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DOI:
10.1152/jn.00144.2016

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Document Version
Peer reviewed version

Citation for published version (Harvard):
MacDonald, H, Cowie, MJ, Cirillo, J & Byblow, WD 2016, 'Proactive modulation of long-interval intracortical inhibition during response inhibition', *Journal of Neurophysiology*, vol. 116, no. 2, pp. 859-867.
https://doi.org/10.1152/jn.00144.2016

Link to publication on Research at Birmingham portal

Publisher Rights Statement:
Published as above, final version of record available at: 10.1152/jn.00144.2016.

Checked 25/7/18.

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Proactive modulation of long-interval intracortical inhibition during response inhibition

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Intracortical Inhibition during Response Inhibition

Keywords

response inhibition; transcranial magnetic stimulation; paired-pulse; motor cortex; intracortical inhibition

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Abstract

Daily activities often require sudden cancellation of pre-planned movement, termed response inhibition. When only a subcomponent of a whole response must be suppressed (required herein on Partial trials), the ensuing component is markedly delayed. The neural mechanisms underlying partial response inhibition remain unclear. We hypothesized that Partial trials would be associated with non-selective corticomotor suppression and that GABA$_B$-receptor mediated inhibition within primary motor cortex might be responsible for the non-selective corticomotor suppression contributing to Partial trial response delays. Sixteen right-handed participants performed a bimanual anticipatory response inhibition task while single and paired-pulse transcranial magnetic stimulation was delivered to elicit motor evoked potentials in the left first dorsal interosseous muscle. Lift times, amplitude of motor evoked potentials and long-interval intracortical inhibition were examined across the different trial types (Go, Stop-Left, Stop-Right, Stop-Both). Go trials produced a tight distribution of lift times around the target, whereas those during Partial trials (Stop-Left and Stop-Right) were substantially delayed. The modulation of motor evoked potential amplitude during Stop-Right trials reflected anticipation, suppression and subsequent re-initiation of movement. Importantly, suppression was present across all Stop trial types, indicative of a “default” non-selective inhibitory process. Compared with blocks containing only Go trials, inhibition increased when Stop trials were introduced but did not differ between trial types. The amount of inhibition was positively correlated with lift times during Stop-Right trials. Tonic levels of inhibition appear to be proactively modulated by task context and influence the speed at which unimanual responses occur after a non-selective “brake” is applied.

New & Noteworthy

The ability to cancel a pre-planned movement, termed response inhibition, is essential for adaptable motor control. Participants performed a bimanual anticipatory response inhibition task while single and paired-pulse transcranial magnetic stimulation was delivered. The modulation of motor evoked potential amplitude during partial response trials reflected anticipation, suppression and subsequent re-initiation of movement. Importantly, suppression was present across all stop trial types, indicative of a "default" non-selective inhibitory process.

Introduction

The ability to cancel a pre-planned movement, termed response inhibition, is essential for adaptable motor control. Response inhibition relies upon a cortico-subcortical network (Aron and Poldrack 2006; Chambers et al. 2006; Coxon et al. 2009; Coxon et al. 2012; Zandbelt et al. 2013) that inhibits corticospinal neurons (CSNs) within the primary motor cortex (M1) in order to suppress descending motor output (Stinear et al., 2009). It is known that gamma-aminobutyric acid (GABA) mediated interneurons within M1 exert powerful inhibitory effects on CSNs (Jones 1993; Keller 1993). However, the role of GABA-ergic inhibition during response inhibition is not fully understood.

Response inhibition can be proactive when stopping demands are anticipated, or reactive when stop signals are presented unexpectedly (Aron and Verbruggen 2008). Transcranial magnetic stimulation (TMS) has been used to assess the temporal modulation of corticomotor excitability (CME) during both types of response inhibition. Proactive stopping is suggested to recruit the indirect basal ganglia pathway to selectively decrease CME for only the movement cued to stop (Aron and Verbruggen 2008; Cai et al. 2011; Majid et al. 2013). A topic of current debate is whether reactive stopping can be achieved selectively (Xu et al. 2014), given that several lines of evidence indicate a transient process in which stopping response preparation suppresses movement non-selectively. For example, when successful stopping can be achieved by inhibiting all movement, CME is reduced in response-irrelevant muscles (Badry et al. 2009; Cai et al. 2012; Coxon et al. 2006; Greenhouse et al. 2012). When only a subcomponent of a prepared response is required to stop (Partial trials), the remaining response is delayed (Coxon et al. 2007; 2009; Coxon et al. 2012; MacDonald et al. 2014; MacDonald et al. 2012). Interestingly there is also a concomitant reduction in CME for the responding left hand on trials when only the right hand is cued to stop (MacDonald et al. 2014), indicative of a non-selective inhibitory process that cancels all prepared effectors. The subsequent delay may arise as a consequence of having to initiate a new response. While these studies suggest reactive response inhibition is non-selective, the primary suppressive mechanism remains unclear.

Intracortical networks within M1 are the final cortical modulators of motor output. Paired-pulse TMS can be used to investigate GABA-ergic inhibition within M1 and identify the contribution of distinct intracortical networks to motor performance (Reis et al. 2008). $GABA_A$-receptor mediated short-interval intracortical inhibition (SICI), assessed using a subthreshold conditioning stimulus followed 1-6 ms later by a suprathreshold test stimulus (Kujirai et al. 1993), is involved with movement initiation and prevention. SICI is selectively reduced during movement initiation (Reynolds and Ashby 1999; Stinear and Byblow 2003; Zoghi et al. 2003). While $GABA_A$-mediated networks within M1 are essential for specific, point-to-point control over motor representations, SICI is non-selectively increased following stop signal presentation during unimanual response inhibition (Coxon et al. 2006). However, MacDonald et al. (2014) could not temporally reconcile non-selective CME suppression with an increase in SICI during partial response inhibition, making it an unlikely candidate mechanism underlying the behavioral and neurophysiological findings observed when only a subcomponent of a prepared response must be terminated.

Within M1, $GABA_B$-receptor mediated inhibition can be assessed as long-interval intracortical inhibition (LICI) using suprathreshold conditioning and test stimuli separated by 50-200 ms (Valls-Solé et al. 1992; Wassermann et al. 1996). LICI engages pre-synaptic receptors (Bettler et al. 2004), typically associated with tonic inhibitory effects. Interestingly, one study reported decreased LICI in a Go/No-Go task (Sohn et al. 2002) but did not assess LICI using an optimal interstimulus interval (Sanger et al. 2001) or use conditioning stimulus intensities that allowed increases in LICI to be observed. Therefore, the role of LICI in reactive response inhibition is yet to be established.

There were three aims of the present study. First, we wanted to confirm and extend on the finding that Partial trials are associated with non-selective CME suppression as demonstrated by MacDonald et al. (2014). We hypothesized that CME, as evident by MEP amplitude, would be reduced during Partial trials, supporting a model of non-selective suppression (MacDonald et al. 2014), and that CME suppression would occur at equivalent time points whether one or both sides were cued to stop. Second, we hypothesized that LICI would be up-regulated during response inhibition trials compared with Go trials irrespective of Stop trial type i.e., indicative of a non-selective inhibitory mechanism. Finally, we wanted to examine CME and LICI at the onset of trials to determine if either could explain why lift times are influenced by previous trial type (Coxon et al. 2007; MacDonald et al. 2012).

Methods

Participants

Sixteen participants without neurological impairment participated in the experiment (mean age 24 y, range 18-49 y, 14 male). Thirteen of these completed the LICI protocol (mean age 25 y, range 18-49 y, 11 male). All were right handed (laterality quotient mean 0.92, range 0.71-1) as determined using a four-item version of the Edinburgh handedness inventory (Veale 2014). Written consent was obtained before participation and the study was approved by the University of Auckland Human Participants Ethics Committee.

Response inhibition task

The experiment utilized a bimanual anticipatory response inhibition task (Coxon et al. 2007; 2009; MacDonald et al. 2014; MacDonald et al. 2012). Participants were seated with forearms resting on a table positioned midway between pronation and supination. This allowed the distal and medial aspect of each index finger to occupy a mechanical switch positioned 55 cm away from the computer monitor. The display consisted of two indicators (vertical rectangles) each 16 cm in length and 1.5 cm in width (Figure 1A). Control of the left or right indicator was via the corresponding left or right switch. Switch “up/down” state was precisely recorded through an Arduino and synchronized to the display through an analog-digital USB interface (NI-DAQmx 9.7; National Instruments). Customized software written in MATLAB (R2011a, version 7.12; The MathWorks) generated the trial order, recorded trial data and controlled the visual output during the task.

Participants were instructed to let the weight of their fingers passively depress the switches. Switch height was adjusted to eliminate any positional related muscle activity. Depression of both switches initiated the trial after a 400-900 ms variable delay. If depression continued, both indicators would ascend vertically at a constant velocity reaching a horizontal line after 800 ms and the top of the display after 1000 ms. Participants were informed that releasing the switch (index finger abduction) would stop the corresponding indicator. Go trials (Go-Left Go-Right; GG) required participants to stop both indicators at the target by releasing both switches (Figure 1B). Stop trials were cued by one or both indicators stopping before the target, requiring participants to inhibit the response of one or both hands (Figures 1C and D). In the protocols a 2:1 ratio of Go to Stop trials existed, establishing Go trials as the default response. When both hands were required to stop (Stop-Both i.e. Stop-Left Stop-Right; SS), both indicators stopped 600 ms into the trial. On Partial trials only one hand was required to stop (Go-Left Stop-Right; GS, or Stop-Left Go-Right; SG). On Partial trials a single indicator stopped 550 ms into the trial while the other continued to ascend. The time the indicator stopped on Stop trials (550 & 600 ms) did not change. This enabled constant TMS times relative to both the stopping of the indicator and the start of the trial. Feedback was visually displayed during each inter-trial interval.

Electromyography

MEP amplitude was recorded using electromyography (EMG) over the left first dorsal interosseous (FDI) muscle as the non-dominant hand is more strongly affected than the dominant hand by the processes required to successfully cancel a subset of a movement (MacDonald et al. 2012). A belly-tendon electrode montage was used with a ground electrode on the posterior hand surface. EMG activity was recorded using a National Instruments A/D acquisition system, displayed using custom LabVIEW software, and stored to disk for offline analysis. Electrical activity was amplified (Grass P511AC), band-pass filtered (10-1000 Hz) and sampled at 2 kHz.

Transcranial magnetic stimulation

To examine CME during successful Stop and Go trials single-pulse TMS was delivered using a single Magstim 200 stimulator (Magstim, Dyfed, United Kingdom). A figure-of-eight coil (70 mm diameter) was held tangentially over the right M1 of the participant. The optimal coil position for eliciting MEPs in the left FDI was determined using a slightly suprathreshold intensity and marked on the scalp. The handle was posteriorly positioned and the coil orientated at a 45°angle to the midline, inducing a posterior to anterior directed current (Brasil-Neto et al. 1992). To examine LICI we delivered paired-pulse TMS from two Magstim 200 units connected via a Bistim unit (Magstim, Dyfed, United Kingdom). The CME protocol always preceded the LICI protocol.

Protocol

To examine CME, Task Motor Threshold (TMT) was determined while the participant rested their index fingers on the switches. TMT was determined as the minimum stimulus intensity required to elicit a MEP of at least 50 µV in the FDI in 4 out of 8 consecutive trials. Stimulus intensity was adjusted in 1-2 % increments from TMT to produce an average MEP amplitude of 0.1-0.2 mV at 200 ms before the target while not disrupting task performance.

This intensity was then used for all remaining stimulated trials. Participants completed an unstimulated practice block of 36 trials containing pseudo-randomized Stop trials.

The task in the CME protocol consisted of 432 trials split into 12 pseudo-randomized blocks of 36 with 288 Go and 144 Stop trials. There were 98 Go trials where TMS was delivered at either 250, 225, 200, 175, 150, 125 or 100 ms before the target to obtain 14 stimuli at each time point. All Stop trials were stimulated and distributed as 84 GS, 30 SG and 30 SS because GS trials were of primary interest. For GS trials, 14 stimuli were delivered 150, 125, 100, 75, 50 and 25 ms before the target. Timing was delayed by 100 ms relative to Go trials because of the expected ~75 - 100 ms delay in the responding hand (Coxon et al. 2007; 2009; Coxon et al. 2012; MacDonald et al. 2014; MacDonald et al. 2012). For SG and SS trials, 15 stimuli were delivered 175 and 200 ms after the stop signal.

To examine LICI, paired-pulse TMS was delivered at an ISI of 100 ms (Sanger et al. 2001). Stimulation intensity was adjusted to elicit a cortical silent period (CSP) duration of 175 ms while left FDI was activated at ~10% of maximum voluntary contraction. This intensity was used in LICI for both the conditioning stimulus (CS) and the test stimulus (TS). CS and TS were then adjusted to produce approximately 50-85% inhibition of the MEP amplitude (%INH). This intensity was used for all following trials.

During the LICI protocol, participants performed a Go Only block consisting of 30 Go trials. %INH was measured at the start of each trial (0 ms). Each participant then performed the task, which consisted of 360 trials split into 10 blocks of 36 trials. Of these, 240 (67%) were Go trials and 120 (33%) were Stop trials. Stop trial types (GS, SG and SS) were equally represented, each condition consisting of 40 trials. The %INH obtained at 0 ms provided information for the previous and upcoming trial. All trials following Stop trials and 185 trials following Go trials were stimulated.

Dependent measures

Peak-to-peak MEP amplitude was calculated from EMG 10 to 50 ms after the stimulus. MEPs were excluded when root mean square (rms) EMG was > 10 µV in the 50 ms preceding stimulation. Also, EMG traces were excluded if any activity was present between the stimulus and MEP evident from visual inspection. Average MEP amplitude was calculated following trimming of the upper and lower 10 % (if > 8 MEPs were present for that time point) or ± 1.5 standard deviations (if 4 – 8 MEPs were present for that time point). To reduce inter-subject variability MEP amplitude was normalised across Trial Types and Stimulations Times such that the condition with the largest mean MEP amplitude was reassigned the value 1, and all other conditions scaled accordingly for the participant. For the LICI protocol, mean stimulated and unstimulated left hand LTs were calculated from Go trials after Go trials. MEP amplitude was calculated for each stimulated trial in the left hand for both CS and TS. The primary dependent measure was %INH, which was calculated as %INH = 100 – (TS MEP amplitude/ CS MEP amplitude) ×100, where TS and CS MEP amplitude are the mean values for each condition from each participant. Δ%INH and ΔCS MEP amplitude was calculated for Partial trials followed and preceded by Go trials. Δ = [(subsequent Go trial – Partial trial)/ Partial trial] × 100.

To assess behaviour, lift times (LTs) were recorded and are reported relative to the target. Mean LTs from Go and successful Partial trials were calculated after the removal of outliers (± 3 SD; 1% removed for Go and Partial trials in CME protocol, 2% removed for Go and Partial trials in LICI protocol). In the LICI protocol only, lift time asynchronies (LTAs) were calculated from LTs in Go trials following Go and successful Stop trials (LTA = [Left hand LT] – [Right hand LT]). For Stop trials, stop signal reaction time (SSRT) and percentage of successful trials were determined. SSRT was calculated using the integration method (Logan and Cowan 1984; Verbruggen et al. 2013).

Statistical analyses

Repeated measures Analysis of Variance (RM ANOVA) were used to test our hypotheses. To test the first hypothesis, normalized MEP amplitude was first compared in an omnibus RM ANOVA with a 2 Trial Type (GG, GS) × 6 Stimulation Time (-225, -200, -175, -150, -125 and -100 ms relative to expected LT i.e. 0 ms on GG, 75 ms on GS) design. To determine if the hypothesised pattern of facilitation, suppression and facilitation on Partial Trials was present, one-way RM ANOVAs with the factor Stimulation Time (6 levels) were run separately on GS and GG trials. Additionally, MEP amplitude for Stop trials was analyzed with a 3 Trial Type (GS, SG, SS) x 2 Stimulation Time (175, 200 ms post stop signal) RM ANOVA. Participants with fewer than 4 MEPs for more than one stimulation time across trial types were excluded from analysis. For all other analyses in the CME protocol, missing data points were replaced with the average of the row and column mean. To determine task compliance behavioral data were analyzed as follows. LTs on Go and Partial trials were analyzed with a two-way RM ANOVA with factors Trial Type (Go, Partial) and Hand (Left, Right). LTAs from Go trials in the LICI protocol were analyzed using a one-way RM ANOVA with Preceding Trial Type (GG, GS, SG, SS). LTs that contributed to LTAs were analyzed in a two-way RM ANOVA with factors Preceding Trial Type (GG, GS, SG, SS) and Hand. A one-way RM ANOVA with factor Stop Trial Type (GS, SG, SS) tested for differences in SSRT.

The second hypothesis was examined in the LICI protocol. A one-way RM ANOVA with 5 Preceding Trial Type (Go Only, GG, GS, SG and SS) was used to analyse CS MEP amplitude and %INH. Linear regression analyses were performed to examine correlations between each of %INH and CS MEP amplitude with LTs of the same trial. To assess the relationship between partial trial CME suppression with both inhibition and response delays, linear regression analyses were performed investigating correlations between GS trial MEP amplitude 175 ms after the stop cue and each of average LICI across trials and GS lift times. To explore the effects of CME and LICI on lift times linear regression analyses were performed to assess the correlations of Δ%INH with LTAs and ΔCS MEP amplitude with LTAs. A paired t-test was used to examine the difference between left hand LTs in stimulated (following GG trials) and unstimulated GG trials.

Statistical significance was determined by $\alpha = 0.05$. *Post hoc* comparisons were performed using t-tests. Normality was assessed prior to ANOVA using the Shapiro-Wilk test. Non-spherical data were reported using Greenhouse-Geisser corrected *P* values. Values are reported as mean ± standard error.

Results

MEP amplitudes and LICI

For normalized MEP amplitudes of GG and GS trials in the CME protocol (Figure 2A) there was a main effect of Time ($F_{5,75} = 23.8$, $P < 0.001$), but not Trial Type ($F_{1,15} = 0.79$, $P = 0.387$) or Trial Type × Time interaction ($F_{5,75} = 1.59$, $P = 0.211$). During GG trials, there was a main effect of Time ($F_{6,90} = 26.6$, $P < 0.001$) where MEP amplitudes at -175, -150, -125 and -100 ms were greater than baseline at -250 ms (all $P < 0.008$). During GS trials, there was a main effect of Time ($F_{5,75} = 8.7$, $P < 0.001$) where MEP amplitudes at -100, ($t_{15} = 3.9$, $P = 0.001$) and -25 ms ($t_{15} = 4.2$, $P < 0.001$) were greater than baseline at -150 ms, whereas -75 ms ($t_{15} = 1.1$, $P = 0.289$) and -50 ms ($t_{15} = 1.7$, $P = 0.096$) were not. Additionally, MEP amplitude at -75 ms was less than -100 ms ($t_{15} = 2.3$, $P = 0.035$), indicative of non-selective braking 175 ms after the stop signal. For Stop trials (Figure 2B; n = 9), there was no main effect of Trial Type ($F_{2,16} = 0.78$, $P = 0.426$) or Time ($F_{1,8} = 32.5$, $P = 0.152$) and no Trial Type × Time interaction ($F_{2,16} = 0.61$, $P = 0.555$). In summary, left FDI MEP amplitudes demonstrated suppression 175 ms after a stop signal even when the left side was not cued to stop (GS trials).

Figure 3 shows averaged left FDI EMG and MEP amplitudes from an individual participant in the LICI protocol during the Go Only block (Figure 3A) and GS trials in the Stop task (Figure 3B). For LICI, there was a main effect of Trial Type ($F_{4,48} = 6.5$, $P = 0.018$). *Post hoc* comparisons revealed that %INH was less during blocks containing only Go trials (53 ± 6 %) compared with all trial types once Stop trials were introduced (all > 70 %; $P < 0.025$) (Figure 4A).

There was a positive correlation between %INH at the start of GS trials and the resulting LT ($r = 0.660$, $P = 0.014$; Figure 4B) such that greater %INH was associated with longer LTs of the left hand during GS trials. There was no correlation for GG trials ($r = 0.032$, $P = 0.917$). There was no correlation between Δ%INH on a GS trial and the LTA on the subsequent GG trial ($r = 0.081$, $P = 0.792$).

For CS MEP amplitude there was a main effect of Trial Type ($F_{4,48} = 3.9$, $P = 0.034$) (Figure 5). *Post hoc* comparisons revealed that CS MEP amplitudes were greater following Go trials in the Stop task (2.3 ± 0.3 mV) than during the Go Only block (1.9 ± 0.3 mV; $t_{12} = 2.4$, $P = 0.034$). Therefore, responding in the context of the Stop task increased CME. Furthermore, CS MEP amplitudes after GS trials (2.4 ± 0.4 mV) were larger than after SG, SS and Go Only trials (all < 2.2 ± 0.3 mV; $P < 0.047$). This indicates that the re-initiation of movement on a Partial trial increased contralateral M1 excitability which persisted to the start of the subsequent trial.

For GS trials, there was an association between MEP amplitude 175 ms post stop cue and LTs ($r = -0.544$) as well as with LICI ($r = -0.504$). However, both correlations failed to reach statistical significance (LTs, $P = 0.054$; LICI, $P = 0.079$). There was no correlation between CS MEP amplitude at the start of a GG or GS trial and the resulting LT (both $r < 0.178$, $P > 0.560$). Likewise, there was no correlation between the ΔCS MEP amplitude on a GS trial and the LTA on the subsequent Go trial ($r = 0.019$, $P = 0.951$).

In the CME protocol, TMT = 38 ± 2% MSO and stimulation intensity = 39 ± 2% MSO (104 ± 2% TMT). In the LICI protocol, TMT = 43 ± 2% MSO, CS and TS = 56 ± 3% MSO (129 ± 3 % TMT). The number of trials excluded for rmsEMG > 10 μV was 28 ± 4 % in the CME and 9 ± 2% in the LICI protocol. In the CME protocol under the GS condition, 7 out of 96 values for MEP amplitude were missing due to pre-trigger EMG and replaced according to the method described.

Lift times and asynchronies

The task was performed successfully as evident in LTs that were close to the target (Table 1), and as noted previously for this task (Coxon et al. 2007; 2009; Coxon et al. 2012; MacDonald et al. 2014; MacDonald et al. 2012). For LTs in the CME protocol, there was a main effect of Trial Type ($F_{1,15} = 100.0$, $P < 0.001$). No main effect of Hand ($F_{1,15} = 0.7$, $P = 0.409$) or Trial Type × Hand interaction ($F_{1,15} = 0.0$, $P = 0.887$) existed. For the LICI protocol, there was a main effect of Trial Type ($F_{1,12} = 111.6$, $P < 0.001$). There was a main effect of Hand ($F_{1,12} = 31.9$, $P < 0.001$) with right LTs (35 ± 4 ms) faster than left (47 ± 4 ms). There was also a Trial Type × Hand interaction ($F_{1,12} = 4.9$, $P = 0.048$), which likely arose from a trend for longer left hand delays (61 ± 5 ms) than right hand delays (55 ± 6 ms; $t_{12} = 2.1$, $P = 0.054$) between Partial and Go trials. There was no difference in left LTs between stimulated (19 ± 3 ms) and unstimulated (21 ± 3 ms; $t_{12} = 1.1$, $P = 0.294$) Go trials.

Lift time asynchronies (LTAs) were analysed from GG trials in the Stop task of the LICI protocol (Table 1). For the Stop task of the LICI protocol, there was a main effect of Preceding Trial Type ($F_{3,36} = 16.1$, $P < 0.001$) such that LTAs decreased after Partial GS compared with after GG trials ($t_{12} = 3.9$, $P = 0.002$). In contrast, LTAs increased after Partial SG compared with after GG trials ($t_{12} = 4.9$, $P < 0.001$). LTAs were not different after SS trials compared with after GG trials ($t_{12} = 0.3$, $P = 0.769$). Figure 6 shows the LTs of GG trials in the Stop task used for LTAs in the LICI protocol. Interestingly, LT on either side was faster on a subsequent GG trial if that side had previously responded on a Partial trial. There was a main effect of Preceding Trial Type ($F_{3,36} = 5.6$, $P = 0.003$) and Hand ($F_{1,12} = 35.6$, $P < 0.001$). There was also a Preceding Trial Type × Hand interaction ($F_{3,36} = 15.4$, $P < 0.001$). Left LTs were faster after GS trials compared with after GG ($t_{12} = 4.6$, $P = 0.001$) and SS trials ($t_{12} = 2.9$, $P = 0.014$) which did not differ from each other ($t_{12} = 1.0$, $P = 0.329$). Similarly, right LTs after SG trials were faster compared with after GG ($t_{12} = 5.3$, $P < 0.001$) and SS trials ($t_{12} = 3.1$, $P = 0.009$) which did not differ from each other ($t_{12} = 0.7$, $P = 0.500$). For the left hand, LTs were faster if the hand had previously stopped on a Partial trial, although to a lesser extent than if it had responded ($t_{12} = 4.6$, $P = 0.001$). For the right hand, LTs were faster after responding versus stopping on a Partial trial ($t_{12} = 3.4$, $P = 0.005$).

Stop signal reaction times and stopping success

Average success on Stop trials was as follows: CME protocol: GS: 76 ± 3%, SG: 61 ± 6%, SS: 58 ± 4%. LICI protocol: GS: 83 ± 3%, SG: 82 ± 3%, SS: 65 ± 3%. In both protocols, average SSRT showed a main effect of Stop Trial Type (CME: $F_{2,30} = 57.3$, $P < 0.001$, LICI: $F_{2,24} = 55.5$, $P < 0.001$). SSRT was shorter for SS (CME: 209 ± 3 ms, LICI: 201 ± 2 ms) than GS (CME: 245 ± 4 ms; $t_{15} = 11.5$, $P < 0.001$, LICI: 236 ± 4 ms; $t_{12} = 9.3$, $P < 0.001$) and SG trials (CME: 256 ± 4 ms; $t_{15} = 8.6$, $P < 0.001$, LICI: 236 ± 4 ms; $t_{12} = 8.1$, $P < 0.001$). Partial trial types did not differ from each other in the LICI protocol ($t_{12} = 0.1$, $P = 0.956$), whereas GS SSRT was shorter than SG in the CME protocol ($t_{15} = 2.3$, $P = 0.038$).

Discussion

This study provides novel insights into the non-selective suppression of motor output in the context of reactive response inhibition. As expected, responses were delayed on Partial trials and temporal modulation of CME for partial response cancellation was consistent with the anticipation, suppression, and subsequent re-initiation of movement. Furthermore, CME suppression was evident when one or both hands were required to stop. CME at trial onset reflected the sum of inhibitory and facilitatory processes required to successfully perform the previous trial. Changes to LTAs after Partial trials were driven by speeding up of LTs of the hand that had previously responded. The magnitude of LICI at trial onset was positively associated with the extent of the delay during GS trials. Interestingly, LICI increased when Stop trials were introduced compared with a block of trials in which stopping was not a possibility. These results may indicate that LICI is a proactive mechanism capable of influencing the interference effect during partial cancellation performed in a reactive context.

Response delays and CME modulation during Stop trials indicated non-selective suppression. As observed previously, LTs in Partial trials were delayed relative to Go trials (Coxon et al. 2007; 2009; Coxon et al. 2012; MacDonald et al. 2014; MacDonald et al. 2012). These substantial delays were observed despite participants achieving relatively high success rates on Partial trials, especially in the LICI protocol (> 80%). It is important to note that response delays were not eliminated, or even reduced, when success rate increased as a result of familiarity with Partial trials; c.f. (Xu et al. 2014). Modulation of MEP amplitude in the CME protocol supported a model of non-selective suppression during Partial trials. Go trials displayed a sustained increase in CME from 200 ms before the target. The delay on Partial trials was a result of an initial facilitation, a dip back to baseline, followed by a secondary increase in CME. This pattern of CME replicates those of MacDonald et al. (2014). At equivalent times relative to the stop signal, MEP amplitude did not differ between the three types of Stop trials. This finding is consistent with functional magnetic resonance imaging studies showing a similar pattern of neural activation between the three Stop trial types (Coxon et al. 2016; Coxon et al. 2009; Coxon et al. 2012). Conversely, functional imaging results from Majid et al. (2013) suggest a distinct role of the selective indirect basal ganglia pathway during partial stopping. Activation of the indirect pathway should have no effect on MEP amplitude in the responding finger during Partial trials. However, all trials in their study were preceded by a warning cue about stopping requirements. The neural activation in response may differ if the cue is unexpected. The present study adds weight to the model of non-selective response inhibition following an unexpected stop cue.

The present study also provides insight into the modulation of intracortical inhibition during response inhibition. Compared with Go Only blocks, LICI increased when Stop trials were introduced. The amount of LICI was comparable between Go and Stop trials suggesting that LICI is not specifically associated with stopping. Previous results using paired-pulse TMS indicated that increased SICI did not coincide with CME suppression in the responding effector during partial response inhibition conditions (MacDonald et al. 2014). Together, these findings indicate that GABAergic circuits within M1 are not primarily responsible for non-selective suppression during reactive response inhibition. Why then, did LICI increase during response inhibition trials? It is likely that increased LICI reflects the proactive modulation of tonic inhibitory circuits as a result of expecting to occasionally stop one or both hands. Studies have demonstrated that CME is modulated as a result of foreknowledge about an ensuing response. When response *execution* is forewarned, SICI and LICI are decreased in the foreperiod for the muscles cued to respond (Sinclair and Hammond 2008) while CME is simultaneously reduced, most likely to prevent a premature response (Davranche et al. 2007; Duque and Ivry 2009). When response *prevention* is forewarned, CME is similarly reduced during the foreperiod (Cai et al. 2011), acting as a mark of advanced inhibitory control. Prior to this study, there had been no examination of ICI modulation as a result of the knowledge that a prepared response may need to be prevented. LICI increased during the foreperiod (trial onset) with the foreknowledge that stopping was a possibility. Therefore, proactive inhibitory control is at least in part, mediated by changes in LICI.

The implications of proactively increasing LICI for reactive response inhibition can be understood within the framework of an activation threshold model (e.g., MacDonald et al. 2014). Tonic levels of inhibition mediate premature response prevention (Duque et al. 2010; Jaffard et al. 2008) requiring a facilitatory process in order to initiate movement. In the present study, a concurrent increase in LICI and CME observed on Go trials when Stop trials were introduced provide candidate mechanisms. The increased CME (facilitation) counteracts the rise in tonic inhibition and Go trial LTs are thereby maintained on target. However on GS trials, LTs were markedly delayed. In response to the stop signal, a reactive inhibitory input is superimposed onto the tonic resting level, raising the threshold for responding (activation threshold) and effectively cancelling all movement. The trend in the association between greater CME suppression and greater non-selective inhibition (LICI) on GS trials in the current study supports such a model. The initial facilitatory process is inadequate to surpass the activation threshold and a second phase of facilitation must be added, resulting in the response delay (MacDonald et al. 2014). It is worth noting that longer GS response delays were associated with higher levels of LICI, supporting the idea that a second phase of facilitation is required to overcome the tonic resting level. The trend between longer response delays and CME suppression for GS trials is in agreement with such a second phase of facilitation. It is interesting that the association between MEP amplitude and response delay was not stronger for CME evaluated closer in time to the response than LICI measured at trial onset. A likely explanation is that MEP amplitude reflects the net excitatory and inhibitory inputs whereas LICI provides a measure of inhibition only. How LICI is modulated within the proactive response inhibition network remains unclear (Majid et al. 2013; Van Belle et al. 2014). The present study supports the idea that proactive and reactive control mechanisms are not independent but rather, reactive stopping depends on ongoing proactive control (Dunovan et al. 2015).

The within trial processes outlined above have neurophysiological and behavioural consequences for the subsequent trial. Left hand LT on a Go trial was quicker if preceded by a GS compared with a Go trial. At the same time, CS MEP amplitude was increased after GS trials compared with other Stop trial types. Therefore, it may be that the second phase of facilitation required to respond on GS trials has a carry-on effect which is evident on the next trial. The second phase of facilitation on SG trials also explains the speeding up of the right hand on a subsequent Go trial. Interestingly, the hand that stops on a Partial trial also speeds up to some degree on the subsequent Go trial. We suspect that Partial trials require "uncoupling" of the two effectors involved in the default Go response, in order to selectively initiate a unimanual response (MacDonald et al. 2012). Some residual effect of uncoupling is still present on the subsequent Go trial as is evident by the heightened LTAs after Partial trials. The presence of (weaker) coupling suggests that the required second phase of facilitation for the unimanual response on the Partial trial will affect the entire bimanual response on the following trial. In other words, the hand that stops on a Partial trial to some extent "comes along for the ride" on a subsequent Go trial. The fact that this dependence is seen more strongly in left hand LTs aligns with the idea that the nondominant hand is more stringently coupled to the dominant than vice versa (Byblow et al. 2000; Carson 1993). Therefore, the after-effects of Partial trials on corticomotor excitability and performance likely result from the second phase of facilitation, rather than any lingering effects of inhibition.

A potential limitation of the present study was the timing of the LICI measurement. At a cellular level, postsynaptic hyperpolarization mediated by $GABA_B$ receptors has been observed up to 500 ms (Lacaille 1991; Otis et al. 1993). However, it is not feasible to record LICI with the required stimulus intensities within the time window between CME suppression and LT without disrupting task performance. Furthermore, it is also difficult to maintain a comparable level of CME or interpret LICI with a constant test stimulus during or immediately following trials in a task where there is dynamic modulation of CME. However, if LICI is responsible for non-selective suppression on Stop trials and the resulting LTAs on the subsequent trials, one would expect LICI to still be modulated at the time we applied TMS (i.e. at the onset of trials where LTAs are present). Stimulation at this time is unlikely to affect task performance (Leocani et al. 2000) with CME variability reduced compared with times closer to the target (Coxon et al. 2006). However CS MEP amplitude varied following different trial types. The strength of the CS influences the amount of LICI, with a higher CS intensity resulting in reduced LICI (Sanger et al. 2001). This has the potential to complicate the comparison of LICI across and between trials. Nonetheless, it is important to note that the mean CS MEP amplitude was between 1.9 and 2.4 mV (~130 % of TMT), where similar amounts of LICI are reported (Opie and Semmler 2014). Furthermore, CS MEP amplitude did not correlate with GS trial LTs. Thus it is unlikely that CS MEP amplitude could solely account for the observed pattern of LICI. It is possible that reduced LICI in Go Only blocks may reflect, in part, an order effect. Go Only trials were always presented first in the LICI protocol. However, an order effect seems unlikely given that all participants had completed the CME protocol prior to the LICI protocol, and stop trials were presented throughout the entire CME protocol.

In summary, this study provides novel insight into the role of LICI during movement cancellation. LICI is a proactive mechanism capable of influencing the interference effect during partial cancellation performed in a reactive context.

Acknowledgements

We thank Clare Turner for assistance with data collection and Terry Corin for technical assistance.

Grants

None.

Disclosures

No conflicts of interest, financial or otherwise, are declared by the authors.

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Figure Captions

Figure 1. Bimanual anticipatory response inhibition task. **A.** Each trial began with the target line (horizontal black bar) displayed and trial type ambiguous. Go trials (GG) were deemed successful if both ascending indicators were stopped within 30 ms of the target line (800 ms into the trial) by lifting the left and right index fingers from switches. To indicate "Success" the target line turned green**. B.** Partial trial (GS = Go-Left Stop-Right): the right indicator automatically stops 550 ms into the trial. This trial type requires the right switch to remain depressed while the left switch must be released as the rising indicator reaches the target line. The target line turned red if the indicator stopped greater than 30 ms of the target line or the hand response was not correctly inhibited (“Miss”). **C.** Stop-Both trial (SS): Both indicators stop automatically 600 ms into the trial and a successful trial is achieved when both switches remain depressed. **D.** Transcranial magnetic stimulation over the right motor cortex. Motor evoked potentials (MEPs) were recorded from the first dorsal interosseous (FDI) muscle during task performance.

Figure 2. Modulation of left first dorsal interosseous normalized motor evoked potential (MEP) amplitude during the corticomotor excitability protocol. **A.** MEP amplitudes before the target (0 ms) during GG (unfilled circles) and GS (shaded squares) trials ($n = 16$). Filled symbols represent values significantly different ($P < 0.05$) to baseline (GG: -250 ms, GS: -150 ms). Note the dip in corticomotor excitability on GS trials at -75 ms. **B.** MEP amplitudes after the stop signal. Bars indicate group means ($n = 9$). Data correspond to -75 and -50 ms relative to lift time from Panel A. Note that MEP amplitudes were suppressed 175 ms after the stop signal regardless of Stop trial type. Error bars indicate 1 SE. * $P < 0.05$. GG = Go trial, GS = Go-Left Stop-Right, SG = Stop-Left Go-Right, SS = Stop-Both.

Figure 3. Representative left first dorsal interosseous electromyography from a single participant in the long-interval intracortical inhibition protocol. Vertical dashed line represents target (800 ms into the trial) and arrows represent average lift time (LT). **A.** Go Only block. % inhibition = 48 %, LT = 786 ms, CS motor evoked potential (MEP) amplitude = 2.2 mV. **B.** Successful GS trials. % inhibition = 72 %, LT = 868 ms, CS MEP amplitude = 2.2 mV. CS = conditioning stimulus, TS = test stimulus.

Figure 4. Group averages (n = 13) for measures of long-interval intracortical inhibition (LICI) at trial onset. **A.** Percent inhibition relative to the previous trial. **B.** Linear regression between % LICI and lift times within GG (unfilled circles) and successful GS trials (filled squares). Error bars indicate 1 SE. * $P < 0.05$. Go Only = block with only Go trials possible, GG = Go trial in the context of the response inhibition task, GS = Go-Left Stop-Right, SG = Stop-Left Go-Right, SS = Stop-Both.

Figure 5. Corticomotor excitability at trial onset. Bars are group averages (n = 13) of the conditioning stimulus (CS) motor evoked potential (MEP) amplitude at trial onset relative to previous trial type. Only data following successful Stop trials were included in the analysis. Error bars indicate 1 SE. * $P < 0.05$. Go Only = block with only Go trials possible, GG = Go trial in the context of the response inhibition task, GS = Go-Left Stop-Right, SG = Stop-Left Go-Right, SS = Stop-Both.

Figure 6. Lift times on Go trials following different trial types. Bars indicate group means (n = 13). Black horizontal lines denote when the hand had previously stopped on a Partial trial. Note that for both hands lift times were faster on a subsequent Go trial if the hand had previously responded on a Partial trial. Error bars indicate 1 SE. * $P < 0.05$, ** $P < 0.001$.

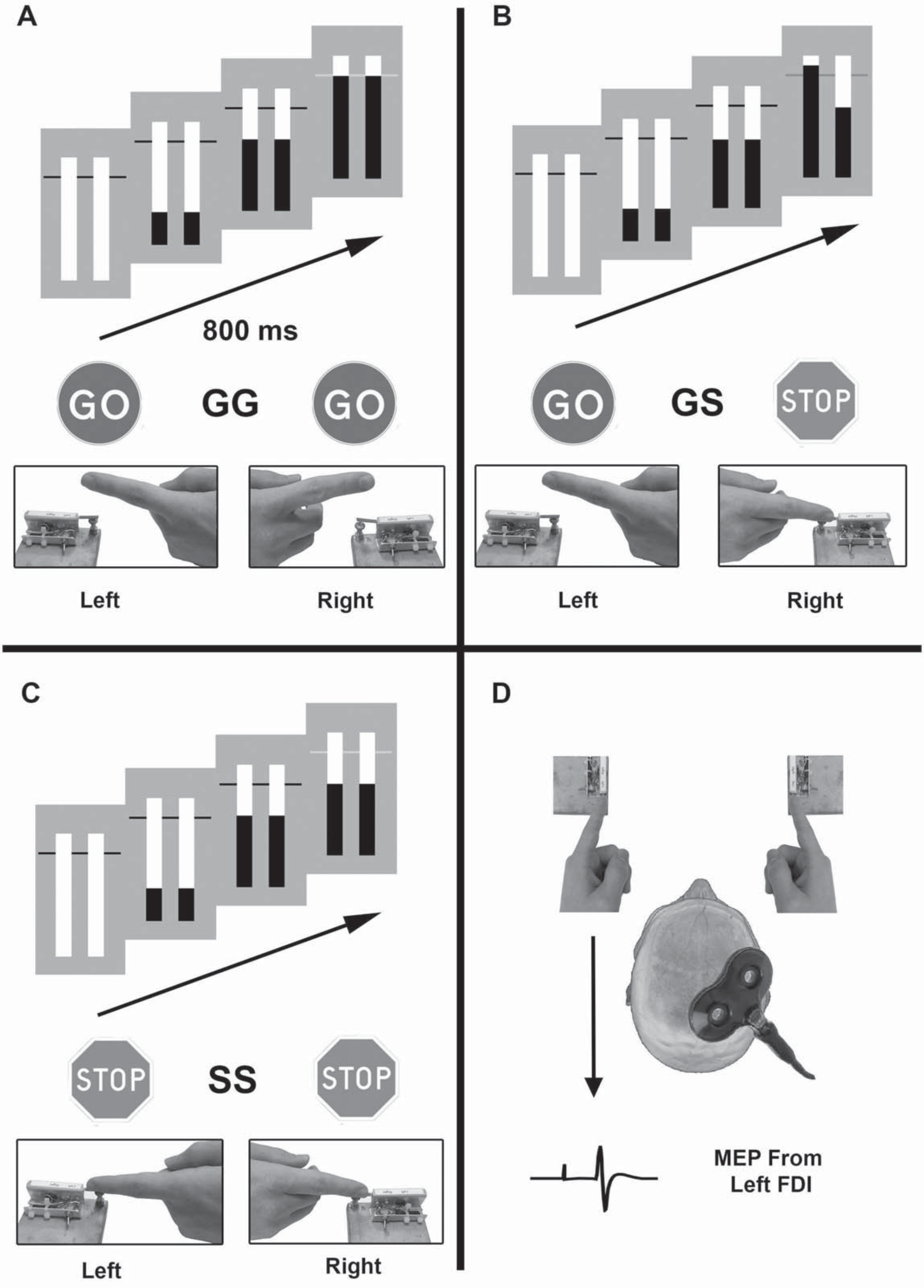
Tables

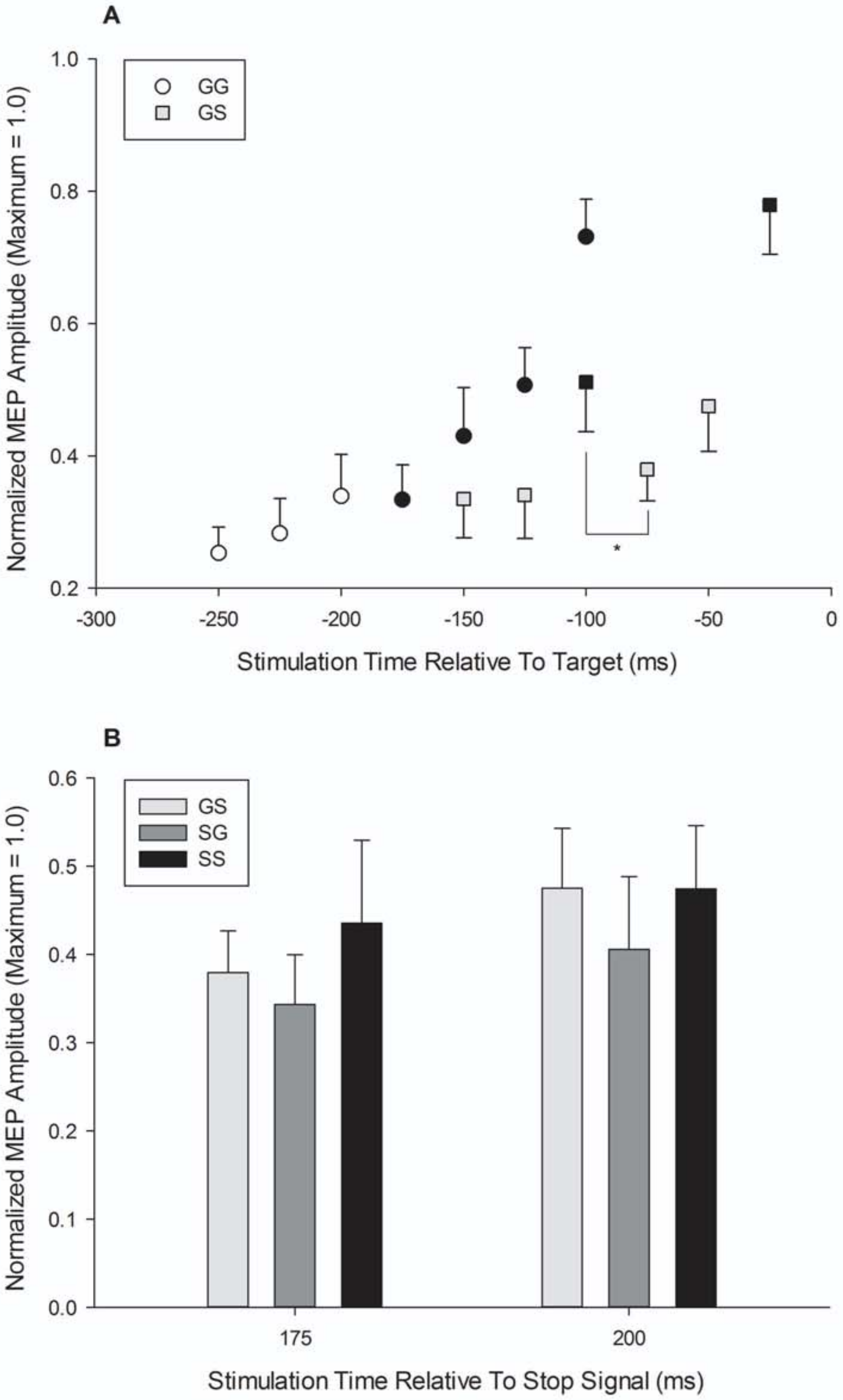
Table 1. Summary of behavioural data from both protocols.

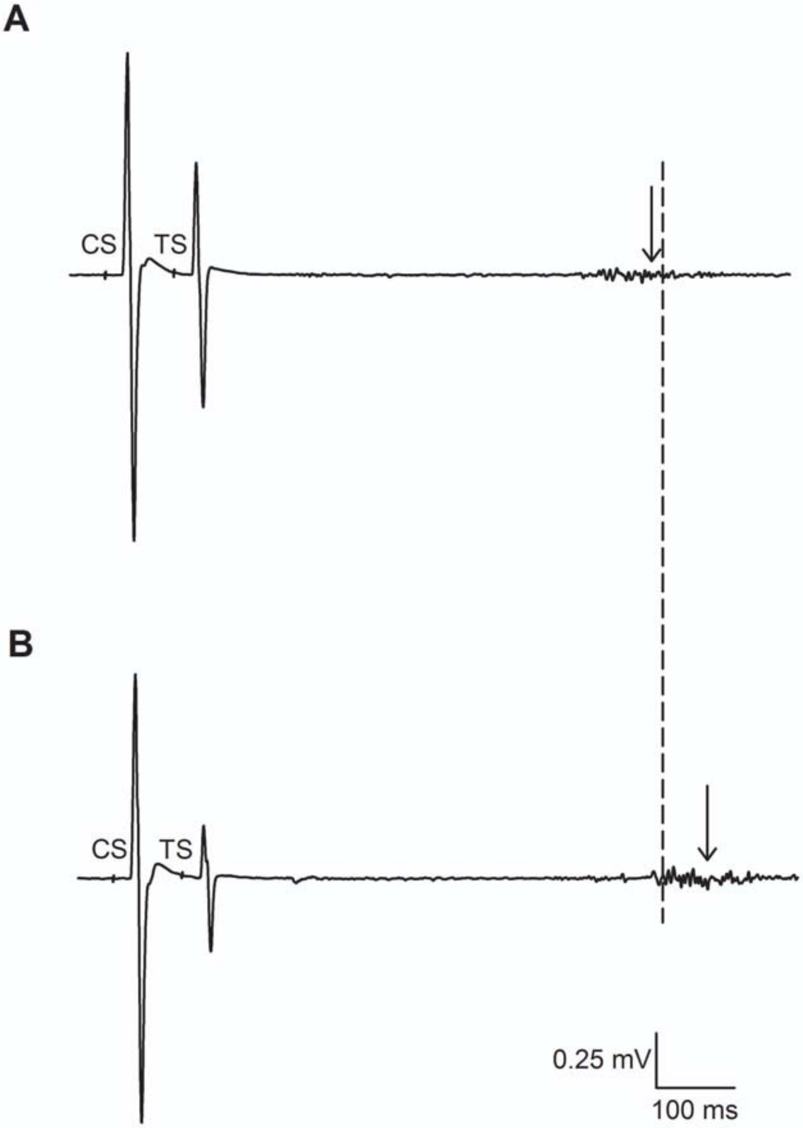
	LTs					
	Go (L)	Go (R)	Go Avg	Partial GS	Partial SG	Partial Avg
CME protocol (ms)	16±3	13±2	14±2	70±8	66±7	68±6*
LICI protocol (ms)	17±2	7±2	12±2	78±6	62±6	70±6*

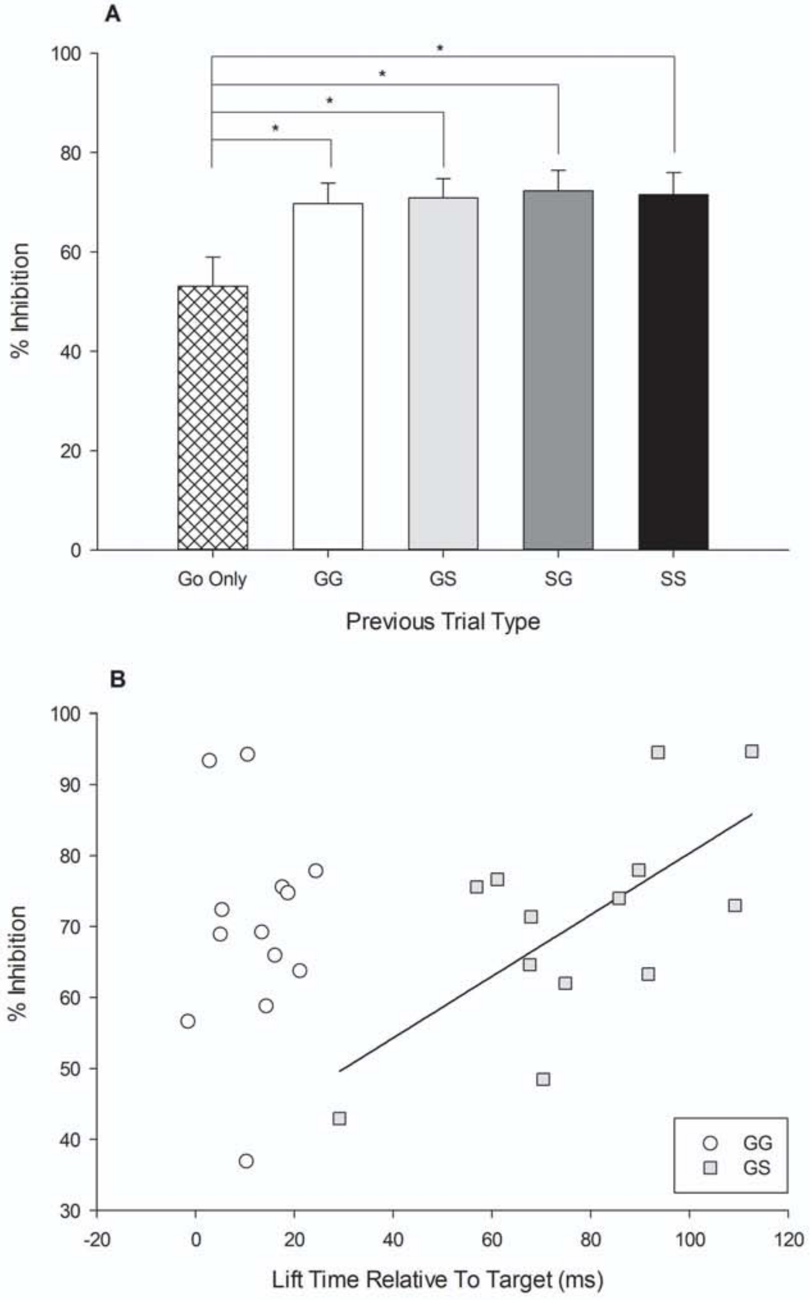
LICI protocol	Preceding trial type			
	Go	Partial GS	Partial SG	Stop Both
LTA (ms)	10±2	3±2†	14±2†	9±1

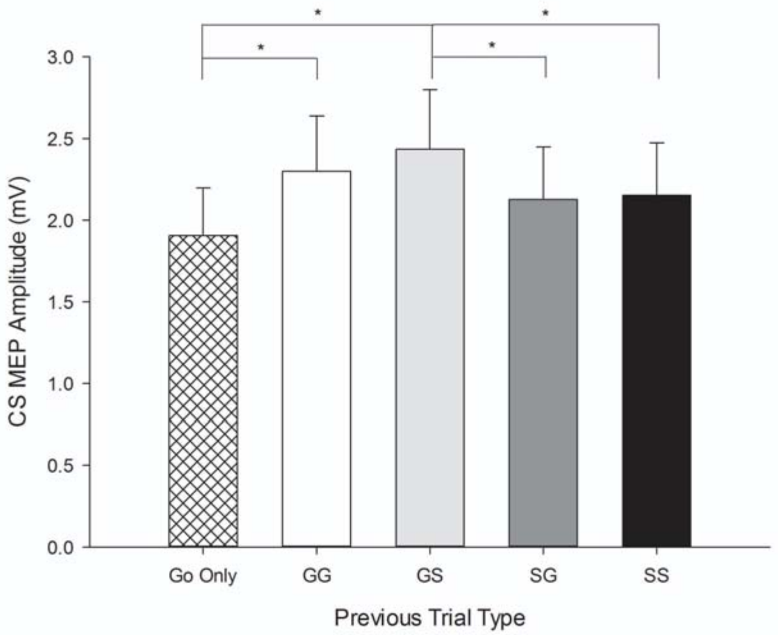
Values are mean±SE lift times (LTs) displayed relative to the target (800 ms). Lift time asynchronies (LTAs) are determined as left LT – right LT in Go trials. GS = Go-Left Stop-Right, SG = Stop-Left Go-Right. * $P < 0.001$ compared with Go Avg, † $P < 0.01$ compared with Go trials.

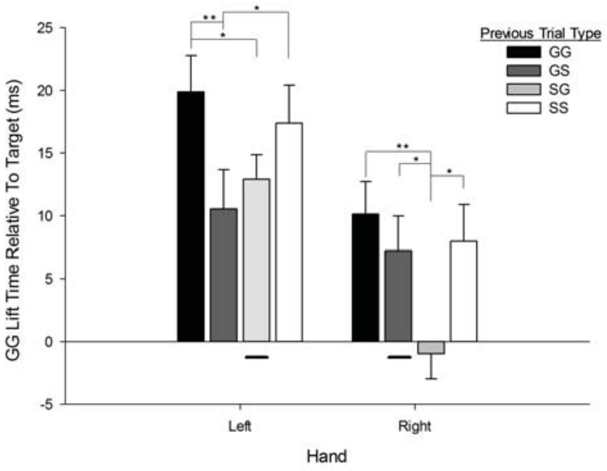

A
800 ms
GO
GG
GO
Left
Right
B
GO
GS
STOP
Left
Right
C
STOP
SS
STOP
Left
Right
D
MEP From
Left FDI


A
○ GG
☐ GS
Normalized MEP Amplitude (Maximum = 1.0)
1.0
0.8
0.6
0.4
0.2
*
-300
-250
-200
-150
-100
-50
0
Stimulation Time Relative To Target (ms)
B
GS
SG
SS
Normalized MEP Amplitude (Maximum = 1.0)
0.6
0.5
0.4
0.3
0.2
0.1
0.0
175
200
Stimulation Time Relative To Stop Signal (ms)


A
CS
TS
B
CS
TS
0.25 mV
100 ms


A
% Inhibition
100
80
60
40
20
0
*
*
*
*
Go Only
GG
GS
SG
SS
Previous Trial Type
B
% Inhibition
100
90
80
70
60
50
40
30
-20
0
20
40
60
80
100
120
Lift Time Relative To Target (ms)
○ GG
□ GS


*
*
*
*
3.0
2.5
2.0
1.5
1.0
0.5
0.0
CS MEP Amplitude (mV)
Go Only
GG
GS
SG
SS
Previous Trial Type



GG Lift Time Relative To Target (ms)
25
20
15
10
5
0
-5
**
*
*
**
*
*
Left
Right
Hand
Previous Trial Type
GG
GS
SG
SS