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Response inhibition activates distinct motor cortical inhibitory processes

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Abbreviations: M1, primary motor cortex; TMS, transcranial magnetic stimulation; GABA, gamma-aminobutyric acid; SICI, short-interval intracortical inhibition; LICI, long-interval intracortical inhibition; MEP, motor evoked potential; EMG, electromyography; FDI, first dorsal interosseous; APB, abductor pollicis brevis; PEST, parameter estimation by sequential testing; RMT, rest motor threshold; AMT, active motor threshold; MS, maybe stop; MSL, maybe stop left; SL, stop left; MSR, maybe stop right; SR, stop right; GG, go-left go-right; GS, go-left stop-right; SG, stop-left go-right; SS, stop-left stop-right; SSRT, stop signal reaction time.

Abstract

We routinely cancel pre-planned movements that are no longer required. If stopping is forewarned, proactive processes are engaged to selectively decrease motor cortex excitability. However, without advance information there is a non-selective reduction in motor cortical excitability. Here we examine modulation of human primary motor cortex inhibitory networks during response inhibition tasks with informative and uninformative cues using paired-pulse transcranial magnetic stimulation. Long- and short-interval intracortical inhibition (LICI and SICI), indicative of $GABA_B$- and $GABA_A$-receptor mediated inhibition respectively, were examined from motor evoked potentials obtained in task-relevant and task-irrelevant hand muscles when response inhibition was preceded by informative and uninformative cues. When the participants (10 male and 8 female) were cued to stop only a subcomponent of the bimanual response, the remaining response was delayed, and the extent of delay was greatest in the more reactive context, when cues were uninformative. For LICI, inhibition was reduced in both muscles during all types of response inhibition trials compared with the pre-task resting baseline. When cues were uninformative and left hand responses were suddenly cancelled, task-relevant LICI positively correlated with response times of the responding right hand. In trials where left hand responding was highly probable or known (informative cues), task-relevant SICI was reduced compared when cued to rest, revealing a motor set indicative of responding. These novel findings indicate that the $GABA_B$-receptor mediated pathway may set a default inhibitory tone according to task context, whereas the $GABA_A$-receptor mediated pathways are recruited proactively with response certainty.

New and Noteworthy

We examined how informative and uninformative cues that trigger both proactive and reactive processes modulate GABA-ergic inhibitory networks within human primary motor cortex. We show that $GABA_B$ inhibition was released during the task regardless of cue type, whereas $GABA_A$ inhibition was reduced when responding was highly probable or known compared with rest. $GABA_B$-receptor-mediated inhibition may set a default inhibitory tone whereas $GABA_A$ circuits may be modulated proactively according to response certainty.

Keywords: response inhibition; transcranial magnetic stimulation; primary motor cortex; intracortical inhibition

Introduction

Response inhibition refers to the innate ability to cancel a planned movement when it is no longer required or is potentially harmful. Response inhibition is commonly studied using a "stop" signal to cancel a planned movement (Verbruggen and Logan 2009). For example, neuroimaging studies have shown that this cancellation may engage a right-lateralized, cortico-subcortical network (Aron et al. 2014; Chikazoe 2010). However, when stopping is forewarned, more proactive inhibitory processes may be engaged (Aron 2011). Reactive and proactive processes are generally deemed separable (Irlbacher et al. 2014), although there is converging evidence that an interaction between these processes may exist, such that proactive inhibitory control can alter the effectiveness of reactive inhibition (Cai et al. 2011; Chen et al. 2010; Dunovan et al. 2015; Jahfari et al. 2012; Zandbelt and Vink 2010). The above studies implicate a critical role for basal ganglia circuitry during proactive and reactive response inhibition.

It is also reasonable to suspect that primary motor cortex (M1) is modulated during response inhibition given its role in shaping descending motor output (Stinear et al. 2009). Transcranial magnetic stimulation (TMS) studies of reactive response inhibition indicate a non-selective reduction in corticomotor excitability (Badry et al. 2009; Cai et al. 2012; Cowie et al. 2016; Coxon et al. 2006; MacDonald et al. 2014; Majid et al. 2012). However, proactive inhibitory processes are amplified and corticomotor excitability is selectively reduced when there is some forewarning that a component of the response might be cancelled (Cai et al. 2011; Claffey et al. 2010; Majid et al. 2013). Currently it is unclear whether corticomotor suppression during response inhibition occurs via modulation of M1 intracortical inhibition or by withdrawal of facilitation.

Intracortical inhibitory networks within M1 possess regulatory effects on descending commands that fine-tune movement. The role of the main inhibitory neurotransmitter gamma-aminobutyric acid (GABA) can be assessed non-invasively in human M1 during functional tasks using paired-pulse TMS (Ziemann et al. 2015). With paired-pulse TMS, measures of long- and short-interval intracortical inhibition (LICI and SICI), mediated respectively by $GABA_B$ (McDonnell et al. 2006; Werhahn et al. 1999) and $GABA_A$ receptors (Ilic et al. 2002; Ziemann et al. 1996), can be examined during response inhibition. LICI engages both pre- and post-synaptic $GABA_B$ receptors (Bettler et al. 2004), and is typically associated with tonic inhibitory effects. A non-selective increase in LICI by response inhibition task context (Cowie et al. 2016) corroborates this association. In contrast, SICI engages $GABA_A$ receptors that directly act on the post-synaptic cell to selectively release the target representation during movement initiation and maintain inhibition over representations in the surround (Reynolds and Ashby 1999; Stinear and Byblow 2003; Zoghi et al. 2003). Measures of SICI may increase (Coxon et al. 2006; MacDonald et al. 2014) or decrease (Duque and Ivry 2009; Sinclair and Hammond 2008) during action preparation, depending on context. Previous studies indicate that TMS with anterior-posterior current direction in the brain is more likely to preferentially activate circuits responsible for SICI (Hanajima et al. 1998), and may provide a more sensitive measure of SICI than a posterior-anterior directed current (Cirillo and Byblow 2016; Sale et al. 2016).

The present study tested three hypotheses relevant to proactive and reactive inhibitory processes when preceding cues were informative or uninformative. First, we hypothesized that response delays would be shorter with informative compared with uninformative cues, owing to more proactive capability (Aron and Verbruggen 2008; Claffey et al. 2010; Majid et al. 2012). Second, we expected a non-selective reduction of LICI in the context of response inhibition

compared with resting tonic levels of LICI at baseline, indicative of a mechanism which sets inhibitory tone. Third, we hypothesized that SICI (obtained with an anterior-posterior current direction) would demonstrate an effector and muscle specific decrease according to response certainty indicated by informative cues.

Methods

Participants. Eighteen participants without neurological impairment were recruited (mean age 26.4 years, range 18-50 years, 8 female). All were right handed (laterality quotient mean 0.92, range 0.75-1) as determined using the abbreviated Edinburgh handedness inventory (Veale 2014). Written informed consent was obtained before participation and the study was approved by the University of Auckland Human Participants Ethics Committee (Ref. 014398).

Response Task. Participants performed a bimanual anticipatory response task (Cowie et al. 2016; Coxon et al. 2007; 2009; MacDonald et al. 2014; MacDonald et al. 2012) which had similarities to unimanual versions of the same task (Coxon et al. 2006; Dunovan et al. 2015; Zandbelt and Vink 2010). Briefly, participants were seated with forearms in a neutral posture, resting on a table surface allowing the distal and medial aspect of each index finger to rest on a mechanical switch. A computer display projected two indicators (as filling bars) (Fig. 1). Switch state was precisely captured with an Arduino and synchronized to the display through an analog-digital interface (NI-DAQmx 9.7; National Instruments). Switch height was adjusted to minimize postural muscle activity. 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 respond by lifting their index fingers (abduction) from the switches to stop the ascending indicators (black) at a horizontal target line (Fig. 1A). Thus, there

were four possible trial types and responses: GG, SS, GS, and SG; where G and S refer to Go and Stop and the position of each refers to the left and right side. Go trials (GG) required lifting both fingers from the switches in order to stop both indicators at the target (800 ms). Stop trials (SS) required both fingers remain on the switches after indicators stop automatically (600 ms). Partial trials (GS, SG) required one finger to remain on the switch (Fig. 1B) after a single indicator stopped (550 ms), while the other finger was lifted from the switch in order to stop the indicator at the target (800 ms).

Each trial was preceded by a warning cue of 1.5 s duration. Once the warning cue disappeared, participants placed their fingers on the switches, and bar filling occurred 500 ms later. Cues consisted of two colored circles on the left and right of the display, corresponding to each hand. Circle color was used to trigger proactive (informative cue) or reactive (uninformative cue) processes (Fig. 1D), and consisted of six possible cue types. The uninformative cue (Maybe Stop, MS) consisted of all trial types. Informative cues (Maybe Stop Left, MSL; Maybe Stop Right, MSR) consisted of three trial types, with a partial trial of cued finger excluded. For MS, MSL, and MSR cues there was a 2-to-1 ratio of Go to Stop trials. Because response complexity may effect inhibitory processes (Greenhouse et al. 2015), catch trials (Stop Both, SS) were maintained (~10%) for the MS, MSL, and MSR cues. Known cues (Stop Left, SL; Stop Right, SR; Rest) consisted of only the specified trial type. Specifically, for SL and SR cue types the subsequent trial types were SG and GS respectively. The ratio of trial types within cue types is shown in Table 1. Measures of corticomotor excitability and inhibition within the block (pre-task, with fingers resting on switches) were obtained in response to an informative “Rest” cue which preceded a SS trial (such that both fingers remained resting on switches and no response was required).

153 *Electromyography.* Surface electromyography (EMG) was collected from the first dorsal
154 interosseous (FDI) and abductor pollicis brevis (APB) muscles of the left hand. The left hand
155 was chosen because processes required to successfully cancel a subset of a movement are most
156 pronounced with the non-dominant hand (MacDonald et al. 2012). A belly-tendon electrode
157 montage recorded activity for FDI and APB using 10-mm-diameter Ag-AgCl surface electrodes
158 (Ambu Blue Sensor Paediatric NS, Ballerup, Denmark). For the left hand, a shared ground
159 electrode was positioned on the posterior hand surface (3M Canada). EMG activity was
160 amplified, bandpass-filtered (10–1000 Hz) and digitized at 10 kHz with a CED interface system
161 (MICRO1401mkII; Cambridge Electronic Design Ltd, UK). Data were recorded onto a computer
162 for offline analysis using Signal Software (Version 6.03; Cambridge Electronic Design Ltd, UK).

163 *Transcranial Magnetic Stimulation.* TMS was delivered with a monophasic current waveform
164 (pulse width 70 μs from onset to peak) using a MagPro X100 + option stimulator (MagVenture
165 A/S, Denmark). A figure-of-eight coil (MC-B70) was held tangentially over the right M1 of the
166 participant with the handle pointing backwards and laterally at an angle ~45° to the midline (Fig.
167 1C). The optimal coil position for eliciting motor evoked potentials (MEPs) in the left FDI was
168 marked on the scalp. The LICI protocol was investigated using a posterior-anterior current
169 direction (Brasil-Neto et al. 1992). The SICI protocol was investigated using an anterior-
170 posterior current direction (coil handle same as posterior-anterior stimulation, but current
171 reversed) (Cirillo and Byblow 2016; Sale et al. 2016).

172 Motor thresholds were determined using parameter estimation by sequential testing using
173 a TMS motor threshold assessment software (Awiszus and Borckardt 2011). For the LICI
174 protocol, a task motor threshold was determined for both FDI and APB of the left hand while the
175 participant rested their index fingers on the switches. Task motor threshold was determined as

the minimum stimulus intensity required to elicit a MEP in the targeted muscle of at least 50 μV. For the SICI protocol, active motor threshold was obtained for left FDI and defined as the minimum stimulus intensity required to elicit a MEP in the FDI muscle of at least 200 μV in amplitude during a low-level voluntary contraction (~10% maximum voluntary contraction).

LICI Protocol. Seventeen participants completed the LICI protocol. For LICI, TMS was delivered with a posterior-anterior current direction using an interstimulus interval of 100 ms (Sanger et al. 2001). Both test and conditioning stimulus intensities were set to 130% of task motor threshold for FDI. If necessary conditioning and test stimuli were equivalently adjusted to produce a conditioned MEP that was ~50% of test. Baseline data for LICI (12 trials) were recorded in the rest condition. This intensity remained constant for all subsequent LICI trials.

Participants performed a practice block of 33 trials containing stimulated and non-stimulated trials for each of the possible warning cues. The response task consisted of 396 trials split into 12 blocks of 33 trials with all cue types randomized within blocks. During stimulated trials, conditioning and test stimuli were given at 450 and 550 ms respectively. This timing was chosen to precede any response related increases in corticomotor excitability and to coincide with the presentation of stop cues at 550 ms (Cowie et al. 2016; MacDonald et al. 2014). For each cue type (MS, MSR, MSL, SR, SL and Rest) 18 trials were stimulated. Non-stimulated trials consisted of 135 MS trials, 51 trials for each of MSR and MSL, 18 trials for each of SL and SR, and 15 trials for Rest cues. Behavioral data were derived from non-stimulated trials given that response times can be contaminated by TMS (Leocani et al. 2000; Ziemann et al. 1997).

SICI Protocol. Sixteen participants completed the SICI protocol. For SICI, TMS was delivered with an anterior-posterior current direction using an ISI of 3 ms (Murase et al. 2015; Peurala et al. 2008). Test stimulus intensity was set to elicit a MEP amplitude of ~0.5 mV while the

participant rested their index fingers on the switches. The conditioning stimulus intensity was set to elicit ~50% inhibition of the test stimulus (i.e. MEP amplitude of ~0.25 mV). Baseline data for SICI (12 conditioned and 12 non-conditioned trials) were recorded in the rest condition. The conditioning and test stimulus intensities remained constant for all subsequent SICI trials.

The response task consisted of 272 trials randomized within 8 blocks of 34 trials. In stimulated trials, the timing of the test stimulus was kept constant to the LICI protocol (550 ms) and the conditioning stimulus occurred at 547 ms. For each of the 6 cue variations (MS, MSR, MSL, SR, SL and Rest) 18 trials elicited conditioned and non-conditioned MEPs respectively. Nine trials were non-stimulated for each of MS, MSR, MSL and Rest cues, whereas 10 trials were non-stimulated for both SL and SR cues.

Dependent Measures. Task performance was determined from non-stimulated trials during the LICI protocol. Because SICI was recorded in a separate experimental session, behavioral data were correlated only to the magnitude of LICI. Lift times were recorded and are reported relative to the target line. Mean lift times from Go and successful Partial trials were calculated after the removal of outliers (±3 SD; 0.8% removed). Partial trial delays were calculated by subtracting the appropriate (left or right) MS-GG trial lift time from the respective Partial trial lift time for informative (MSL, MSR) or uninformative (MS) cues. Stop signal reaction time (SSRT) and the percentage of successful trials were determined. The integration method was used to calculate SSRT:

(SSRT = stop signal delay + *n*th lift time)

where *n* is the probability of failing to stop for the given trial multiplied by the number of lift times in the ordered lift time distribution, and the stop signal delay is the bar stop time (550 or

600 ms) subtracted from target time (800 ms) for the given stop trial (Logan et al. 1984; Verbruggen et al. 2013).

Peak-to-peak MEP amplitude was calculated from EMG 10 to 45 ms after the stimulus. MEPs were excluded when root mean square (rms) EMG was >10 μV in the 50 ms preceding stimulation. Data from one participant was removed for APB in the SICI protocol because background EMG activity was consistently >10 μV. The mean MEP amplitude from FDI and APB was calculated following trimming of the upper and lower 10% of trials (Stinear and Byblow 2004; Wilcox 2010). For both SICI and LICI, the magnitude of inhibition was calculated as:

Percent inhibition = [1 – (conditioning stimulus MEP amplitude / test stimulus MEP amplitude)] × 100

where the conditioning and test stimulus MEP amplitude were the mean for each condition from each participant. To reduce inter-subject variability, MEPs during the task context where the participant was instructed to remain on the switches (i.e. rest cue type) were normalized to the baseline data recorded in the rest condition (pre-task resting baseline; 1.0). For APB SICI there was no inhibition in the baseline condition (pre-task resting inhibition) for one participant, whereas the normalized rest-cue inhibition was considered an outlier (>3 SD of the mean) in another participant. Both participants were excluded from the APB SICI analyses.

Experimental Design and Statistical Analysis. Both experiments employed repeated-measures designs with Factors Cue Type, Hand and Trial Type as described below. To assess the effect of Cue Type on lift times, two-way repeated measures analysis of variance (RM ANOVA) with factors Cue Type (MS, MSL, SL, MSR, SR) and Hand (Left, Right) were performed for both Partial (one hand response) and Go trial lift times (both hands respond). Partial trial delays (MS,

MSL, MSR) were assessed with a one-way RM ANOVA for Trial Type. For Stop trials (MS-SG, MS-GS, MS-SS, MSL-SG, MSR-GS), one-way RM ANOVAs were performed for stopping success rate and SSRT.

To assess the effect of Cue Type on corticomotor excitability and inhibition, one-way RM ANOVAs with 6 Cue Types (Rest, MS, MSL, SL, MSR, SR) were used to examine both non-conditioned MEP amplitudes and percent inhibition from LICI and SICI protocols. To assess effector specific modulation of SICI, cued responses (MS, MSL, SL, MSR, SR) were compared to Rest cues, and the inhibition difference between Rest and MSR, Rest and SR, and Rest and MS conditions were compared directly with paired t-tests. The effect of task context on corticomotor excitability and inhibition was assessed using a one-sample *t*-test (hypothesized mean = pre-task resting condition) for mean non-conditioned MEP amplitude and percent inhibition. Finally, to investigate whether the extent of LICI was associated with the stopping interference effect, linear regression analyses were performed for percent inhibition of uninformative (MS) and informative (MSL and MSR) cues and the respective Partial trial delays. Linear regression analyses were also performed for percent LICI of MSL and MSR cues and the difference in lift time between left and right hand responses (Trial type GG).

Normality was assessed prior to ANOVA using the Shapiro-Wilk test. Non-normal data were logarithmically transformed. Statistical tests were performed and reported for the transformed data. The criterion for statistical significance was set to $\alpha = 0.05$. Non-transformed means ± standard error (SE) are reported. Non-spherical data were determined by Mauchly's Test of Sphericity and are reported with Greenhouse-Geisser corrected *P* values. Two-tailed paired t-tests were performed to explore main effects and interactions and corrected for multiple comparisons (Rom 1990).

Results

Behavioral Data

Participants performed the task accurately. Lift times indicated that there was a cost-benefit trade-off with Cue Type, and an interference effect from stopping one side and lifting with the other on Partial trials. For Partial trials, there was a main effect of Cue Type ($F_{2,34}$ = 112.9, P < 0.001). Lift times were later for MS (69 ms ± 5 ms) than MSL/R (45 ms ± 8 ms; t_{17} = 6.1, corrected P < 0.001) and SL/R (3 ms ± 5 ms; t_{17} = 16.7, corrected P < 0.001) cues, which also differed from each other (t_{17} = 8.0, corrected P < 0.001). There was no main effect of Hand ($F_{1,17}$ = 3.1, P = 0.095) and no Cue Type x Hand interaction ($F_{2,34}$ = 2.6, P = 0.085). On Partial trials there was a main effect of Cue Type ($F_{1.9,32.7}$ = 7.2, P < 0.01) for lift time delay. For GS trials, lift time delays were shorter for MSR (24.3 ± 9.9 ms) than MS (53.3 ± 5.5 ms; t_{17} = 4.5, corrected P = 0.001) cues. Similarly, for SG trials, lift time delays were shorter for MSL (25.7 ± 5.2 ms) than MS (44.6 ± 5.1 ms; t_{17} = 3.7, corrected P = 0.007) cues.

During Go trials, there was a main effect of Hand ($F_{1,17}$ = 13.0, P = 0.002), with faster lift times for the right hand (13 ± 2 ms) compared with the left (23 ± 3 ms). There was a Cue Type x Hand interaction ($F_{2,34}$ = 42.1, P < 0.001), but no main effect of Cue Type ($F_{2,34}$ = 1.2, P = 0.316). For the left hand (Fig. 2A), lift times were shorter with MSR cues (14 ± 3 ms) than both MS (25 ± 3 ms; t_{17} = 4.3, corrected P = 0.003) and MSL (30 ± 3 ms; t_{17} = 5.2, corrected P < 0.001) cues. For the right hand (Fig. 2B), lift times were shorter with MSL cues (4 ± 3 ms) than both MSR (19 ± 3 ms; t_{17} = 4.4, corrected P = 0.003) and MS (15 ± 3 ms; t_{17} = 4.0, corrected P = 0.015) cues. Lift times were slower on the left than right with MS cues (t_{17} = 3.4, corrected P = 0.024) and MSL cues (t_{17} = 7.0, corrected P < 0.001). These results indicate that proactive "braking" is expressed to a greater extent in the non-dominant side.

There was no effect of Trial Type ($F_{4,68} = 1.5$, $P = 0.215$) on stopping success rates (Table 2). For SSRTs there was a main effect of Trial Type ($F_{4,68} = 22.6$, $P < 0.001$), with SSRTs shorter for SS trials (202 ± 6 ms) than all other Trial Types (SSRTs all > 248.4 ± 6 ms; all $t_{17} > 6.0$, all $P < 0.001$). Therefore, Partial trials were associated with longer stopping processes than when both hands required stopping.

Stimulation Parameters

For the LICI protocol, task motor threshold was 47 ± 2% MSO for FDI and 51 ± 2% MSO for APB. Task stimulation intensity was set at 65 ± 2% MSO (138% of task motor threshold for FDI). Average pre-task resting inhibition was 64.3 ± 4.8% for FDI and 70.0 ± 5.2% for APB. Average pre-task unconditioned MEP amplitude was 1.9 ± 0.4 mV in FDI and 0.8 ± 0.2 mV in APB.

For the SICI protocol, active motor threshold was 53 ± 2% MSO. Average test stimulus intensity was 76 ± 4% MSO while conditioning stimulus intensity was 39 ± 4% MSO (74% of active motor threshold). Average pre-task resting inhibition was 54.7 ± 3.8% for FDI and 50.3 ± 6.2% for APB. Average pre-task unconditioned MEP amplitude was 0.6 ± 0.1 mV for FDI and 0.5 ± 0.2 mV for APB.

Corticomotor Excitability

Figure 3A shows EMG traces with MEPs from the LICI protocol for an individual participant. For corticomotor excitability of FDI in the LICI protocol (FDI, $n = 17$; Fig. 4A), there was no main effect of Cue Type ($F_{5,80} = 2.9$, $P = 0.053$). However, non-conditioned MEP amplitude (2.8 ± 0.5 mV) increased by 58.9 ± 21% during the task compared with the pre-task resting condition ($t_{16} = 2.8$, $P = 0.012$; Fig. 4B). For APB, there was an effect of Cue Type ($F_{5,80} = 5.0$, $P = 0.005$), with greater MEP amplitude for SL cues (0.9 ± 0.2 mV) compared with both Rest (0.8 ± 0.2 mV;

313 t_{16} = 3.8, corrected P = 0.013) and SR (0.8 ± 0.2 mV; t_{16} = 4.7, corrected P = 0.002). Task and
314 pre-task APB MEP amplitudes did not differ (5.0 ± 14.8 %; t_{16} = 0.3, P = 0.741). Thus,
315 corticomotor excitability increased for the task-relevant FDI only.
316 Figure 3B shows EMG traces of the left hand with MEPs from the SICI protocol for an
317 individual participant. For corticomotor excitability in the SICI protocol (FDI n =16, APB n =
318 15; Fig. 4C), there was no main effect of Cue Type for FDI ($F_{5,75}$ = 0.3, P = 0.857) or APB ($F_{5,70}$
319 = 2.7, P = 0.084). For FDI, MEP amplitude increased by 82.9 ± 27.7% during the task compared
320 with the pre-task resting condition (t_{15} = 3.0, P = 0.009; Fig. 4D). MEP amplitude for APB did
321 not significantly change between the pre-task resting and task conditions (t_{14} = 0.5, P = 0.599).
322 Thus, corticomotor excitability increased for the task-relevant muscle only.

323 *Inhibition*

324 For the LICI protocol (n = 17; Fig. 5A), there was no main effect of Cue Type for either muscle
325 (FDI: $F_{5,80}$ = 0.9, P = 0.458; APB: $F_{5,80}$ = 2.2, P = 0.063). For FDI, inhibition decreased during
326 the task by 73.1 ± 22.0% compared with the pre-task resting condition (t_{16} = 3.3; P = 0.004, Fig.
327 5B). For APB, inhibition also decreased by 70.3 ± 17.6% during the task compared with the pre-
328 task resting condition (t_{16} = 4.0, P = 0.001), indicating a non-selective disinhibition within task
329 context.
330 The SICI protocol produced distinct results across the two muscles (FDI n =16, APB n =
331 14). For FDI (Fig. 5C), there was a main effect of Cue Type ($F_{5,75}$ = 2.5, P = 0.037) with greater
332 inhibition during Rest cues (46.0 ± 5.8%) compared with MSR (32.7 ± 6.9%; t_{15} = 3.5, corrected
333 P = 0.016) and SR (31.9 ± 6.7%; t_{15} = 3.5, corrected P = 0.015) cues. Inhibition observed with
334 MSL and SL cue types did not differ from inhibition at Rest cues (all corrected P > 0.12). As can
335 be seen in Fig. 5C, inhibition decreased (albeit non-significantly; t_{15} = 2.6, corrected P = 0.105)

with the introduction of uninformative MS cues, where the default response is to prepare to respond with both sides. The decrease in inhibition was significant only when responding became highly likely or certain with MSR or SR cues. However, directly comparing the differences in inhibition between Rest and MS (14.0 ± 5.5%) with Rest and MSR (13.2 ± 3.8%) yielded no difference (P = 0.873) nor between Rest and SR (14.1 ± 4.0%; P = 0.996). Also for FDI, SICI was similar between the pre-task and task resting conditions (P = 0.842; Fig. 5D). For APB, there was no main effect of Cue Type ($F_{5,65}$ = 2.0, P = 0.091) and no significant difference in the amount of inhibition between the pre-task and task resting conditions (P = 0.382; Fig. 5D).

Linear regression

For MS conditions, there was a positive correlation between LICI and Partial trial delays for the FDI (r = 0.620, P = 0.016; Fig. 6A), such that less inhibition was associated with shorter delays. For APB, there was a weak association between LICI and Partial trial delays (r = 0.522, P = 0.062, Fig. 6B). For MSL and MSR conditions there were no correlations between LICI and trial delays for either FDI or APB (all P > 0.199). Furthermore, there were no correlations between LICI and the difference in lift time between left and right hand responses (GG trials) for MSL and MSR conditions (all P > 0.187).

Discussion

The present study provides novel insights into the modulation of primary motor cortex excitability and inhibition of reactive and proactive processes in response inhibition preceded by informative or uninformative cues. As expected, the delay in response times on Partial trials was reduced when advanced information was provided to forewarn stopping. Corticomotor excitability increased during the task relative to rest, but was not modulated by cue type. For LICI, inhibition was reduced during the task for both task-relevant and irrelevant muscles

irrespective of cue type. In contrast, compared to when cued to rest, SICI was reduced when responding was highly probable or known. These results provide preliminary evidence for distinct roles for M1 GABA mediated networks during response inhibition. While $GABA_B$-receptor mediated inhibition may set overall inhibitory tone related to task demands, $GABA_A$-receptor mediated inhibition may be critical for preventing premature responding in a task-relevant manner.

Cue Information on Proactive and Reactive Processes in Response Inhibition

For partial trials, lift time was close to the target when trial type was known (SR and SL) and delayed when it was not, for both uninformative (MS) and informative (MSR and MSL) cues. These lift-time delays are indicative of an interference effect between stopping and going processes (Aron and Verbruggen 2008; Coxon et al. 2007; 2009; MacDonald et al. 2014). As in previous studies, the response delay was not eliminated or reduced despite a relatively high success rate (~60%) (Cowie et al. 2016). This finding challenges the view that the interference effect may be eliminated with familiarity or training (Xu et al. 2015). Instead, the present study demonstrates that interference effects and slower lift times accompany reactive and proactive processes for both informative and uninformative cues and that uninformative cues typically produce greater delays than informative cues (Aron and Verbruggen 2008; Claffey et al. 2010; Majid et al. 2012). Lift times were longer for the (left) hand when it was cued to stop (MSL), inducing delays similar to trials with uninformative cues (MS). These prolonged lift times with informative cues may indicate a temporary "braking" mechanism (Aron 2011; Jahfari et al. 2010; Majid et al. 2013).

The anticipatory task did not modulate MEP amplitude between cue-types for task-relevant FDI. This finding is in contrast to studies that have shown suppression of MEP

amplitude (corticomotor excitability suppression) preceding responses (e.g., Duque et al. 2017). The reason for this discrepancy may be related to the timing of TMS. Here, corticomotor excitability was assessed 250 (SICI) - 350 (LICI) ms before the target, a time period that closely coincides with the stop cue presentation. Corticomotor excitability suppression has been observed in the anticipatory task when TMS is delivered after the stop imperative (Cowie et al. 2016; MacDonald et al. 2014). The anticipatory task differs from stop-signal tasks which seem to produce suppression from trial onset, and has been interpreted in a model of "impulse control" where selected responses are suppressed to ensure they are not made before required (Duque and Ivry 2009; Duque et al. 2012; Duque et al. 2010; Labruna et al. 2014).

Intracortical Inhibition

LICI is typically associated with tonic inhibitory effects. The LICI procedure showed reduced inhibition in the context of response inhibition (compared with baseline), although the magnitude of inhibition was similar between informative and uninformative cue types and corroborates previous findings (Cowie et al. 2016). Conversely, Sinclair and Hammond (2008) found that LICI was reduced on trials when unimanual right hand responses were warned (informative) compared with unwarned (uninformative). One possible explanation for the discrepancy between studies may relate to the intensity used for the conditioning and test stimuli (Sanger et al. 2001). In the present study the stimulus intensities were adjusted to produce a conditioned MEP amplitude that was ~50% of non-conditioned. In contrast, Sinclair and Hammond (2008) set both conditioning and test stimulus intensities to 110% RMT (warned unconditioned MEP, 2-3 mV; unwarned unconditioned MEP, 3-4 mV). Task differences may also have contributed. Sinclair and Hammond (2008) had only two cue types (warned and unwarned) for a response initiation task, whereas the present study had six variants that included both action stopping and

preparation. Previously, we found greater inhibition with LICI for blocks containing reactive inhibition trials, compared with blocks where stopping was never signaled (Cowie et al. 2016). It may be that tonic levels of LICI are adjusted based on task-expectations as part of an "activation threshold" (MacDonald et al. 2017). Increasing attentional demand may also reduce LICI (Conte et al. 2007). Although attention was not assessed explicitly, attentional demand would conceivably be much greater during response inhibition than during the baseline procedure. The association between LICI and response delays on Partial trials, as observed previously (Cowie et al. 2016), lends further support to the idea that a functional modulation of LICI occurs according to task-requirements. In summary, it appears that LICI is modulated by task context, but does not seem to be modulated differentially between reactive and proactive processes in response inhibition preceded by informative or uninformative cues.

In the present study, task-relevant (FDI) SICI was influenced by cue type. Our effector-specific hypothesis about SICI modulation was not supported when directly comparing inhibition differences between Rest and informative cues (MSR, SR) and Rest and uninformative cues (MS). However, there was evidence in support of a step-wise release of inhibition with accumulating advance information. Compared with being cued to Rest there was a non-significant decrease in inhibition with the introduction of uninformative MS cues (Fig. 5C). Inhibition reduced further in the task relevant FDI only, once responding was highly likely (MSR) or known (SR). However, inhibition did not increase when stopping was more likely (MSL and SL). Together, these findings support the contention that a release of $GABA_A$-mediated intracortical inhibition occurs immediately before movement (Coxon et al. 2006; Sinclair and Hammond 2008; Stinear and Byblow 2003), and supports a model whereby motor inhibition assists action selection (Duque and Ivry 2009; Sinclair and Hammond 2008). Overall,

the present findings indicate that informative cues may trigger more proactive processes which modulate SICI when a response is about to occur. In contrast, the absence of effect of cue type in the task irrelevant APB is inconclusive because TMS parameters were optimized to obtain maximum sensitivity in FDI only. This study was the first to utilize anterior-posterior stimulation to assess SICI in the context of response inhibition and further investigations which examine the time course of SICI modulation may be warranted.

A dissociation in muscle specificity between LICI and unconditioned MEP amplitudes during the task relative to pre-task baseline was evident in the present study. A lack of muscle specificity accompanying LICI may not be surprising because of its association with tonic inhibition, acting on both pre- and post-synaptic $GABA_B$ receptors (Bettler et al. 2004). In contrast, the increased unconditioned MEP amplitude observed in the task-relevant (FDI), but not task-irrelevant (APB), effector may reflect excitability of $GABA_A$-ergic networks that spatially and temporally regulate control over M1 corticospinal output (Stinear and Byblow 2003). However, this explanation seems unlikely because SICI was reduced only when responses were highly likely or required. What leads to the muscle-specific increase in corticomotor excitability during task context remains to be elucidated, but other cortical connections (i.e. increased excitatory circuits within M1) or subcortical mechanisms may contribute.

Response inhibition and the role of M1 intracortical inhibition

Neuroimaging studies have proposed recent advances on the race model (Logan et al. 1984) to account for an interaction between proactive and reactive processes (Jahfari et al. 2012; Zandbelt et al. 2013), given a proposed shared circuitry (Dunovan et al. 2015). Recently we proposed an "activation threshold" framework to explain response inhibition dynamics as well as account for the large interference effects in reactive response inhibition contexts such as observed here, that

are difficult to reconcile within the race model (MacDonald et al. 2014; MacDonald et al. 2017). Within the activation threshold framework, proactive modulation of intracortical inhibition may influence reactive response inhibition performance by altering the position of the "finish line". There was a non-selective reduction of LICI with task context, consistent with our previous study (Cowie et al. 2016). Reduced LICI may promote responding by reducing the activation threshold. Conversely, increased LICI may strengthen inhibitory control, which would concurrently increase the activation threshold for re-initiated movement, and result in even slower response times (even greater interference effects). Both scenarios can be accommodated within the activation threshold model, which adjusts tonic levels of inhibition in a task-dependent manner (MacDonald et al. 2014). As expected, SICI reduced when responses were highly likely or required compared with being cued to rest (Duque and Ivry 2009). Less SICI may proactively lower the activation threshold, improving the likelihood of lift times that are closer to the target. Therefore, it seems likely that SICI is reduced mainly prior to movement i.e., it is a mechanism which is permissive for voluntary movement to occur (Reynolds and Ashby 1999; Stinear and Byblow 2003). With uncertainty, lift times were slowed. Proactively, SICI may be maintained at a higher level in an attempt to "hold" a commenced Go process until response certainty is available. Overall, the present results may indicate that LICI is used to set general inhibitory tone relative to response-expectations, whereas SICI is modulated until response decisions are confirmed. The present study identifies potential mechanisms within M1 which may support both proactive and reactive processes.

In conclusion, this current study provides novel insight into the role of primary motor cortex function in engaging proactive and reactive processes during movement cancellation when preceded by informative or uninformative cues. The magnitude of LICI was reduced by task

context, but was similar between cue types (informative and uninformative). Similar differences in SICI relative to rest were observed with informative and uninformative cues. However, compared with rest, less SICI was evident when responding was highly probable or known. We propose that $GABA_B$-receptor mediated pathways play a role in setting inhibitory tone according to task context and not cue information, and $GABA_A$-receptor mediated pathways may be modulated proactively with response certainty to optimize task performance.

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Figure Legends

Figure 1. Trials began when both switches were pressed. After 500 ms the indicators would rise at a constant velocity and reach the top in exactly 1 s. Participants were instructed to stop the left, right or both indicators at the target line (800 ms) by abducting the corresponding index finger(s) to release the switches. A. The majority of trials were Go trials (Go-Left Go-Right), which required the simultaneous left and right index finger abduction. B. Top panel shows partial trial (Go-Left Stop-Right), whereby the right indicator stopped automatically at 550 ms, and required left response was delayed relative to target. These 'interference effects' were larger for uninformative than informative conditions. Bottom panel shows Stop-Both condition where both indicators stopped 600 ms into the trial, and both responses were successfully inhibited. Successful trials were represented by a green target line when lift times were within 30 ms of the target, otherwise a red target line was indicated. C. Transcranial magnetic stimulation was delivered over the right motor cortex to elicit motor-evoked potentials in the left first dorsal interosseous and abductor pollicis brevis. D. Four warning cues (cue type) were combined to produce six task variants (trial type). Uninformative cues were indicated by two yellow circles. Informative cues were indicated by a green circle for the responding hand and a yellow circle for the hand that might be cued to stop. Known cues were indicated by a green circle for the responding hand and a red circle for the non-responding hand. Rest cues were indicated by two red circles to specify that no response was required.

Figure 2. Lift times relative to informative and uninformative warning cues. Lift times are indicated by the time between response and target. Partial trial and Go trial lift times relative to cue for the left (A) and right (B) hand. Uninformative cues (Maybe Stop; MS) required the left, right or both hands to occasionally stop. Informative cues (Maybe Stop Left and Maybe Stop

Right; MSL and MSR) required only the cued hand to occasionally stop, except on catch trials. Known cues (Stop Left and Stop Right; SL and SR) required the cued hand to always stop. Bars represent the group mean (n = 18). Error bars indicate SE. ‡ $P < 0.05$ MS compared with MSR. † $P < 0.05$ MSL compared with MSR. * $P < 0.05$ MS compared with MSL. # $P < 0.05$ compared with left for the given cue.

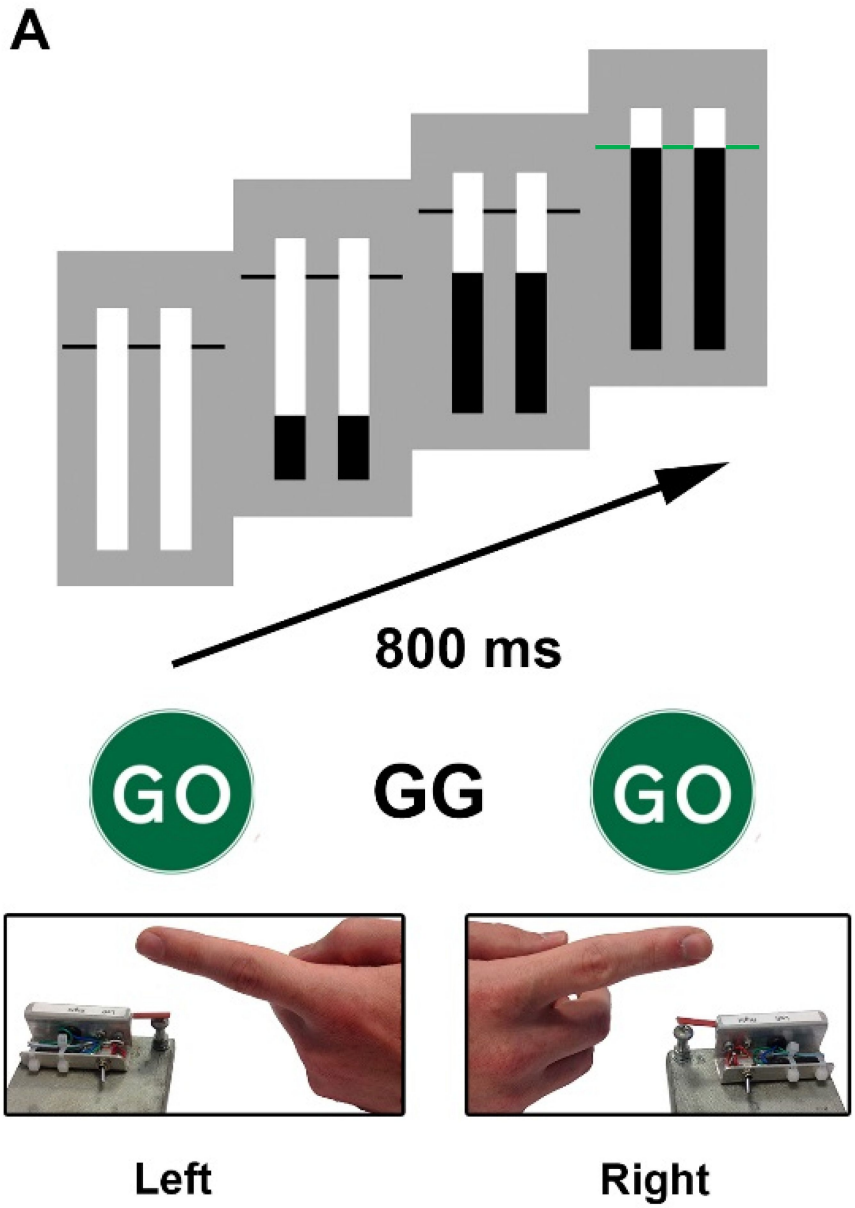
Figure 3. Representative electromyography traces with motor evoked potentials in the left first dorsal interosseous muscle. A. On Rest trials, long-interval intracortical inhibition (LICI) was weaker during the task than during the pre-task resting condition as indicated by the difference in conditioned (second) MEP size. B. Similarly, short-interval intracortical inhibition (SICI) was weaker for Maybe Stop Right (MSR) trials compared with Rest trials. For both LICI and SICI the test stimulus was delivered at 550 ms, and conditioning stimulus at 450 ms and 547 ms respectively. CS, conditioning stimulus; TS, test stimulus.

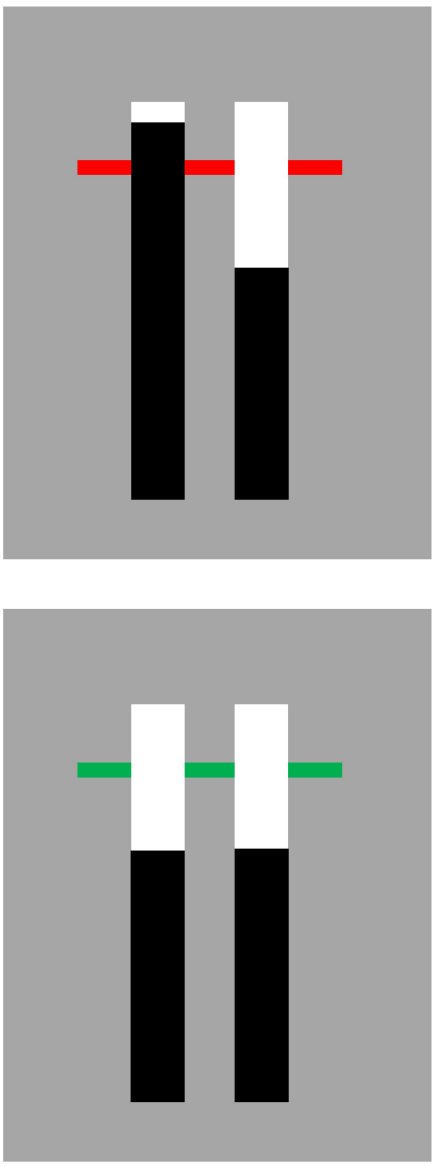
Figure 4. Corticomotor excitability was indicated by MEP amplitude. First dorsal interosseous non-conditioned motor evoked potential (MEP) amplitude for long-interval intracortical inhibition (A. LICI, $n = 17$) and short-interval intracortical inhibition (C. SICI, $n = 16$). Non-conditioned MEP amplitude between pre-task and task context for LICI (B) and SICI (D). Pre-task and task rest conditions are normalized and scaled according to pre-task values (1.0, dashed line). MS, Maybe Stop; MSL, Maybe Stop Left; SL, Stop Left; MSR, Maybe Stop Right; SR, Stop Right. Mean ± SE bars represent non-transformed data. *$P < 0.05$.

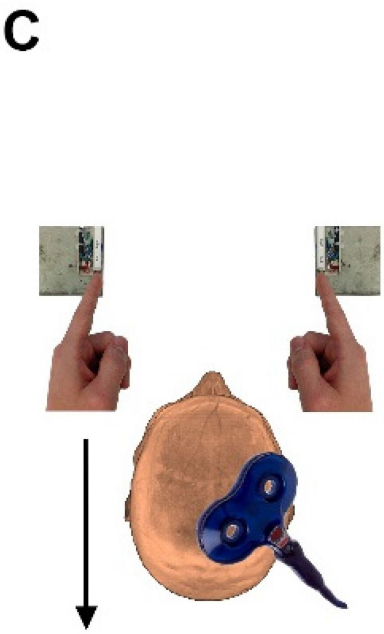
Figure 5. Intracortical inhibition was expressed as a percentage with greater values indicative of more inhibition. First dorsal interosseous long-interval intracortical inhibition (A. LICI, $n = 17$) and short-interval intracortical inhibition (C. SICI, $n = 16$). %Inhibition between pre-task and

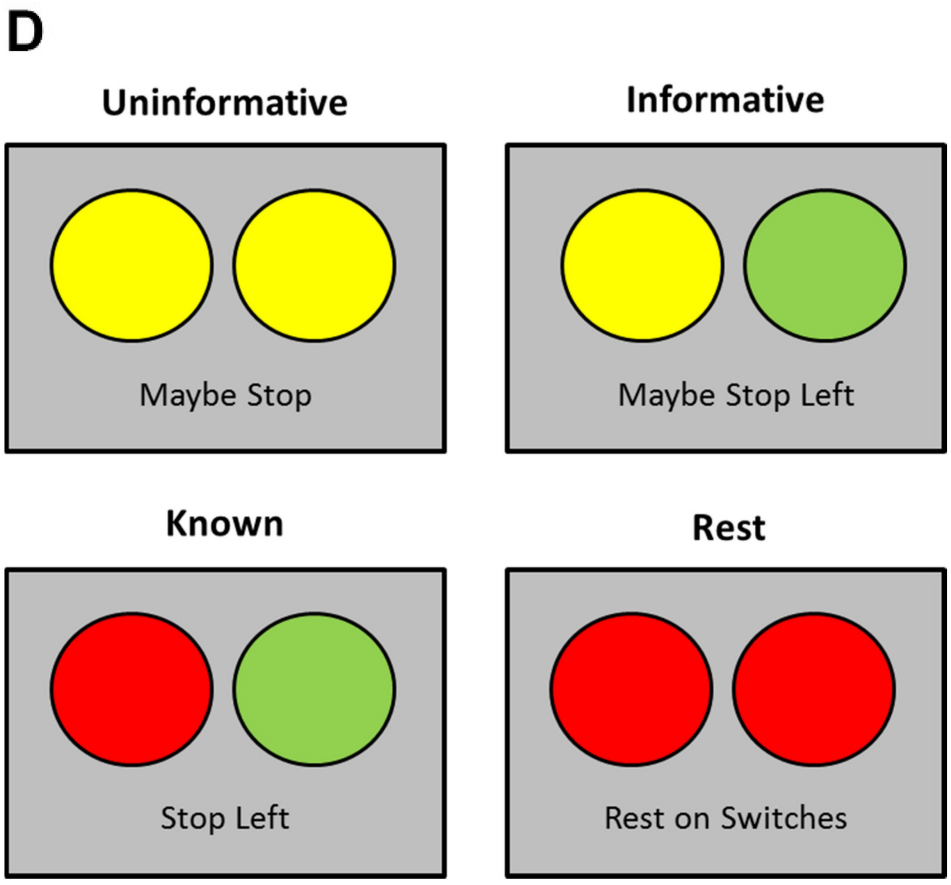
task context for LICI (B) and SICI (D). Intracortical inhibition of pre-task and task rest conditions are normalized and scaled according to pre-task values (1.0, dashed line). MS, Maybe Stop; MSL, Maybe Stop Left; SL, Stop Left; MSR, Maybe Stop Right; SR, Stop Right. Mean ± SE bars represent non-transformed data. *P < 0.05.

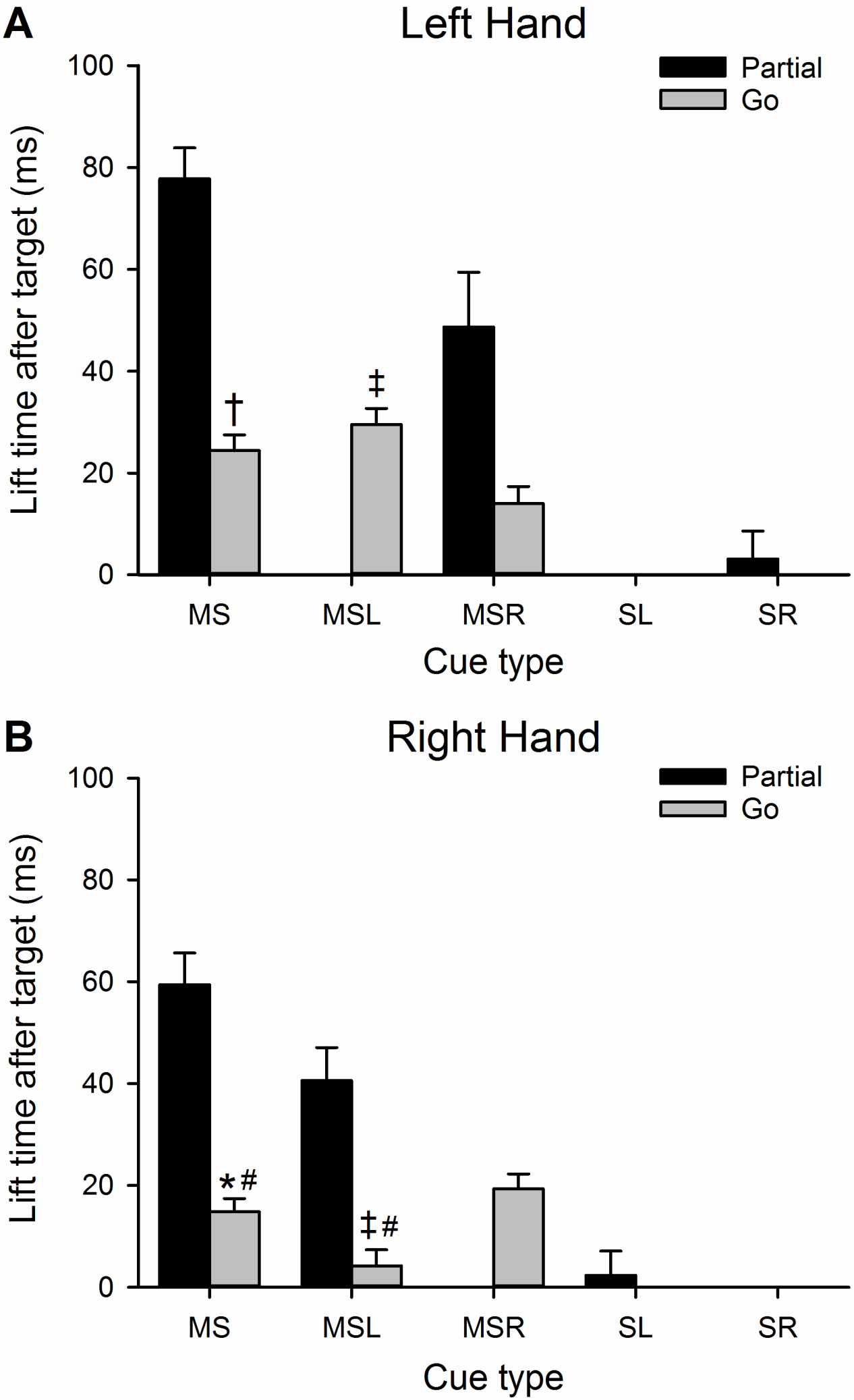
Figure 6. Correlations between LICI (% INH) and Partial trial delays of right hand responses for trials preceded by uninformative cues (Maybe Stop; $n = 17$). A. Task-relevant first dorsal interosseous ($r = 0.620$, $P = 0.016$). B. Task-irrelevant abductor pollicis brevis ($r = 0.522$, $P = 0.062$).

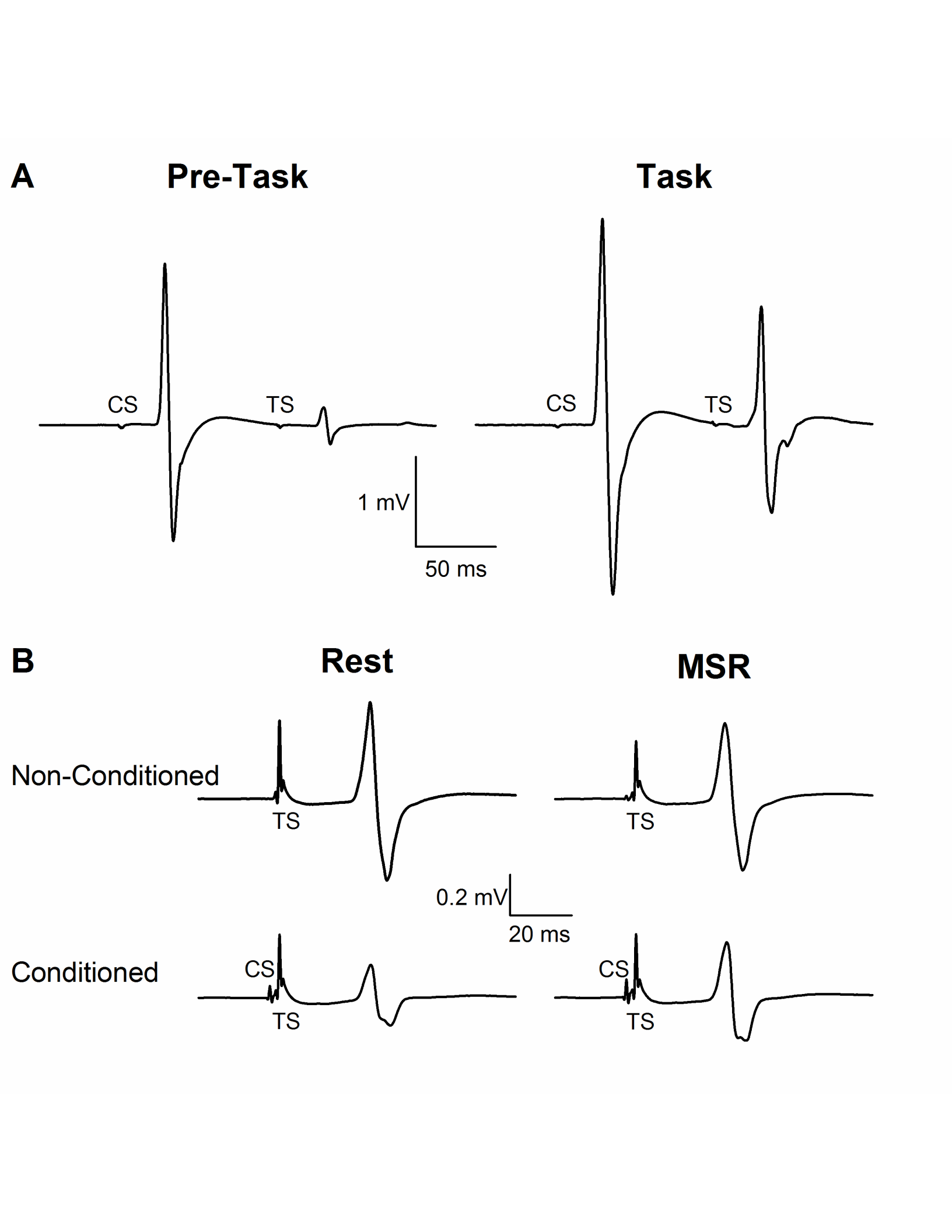

A
800 ms
GO
GG
GO
Left
Right

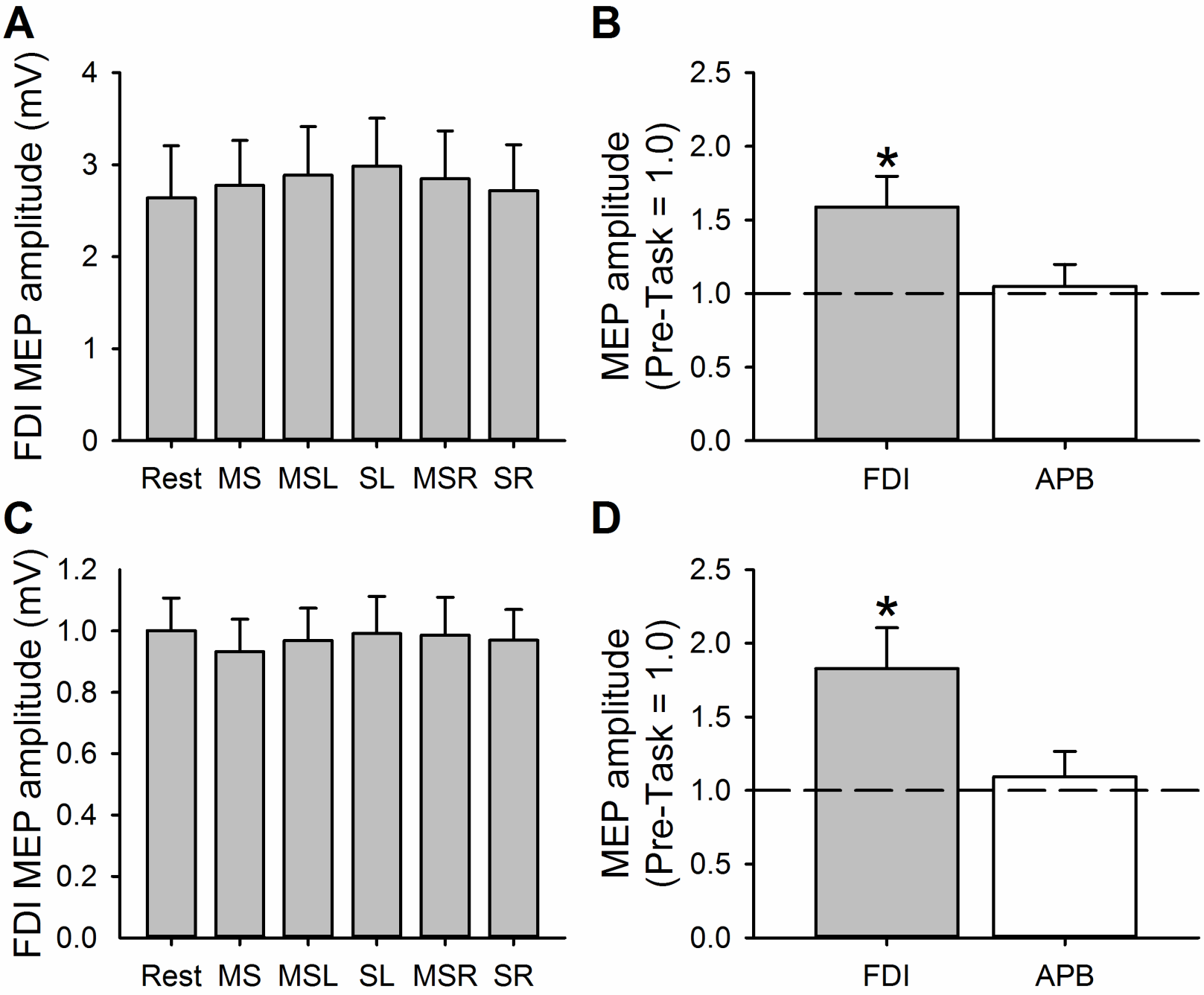

B

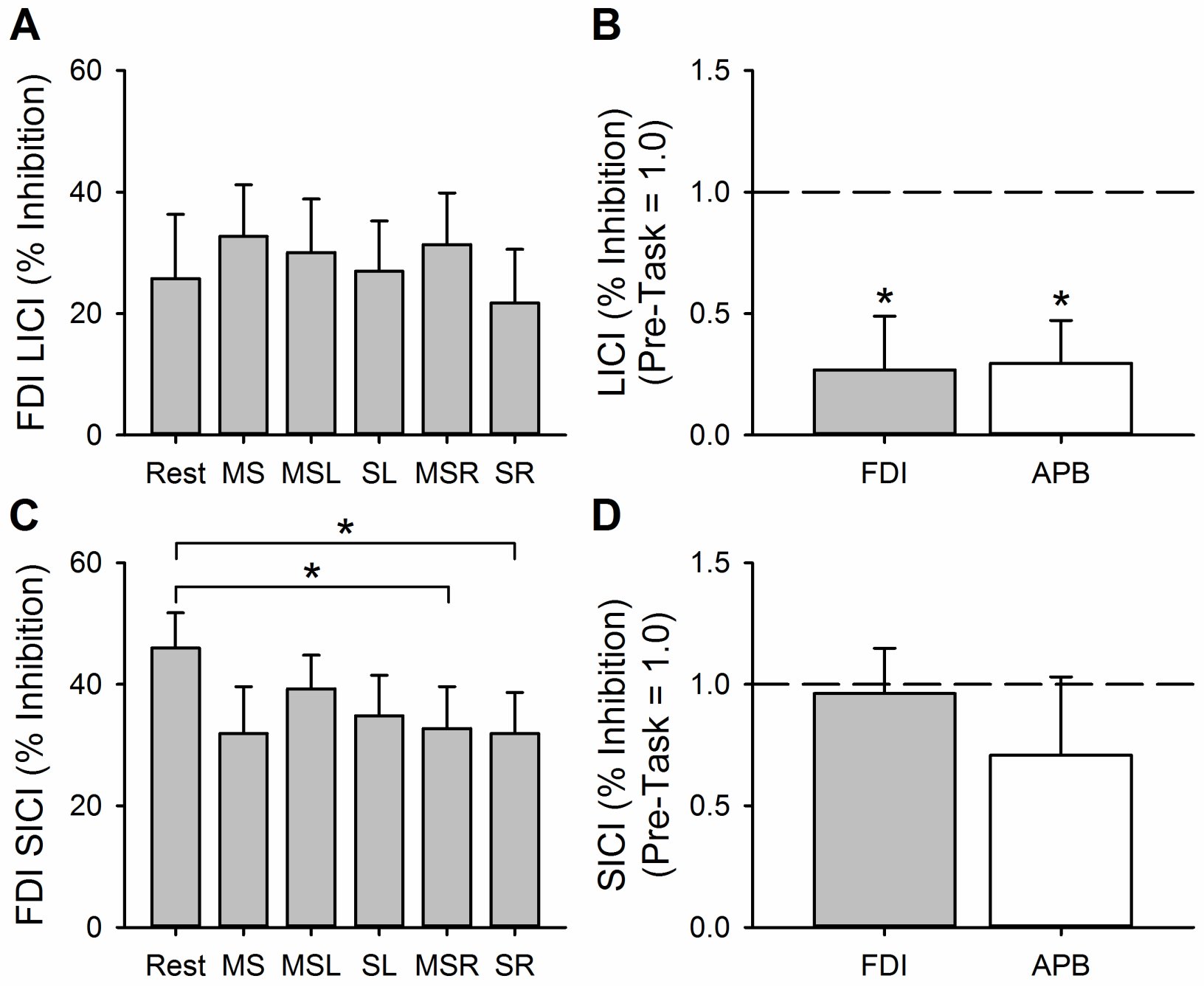

C
MEP From
Left FDI


D
Uninformative
Maybe Stop
Informative
Maybe Stop Left
Known
Stop Left
Rest
Rest on Switches


A
Left Hand
Partial
Go
Lift time after target (ms)
100
80
60
40
20
0
†
‡
MS
MSL
MSR
SL
SR
Cue type
B
Right Hand
Partial
Go
Lift time after target (ms)
100
80
60
40
20
0
*#
‡#
MS
MSL
MSR
SL
SR
Cue type


A
Pre-Task
Task
CS
TS
CS
TS
1 mV
50 ms
B
Rest
MSR
Non-Conditioned
TS
TS
0.2 mV
20 ms
Conditioned
CS
TS
CS
TS


A
FDI MEP amplitude (mV)
4
3
2
1
0
Rest
MS
MSL
SL
MSR
SR
B
MEP amplitude
(Pre-Task = 1.0)
2.5
2.0
1.5
1.0
0.5
0.0
*
FDI
APB
C
FDI MEP amplitude (mV)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Rest
MS
MSL
SL
MSR
SR
D
MEP amplitude
(Pre-Task = 1.0)
2.5
2.0
1.5
1.0
0.5
0.0
*
FDI
APB


A
FDI LICI (% Inhibition)
60
40
20
0
Rest
MS
MSL
SL
MSR
SR
B
LICI (% Inhibition)
(Pre-Task = 1.0)
1.5
1.0
0.5
0.0
*
*
FDI
APB
C
FDI SICI (% Inhibition)
60
40
20
0
*
*
Rest
MS
MSL
SL
MSR
SR
D
SICI (% Inhibition)
(Pre-Task = 1.0)
1.5
1.0
0.5
0.0
FDI
APB

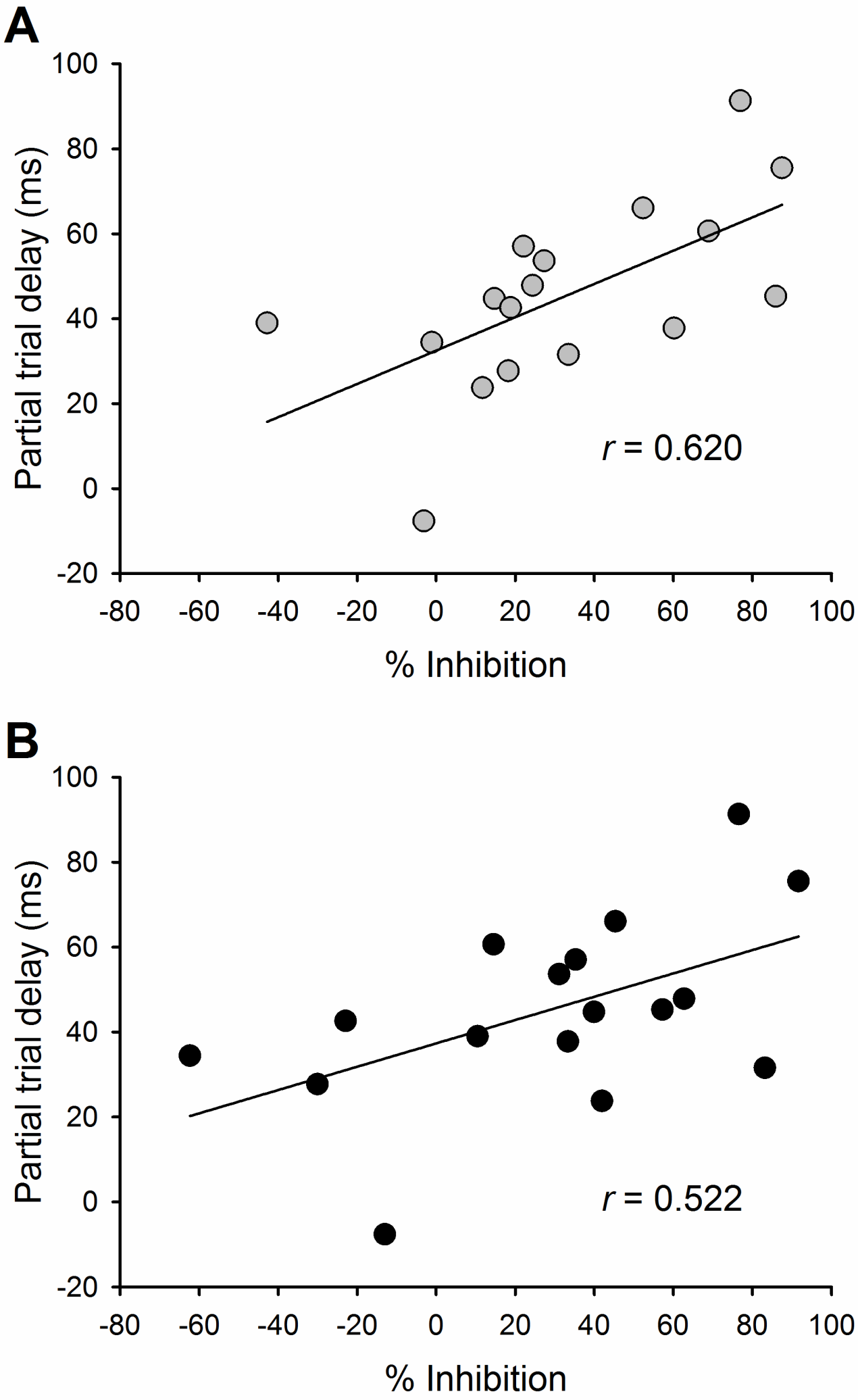

A
Partial trial delay (ms)
100
80
60
40
20
0
-20
-80
-60
-40
-20
0
20
40
60
80
100
% Inhibition
r = 0.620
B
Partial trial delay (ms)
100
80
60
40
20
0
-20
-80
-60
-40
-20
0
20
40
60
80
100
% Inhibition
r = 0.522

Table 1. *Distribution of trial types following cue types*

Cue Type	**Distribution of Trials (%)**			
	GG	GS	SG	SS
MS	67	11	11	11
MSL	67	0	22	11
SL	0	0	100	0
MSR	67	22	0	11
SR	0	100	0	0
Rest	0	0	0	100

Cue Type: MS Maybe Stop; MSL Maybe Stop Left; MSR Maybe Stop Right; SR Stop Right; SL Stop Left. Trial Type: GG Go-Left Go-Right; GS Go-Left Stop-Right; SG Stop-Left Go-Right; SS Stop Both.

Table 2. *Behavioral results (LICI protocol)*

	Stop Trials – Trial Type(Cue Type)						
	MS (SG)	MS (GS)	MS (SS)	MSL (SG)	MSR (GS)	SL (SG)	SR (GS)
Success Rate (%)	66 ± 6	59 ± 8	66 ± 6	69 ± 6	57 ± 7	96 ± 2	96 ± 2
Partial Delay (ms)	45 ± 5	53 ± 5	-	26 ± 5	24 ± 10	-	-
SSRT (ms)	248 ± 6	266 ± 10	202 ± 6*	256 ± 6	254 ± 7	-	-

Behavioral values include stopping success rates, partial trial delays (relative to MS-GG trials) and stop-signal reaction time (SSRT). Cue Types: MS, Maybe Stop; MSL, Maybe Stop Left; MSR, Maybe Stop Right; SR, Stop Right, SL, Stop Left. Trial Types: SG, Stop-Left Go-Right; GS, Go-Left Stop-Right; SS, Stop-Left Stop-Right. Values are reported as mean (n = 18) ± SE. *P < 0.001 compared with all other trial types.