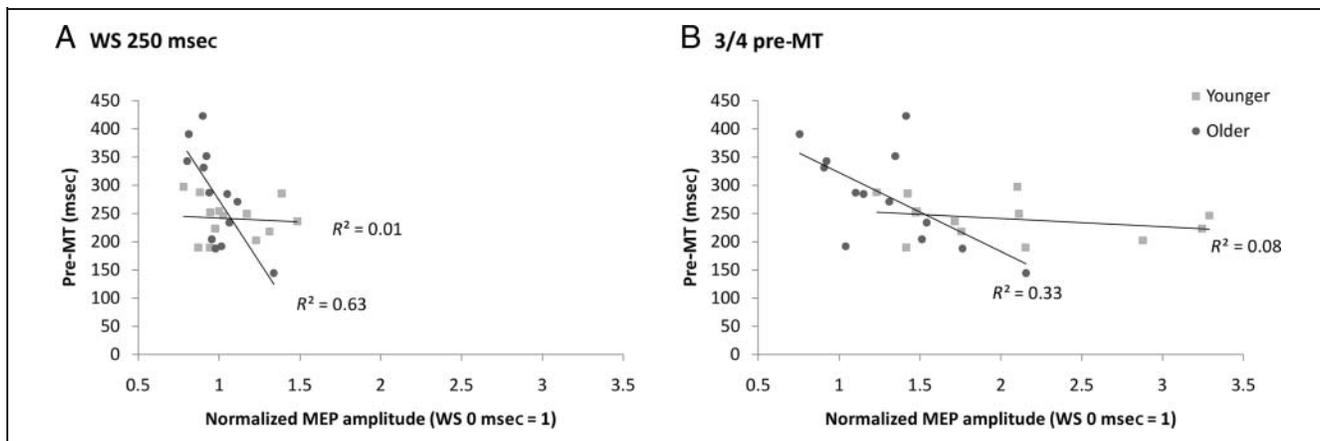


Figure 5. Correlations between pre-MT and normalized MEP amplitude (relative to WS 0 msec) at WS 250 msec (A) and 3/4 pre-MT (B) in younger and older adults. Circles are data from older adults, and squares are data from younger adults.

their excitability earlier during movement generation than older adults (i.e., at 1/2 pre-MT; see Figure 3). With respect to the time course of intracortical inhibition, we predicted and found (see Figure 4) that a release of inhibition, which was of similar magnitude for both age groups, was manifested just before the movement onset. This release of inhibition was not apparent earlier in movement preparation or generation for either group. Taken together, these results provide further evidence to suggest corticospinal excitability and SICI are mediated independently during movement preparation and execution and are affected differently by aging.

Younger adults demonstrated suppression of corticospinal excitability around 60 msec (1/4 pre-MT) following the onset of the IS. Note that the MEP depression at 1/4 pre-MT was also observed in catch trials in which there was no IS, suggesting that the depression of MEP amplitude was associated with preparatory processes rather than because of the processing of IS. The MEP suppression has been reported in previous studies (Tandonnet et al., 2010; Duque & Ivry, 2009; Sinclair & Hammond, 2008) and linked to the prevention of a premature response during movement preparation (Sinclair & Hammond, 2008). In contrast to younger adults, as we hypothesized older adults in the current study did not show the suppression of corticospinal excitability early in the response generation period relative to the excitability noted in the WS period. However, because the increase in excitability in the warning period was less prominent for older adults, a subsequent reduction in excitability (to prevent a premature release of the planned action) may not have been necessary. The discrepancy between modulations of MEP amplitude and SICI suggested that the changes in these parameters were controlled by different mechanisms. It is likely that the suppression of MEPs was produced not via intracortical interneurons but rather via projections from superior (pre)motor areas to M1 (Cohen et al., 2010).

Age-related differences were also evident in the response generation period. Younger adults showed earlier

MEP increases before EMG onset in comparison with older adults. This gradual increase of corticospinal excitability before EMG onset in young adults is in line with previous studies (Tandonnet et al., 2011; Yamanaka et al., 2002; Chen et al., 1998; Rossini et al., 1988). Corticospinal excitability increase in older adults, however, was limited to the period immediately before the onset of EMG activity. It is possible that the time required for corticospinal excitability to reach motor unit activation threshold was shorter in younger adults because corticospinal excitability was already potentiated and the level of the excitability was closer to the threshold, whereas in older adults stronger and longer activation of the corticospinal excitability may be necessary to reach to the threshold. This result is consistent with the findings by Yordanova et al. (2004), demonstrating greater and prolonged motor-related brain potentials in older adults. In contrast to the present results, Levin and colleagues (2011) reported that in a simple RT task increases in corticospinal excitability during the response generation period (i.e., following the IS) occurred earlier for older adults compared with younger adults. There was, however, no age-related difference in RT, suggesting that the earlier increase in corticospinal excitability in older adults may have compensated for any RT slowing that may have otherwise been expected. It is also likely that the early facilitation of MEPs in older adults occurred because in the simple RT paradigm the motor response is completely predictable. In this study, however, there was uncertainty with regard to the required response (i.e., 70% go and 30% no-go) and older adults did not appear to use the WS to prepare the more probable go response. The lack of preparatory changes in corticospinal facilitation, therefore, may reflect a strategy adopted by older adults to reduce the likelihood of behavioral errors caused by making a response to a no-go signal. The prioritization of accuracy over speed in older adults has been noted in a number of contexts (e.g., Smith & Brewer, 1995; Goggin & Stelmach, 1990; Salthouse & Somberg, 1982).

The two groups of participants did not show statistically significant differences in intracortical inhibition (SICI) across the two response types and TMS intervals. There was little change in SICI (relative to the onset of WS) during the warning period, following the IS during no-go trials, or during the early phase of the motor generation period for go responses. Immediately before the onset of EMG activity in go trials, however, there was a release of intracortical inhibition when a go response was required. The reduced level of intracortical inhibition immediately before movement initiation has been observed in other RT tasks (Fujiyama et al., 2011; Sinclair & Hammond, 2008, 2009; Sohn, Wiltz, & Hallett, 2002; Waldvogel et al., 2000; Reynolds & Ashby, 1999) and may contribute to an increase in the net activation of the corticospinal pathway. Although there is some evidence of deficits in intracortical inhibitory function in older adults (Hortobágyi & DeVita, 2006; Peinemann et al., 2001), this study indicates that the time course of SICI modulation mechanisms during response preparation and response generation may be preserved in healthy aging.

Importantly, the significant negative correlations at WS 250 msec and 3/4 pre-MT between MEP amplitude and pre-MT observed in older adults suggest that greater potentiation of corticospinal excitability during the preparation period as well as immediately before the response execution was associated with faster pre-MT for older adults. It has been suggested that nonspecific arousal is important for maintaining sustained attention in an RT task, which requires occasional response inhibition (Shalgi, O'Connell, Deouell, & Robertson, 2007). Therefore, the significant negative correlation between MEP amplitude in the WS interval and pre-MT may reflect the contribution of arousal to faster responding in older adults. Interestingly, intracortical inhibition, which reflects the involvement of intracortical GABA_A-ergic circuits, during the warning interval also showed a significant correlation to pre-MT in older adults indicating that higher levels of intracortical inhibition were associated with faster responses to go signals. This finding, together with the significant correlation of MEP amplitude, suggests that concurrent facilitations of two functionally opposing mechanisms, increase of corticospinal excitability and intracortical inhibition, may be beneficial to faster responses to go signals in older adults. Cohen and colleagues (2010) suggested that there are two functionally opposing processes operating during preparation for movements: increased excitability in corticospinal pathways to prepare fast responses, while M1 cortical inhibition is also potentiated by the influence of dorsal premotor cortex to prevent premature responses. The lack of significant correlations between MEP amplitude and pre-MT in young adults may be partly because of the elevated level of corticospinal excitability at WS onset (relative to the rest) and at all time points during the task in the younger group. That is, because the corticospinal excitability was already

potentiated from the resting state in young adults, further increase of excitability in the corticospinal pathway may not have substantial impact on the production of fast response.

This study provided the first known assessment of the time course in corticospinal excitability and inhibitory process in preparation and response generation during a go/no-go RT task in older adults. In conclusion, age-related changes in this task were characterized by reduced modulation of corticospinal drive during the period between a WS and the IS along with a smaller and delayed increase of corticospinal excitability before EMG onset. As such, the results of this study provide important advances in our understanding of how changes within the corticospinal tract that occur with normal aging are related to the slowing of motor responses.

Acknowledgments

We thank Dr. Oron Levin for his valuable comments on an earlier draft of the manuscript. This research was supported under Australian Research Council's Discovery Projects funding scheme (Project No. DP0770568).

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