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Response inhibition activates distinct motor cortical inhibitory processes

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DOI:

[10.1152/jn.00784.2017](https://doi.org/10.1152/jn.00784.2017)

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Document Version

Peer reviewed version

Citation for published version (Harvard):

Cirillo, J, Cowie, MJ, MacDonald, HJ & Byblow, WD 2018, 'Response inhibition activates distinct motor cortical inhibitory processes' *Journal of Neurophysiology*, vol. 119, no. 3, pp. 877-886.
<https://doi.org/10.1152/jn.00784.2017>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

Published as above, final version of record available at: <https://doi.org/10.1152/jn.00784.2017>.

Checked 25/7/18.

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31 **Abstract**

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

52

53 **New and Noteworthy**

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

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

62 **Introduction**

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

74 It is also reasonable to suspect that primary motor cortex (M1) is modulated during
75 response inhibition given its role in shaping descending motor output (Stinear et al. 2009).
76 Transcranial magnetic stimulation (TMS) studies of reactive response inhibition indicate a non-
77 selective reduction in corticomotor excitability (Badry et al. 2009; Cai et al. 2012; Cowie et al.
78 2016; Coxon et al. 2006; MacDonald et al. 2014; Majid et al. 2012). However, proactive
79 inhibitory processes are amplified and corticomotor excitability is selectively reduced when there
80 is some forewarning that a component of the response might be cancelled (Cai et al. 2011;
81 Claffey et al. 2010; Majid et al. 2013). Currently it is unclear whether corticomotor suppression
82 during response inhibition occurs via modulation of M1 intracortical inhibition or by withdrawal
83 of facilitation.

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

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

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

111 **Methods**

112 *Participants.* Eighteen participants without neurological impairment were recruited (mean age
113 26.4 years, range 18-50 years, 8 female). All were right handed (laterality quotient mean 0.92,
114 range 0.75-1) as determined using the abbreviated Edinburgh handedness inventory (Veale
115 2014). Written informed consent was obtained before participation and the study was approved
116 by the University of Auckland Human Participants Ethics Committee (Ref. 014398).

117 *Response Task.* Participants performed a bimanual anticipatory response task (Cowie et al. 2016;
118 Coxon et al. 2007; 2009; MacDonald et al. 2014; MacDonald et al. 2012) which had similarities
119 to unimanual versions of the same task (Coxon et al. 2006; Dunovan et al. 2015; Zandbelt and
120 Vink 2010). Briefly, participants were seated with forearms in a neutral posture, resting on a
121 table surface allowing the distal and medial aspect of each index finger to rest on a mechanical
122 switch. A computer display projected two indicators (as filling bars) (Fig. 1). Switch state was
123 precisely captured with an Arduino and synchronized to the display through an analog-digital
124 interface (NI-DAQmx 9.7; National Instruments). Switch height was adjusted to minimize
125 postural muscle activity. Customized software written in MATLAB (R2011a, version 7.12; The
126 MathWorks) generated the trial order, recorded trial data and controlled the visual output during
127 the task.

128 Participants were instructed to respond by lifting their index fingers (abduction) from the
129 switches to stop the ascending indicators (black) at a horizontal target line (Fig. 1A). Thus, there

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

137 Each trial was preceded by a warning cue of 1.5 s duration. Once the warning cue
138 disappeared, participants placed their fingers on the switches, and bar filling occurred 500 ms
139 later. Cues consisted of two colored circles on the left and right of the display, corresponding to
140 each hand. Circle color was used to trigger proactive (informative cue) or reactive
141 (uninformative cue) processes (Fig. 1D), and consisted of six possible cue types. The
142 uninformative cue (Maybe Stop, MS) consisted of all trial types. Informative cues (Maybe Stop
143 Left, MSL; Maybe Stop Right, MSR) consisted of three trial types, with a partial trial of cued
144 finger excluded. For MS, MSL, and MSR cues there was a 2-to-1 ratio of Go to Stop trials.
145 Because response complexity may effect inhibitory processes (Greenhouse et al. 2015), catch
146 trials (Stop Both, SS) were maintained (~10%) for the MS, MSL, and MSR cues. Known cues
147 (Stop Left, SL; Stop Right, SR; Rest) consisted of only the specified trial type. Specifically, for
148 SL and SR cue types the subsequent trial types were SG and GS respectively. The ratio of trial
149 types within cue types is shown in Table 1. Measures of corticomotor excitability and inhibition
150 within the block (pre-task, with fingers resting on switches) were obtained in response to an
151 informative “Rest” cue which preceded a SS trial (such that both fingers remained resting on
152 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 μ s 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 $\sim 45^\circ$ 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

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

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

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

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

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

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

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

$$218 \quad (\text{SSRT} = \text{stop signal delay} + n\text{th lift time})$$

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

221 600 ms) subtracted from target time (800 ms) for the given stop trial (Logan et al. 1984;
222 Verbruggen et al. 2013).

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

230 Percent inhibition = $[1 - (\text{conditioning stimulus MEP amplitude} / \text{test stimulus MEP}$
231 $\text{amplitude})] \times 100$

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

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

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

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

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

267 **Results**

268 *Behavioral Data*

269 Participants performed the task accurately. Lift times indicated that there was a cost-benefit
270 trade-off with Cue Type, and an interference effect from stopping one side and lifting with the
271 other on Partial trials. For Partial trials, there was a main effect of Cue Type ($F_{2,34} = 112.9, P <$
272 0.001). Lift times were later for MS ($69 \text{ ms} \pm 5 \text{ ms}$) than MSL/R ($45 \text{ ms} \pm 8 \text{ ms}; t_{17} = 6.1,$
273 $\text{corrected } P < 0.001$) and SL/R ($3 \text{ ms} \pm 5 \text{ ms}; t_{17} = 16.7, \text{corrected } P < 0.001$) cues, which also
274 differed from each other ($t_{17} = 8.0, \text{corrected } P < 0.001$). There was no main effect of Hand ($F_{1,17}$
275 $= 3.1, P = 0.095$) and no Cue Type x Hand interaction ($F_{2,34} = 2.6, P = 0.085$). On Partial trials
276 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,
277 lift time delays were shorter for MSR ($24.3 \pm 9.9 \text{ ms}$) than MS ($53.3 \pm 5.5 \text{ ms}; t_{17} = 4.5,$
278 $\text{corrected } P = 0.001$) cues. Similarly, for SG trials, lift time delays were shorter for MSL ($25.7 \pm$
279 5.2 ms) than MS ($44.6 \pm 5.1 \text{ ms}; t_{17} = 3.7, \text{corrected } P = 0.007$) cues.

280 During Go trials, there was a main effect of Hand ($F_{1,17} = 13.0, P = 0.002$), with faster lift
281 times for the right hand ($13 \pm 2 \text{ ms}$) compared with the left ($23 \pm 3 \text{ ms}$). There was a Cue Type x
282 Hand interaction ($F_{2,34} = 42.1, P < 0.001$), but no main effect of Cue Type ($F_{2,34} = 1.2, P =$
283 0.316). For the left hand (Fig. 2A), lift times were shorter with MSR cues ($14 \pm 3 \text{ ms}$) than both
284 MS ($25 \pm 3 \text{ ms}; t_{17} = 4.3, \text{corrected } P = 0.003$) and MSL ($30 \pm 3 \text{ ms}; t_{17} = 5.2, \text{corrected } P <$
285 0.001) cues. For the right hand (Fig. 2B), lift times were shorter with MSL cues ($4 \pm 3 \text{ ms}$) than
286 both MSR ($19 \pm 3 \text{ ms}; t_{17} = 4.4, \text{corrected } P = 0.003$) and MS ($15 \pm 3 \text{ ms}; t_{17} = 4.0, \text{corrected } P =$
287 0.015) cues. Lift times were slower on the left than right with MS cues ($t_{17} = 3.4, \text{corrected } P =$
288 0.024) and MSL cues ($t_{17} = 7.0, \text{corrected } P < 0.001$). These results indicate that proactive
289 “braking” is expressed to a greater extent in the non-dominant side.

290 There was no effect of Trial Type ($F_{4,68} = 1.5, P = 0.215$) on stopping success rates
291 (Table 2). For SSRTs there was a main effect of Trial Type ($F_{4,68} = 22.6, P < 0.001$), with SSRTs
292 shorter for SS trials (202 ± 6 ms) than all other Trial Types (SSRTs all $> 248.4 \pm 6$ ms; all $t_{17} >$
293 6.0 , all $P < 0.001$). Therefore, Partial trials were associated with longer stopping processes than
294 when both hands required stopping.

295 *Stimulation Parameters*

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

301 For the SICI protocol, active motor threshold was $53 \pm 2\%$ MSO. Average test stimulus
302 intensity was $76 \pm 4\%$ MSO while conditioning stimulus intensity was $39 \pm 4\%$ MSO (74% of
303 active motor threshold). Average pre-task resting inhibition was $54.7 \pm 3.8\%$ for FDI and $50.3 \pm$
304 6.2% for APB. Average pre-task unconditioned MEP amplitude was 0.6 ± 0.1 mV for FDI and
305 0.5 ± 0.2 mV for APB.

306 *Corticomotor Excitability*

307 Figure 3A shows EMG traces with MEPs from the LICI protocol for an individual participant.
308 For corticomotor excitability of FDI in the LICI protocol (FDI, $n = 17$; Fig. 4A), there was no
309 main effect of Cue Type ($F_{5,80} = 2.9, P = 0.053$). However, non-conditioned MEP amplitude (2.8
310 ± 0.5 mV) increased by $58.9 \pm 21\%$ during the task compared with the pre-task resting condition
311 ($t_{16} = 2.8, P = 0.012$; Fig. 4B). For APB, there was an effect of Cue Type ($F_{5,80} = 5.0, P = 0.005$),
312 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 $P = 0.105$)

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

344 *Linear regression*

345 For MS conditions, there was a positive correlation between LICI and Partial trial delays for the
346 FDI ($r = 0.620$, $P = 0.016$; Fig. 6A), such that less inhibition was associated with shorter delays.
347 For APB, there was a weak association between LICI and Partial trial delays ($r = 0.522$, $P =$
348 0.062 , Fig. 6B). For MSL and MSR conditions there were no correlations between LICI and trial
349 delays for either FDI or APB (all $P > 0.199$). Furthermore, there were no correlations between
350 LICI and the difference in lift time between left and right hand responses (GG trials) for MSL
351 and MSR conditions (all $P > 0.187$).

352 **Discussion**

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

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

365 *Cue Information on Proactive and Reactive Processes in Response Inhibition*

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

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

382 amplitude (corticomotor excitability suppression) preceding responses (e.g., Duque et al. 2017).
383 The reason for this discrepancy may be related to the timing of TMS. Here, corticomotor
384 excitability was assessed 250 (SICI) - 350 (LICI) ms before the target, a time period that closely
385 coincides with the stop cue presentation. Corticomotor excitability suppression has been
386 observed in the anticipatory task when TMS is delivered after the stop imperative (Cowie et al.
387 2016; MacDonald et al. 2014). The anticipatory task differs from stop-signal tasks which seem to
388 produce suppression from trial onset, and has been interpreted in a model of “impulse control”
389 where selected responses are suppressed to ensure they are not made before required (Duque and
390 Ivry 2009; Duque et al. 2012; Duque et al. 2010; Labruna et al. 2014).

391 *Intracortical Inhibition*

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

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

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

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

434 A dissociation in muscle specificity between LICI and unconditioned MEP amplitudes
435 during the task relative to pre-task baseline was evident in the present study. A lack of muscle
436 specificity accompanying LICI may not be surprising because of its association with tonic
437 inhibition, acting on both pre- and post-synaptic GABA_B receptors (Bettler et al. 2004). In
438 contrast, the increased unconditioned MEP amplitude observed in the task-relevant (FDI), but
439 not task-irrelevant (APB), effector may reflect excitability of GABA_A-ergic networks that
440 spatially and temporally regulate control over M1 corticospinal output (Stinear and Byblow
441 2003). However, this explanation seems unlikely because SICI was reduced only when responses
442 were highly likely or required. What leads to the muscle-specific increase in corticomotor
443 excitability during task context remains to be elucidated, but other cortical connections (i.e.
444 increased excitatory circuits within M1) or subcortical mechanisms may contribute.

445 *Response inhibition and the role of M1 intracortical inhibition*

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

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

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

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

480 **Acknowledgments:** We thank Ms April Ren, Mr Pablo Ortega Auriol and Mr Terry Corrin for
481 help with data collection and technical assistance.

482 **Grants:** None.

483 **Disclosures:** The authors declare no conflict of interest.

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623

624 **Figure Legends**

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

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

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

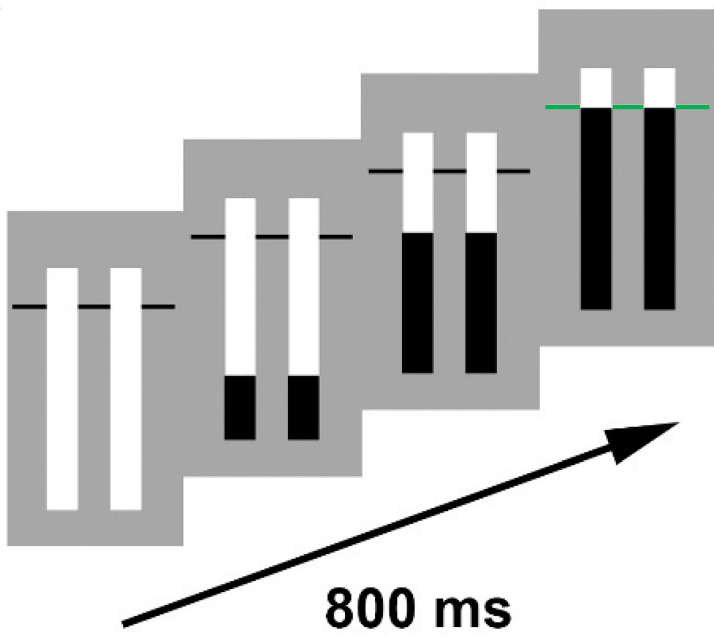
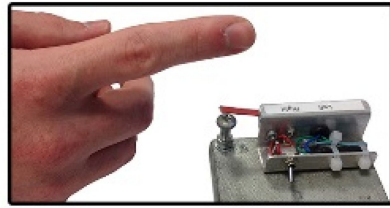
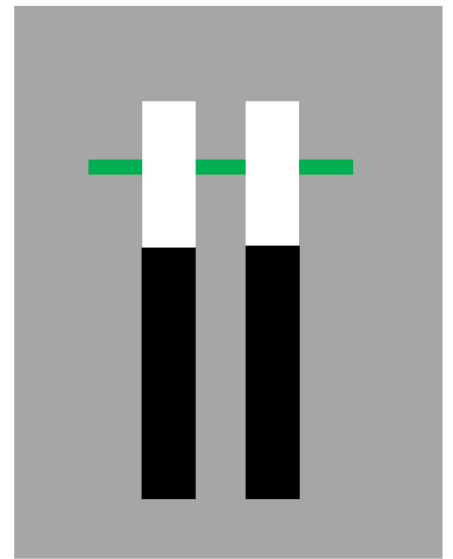
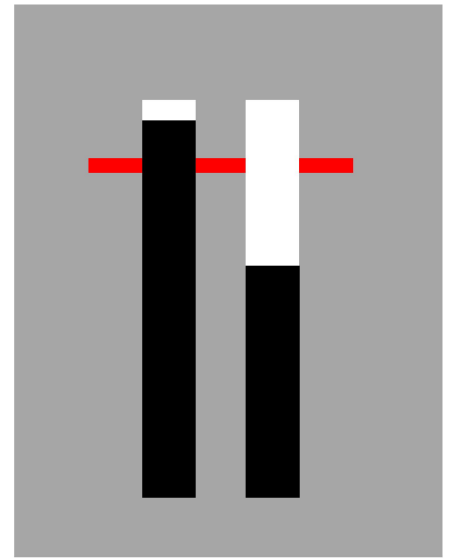
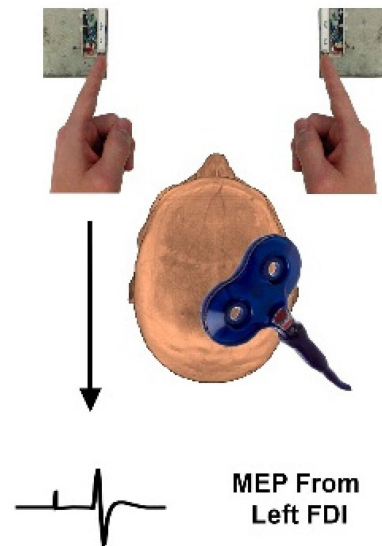
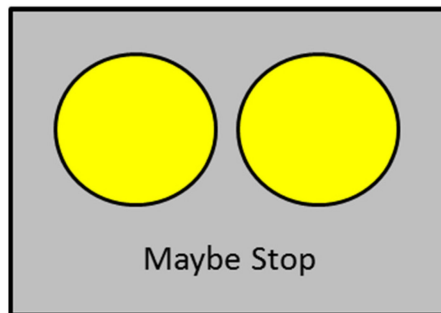
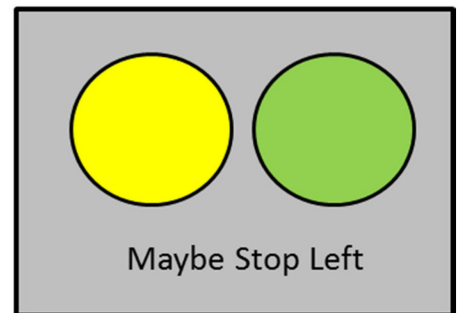
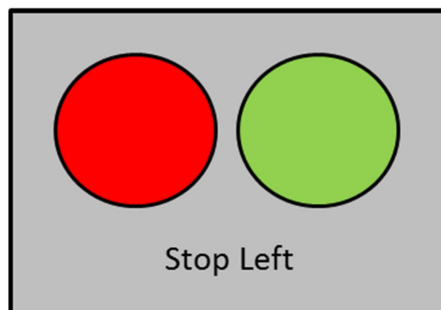
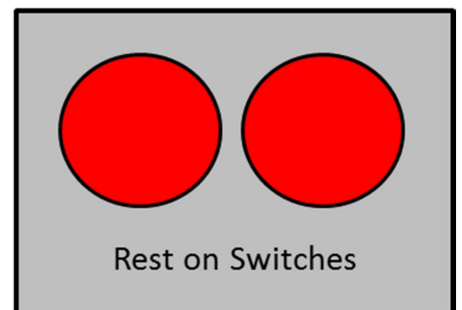
652 **Figure 3.** Representative electromyography traces with motor evoked potentials in the left first
653 dorsal interosseous muscle. A. On Rest trials, long-interval intracortical inhibition (LICI) was
654 weaker during the task than during the pre-task resting condition as indicated by the difference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

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

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

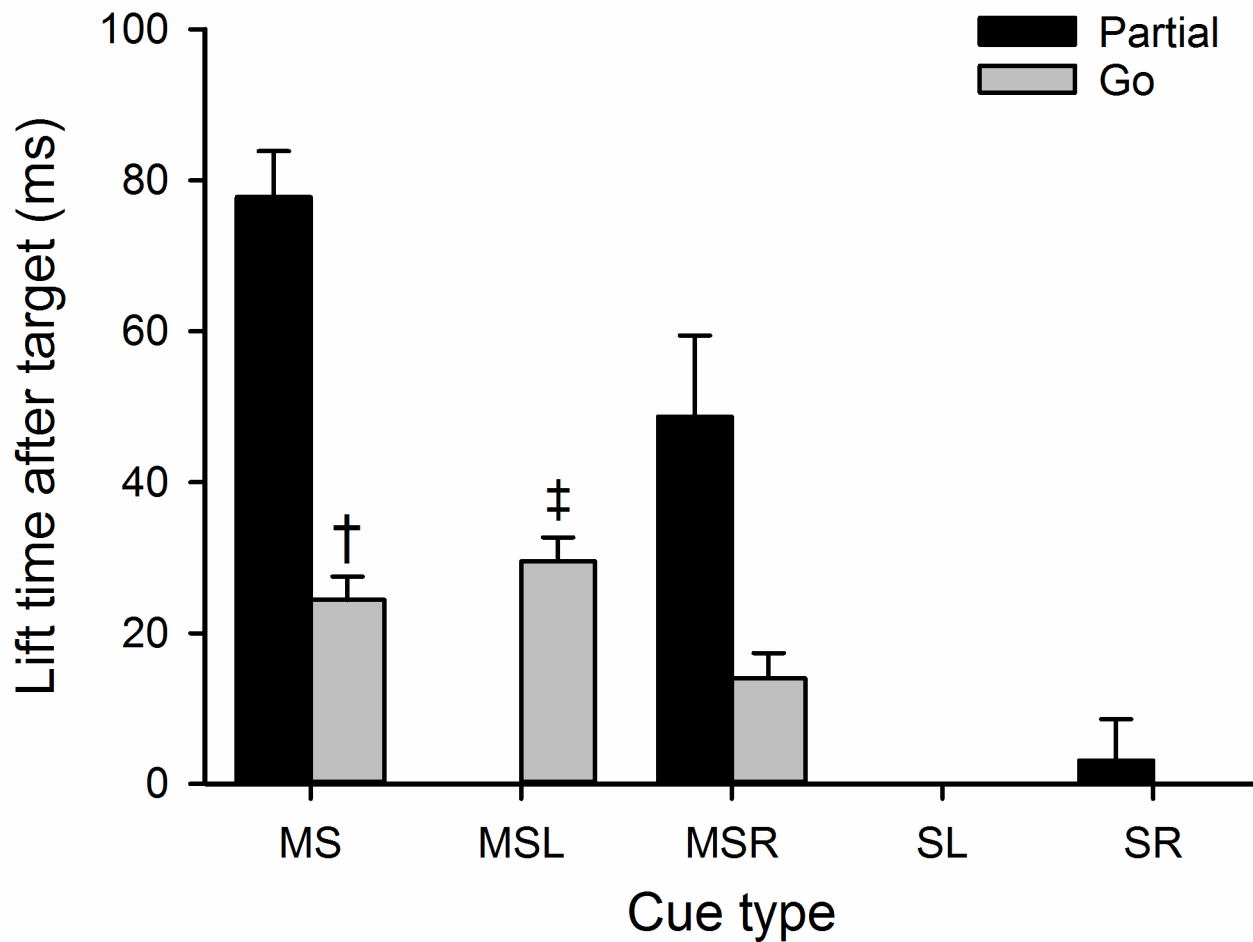
669 task context for LICI (B) and SICI (D). Intracortical inhibition of pre-task and task rest
670 conditions are normalized and scaled according to pre-task values (1.0, dashed line). MS, Maybe
671 Stop; MSL, Maybe Stop Left; SL, Stop Left; MSR, Maybe Stop Right; SR, Stop Right. Mean \pm
672 SE bars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

673 **Figure 6.** Correlations between LICI (% INH) and Partial trial delays of right hand responses for
674 trials preceded by uninformative cues (Maybe Stop; $n = 17$). A. Task-relevant first dorsal
675 interosseous ($r = 0.620$, $P = 0.016$). B. Task-irrelevant abductor pollicis brevis ($r = 0.522$, $P =$
676 0.062).

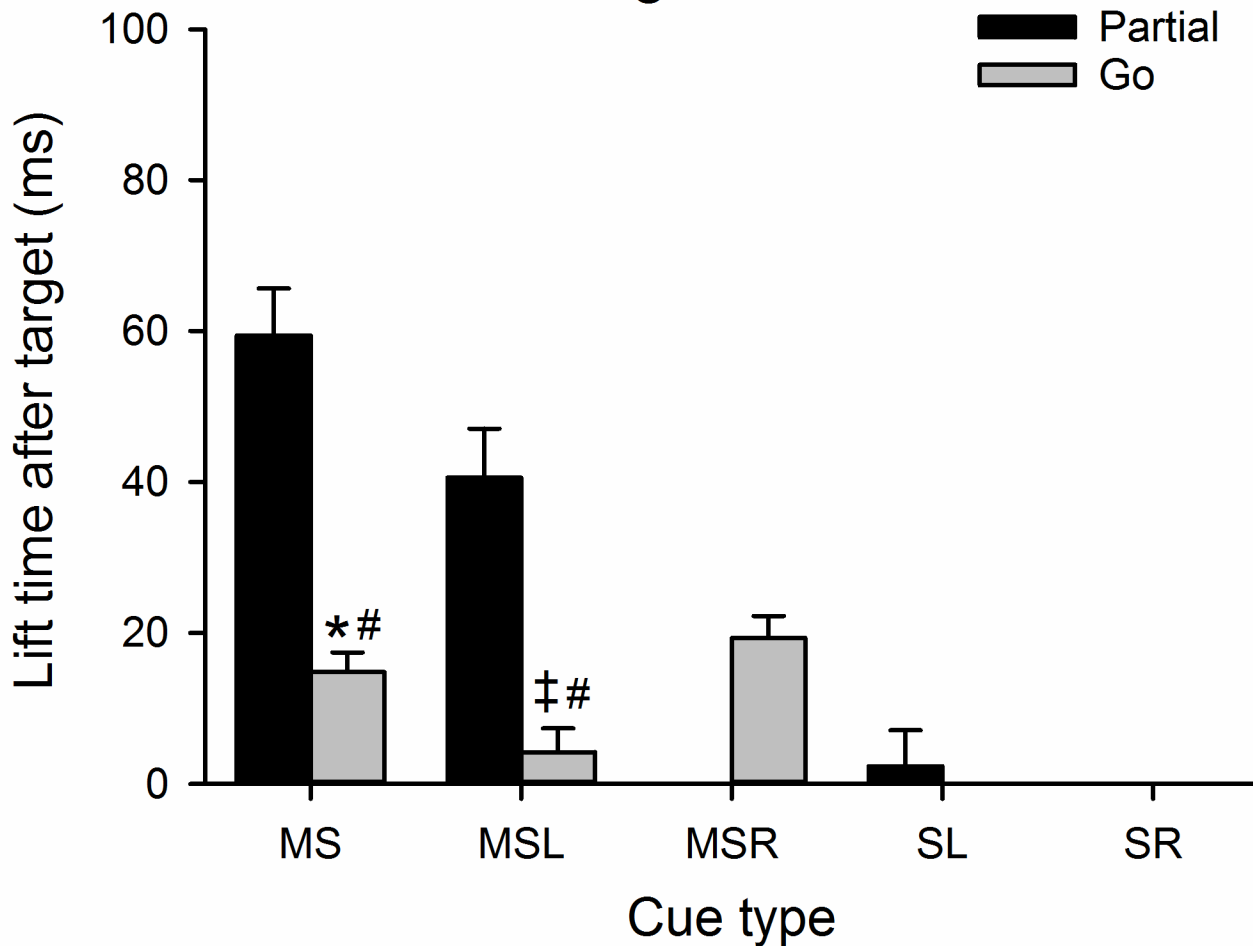
A**GO****GG****GO****Left****Right****B****C****D****Uninformative****Informative****Known****Rest**

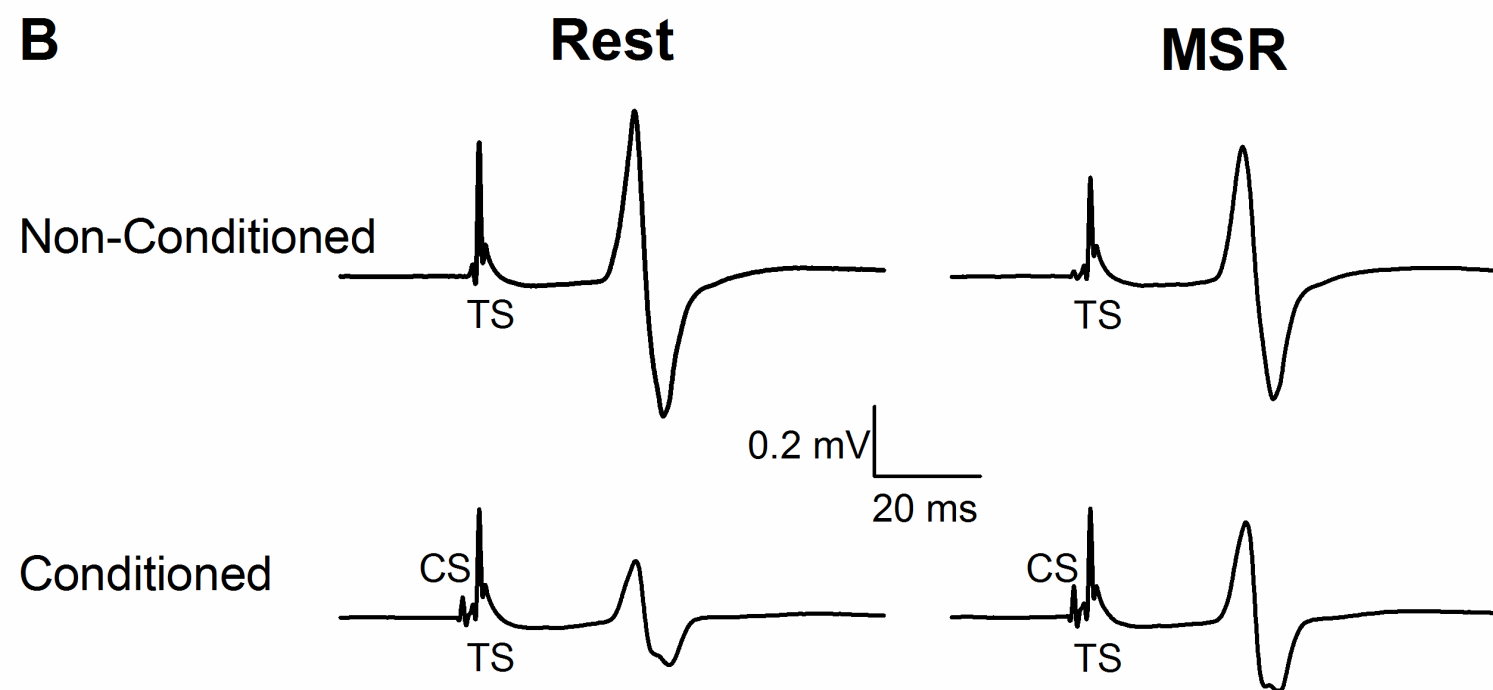
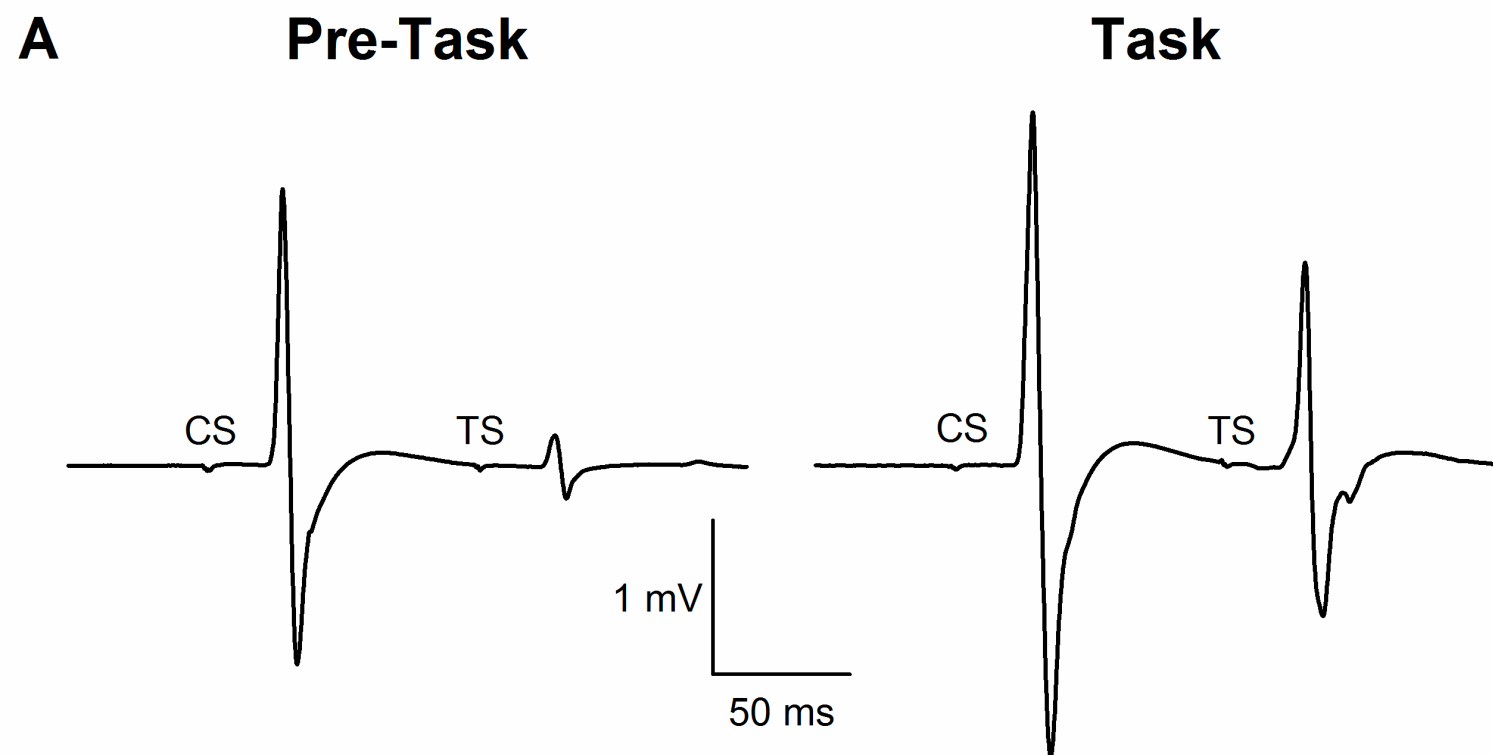
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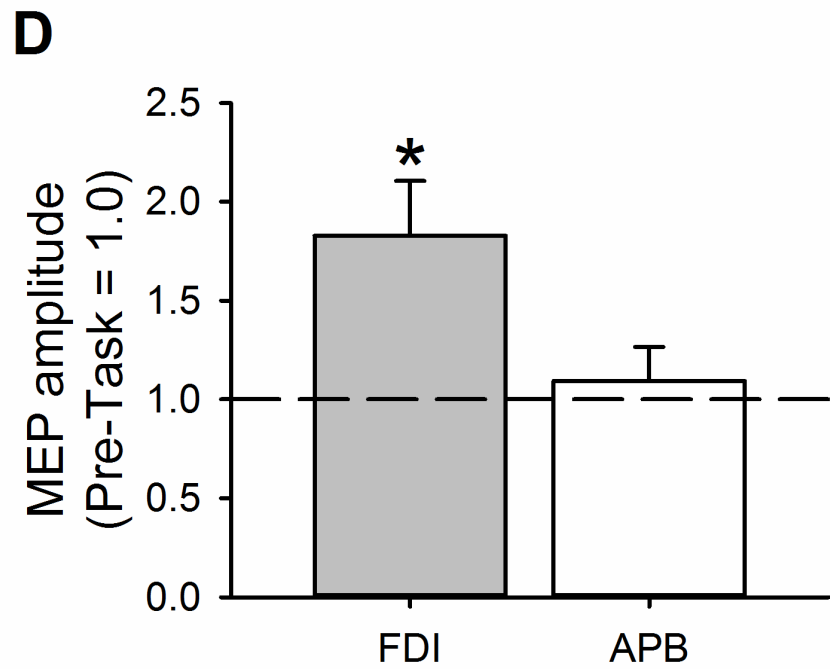
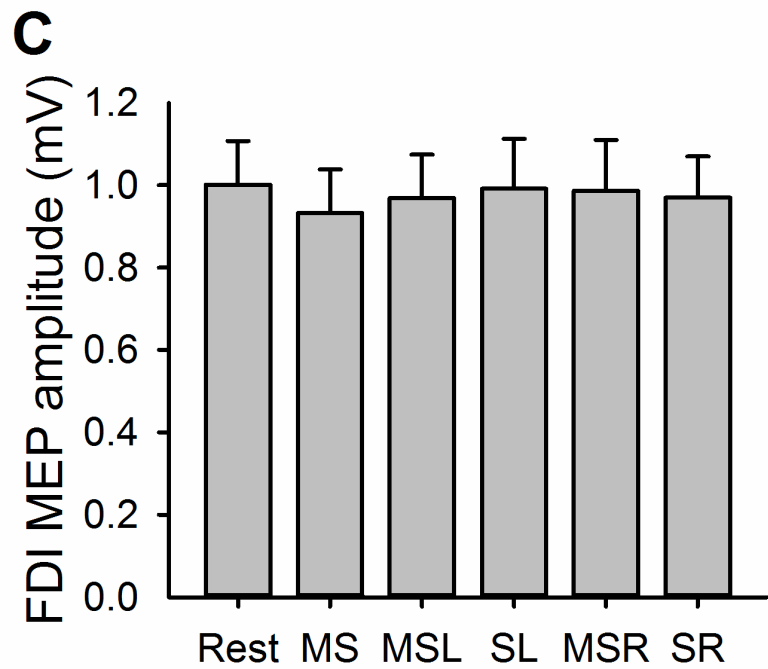
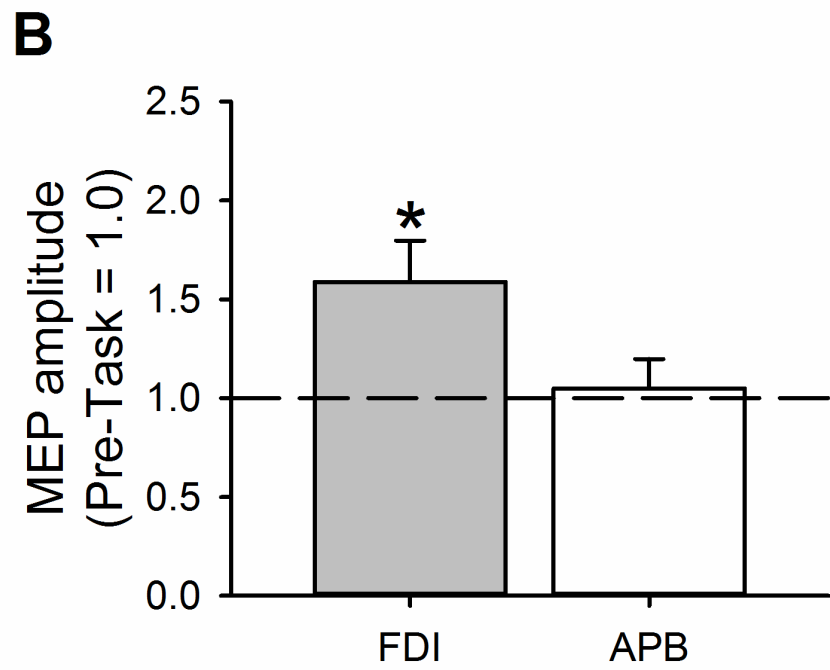
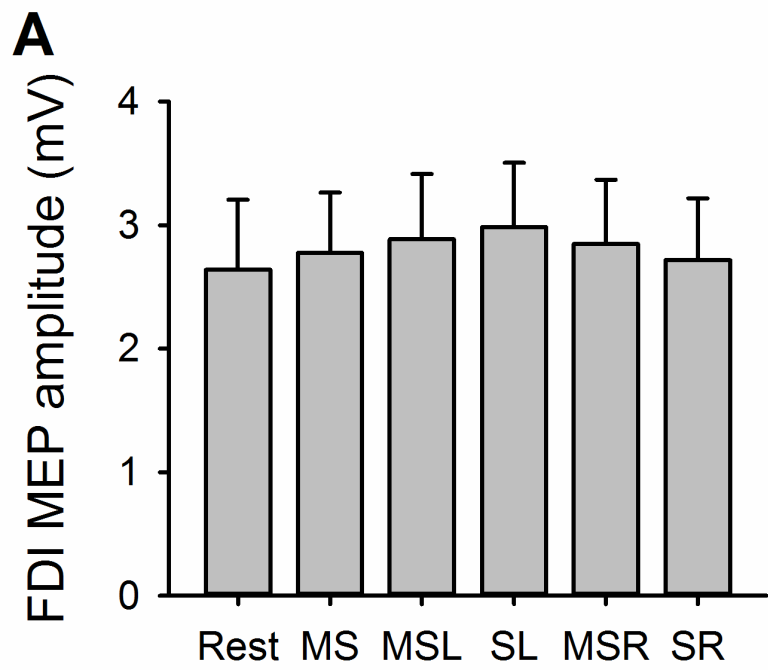
Left Hand

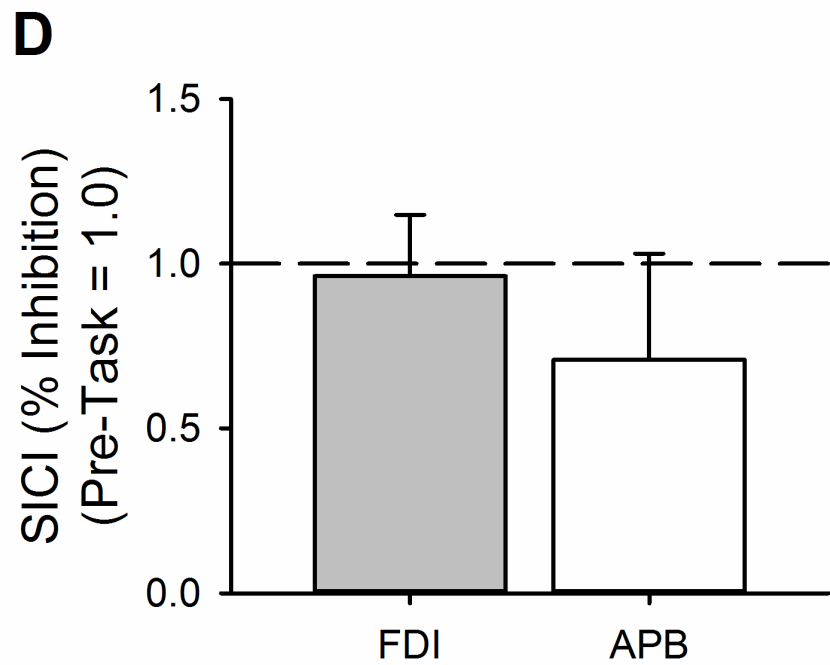
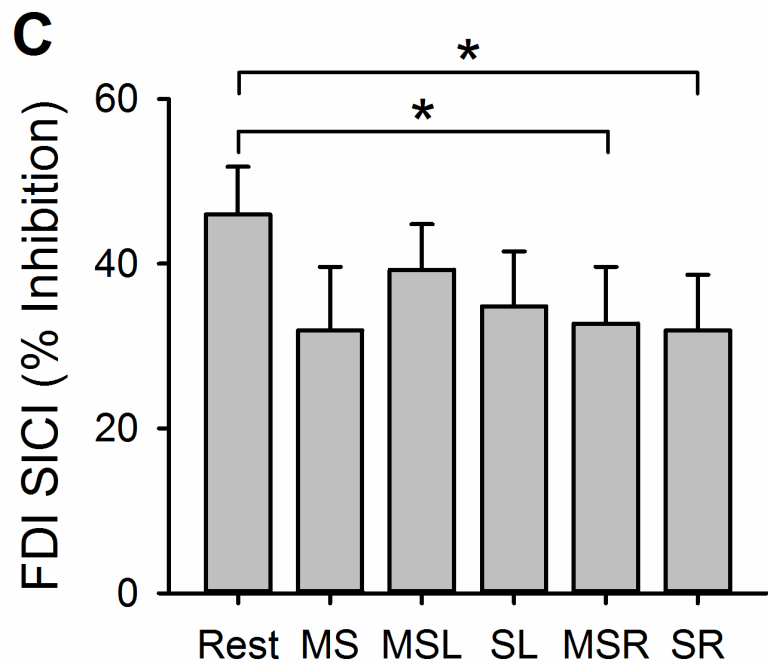
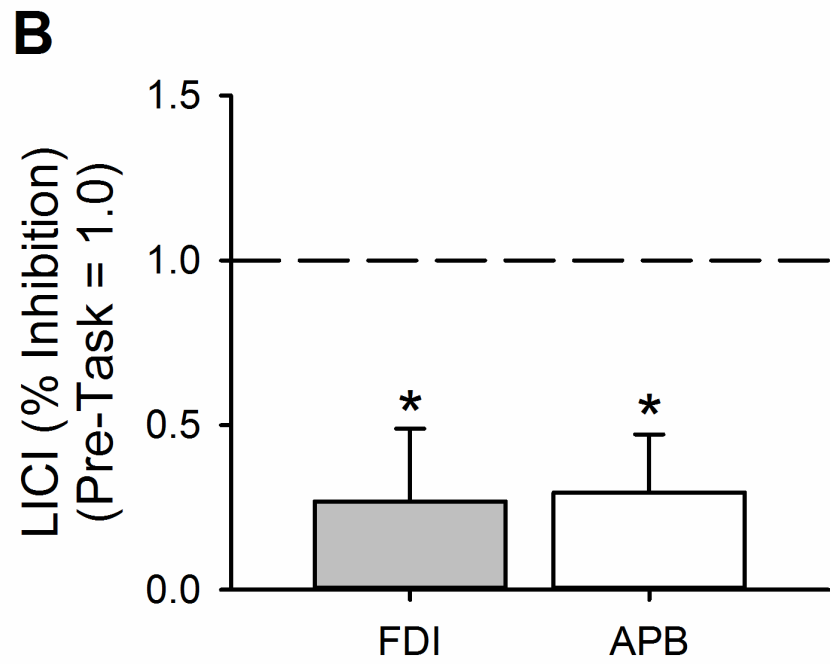
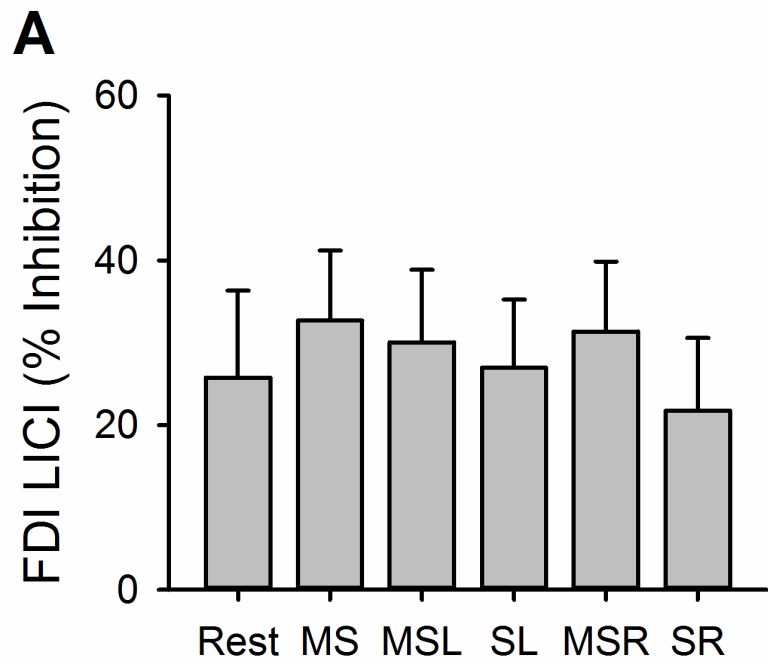
**B**

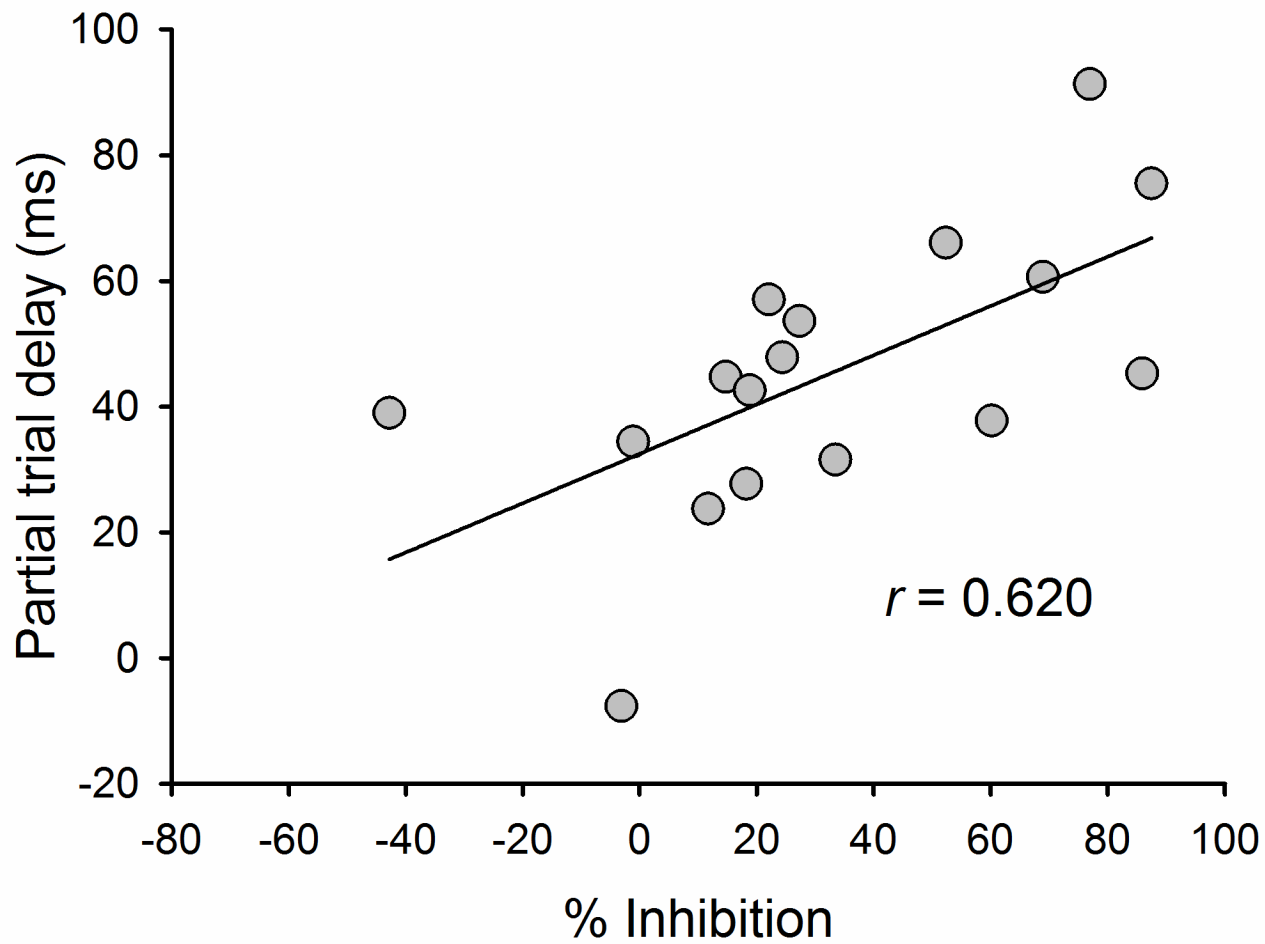
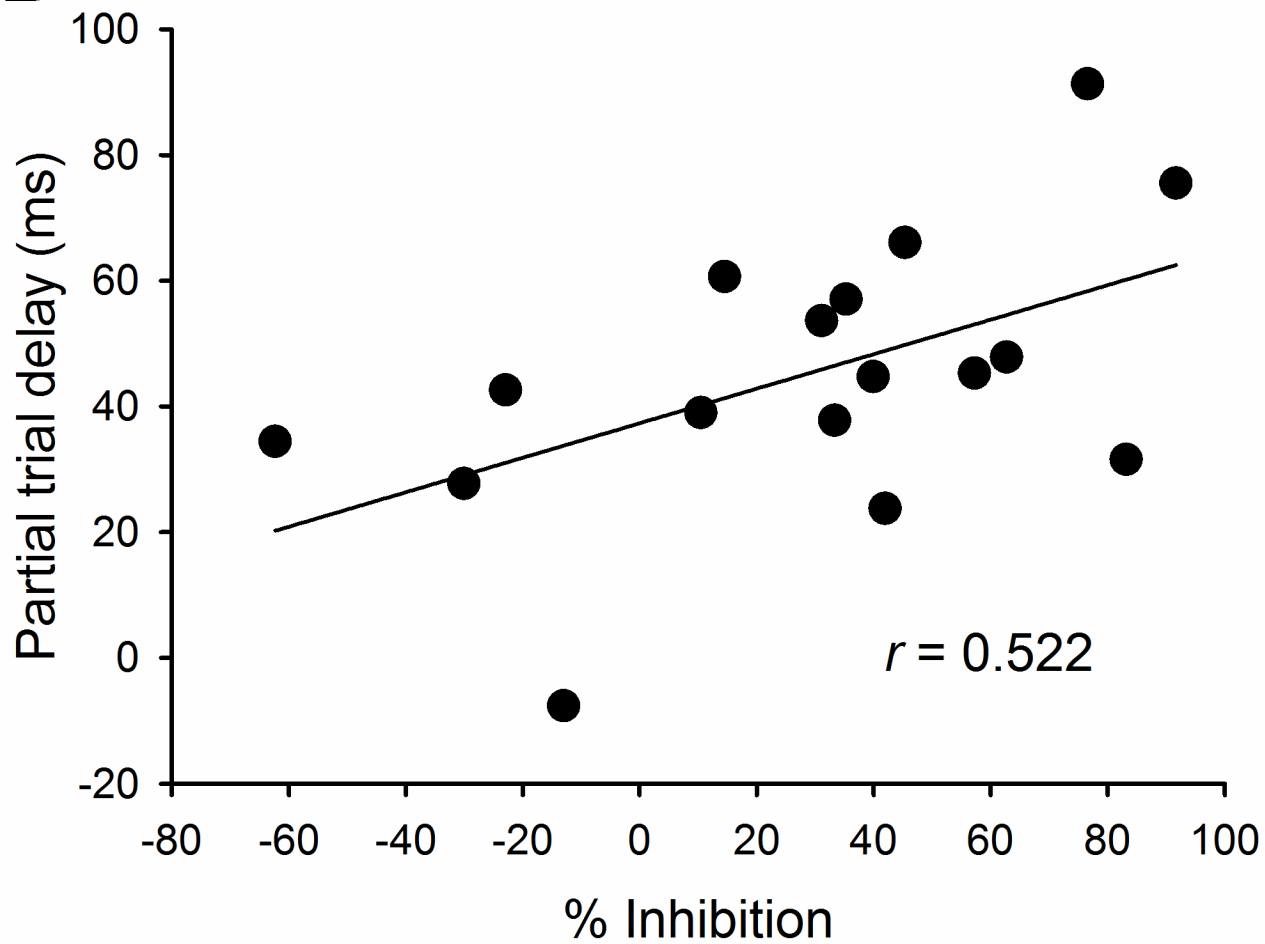
Right Hand









A**B**

1 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

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

1 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	-	-

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