

# Proactive modulation of long-interval intracortical inhibition during response inhibition

MacDonald, Hayley; Cowie, Matthew J.; Cirillo, John; Byblow, Winston D.

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1 **Proactive modulation of long-interval intracortical inhibition during response inhibition**

2

3 Matthew J. Cowie<sup>1,2,\*</sup>, Hayley J. MacDonald<sup>1,2,\*</sup>, John Cirillo<sup>1,2</sup>, Winston D. Byblow<sup>1,2</sup>

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5 <sup>1</sup> Movement Neuroscience Laboratory, Department of Exercise Sciences, The University of Auckland,  
6 Auckland 1142, New Zealand

7 <sup>2</sup> Centre for Brain Research, The University of Auckland, Auckland 1142, New Zealand

8 \*these authors contributed equally

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10 **Running head**

11 Intracortical Inhibition during Response Inhibition

12

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15 inhibition

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17 Contact information:

18 Professor Winston Byblow

19 Centre for Brain Research, The University of Auckland

20 Private Bag 92019, Auckland, New Zealand

21 Phone: +64 9 373 7599 ext 86844

22 Email: w.byblow@auckland.ac.nz

23 **Abstract**

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

45

46

47 **New & Noteworthy**

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

55

56 **Introduction**

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

65           Response inhibition can be proactive when stopping demands are anticipated, or  
66 reactive when stop signals are presented unexpectedly (Aron and Verbruggen 2008).  
67 Transcranial magnetic stimulation (TMS) has been used to assess the temporal modulation of  
68 corticomotor excitability (CME) during both types of response inhibition. Proactive stopping  
69 is suggested to recruit the indirect basal ganglia pathway to selectively decrease CME for  
70 only the movement cued to stop (Aron and Verbruggen 2008; Cai et al. 2011; Majid et al.  
71 2013). A topic of current debate is whether reactive stopping can be achieved selectively (Xu  
72 et al. 2014), given that several lines of evidence indicate a transient process in which  
73 stopping response preparation suppresses movement non-selectively. For example, when  
74 successful stopping can be achieved by inhibiting all movement, CME is reduced in  
75 response-irrelevant muscles (Badry et al. 2009; Cai et al. 2012; Coxon et al. 2006;  
76 Greenhouse et al. 2012). When only a subcomponent of a prepared response is required to  
77 stop (Partial trials), the remaining response is delayed (Coxon et al. 2007; 2009; Coxon et al.  
78 2012; MacDonald et al. 2014; MacDonald et al. 2012). Interestingly there is also a  
79 concomitant reduction in CME for the responding left hand on trials when only the right hand  
80 is cued to stop (MacDonald et al. 2014), indicative of a non-selective inhibitory process that

81 cancels all prepared effectors. The subsequent delay may arise as a consequence of having to  
82 initiate a new response. While these studies suggest reactive response inhibition is non-  
83 selective, the primary suppressive mechanism remains unclear.

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

98 Within M1, GABA<sub>B</sub>-receptor mediated inhibition can be assessed as long-interval  
99 intracortical inhibition (LICI) using suprathreshold conditioning and test stimuli separated by  
100 50-200 ms (Valls-Solé et al. 1992; Wassermann et al. 1996). LICI engages pre-synaptic  
101 receptors (Bettler et al. 2004), typically associated with tonic inhibitory effects. Interestingly,  
102 one study reported decreased LICI in a Go/No-Go task (Sohn et al. 2002) but did not assess  
103 LICI using an optimal interstimulus interval (Sanger et al. 2001) or use conditioning stimulus  
104 intensities that allowed increases in LICI to be observed. Therefore, the role of LICI in  
105 reactive response inhibition is yet to be established.

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

## 116 **Methods**

### 117 *Participants*

118 Sixteen participants without neurological impairment participated in the experiment (mean  
119 age 24 y, range 18-49 y, 14 male). Thirteen of these completed the LICI protocol (mean age  
120 25 y, range 18-49 y, 11 male). All were right handed (laterality quotient mean 0.92, range  
121 0.71-1) as determined using a four-item version of the Edinburgh handedness inventory  
122 (Veale 2014). Written consent was obtained before participation and the study was approved  
123 by the University of Auckland Human Participants Ethics Committee.

### 124 *Response inhibition task*

125           The experiment utilized a bimanual anticipatory response inhibition task (Coxon et al.  
126 2007; 2009; MacDonald et al. 2014; MacDonald et al. 2012). Participants were seated with  
127 forearms resting on a table positioned midway between pronation and supination. This  
128 allowed the distal and medial aspect of each index finger to occupy a mechanical switch  
129 positioned 55 cm away from the computer monitor. The display consisted of two indicators

130 (vertical rectangles) each 16 cm in length and 1.5 cm in width (Figure 1A). Control of the left  
131 or right indicator was via the corresponding left or right switch. Switch “up/down” state was  
132 precisely recorded through an Arduino and synchronized to the display through an analog-  
133 digital USB interface (NI-DAQmx 9.7; National Instruments). Customized software written  
134 in MATLAB (R2011a, version 7.12; The MathWorks) generated the trial order, recorded trial  
135 data and controlled the visual output during the task.

136 Participants were instructed to let the weight of their fingers passively depress the  
137 switches. Switch height was adjusted to eliminate any positional related muscle activity.  
138 Depression of both switches initiated the trial after a 400-900 ms variable delay. If depression  
139 continued, both indicators would ascend vertically at a constant velocity reaching a horizontal  
140 line after 800 ms and the top of the display after 1000 ms. Participants were informed that  
141 releasing the switch (index finger abduction) would stop the corresponding indicator. Go  
142 trials (Go-Left Go-Right; GG) required participants to stop both indicators at the target by  
143 releasing both switches (Figure 1B). Stop trials were cued by one or both indicators stopping  
144 before the target, requiring participants to inhibit the response of one or both hands (Figures  
145 1C and D). In the protocols a 2:1 ratio of Go to Stop trials existed, establishing Go trials as  
146 the default response. When both hands were required to stop (Stop-Both i.e. Stop-Left Stop-  
147 Right; SS), both indicators stopped 600 ms into the trial. On Partial trials only one hand was  
148 required to stop (Go-Left Stop-Right; GS, or Stop-Left Go-Right; SG). On Partial trials a  
149 single indicator stopped 550 ms into the trial while the other continued to ascend. The time  
150 the indicator stopped on Stop trials (550 & 600 ms) did not change. This enabled constant  
151 TMS times relative to both the stopping of the indicator and the start of the trial. Feedback  
152 was visually displayed during each inter-trial interval.



153 *Electromyography*

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

162 *Transcranial magnetic stimulation*

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

172 *Protocol*

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

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

180 The task in the CME protocol consisted of 432 trials split into 12 pseudo-randomized  
181 blocks of 36 with 288 Go and 144 Stop trials. There were 98 Go trials where TMS was  
182 delivered at either 250, 225, 200, 175, 150, 125 or 100 ms before the target to obtain 14  
183 stimuli at each time point. All Stop trials were stimulated and distributed as 84 GS, 30 SG  
184 and 30 SS because GS trials were of primary interest. For GS trials, 14 stimuli were delivered  
185 150, 125, 100, 75, 50 and 25 ms before the target. Timing was delayed by 100 ms relative to  
186 Go trials because of the expected ~75 - 100 ms delay in the responding hand (Coxon et al.  
187 2007; 2009; Coxon et al. 2012; MacDonald et al. 2014; MacDonald et al. 2012). For SG and  
188 SS trials, 15 stimuli were delivered 175 and 200 ms after the stop signal.

189 To examine LICI, paired-pulse TMS was delivered at an ISI of 100 ms (Sanger et al.  
190 2001). Stimulation intensity was adjusted to elicit a cortical silent period (CSP) duration of  
191 175 ms while left FDI was activated at ~10% of maximum voluntary contraction. This  
192 intensity was used in LICI for both the conditioning stimulus (CS) and the test stimulus (TS).  
193 CS and TS were then adjusted to produce approximately 50-85% inhibition of the MEP  
194 amplitude (%INH). This intensity was used for all following trials.

195 During the LICI protocol, participants performed a Go Only block consisting of 30  
196 Go trials. %INH was measured at the start of each trial (0 ms). Each participant then  
197 performed the task, which consisted of 360 trials split into 10 blocks of 36 trials. Of these,  
198 240 (67%) were Go trials and 120 (33%) were Stop trials. Stop trial types (GS, SG and SS)  
199 were equally represented, each condition consisting of 40 trials. The %INH obtained at 0 ms  
200 provided information for the previous and upcoming trial. All trials following Stop trials and  
201 185 trials following Go trials were stimulated.

202 *Dependent measures*

203 Peak-to-peak MEP amplitude was calculated from EMG 10 to 50 ms after the  
204 stimulus. MEPs were excluded when root mean square (rms) EMG was  $> 10 \mu\text{V}$  in the 50 ms  
205 preceding stimulation. Also, EMG traces were excluded if any activity was present between  
206 the stimulus and MEP evident from visual inspection. Average MEP amplitude was  
207 calculated following trimming of the upper and lower 10 % (if  $> 8$  MEPs were present for  
208 that time point) or  $\pm 1.5$  standard deviations (if 4 – 8 MEPs were present for that time point).  
209 To reduce inter-subject variability MEP amplitude was normalised across Trial Types and  
210 Stimulation Times such that the condition with the largest mean MEP amplitude was  
211 reassigned the value 1, and all other conditions scaled accordingly for the participant. For the  
212 LICI protocol, mean stimulated and unstimulated left hand LTs were calculated from Go  
213 trials after Go trials. MEP amplitude was calculated for each stimulated trial in the left hand  
214 for both CS and TS. The primary dependent measure was %INH, which was calculated as  
215  $\%INH = 100 - (\text{TS MEP amplitude} / \text{CS MEP amplitude}) \times 100$ , where TS and CS MEP  
216 amplitude are the mean values for each condition from each participant.  $\Delta\%INH$  and  $\Delta\text{CS}$   
217 MEP amplitude was calculated for Partial trials followed and preceded by Go trials.  $\Delta =$   
218  $[(\text{subsequent Go trial} - \text{Partial trial}) / \text{Partial trial}] \times 100$ .

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

227 *Statistical analyses*

228 Repeated measures Analysis of Variance (RM ANOVA) were used to test our  
229 hypotheses. To test the first hypothesis, normalized MEP amplitude was first compared in an  
230 omnibus RM ANOVA with a 2 Trial Type (GG, GS)  $\times$  6 Stimulation Time (-225, -200, -175,  
231 -150, -125 and -100 ms relative to expected LT i.e. 0 ms on GG, 75 ms on GS) design. To  
232 determine if the hypothesised pattern of facilitation, suppression and facilitation on Partial  
233 Trials was present, one-way RM ANOVAs with the factor Stimulation Time (6 levels) were  
234 run separately on GS and GG trials. Additionally, MEP amplitude for Stop trials was  
235 analyzed with a 3 Trial Type (GS, SG, SS)  $\times$  2 Stimulation Time (175, 200 ms post stop  
236 signal) RM ANOVA. Participants with fewer than 4 MEPs for more than one stimulation  
237 time across trial types were excluded from analysis. For all other analyses in the CME  
238 protocol, missing data points were replaced with the average of the row and column mean. To  
239 determine task compliance behavioral data were analyzed as follows. LTs on Go and Partial  
240 trials were analyzed with a two-way RM ANOVA with factors Trial Type (Go, Partial) and  
241 Hand (Left, Right). LTAs from Go trials in the LICI protocol were analyzed using a one-way  
242 RM ANOVA with Preceding Trial Type (GG, GS, SG, SS). LTs that contributed to LTAs  
243 were analyzed in a two-way RM ANOVA with factors Preceding Trial Type (GG, GS, SG,  
244 SS) and Hand. A one-way RM ANOVA with factor Stop Trial Type (GS, SG, SS) tested for  
245 differences in SSRT.

246 The second hypothesis was examined in the LICI protocol. A one-way RM ANOVA  
247 with 5 Preceding Trial Type (Go Only, GG, GS, SG and SS) was used to analyse CS MEP  
248 amplitude and %INH. Linear regression analyses were performed to examine correlations  
249 between each of %INH and CS MEP amplitude with LTs of the same trial. To assess the  
250 relationship between partial trial CME suppression with both inhibition and response delays,  
251 linear regression analyses were performed investigating correlations between GS trial MEP

252 amplitude 175 ms after the stop cue and each of average LICI across trials and GS lift times.  
253 To explore the effects of CME and LICI on lift times linear regression analyses were  
254 performed to assess the correlations of  $\Delta\%INH$  with LTAs and  $\Delta CS$  MEP amplitude with  
255 LTAs. A paired t-test was used to examine the difference between left hand LTs in stimulated  
256 (following GG trials) and unstimulated GG trials.

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

## 261 **Results**

### 262 *MEP amplitudes and LICI*

263 For normalized MEP amplitudes of GG and GS trials in the CME protocol (Figure  
264 2A) there was a main effect of Time ( $F_{5,75} = 23.8, P < 0.001$ ), but not Trial Type ( $F_{1,15} = 0.79,$   
265  $P = 0.387$ ) or Trial Type  $\times$  Time interaction ( $F_{5,75} = 1.59, P = 0.211$ ). During GG trials, there  
266 was a main effect of Time ( $F_{6,90} = 26.6, P < 0.001$ ) where MEP amplitudes at -175, -150, -  
267 125 and -100 ms were greater than baseline at -250 ms (all  $P < 0.008$ ). During GS trials, there  
268 was a main effect of Time ( $F_{5,75} = 8.7, P < 0.001$ ) where MEP amplitudes at -100, ( $t_{15} = 3.9,$   
269  $P = 0.001$ ) and -25 ms ( $t_{15} = 4.2, P < 0.001$ ) were greater than baseline at -150 ms, whereas -  
270 75 ms ( $t_{15} = 1.1, P = 0.289$ ) and -50 ms ( $t_{15} = 1.7, P = 0.096$ ) were not. Additionally, MEP  
271 amplitude at -75 ms was less than -100 ms ( $t_{15} = 2.3, P = 0.035$ ), indicative of non-selective  
272 braking 175 ms after the stop signal. For Stop trials (Figure 2B;  $n = 9$ ), there was no main  
273 effect of Trial Type ( $F_{2,16} = 0.78, P = 0.426$ ) or Time ( $F_{1,8} = 32.5, P = 0.152$ ) and no Trial  
274 Type  $\times$  Time interaction ( $F_{2,16} = 0.61, P = 0.555$ ). In summary, left FDI MEP amplitudes

275 demonstrated suppression 175 ms after a stop signal even when the left side was not cued to  
276 stop (GS trials).

277 Figure 3 shows averaged left FDI EMG and MEP amplitudes from an individual  
278 participant in the LICI protocol during the Go Only block (Figure 3A) and GS trials in the  
279 Stop task (Figure 3B). For LICI, there was a main effect of Trial Type ( $F_{4,48} = 6.5$ ,  $P =$   
280  $0.018$ ). *Post hoc* comparisons revealed that %INH was less during blocks containing only Go  
281 trials ( $53 \pm 6\%$ ) compared with all trial types once Stop trials were introduced (all  $> 70\%$ ;  $P$   
282  $< 0.025$ ) (Figure 4A).

283 There was a positive correlation between %INH at the start of GS trials and the  
284 resulting LT ( $r = 0.660$ ,  $P = 0.014$ ; Figure 4B) such that greater %INH was associated with  
285 longer LTs of the left hand during GS trials. There was no correlation for GG trials ( $r =$   
286  $0.032$ ,  $P = 0.917$ ). There was no correlation between  $\Delta\%$ INH on a GS trial and the LTA on  
287 the subsequent GG trial ( $r = 0.081$ ,  $P = 0.792$ ).

288 For CS MEP amplitude there was a main effect of Trial Type ( $F_{4,48} = 3.9$ ,  $P = 0.034$ )  
289 (Figure 5). *Post hoc* comparisons revealed that CS MEP amplitudes were greater following  
290 Go trials in the Stop task ( $2.3 \pm 0.3$  mV) than during the Go Only block ( $1.9 \pm 0.3$  mV;  $t_{12} =$   
291  $2.4$ ,  $P = 0.034$ ). Therefore, responding in the context of the Stop task increased CME.  
292 Furthermore, CS MEP amplitudes after GS trials ( $2.4 \pm 0.4$  mV) were larger than after SG,  
293 SS and Go Only trials (all  $< 2.2 \pm 0.3$  mV;  $P < 0.047$ ). This indicates that the re-initiation of  
294 movement on a Partial trial increased contralateral M1 excitability which persisted to the start  
295 of the subsequent trial.

296 For GS trials, there was an association between MEP amplitude 175 ms post stop cue  
297 and LTs ( $r = -0.544$ ) as well as with LICI ( $r = -0.504$ ). However, both correlations failed to  
298 reach statistical significance (LTs,  $P = 0.054$ ; LICI,  $P = 0.079$ ). There was no correlation

299 between CS MEP amplitude at the start of a GG or GS trial and the resulting LT (both  $r <$   
300  $0.178$ ,  $P > 0.560$ ). Likewise, there was no correlation between the  $\Delta$ CS MEP amplitude on a  
301 GS trial and the LTA on the subsequent Go trial ( $r = 0.019$ ,  $P = 0.951$ ).

302 In the CME protocol, TMT =  $38 \pm 2\%$  MSO and stimulation intensity =  $39 \pm 2\%$   
303 MSO ( $104 \pm 2\%$  TMT). In the LICI protocol, TMT =  $43 \pm 2\%$  MSO, CS and TS =  $56 \pm 3\%$   
304 MSO ( $129 \pm 3\%$  TMT). The number of trials excluded for rmsEMG  $> 10 \mu\text{V}$  was  $28 \pm 4\%$   
305 in the CME and  $9 \pm 2\%$  in the LICI protocol. In the CME protocol under the GS condition, 7  
306 out of 96 values for MEP amplitude were missing due to pre-trigger EMG and replaced  
307 according to the method described.

### 308 *Lift times and asynchronies*

309 The task was performed successfully as evident in LTs that were close to the target  
310 (Table 1), and as noted previously for this task (Coxon et al. 2007; 2009; Coxon et al. 2012;  
311 MacDonald et al. 2014; MacDonald et al. 2012). For LTs in the CME protocol, there was a  
312 main effect of Trial Type ( $F_{1,15} = 100.0$ ,  $P < 0.001$ ). No main effect of Hand ( $F_{1,15} = 0.7$ ,  $P =$   
313  $0.409$ ) or Trial Type  $\times$  Hand interaction ( $F_{1,15} = 0.0$ ,  $P = 0.887$ ) existed. For the LICI  
314 protocol, there was a main effect of Trial Type ( $F_{1,12} = 111.6$ ,  $P < 0.001$ ). There was a main  
315 effect of Hand ( $F_{1,12} = 31.9$ ,  $P < 0.001$ ) with right LTs ( $35 \pm 4$  ms) faster than left ( $47 \pm 4$   
316 ms). There was also a Trial Type  $\times$  Hand interaction ( $F_{1,12} = 4.9$ ,  $P = 0.048$ ), which likely  
317 arose from a trend for longer left hand delays ( $61 \pm 5$  ms) than right hand delays ( $55 \pm 6$   
318 ms;  $t_{12} = 2.1$ ,  $P = 0.054$ ) between Partial and Go trials. There was no difference in left LTs  
319 between stimulated ( $19 \pm 3$  ms) and unstimulated ( $21 \pm 3$  ms;  $t_{12} = 1.1$ ,  $P = 0.294$ ) Go trials.

320 Lift time asynchronies (LTAs) were analysed from GG trials in the Stop task of the  
321 LICI protocol (Table 1). For the Stop task of the LICI protocol, there was a main effect of  
322 Preceding Trial Type ( $F_{3,36} = 16.1$ ,  $P < 0.001$ ) such that LTAs decreased after Partial GS

323 compared with after GG trials ( $t_{12} = 3.9, P = 0.002$ ). In contrast, LTAs increased after Partial  
324 SG compared with after GG trials ( $t_{12} = 4.9, P < 0.001$ ). LTAs were not different after SS  
325 trials compared with after GG trials ( $t_{12} = 0.3, P = 0.769$ ). Figure 6 shows the LTs of GG  
326 trials in the Stop task used for LTAs in the LICI protocol. Interestingly, LT on either side was  
327 faster on a subsequent GG trial if that side had previously responded on a Partial trial. There  
328 was a main effect of Preceding Trial Type ( $F_{3,36} = 5.6, P = 0.003$ ) and Hand ( $F_{1,12} = 35.6, P <$   
329  $0.001$ ). There was also a Preceding Trial Type  $\times$  Hand interaction ( $F_{3,36} = 15.4, P < 0.001$ ).  
330 Left LTs were faster after GS trials compared with after GG ( $t_{12} = 4.6, P = 0.001$ ) and SS  
331 trials ( $t_{12} = 2.9, P = 0.014$ ) which did not differ from each other ( $t_{12} = 1.0, P = 0.329$ ).  
332 Similarly, right LTs after SG trials were faster compared with after GG ( $t_{12} = 5.3, P < 0.001$ )  
333 and SS trials ( $t_{12} = 3.1, P = 0.009$ ) which did not differ from each other ( $t_{12} = 0.7, P = 0.500$ ).  
334 For the left hand, LTs were faster if the hand had previously stopped on a Partial trial,  
335 although to a lesser extent than if it had responded ( $t_{12} = 4.6, P = 0.001$ ). For the right hand,  
336 LTs were faster after responding versus stopping on a Partial trial ( $t_{12} = 3.4, P = 0.005$ ).

### 337 *Stop signal reaction times and stopping success*

338 Average success on Stop trials was as follows: CME protocol: GS:  $76 \pm 3\%$ , SG:  $61 \pm$   
339  $6\%$ , SS:  $58 \pm 4\%$ . LICI protocol: GS:  $83 \pm 3\%$ , SG:  $82 \pm 3\%$ , SS:  $65 \pm 3\%$ . In both protocols,  
340 average SSRT showed a main effect of Stop Trial Type (CME:  $F_{2,30} = 57.3, P < 0.001$ , LICI:  
341  $F_{2,24} = 55.5, P < 0.001$ ). SSRT was shorter for SS (CME:  $209 \pm 3$  ms, LICI:  $201 \pm 2$  ms) than  
342 GS (CME:  $245 \pm 4$  ms;  $t_{15} = 11.5, P < 0.001$ , LICI:  $236 \pm 4$  ms;  $t_{12} = 9.3, P < 0.001$ ) and SG  
343 trials (CME:  $256 \pm 4$  ms;  $t_{15} = 8.6, P < 0.001$ , LICI:  $236 \pm 4$  ms;  $t_{12} = 8.1, P < 0.001$ ). Partial  
344 trial types did not differ from each other in the LICI protocol ( $t_{12} = 0.1, P = 0.956$ ), whereas  
345 GS SSRT was shorter than SG in the CME protocol ( $t_{15} = 2.3, P = 0.038$ ).



346 **Discussion**

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

359 Response delays and CME modulation during Stop trials indicated non-selective  
360 suppression. As observed previously, LTs in Partial trials were delayed relative to Go trials  
361 (Coxon et al. 2007; 2009; Coxon et al. 2012; MacDonald et al. 2014; MacDonald et al. 2012).  
362 These substantial delays were observed despite participants achieving relatively high success  
363 rates on Partial trials, especially in the LICI protocol (> 80%). It is important to note that  
364 response delays were not eliminated, or even reduced, when success rate increased as a result  
365 of familiarity with Partial trials; c.f. (Xu et al. 2014). Modulation of MEP amplitude in the  
366 CME protocol supported a model of non-selective suppression during Partial trials. Go trials  
367 displayed a sustained increase in CME from 200 ms before the target. The delay on Partial  
368 trials was a result of an initial facilitation, a dip back to baseline, followed by a secondary  
369 increase in CME. This pattern of CME replicates those of MacDonald et al. (2014). At  
370 equivalent times relative to the stop signal, MEP amplitude did not differ between the three

371 types of Stop trials. This finding is consistent with functional magnetic resonance imaging  
372 studies showing a similar pattern of neural activation between the three Stop trial types  
373 (Coxon et al. 2016; Coxon et al. 2009; Coxon et al. 2012). Conversely, functional imaging  
374 results from Majid et al. (2013) suggest a distinct role of the selective indirect basal ganglia  
375 pathway during partial stopping. Activation of the indirect pathway should have no effect on  
376 MEP amplitude in the responding finger during Partial trials. However, all trials in their study  
377 were preceded by a warning cue about stopping requirements. The neural activation in  
378 response may differ if the cue is unexpected. The present study adds weight to the model of  
379 non-selective response inhibition following an unexpected stop cue.

380         The present study also provides insight into the modulation of intracortical inhibition  
381 during response inhibition. Compared with Go Only blocks, LICI increased when Stop trials  
382 were introduced. The amount of LICI was comparable between Go and Stop trials suggesting  
383 that LICI is not specifically associated with stopping. Previous results using paired-pulse  
384 TMS indicated that increased SICI did not coincide with CME suppression in the responding  
385 effector during partial response inhibition conditions (MacDonald et al. 2014). Together,  
386 these findings indicate that GABAergic circuits within M1 are not primarily responsible for  
387 non-selective suppression during reactive response inhibition. Why then, did LICI increase  
388 during response inhibition trials? It is likely that increased LICI reflects the proactive  
389 modulation of tonic inhibitory circuits as a result of expecting to occasionally stop one or  
390 both hands. Studies have demonstrated that CME is modulated as a result of foreknowledge  
391 about an ensuing response. When response *execution* is forewarned, SICI and LICI are  
392 decreased in the foreperiod for the muscles cued to respond (Sinclair and Hammond 2008)  
393 while CME is simultaneously reduced, most likely to prevent a premature response  
394 (Davranche et al. 2007; Duque and Ivry 2009). When response *prevention* is forewarned,  
395 CME is similarly reduced during the foreperiod (Cai et al. 2011), acting as a mark of

396 advanced inhibitory control. Prior to this study, there had been no examination of ICI  
397 modulation as a result of the knowledge that a prepared response may need to be prevented.  
398 LICI increased during the foreperiod (trial onset) with the foreknowledge that stopping was a  
399 possibility. Therefore, proactive inhibitory control is at least in part, mediated by changes in  
400 LICI.

401         The implications of proactively increasing LICI for reactive response inhibition can  
402 be understood within the framework of an activation threshold model (e.g., MacDonald et al.  
403 2014). Tonic levels of inhibition mediate premature response prevention (Duque et al. 2010;  
404 Jaffard et al. 2008) requiring a facilitatory process in order to initiate movement. In the  
405 present study, a concurrent increase in LICI and CME observed on Go trials when Stop trials  
406 were introduced provide candidate mechanisms. The increased CME (facilitation) counteracts  
407 the rise in tonic inhibition and Go trial LTs are thereby maintained on target. However on GS  
408 trials, LTs were markedly delayed. In response to the stop signal, a reactive inhibitory input is  
409 superimposed onto the tonic resting level, raising the threshold for responding (activation  
410 threshold) and effectively cancelling all movement. The trend in the association between  
411 greater CME suppression and greater non-selective inhibition (LICI) on GS trials in the  
412 current study supports such a model. The initial facilitatory process is inadequate to surpass  
413 the activation threshold and a second phase of facilitation must be added, resulting in the  
414 response delay (MacDonald et al. 2014). It is worth noting that longer GS response delays  
415 were associated with higher levels of LICI, supporting the idea that a second phase of  
416 facilitation is required to overcome the tonic resting level. The trend between longer response  
417 delays and CME suppression for GS trials is in agreement with such a second phase of  
418 facilitation. It is interesting that the association between MEP amplitude and response delay  
419 was not stronger for CME evaluated closer in time to the response than LICI measured at trial  
420 onset. A likely explanation is that MEP amplitude reflects the net excitatory and inhibitory

421 inputs whereas LICl provides a measure of inhibition only. How LICl is modulated within  
422 the proactive response inhibition network remains unclear (Majid et al. 2013; Van Belle et al.  
423 2014). The present study supports the idea that proactive and reactive control mechanisms are  
424 not independent but rather, reactive stopping depends on ongoing proactive control (Dunovan  
425 et al. 2015).

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

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

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

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477            **Disclosures**

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

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600

601

602 **Figure Captions**

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

616

617 **Figure 2.** Modulation of left first dorsal interosseous normalized motor evoked potential  
618 (MEP) amplitude during the corticomotor excitability protocol. **A.** MEP amplitudes before  
619 the target (0 ms) during GG (unfilled circles) and GS (shaded squares) trials (n = 16). Filled  
620 symbols represent values significantly different ( $P < 0.05$ ) to baseline (GG: -250 ms, GS: -  
621 150 ms). Note the dip in corticomotor excitability on GS trials at -75 ms. **B.** MEP amplitudes  
622 after the stop signal. Bars indicate group means (n = 9). Data correspond to -75 and -50 ms  
623 relative to lift time from Panel A. Note that MEP amplitudes were suppressed 175 ms after  
624 the stop signal regardless of Stop trial type. Error bars indicate 1 SE. \*  $P < 0.05$ . GG = Go  
625 trial, GS = Go-Left Stop-Right, SG = Stop-Left Go-Right, SS = Stop-Both.

626 **Figure 3.** Representative left first dorsal interosseous electromyography from a single  
627 participant in the long-interval intracortical inhibition protocol. Vertical dashed line  
628 represents target (800 ms into the trial) and arrows represent average lift time (LT). **A.** Go  
629 Only block. % inhibition = 48 %, LT = 786 ms, CS motor evoked potential (MEP) amplitude  
630 = 2.2 mV. **B.** Successful GS trials. % inhibition = 72 %, LT = 868 ms, CS MEP amplitude =  
631 2.2 mV. CS = conditioning stimulus, TS = test stimulus.

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

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

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

648

649

650 **Tables**

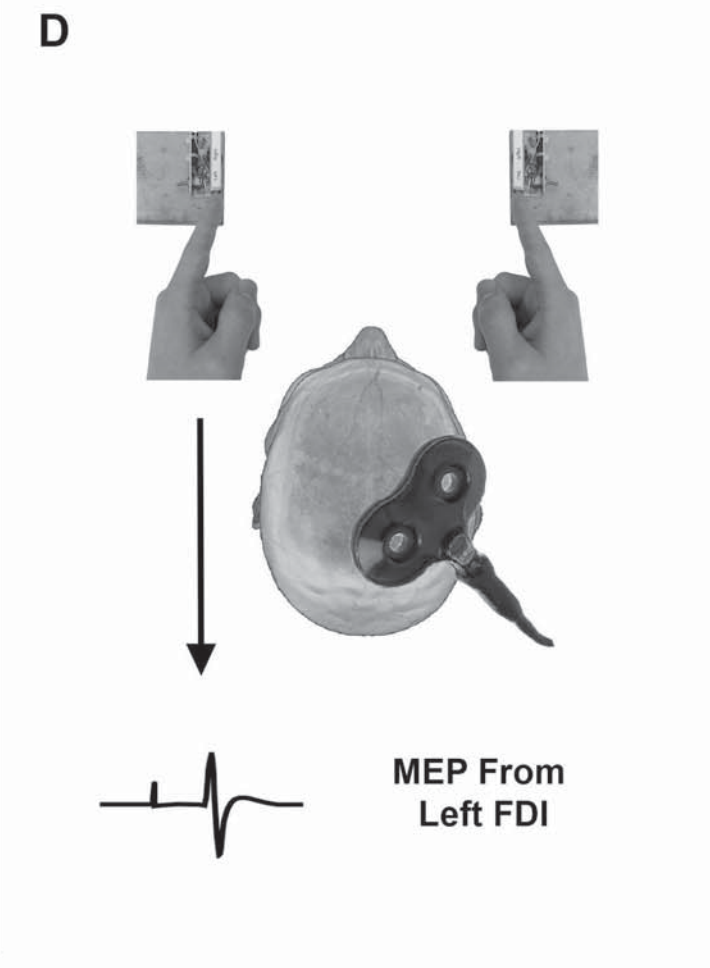
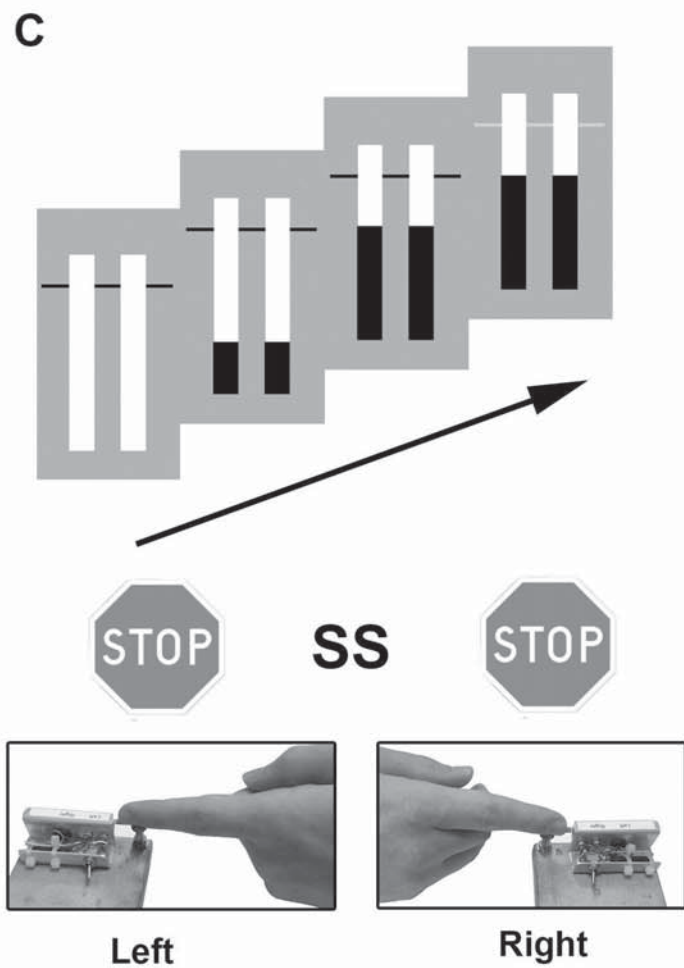
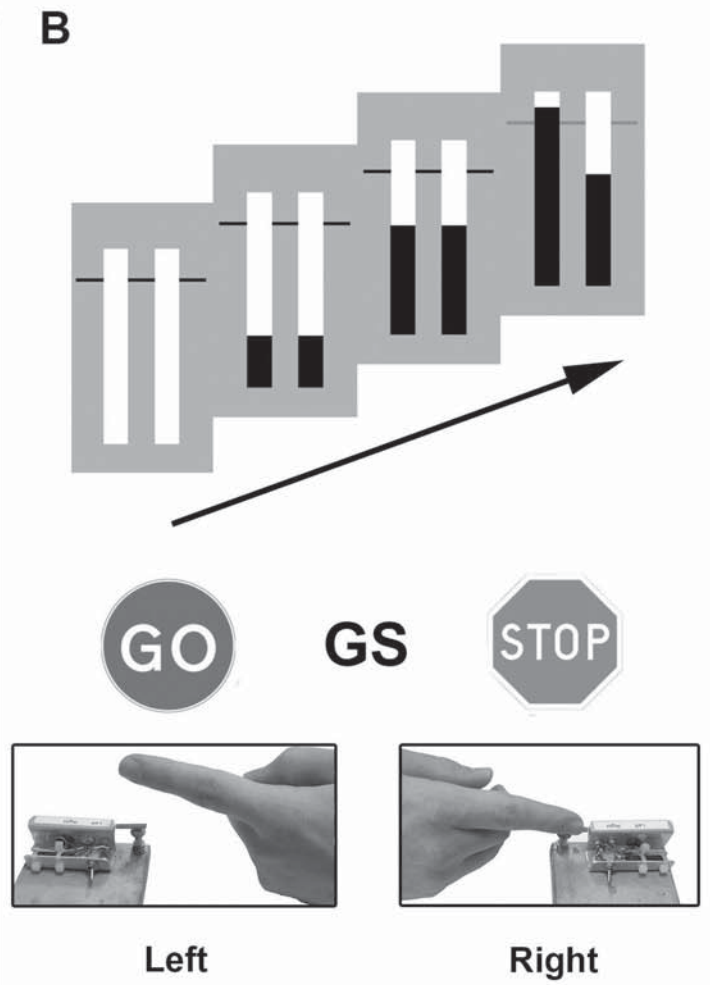
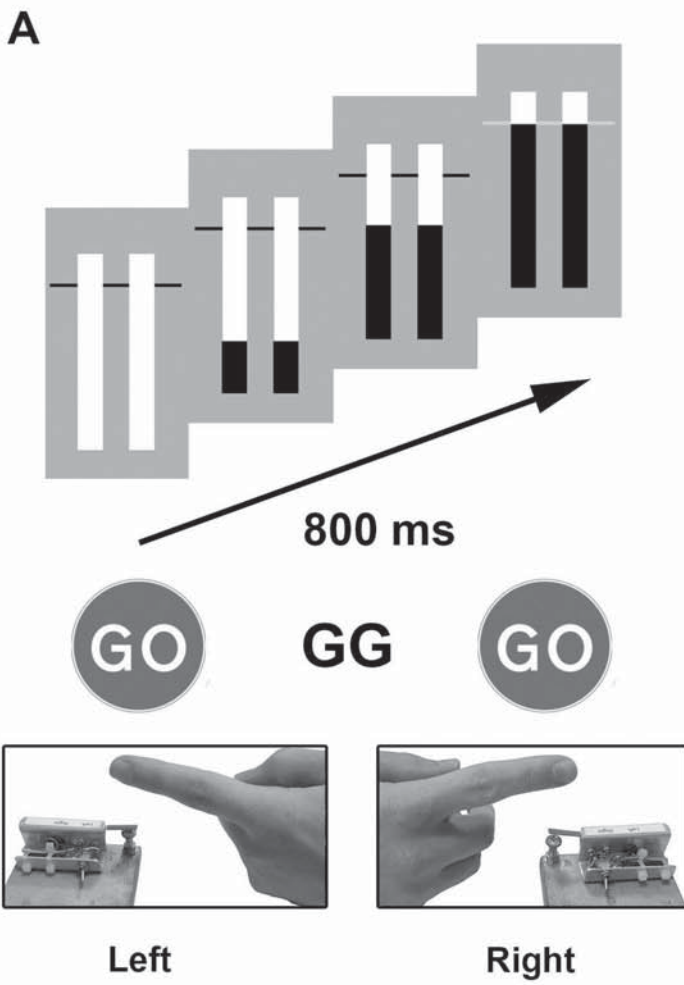
651 **Table 1.** Summary of behavioural data from both protocols.

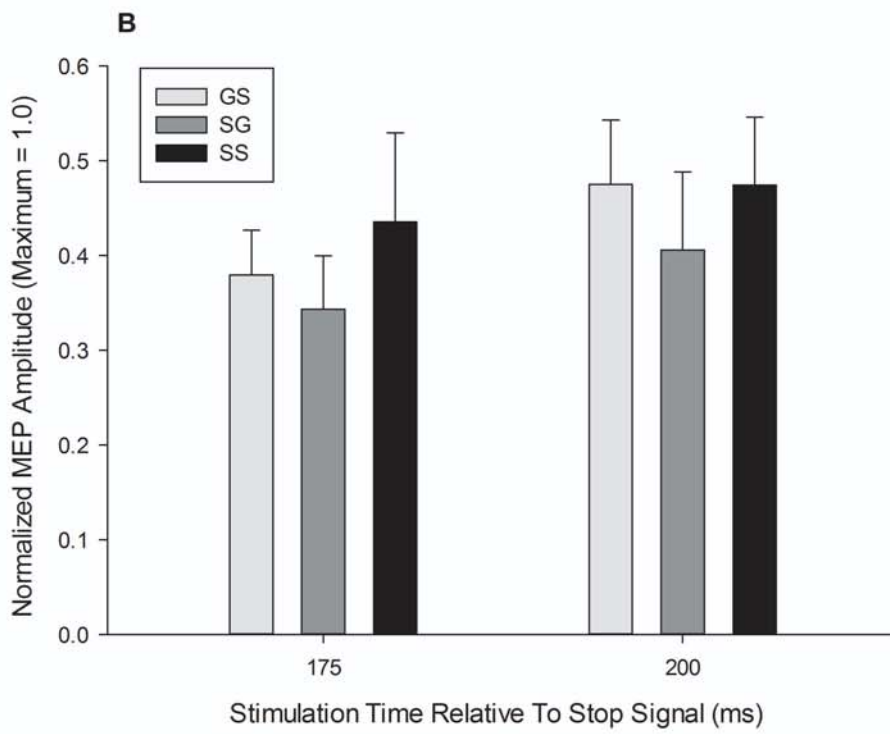
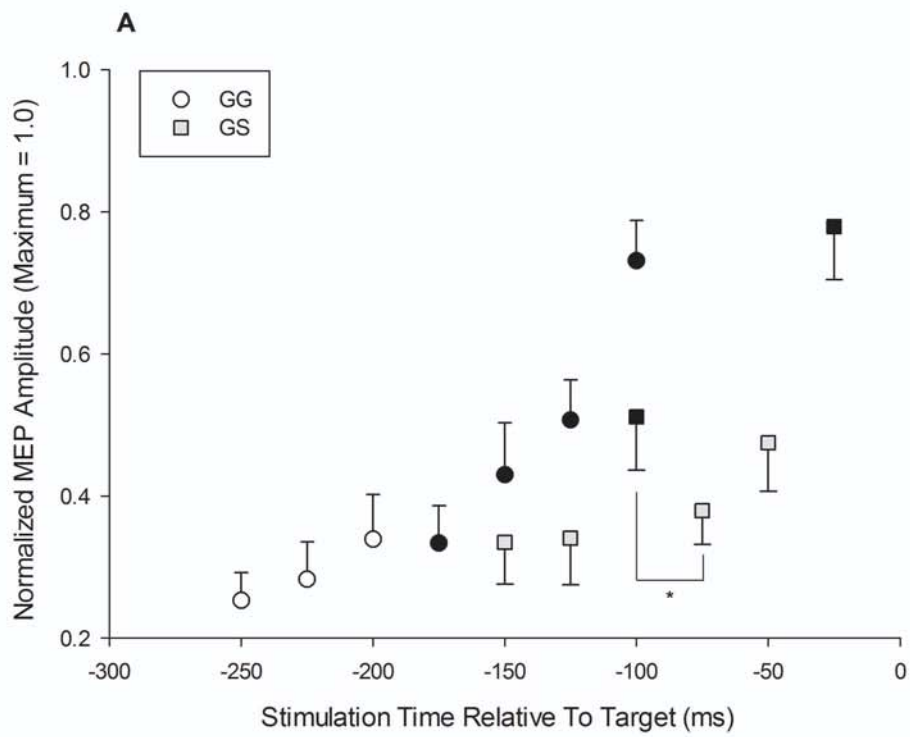
	LTs					
	Go (L)	Go (R)	Go Avg	Partial GS	Partial SG	Partial Avg
CME protocol (ms)	16±3	13±2	14±2	70±8	66±7	68±6*
LICI protocol (ms)	17±2	7±2	12±2	78±6	62±6	70±6*
LICI protocol	Preceding trial type					
	Go	Partial GS	Partial SG	Stop Both		
LTA (ms)	10±2	3±2†	14±2†	9±1		

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

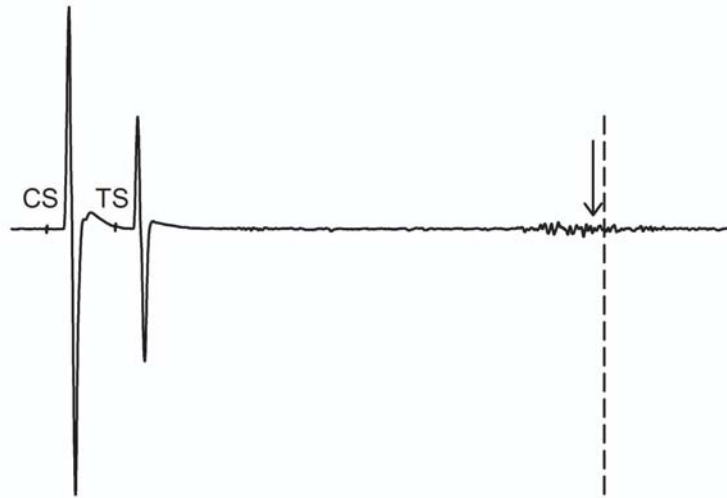
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**A**



**B**

