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The Role of Interhemispheric Communication During Complete and Partial Cancellation of Bimanual Responses

Hayley J. MacDonald[#1], Chotica Laksanaphuk[2], Alice Day[1], Winston D Byblow[3], Ned Jenkinson[1]

[1]School of Sport, Exercise and Rehabilitation Sciences

Centre for Human Brain Health

University of Birmingham, Birmingham B15 2TT, United Kingdom

[2]Faculty of Physical Therapy and Sports Medicine

Rangsit University, Pathumthani, Thailand

[3]Department of Exercise Sciences

Centre for Brain Research

University of Auckland, Auckland 1142, New Zealand

[#]*Corresponding author:*

Dr Hayley MacDonald

School of Sport, Exercise and Rehabilitation Sciences

The University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom

Phone: +441214147242

Email: h.j.macdonald@bham.ac.uk

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Abstract

Precise control of upper limb movements in response to external stimuli is vital to effectively interact with the environment. Accurate execution of bimanual movement is known to rely on finely orchestrated interhemispheric communication between the primary motor cortices (M1s). However, relatively little is known about the role of interhemispheric communication during sudden cancellation of prepared bimanual movement. The current study investigated the role of interhemispheric interactions during complete and partial cancellation of bimanual movement. In two experiments, healthy young human participants received transcranial magnetic stimulation to both M1s during a bimanual response inhibition task. The increased corticomotor excitability in anticipation of bimanual movement was accompanied by a release of inhibition from both M1s. After a stop cue, inhibition was re-engaged onto both hemispheres to successfully cancel the complete bimanual response. However, when the stop cue signalled partial cancellation (stopping of one digit only), inhibition was re-engaged with regard to the cancelled digit, but the responding digit representation was facilitated. This bifurcation in interhemispheric communication between M1s occurred 75 ms later in the more difficult condition when the non-dominant, as opposed to dominant, hand was still responding. Our results demonstrate that interhemispheric communication is integral to response inhibition once a bimanual response has been prepared. Interestingly, M1-M1 interhemispheric circuitry does not appear to be responsible for the non-selective suppression of all movement components that has been observed during partial cancellation. Instead such interhemispheric communication enables uncoupling of bimanual response components and facilitates the selective initiation of just the required unimanual movement.

New & Noteworthy

We provide the first evidence that interhemispheric communication plays an important role during sudden movement cancellation of two-handed responses. Simultaneously increased inhibition onto both hemispheres assists with two-handed movement cancellation. However, this network is not responsible for the widespread suppression of motor activity observed when only one of the two hands is cancelled. Instead, communication between hemispheres enables the separation of motor activity for the two hands and helps to execute the required one-handed response.

Introduction

Precise control of upper limb movements is crucial for human behaviour. Both unimanual and bimanual movements rely on finely orchestrated interhemispheric interactions between primary motor cortices (M1s). During unimanual movement, corticomotor excitability (CME) is facilitated in ipsilateral M1 through crossed-facilitation (Muellbacher et al. 2000). This interhemispheric interaction may also constitute inhibitory processes to suppress homologous representations and prevent mirror movements, as evidenced through neuroimaging (Newton et al. 2005) and neurophysiology (Giovannelli et al. 2009; Liang et al. 2014; Perez and Cohen 2008). Meanwhile, performing in-phase bimanual movement produces bilaterally increased CME and decreased inhibition (Byblow et al. 2012). Asymmetric bimanual movements also require the integrity of interhemispheric connections (Loehrer et al. 2016; Tuller and Kelso 1989), without which the necessary decrease in interhemispheric coupling is impossible (Cardoso de Oliveira et al. 2001; Serrien et al. 2003). As such, interhemispheric communication is a key mechanism in upper limb coordination (Carson 2005; Liuzzi et al. 2011).

Interhemispheric communication is often measured via transcranial magnetic stimulation (TMS). A suprathreshold conditioning pulse applied to M1 10 or 40 ms before a test pulse to the contralateral M1, reduces the size of the test motor evoked potential (MEP) (Ferbert et al. 1992). The timings between the pulses target different interhemispheric circuits (Chen et al. 2003; Ferbert et al. 1992). An interstimulus interval (ISI) of 40 ms is thought to interrogate mechanisms of longer-latency interhemispheric inhibition (IHI) mediated by postsynaptic $GABA_B$ receptors (Kukaswadia et al. 2005). Whereas a 10 ms ISI is thought to measure the effect of activating glutamatergic transcallosal neurons that synapse onto $GABA_A$ interneurons which inhibit pyramidal neurons descending from the contralateral M1 (Daskalakis et al. 2002; Reis et al. 2008). The magnitude of this short-latency IHI is modulated during both unimanual (Duque et al. 2007; Murase et al. 2004; Talelli et al. 2008; Wischnewski et al. 2016) and bimanual movement (Wahl et al. 2016).

Relatively little is known about interhemispheric communication during response inhibition i.e. the sudden cancellation of prepared movement. Complete cancellation of a bimanual response can be achieved at a comparable latency to cancellation of unimanual movement (e.g. Coxon et al. 2007; Aron and Poldrack, 2006). Both types of response inhibition engage a right-lateralized inhibitory control network that recruits the supplementary motor area, inferior frontal cortex, basal ganglia and related thalamic regions (Aron and Poldrack 2006; Rubia et al. 2003; Zandbelt et al. 2013). M1 is a target for this network where excitability is modulated to prevent prepared voluntary movement. This interaction could take place via direct postsynaptic inhibition of M1 neurons, or excitation of the inhibitory interneurons targeting pyramidal neurons. While unimanual movement cancellation includes intracortical inhibitory mechanisms (Coxon et al. 2006; Hermans et al. 2019), the role of inhibitory – and especially interhemispheric - circuits in bimanual cancellation is less clear.

When only one side of a pre-prepared bimanual response is cancelled during an anticipatory response inhibition task, two consistent behaviours reveal themselves: 1) a robust response delay in the remaining movement component, and 2) people are less accurate at partial cancellation than complete bimanual cancellation. Evidence exists for a widespread effect on the motor system during such partial cancellations (Ko and Miller 2011), where CME is suppressed in the remaining executed hand 175 ms after the (irrelevant) stop cue (Cowie et al. 2016; MacDonald et al. 2014). It is suggested this global suppression is followed by uncoupling of the functionally-coupled bimanual components, before selective initiation of the required component can occur (MacDonald et al. 2017). The neural circuits responsible for the non-selective suppression and uncoupling during partial cancellation remain elusive.

Our aim was to investigate M1-M1 interhemispheric communication during complete and partial cancellation of bimanual movement. In *experiment 1*, we hypothesized IHI would increase bi-directionally 175 ms after the stop cue during both bimanual and partial cancellation. An increase in IHI onto both hemispheres would indicate interhemispheric communication is contributing to the global braking of movement observed following selective and non-selective stop cues. Following *experiment 1*, we investigated whether the same pattern of IHI modulation observed during partial cancellation when the dominant hand responded, could be observed (albeit at a later time point) when the non-dominant hand responded. A comparable pattern of modulation between partial cancellation conditions would support a role for IHI in response uncoupling and selective movement initiation. We expected that the dissociation in interhemispheric communication would occur later when the non-dominant hand was responding given the greater difficulty in uncoupling responses during this condition.

Materials and Methods

Participants

Healthy, self-reported right-handed adults with no known neurological impairment participated in this study (*Experiment 1*: N = 26, mean age 25 ± 6 years, range 19 – 47 years, 10 male; *Experiment 2*: N = 20, mean age 28 ± 6 years, range 21 – 48 years, 12 male). Ethical approval was obtained from the University of Birmingham Ethics Committee (ERN_17-1541AP1) and all participants gave written informed consent.

Experimental Design

Response inhibition task

An anticipatory response inhibition (ARI) task was performed by participants. The task was displayed on a computer monitor (47.8 x 27 cm) approximately 1 m in front of the participant. The display consisted of two indicators (vertical bars), each 21.6 cm in length and 1.8 cm in width. Participants were seated with forearms resting on a table positioned midway between pronation and supination so that the medial surface of each index finger rested on a custom-made microswitch. Control of the left or right bar was via the corresponding left or right switch. Switch "up/down" state was precisely recorded through an Arduino (Uno; Arduino.cc) and synchronized to the display through an analogue-digital USB interface (NI-DAQmx 9.7; National Instruments). Customized software written in MATLAB (R2016a, version 9.0; The MathWorks) generated the trial order, recorded trial data, and controlled the visual output during the task.

Participants were instructed to let the weight of their fingers passively depress the switches. Depression of both switches initiated the trial after a 400 - 900 ms variable delay. As long as the switches remained depressed, both bars would fill from the bottom at a constant velocity, reaching a horizontal stationary target line after 800 ms and the top of the

display after 1000 ms. Participants were informed that releasing the switch (index finger abduction) would stop the corresponding bar from filling (Fig. 1). The majority of trials (70%) involved bimanual index finger abduction to release both switches in time to intercept both bars with the target line (Go Bimanual trials, Go Left – Go Right; GG). Visual feedback was displayed at the completion of each trial, indicating whether the bar(s) were sufficiently close to the target (within 30 ms), to emphasize that trials were to be performed as accurately as possible (Fig. 1A). Occasionally one or both bars stopped automatically before reaching the target, cueing the participant to cancel responding with the corresponding digit(s) (Stop trials). There were three types of trials requiring response inhibition: Stop Bimanual trials (Stop Left – Stop Right; SS), when both bars stopped automatically, and Stop Unimanual trials which included Stop Left - Go Right (SG) and Go Left - Stop Right (GS), when only the left or right bar stopped, respectively. The pairing of letters denotes the spatial mapping of index fingers (Fig. 1A). The bar(s) were initially programmed to stop 200 ms before the target, and a separate staircase procedure ensured convergence on an individualized 50 % stopping success rate for each Stop trial type. The bar(s) stopped 25 ms later/earlier following a successful/unsuccessful Stop trial, respectively.

All participants completed preliminary practice blocks comprised of only GG trials. Practice blocks ensured familiarization and were used to set TMS intensities. The main ten blocks were comprised of 600 trials of which 420 were GG trials (120 stimulated) and 180 were Stop trials pseudo-randomized across the blocks (all stimulated). In *experiment 1*, there were 60 trials for each stop type whereas for *experiment 2*, 120 of the 180 Stop trials were GS trials to enable a wider range of stimulation times during this main trial type of interest. Participants had a rest of at least 1 minute between each block to minimise fatigue and were told they could rest between trials if needed as the trial wouldn't start until both switches were depressed.

177 *Transcranial magnetic stimulation*

178 Surface electromyography (EMG) was recorded over the first-dorsal interosseous (FDI)
179 muscle of each hand, with a ground electrode placed on the bony prominence of the left
180 elbow. Electrode signals were amplified, filtered (20-1000 Hz), and sampled at 2 kHz
181 (Cambridge Electronic Designs 1401, Cambridge, United Kingdom) for offline analysis with
182 Signal (CED, version 6.04) and custom MATLAB software. Triggering of the TMS machines
183 and Signal software was controlled by the Arduino device to accurately integrate pulse timing
184 with the timing in the behavioural trial.

185 Each M1 was stimulated using a flat, figure-of-eight (wing diameter 70mm) TMS coil
186 and Magstim200 unit (Magstim, Dyfed, United Kingdom) generating a bi-phasic pulse
187 waveform. The TMS coils were positioned tangentially to the head and the optimal position
188 was found (and marked on the scalp) that elicited MEPs of the largest amplitude in each FDI
189 using a slightly supra-threshold stimulus intensity. Task motor threshold (TMT) was
190 determined for each hemisphere as the minimum percentage of maximum stimulator output
191 (%MSO) required to obtain a MEP of at least 0.05 mV in four out of eight consecutive
192 stimulations when the participant was resting their fingers on the switches. The handle of the
193 coil delivering the test stimulus (TS) remained in a posterior direction at a 45-degree angle to
194 the midline of the head, inducing a posterior-anterior current. Positioning the conditioning
195 stimulus (CS) coil in the same orientation caused difficulties fitting both coils on the head and
196 therefore non-optimal coil placements in terms of scalp position. Instead, the handle for the CS coil
197 was subsequently rotated to 90 degrees after thresholding, inducing a lateral-medial current
198 (Fig. 1B), allowing both coils to remain at the optimal scalp position. Interhemispheric effects can
199 be reliably measured using this combination of coil orientations (Chen et al. 2003; Duque et
200 al. 2007; Murase et al. 2004; Uehara et al. 2014) with the CS coil orientation thought to
201 produce mainly direct and I1 waves (Sakai et al. 1997; Schnitzler et al. 1996; Werhahn et al.

202 1994). Nevertheless, the two different coil orientations necessitated a between-groups study
203 design as the TS and CS were not equivalent and therefore not interchangeable. MEPs were
204 recorded from the left FDI corresponding to the TS over the right M1 in one group and
205 recorded from the right FDI corresponding to TS over the left M1 in the other group. Coil
206 orientations were consistently checked throughout the session to ensure both coils were
207 stimulating optimally.

208 During practice blocks on the task, TMS was administered -600 ms relative to the
209 target and TS intensity was adjusted in 1 - 2 %MSO increments from TMT to produce an
210 average non-conditioned (NC) MEP of 1 mV. To measure IHI, the CS intensity was initially
211 set to 120 % TMT (Ferbert et al. 1992) and adjusted in 1 – 2 % increments to produce 50 %
212 inhibition of the NC MEP during practice blocks, at a 10 ms inter-stimulus interval
213 (Daskalakis et al. 2002; Duque et al. 2007; Ferbert et al. 1992). Intensities for TS and CS
214 remained constant after the practice blocks. During the main task, 30 NC and 30 conditioned
215 (C) MEPs were recorded at each of the stimulation times during Go and Stop trials
216 (*experiment 1* Fig. 1C top, *experiment 2* Fig. 1C bottom). CS and TS were always applied but
217 order of stimulation determined whether MEP corresponded to a NC or C trial (e.g. test
218 stimulus applied first = NC MEP trial). During GG trials of both experiments, MEPs were
219 recorded 600, 225, 175 and 125 ms before the target. During all Stop trials in *experiment 1*,
220 TMS occurred 175 ms after the stop cue which was left to vary according to the staircase
221 algorithm. This timing on Stop trials corresponded to the MEP suppression observed
222 previously (Cowie et al. 2016; MacDonald et al. 2014). Later stimulation times were
223 investigated on GS trials in *experiment 2* only at 200, 225 and 250 ms after the stop cue. The
224 increased number of stimulation times necessitated an increase in the number of GS trials.
225 However, to make overall behavioural performance comparable and to keep the task a

tolerable duration, the total number of trials remained the same as *experiment 1* by necessarily decreasing the number of SS and SG trials.

Analysis

Dependent measures

To assess behaviour in both experiments, lift times (LTs) were recorded for all Go Bimanual trials and from the responding digit on successful Stop Unimanual trials. LTs are reported relative to the target and were trimmed to remove outliers greater than 3 standard deviations (SDs) from the mean LT. LTs on unstimulated versus stimulated Go Bimanual trials were compared to confirm that the TMS pulse did not influence behaviour. Stop signal reaction time (SSRT) was calculated using the integration method (Logan and Cowan 1984) for each Stop trial type. This involved LTs for GG, GS and SG trials being rank ordered and the *n*th number selected, with *n* obtained by multiplying the number of successful trials by the probability of a response on the corresponding Stop trial type (LTs on GG trials used for calculation of SS SSRT). The time at which the staircase procedure stopped the indicator to achieve 50 % success was also recorded for each Stop trial type and used in the SSRT calculation.

Average peak-to-peak amplitudes for NC and C MEPs were calculated in the target FDI (corresponding to TS) for each trial type and stimulation time by trimming the top and bottom 10% of MEPs from successful trials. The primary dependent measure was percent inhibition (%IHI) which was calculated as 100 – ((C MEP / NC MEP) x 100). Larger IHI values indicate greater levels of inhibition and negative values reflect facilitation/disinhibition. Root-mean-squared (rms) EMG was calculated over a 50ms window preceding stimulation and trials with rmsEMG values >15μV were excluded from

analysis (Ferbert et al. 1992). Trials were also excluded through visual inspection if any EMG activity was present between the TMS pulse and MEP.

Statistical analyses

A paired *t*-test examined the difference between LTs in stimulated versus unstimulated GG trials for each group. A mixed effects (ME), repeated-measures analysis of variance (rmANOVA) was run on all remaining behavioural dependent measures. LT was analysed with a 2 Group (Left, Right) x 2 Digit (LeftFDI, RightFDI) x 2 Trial Type (Go, Stop Unimanual) design. SSRT and indicator stop time were subjected to 2 Group x 3 Stop Trial Type (SS, SG, GS) ME rmANOVAs.

A 2 Group x 4 Stimulation Time (-600, -225, -175, -125 ms relative to target) ME rmANOVA tested for differences in Go trial excitability (NC MEP amplitude), %IHI and rmsEMG in both experiments. To test our main hypotheses in *experiment 1*, a 2 Group x 3 Stop Trial Type ME rmANOVA was run for %IHI, NC MEP amplitude and rmsEMG. For *experiment 2*, the main hypothesis was investigated using a 2 Group x 3 Stimulation Time (200, 225, 250 ms relative to stop cue) ME rmANOVA on %IHI and rmsEMG data from GS trials.

Effect sizes are reported for all significant ANOVA results and statistical significance is set at $\alpha \leq 0.05$. The conservative Greenhouse-Geisser *P* value is reported for data that violate the assumption of sphericity. Post hoc *t*-tests were used to investigate ANOVA interactions and main effects. Values are reported as mean ± standard error (SE).

Results

Experiment 1

Behavioural data - Go trials

Behavioural data are presented for all twenty-six participants (Left FDI Group N = 13, Right FDI Group N = 13). LTs were as expected for this task compared to previous data e.g. (MacDonald et al. 2014) and confirmed that participants were performing the task correctly. TMS had no effect on participant behaviour as the paired *t*-tests revealed that LT was comparable between stimulated and unstimulated GG trials in both groups (Left FDI p = 0.073, Cohen's d = 0.009; Right FDI p = 0.429, Cohen's d = 0.019). There was a main effect of Trial Type ($F_{1,24}$ = 56.96, p < 0.001, η_p^2 = 0.704) with the average LT on Stop Unimanual trials delayed by an average of 48 ms compared to GG trials (see Table 1). Both groups showed the expected LT delay on Stop Unimanual compared to Go trials, and this delay was comparable between the left and right digits. There were no other main effects or interactions for LT (all p > 0.145).

Behavioural data - Stop trials

Successful stopping percentage for SS trials was not different to 50% (49 ± 0.4 %, p = 0.154) but was slightly below 50% for both SG (46 ± 1.3 %, p = 0.005) and GS trials (43 ± 1.6 %, p < 0.001), reflecting the increased difficulty of partial compared to bimanual cancellation. For SSRT (Fig. 2), there was a main effect of Stop Trial Type ($F_{1.4,33.4}$ = 15.177, p < 0.001, η_p^2 = 0.387); with a difference of 64 ± 14 ms (p < 0.001) between the SSRT for SS (231 ± 6 ms) and SG (295 ± 12 ms) trials, and a difference of 118 ± 28 ms (p < 0.001) between SS and GS (350 ± 28 ms) trials. Of note, there was a significant difference of 54 ± 24 ms between SG and GS trials (p = 0.034) with GS trials producing longer SSRTs. There were no other main effects or interactions (all p > 0.312).

The SSRT results were precipitated by an effect of Stop Trial Type ($F_{2,50}$ = 16.087, p < 0.001, η_p^2 = 0.392) for the time at which the staircase procedure stopped the indicator(s) to

achieve 50 % success. The indicators stopped later on SS (577 ± 6 ms) compared to both SG (479 ± 25 ms, $p < 0.001$) and GS trials (438 ± 33 ms, $p < 0.001$). Despite the differences in SSRT, the indicator stop times were comparable between SG and GS trials ($p = 0.086$), with no other main effects or interactions (all $p > 0.085$). Replicating previous studies (Coxon et al. 2007; Coxon et al. 2012; MacDonald et al. 2014; MacDonald et al. 2012), stopping all components of the prepared response was faster than stopping either component individually. Notably, stopping the non-dominant left hand and continuing with the *dominant* right hand on SG trials was a faster process than having to stop the dominant hand and continue with the *non-dominant* on GS trials, despite being cued at similar times by the stop cue.

Neurophysiological data – Go trials

Data are presented for N = 10 for Left and N = 10 for Right FDI Groups (Left: 2 male, 24 ± 5 years; Right: 5 male, 27 ± 8 years) as TMS data could not be collected or was rejected from the analysis for the remaining participants e.g. TMT > 70 % MSO, rmsEMG > 15μV on too many trials. Average stimulation intensities were as follows: Left M1: TMT 42 ± 2 % MSO, TS 52 ± 3 % MSO (118 ± 2 % TMT), CS 57 ± 1 % MSO (121 ± 2 % TMT); Right M1: TMT 48 ± 2 % MSO, TS 58 ± 2 % MSO (118 ± 2 % TMT), CS 58 ± 2 % MSO (123 ± 3 % TMT). CS intensity around 120 % of motor threshold is appropriate to produce robust levels of IHI (Uehara et al. 2014). EMG traces from a representative participant in the Right FDI Group are shown in Fig 3 illustrating NC and C MEP amplitudes and the presence/release of IHI.

For NC MEP amplitude (Fig 4A&B) there was a main effect of Stimulation Time ($F_{3,54} = 10.388$, $p < 0.001$, $\eta_p^2 = 0.366$), with no other main effects or interactions ($p > 0.403$). Collapsed across FDI (i.e. Group), there were no differences in NC MEP amplitude between early in GG trials (-600 ms: 0.94 ± 0.16 mV) and at -225 (0.74 ± 0.11 mV; $p = 0.085$) or -175 ms (0.88 ± 0.11 mV; $p = 0.686$) relative to target. However, there was a significant increase

from -600 ms by -125 ms (1.36 ± 0.12 mV, $p = 0.003$). For pre-trigger rmsEMG there were no main effects or interactions (all $p > 0.263$). Therefore, excitability was seen to 'ramp up' for both movement components when the bars got close to the target line on Go trials, replicating previous findings (Cowie et al. 2016; MacDonald et al. 2014).

For % IHI (Fig. 4C&D), there was a main effect of Stimulation Time ($F_{2.0,35.5} = 5.857$, $p = 0.007$, $\eta_p^2 = 0.246$), with no other main effects or interactions ($p > 0.115$). Collapsed across Group, there was not yet a difference in % IHI from -600 ms (31 ± 7 %) at -225 ms (17 ± 6 %, $p = 0.091$), but there was a decrease by -175 ms ($p = 0.001$) that remained at -125 ms ($p = 0.004$). There were no main effects or interactions in the rmsEMG data (all $p > 0.125$). Both FDIs therefore showed a comparable release of IHI during Go trials.

Neurophysiological data – Stop trials

There were no main effects or interactions for NC MEP amplitude (all $p > 0.545$). Corticomotor excitability was comparable across muscles and across Stop trial types at the time of %IHI calculation. The ANOVA on %IHI recorded 175 ms after the stop cue on Stop trials (Fig. 5A) produced a main effect of Stop Trial Type ($F_{2, 36} = 3.688$, $p = 0.049$, $\eta_p^2 = 0.170$) and a Stop Trial Type x Group interaction ($F_{2,36} = 9.963$, $p = 0.001$, $\eta_p^2 = 0.356$), but no effect of Group ($F_{1,18} = 3.457$, $p = 0.079$). Compared to SS trials, SG trials showed a reduction in %IHI onto the hemisphere controlling the right FDI (-46 ± 21 vs 20 ± 9 %, $p = 0.025$) and an increase in %IHI onto the hemisphere controlling the left FDI (27 ± 7 % vs 8 ± 7 %, $p = 0.037$). Only SG trials showed a difference in %IHI onto the cancelled versus responding digits (left FDI: 27 ± 7 %; right FDI: -46 ± 21 %, $p = 0.004$; all other $p > 0.268$). Compared to simple bimanual cancellation, SG trials showed an increase in IHI onto the M1 corresponding to the cancelled digit and a release of IHI for the responding digit 175 ms after

343 the stop cue. This pattern of IHI modulation was not present 175 ms after the stop cue on GS
344 trials.

345 For rmsEMG there was a main effect of Stop Trial Type ($F_{1.5, 27.7} = 7.577$, $p = 0.004$,
346 $\eta_p^2 = 0.296$) were SS trials showed higher average rmsEMG (3.5 ± 0.3 μV) compared to both
347 SG (2.9 ± 0.2 μV, $p = 0.022$) and GS trials (2.5 ± 0.2 μV, $p = 0.005$). Importantly, this effect
348 of Stop Trial Type cannot account for the interaction seen in the IHI data. There were no
349 other main effects or interactions for pretrigger rmsEMG (all $p > 0.075$).

350 *Experiment 2*

351 The novel finding from *experiment 1* was that partial cancellation on SG trials required a
352 dissociation in interhemispheric communication onto the two FDI representations compared
353 to bimanual cancellation. This finding may indicate that interhemispheric communication
354 was involved in the uncoupling of response components by directing IHI onto the M1 of the
355 cancelled side and releasing IHI from the M1 of responding side. This working hypothesis for
356 the role of interhemispheric communication in partial cancellation would necessitate an
357 equivalent dissociation during GS trials, although none was seen 175 ms after the stop cue.
358 *Experiment 2* was conducted to test the working hypothesis that this dissociation in
359 interhemispheric communication would occur on GS trials at a later time point given the
360 longer SSRTs in GS compared to SG trials. GS trials were therefore the main trial type of
361 interest in *experiment 2* and %IHI was measured 200, 225 and 250 ms after the stop cue. Go
362 trial results are reported primarily as comparison to *experiment 1*. Behavioural and
363 neurophysiological data are presented from all twenty participants (Left FDI Group: N = 10,
364 8 male, 30 ± 7 years; Right FDI Group: N = 10, 4 male, 27 ± 3 years).

365 *Behavioural data - Go trials*

Lift time results replicated those in *experiment 1* with a main effect of Trial Type ($F_{1,18}$ = 24.65, $p < 0.001$, $\eta_p^2 = 0.578$) and no other main effects or interactions (all $p > 0.213$). Average LT on Stop Unimanual trials was delayed by an average of 50 ms compared to GG trials.

Neurophysiological data – Go trials

The pattern for NC MEP amplitude closely matched *experiment 1*. There was a main effect of Stimulation Time ($F_{3,54} = 14.682$, $p < 0.001$, $\eta_p^2 = 0.449$) with a significant increase in CME at -125 ms (1.47 ± 0.17 mV) compared to -600 ms (1.06 ± 0.13 mV, $p = 0.029$). A Stimulation Time x Group interaction ($F_{3,54} = 3.505$, $p = 0.037$, $\eta_p^2 = 0.163$) also arose as CME at -600 ms was higher in the Right FDI Group (1.39 ± 0.18 mV) compared to the Left FDI Group (0.74 ± 0.18 mV, $p = 0.022$). There was no main effect of Group ($F_{1,18} = 1.032$, $p = 0.323$). Importantly, both groups showed the same increase in CME prior to movement execution seen in *experiment 1*.

%IHI results also closely matched those in *experiment 1*. There was a main effect of Stimulation Time ($F_{3,54} = 4.487$, $p = 0.029$, $\eta_p^2 = 0.200$) as %IHI decreased compared to -600 ms (22 ± 6 %) from -225 ms (-5 ± 8 %, $p = 0.006$) onwards (-175 ms: -32 ± 20 %, $p = 0.018$; -125 ms: 7 ± 6 %, $p = 0.056$). A Stimulation Time x Group interaction arose ($F_{3,54} = 4.527$, $p = 0.029$, $\eta_p^2 = 0.201$) despite %IHI not being significantly different between groups at any single timepoint (all $p > 0.064$). There were no main effects or interactions in the rmsEMG data (all $p > 0.804$). Importantly, both groups showed a pattern of IHI release over the course of Go trials that was comparable to e*xperiment 1*.

Neurophysiological data – GS trials

There were no main effects for NC MEP amplitude (both $p > 0.077$) and most importantly no Stimulation Time x Group interaction ($p = 0.481$). Corticomotor excitability was comparable

across muscles and stimulation times at the time of %IHI calculation. The hypothesis-driven unpaired t-tests showed the dissociation in %IHI between left and right FDIs was significant at 250 ms post stop cue (p = 0.037, Fig. 5B) but not at the earlier stimulation times (both p > 0.731), despite the Stimulation Time x Group interaction not reaching significance ($F_{2,36}$ = 1.972, p = 0.154). The main effects of Stimulation Time and Group were not significant (p > 0.193). Pretrigger rmsEMG data showed a Stimulation Time x Group interaction that approached significance ($F_{2,36}$ = 3.161, p = 0.054, η_p^2 = 0.149) but that did not deconstruct meaningfully. Crucially, there was no difference in rmsEMG between left and right FDI at 250 ms (p = 0.570) that could account for the difference in %IHI.

A post-hoc linear regression tested for a correlation between the release of IHI in the left FDI at 250 ms post stop cue and SSRT for GS trials. Figure 6 illustrates that individuals who showed a greater decrease in %IHI onto the responding digit at this critical time point tended to have shorter SSRTs, although this did not reach significance (R = 0.530, p = 0.115).

Discussion

Our findings demonstrate a previously unknown and differential role for interhemispheric communication between M1s during complete versus partial cancellation of bimanual movements (see Figure 7). As expected, there was a release of IHI from both hemispheres during anticipation of a bimanual movement (Go Bimanual trials). After stop cue presentation, IHI was re-engaged bi-directionally on trials that required bimanual cancellation. However, after a partial cancellation cue, IHI was re-engaged in the M1 corresponding to the cancelled digit but further released in the responding M1. The dissociation in interhemispheric communication between hemispheres appears necessary to uncouple the two response components for successful partial cancellation, as it was observed in both types of Stop Unimanual conditions. Confirming our second hypothesis, the

uncoupling occurred later (by 75 ms) in the more difficult Stop Unimanual trials when only the non-dominant hand was responding. This delayed uncoupling mirrors the longer SSRTs in this condition. Importantly, there was no difference in NC MEP amplitude between Stop trial types or between stimulation times for GS Stop Unimanual trials. Therefore, it seems unlikely that the IHI modulation discussed above merely reflects changes in NC MEP amplitude. Overall, our results indicate that M1-M1 interhemispheric communication enables the uncoupling of bimanual response components to allow the selective re-initiation of just the required unimanual movement.

The anticipation of bimanual action modulated the excitability of both motor representations prior to execution in a familiar pattern of facilitation (Chen et al. 1998; Duque et al. 2010; Marinovic et al. 2013; Marinovic et al. 2011). This facilitation supports previous evidence that CME reliably increases in a temporally predictable manner during pre-prepared movements on the ARI task (Cowie et al. 2016; Coxon et al. 2006; MacDonald et al. 2014). The equivalent pattern between movement components reflects the highly synchronized neural activity between M1s during in-phase, functionally-coupled bimanual movements (Cardoso de Oliveira et al. 2001; Gerloff and Andres 2002; Loehrer et al. 2016; Murthy and Fetz 1996; Wahl et al. 2016). CME increase was accompanied by a release of IHI during movement anticipation (Liuzzi et al. 2011) to a point of reversal into facilitation, similar to unimanual movement preparation (Duque et al. 2007; Murase et al. 2004). However, it is worth acknowledging that the IHI decrease may reflect, in part, the NC MEP increase (Crone et al. 1990). Nevertheless, the balanced release of IHI between effectors provides further evidence that synchronous bimanual movements are neurally coupled together into a single bimanual response.

An increase in transcallosal inhibition was evident during movement cancellation, as a re-engagement of bi-directional IHI between homologous muscle representations was seen

during successful bimanual cancellation. Compared to the disinhibition across Go Bimanual trials, IHI had to be increased again onto both FDI representations following a non-selective stop cue. To our knowledge, the current study is the first to directly measure IHI modulation *during* action cancellation. The dual-coil TMS protocol used in the current study allows snapshot measures of interhemispheric communication mechanisms that directly related to the behavioural outcome on that trial.

Successful partial cancellation required a clear dissociation in interhemispheric communication onto each muscle representation comprising the bimanual response. This bifurcation of IHI reflects the rapid neural and functional uncoupling of the motor representations (MacDonald et al. 2012), that allows a response with a unimanual movement. Such downregulation of spatiotemporal coupling is achieved through modulation of interhemispheric connections (Kajal et al. 2017) which decrease interhemispheric coherence (Serrien et al. 2003). An inability to release IHI during bimanual uncoupling is associated with decreased bimanual finger coordination in older participants (Loehrer et al. 2016). An equivalent link between neural uncoupling and behavioural performance is suggested for young healthy adults in the current study as participants with longer SSRTs during the more difficult partial cancellation condition tended to show an attenuated release of IHI from the responding digit. The fact that divergent modulation in interhemispheric communication is seen later when the non-dominant - rather than dominant - hand is responding reflects studies which suggest that the non-dominant hand is more strongly coupled to the dominant than vice versa (Byblow et al. 2000; Carson 1993). Interestingly, the pattern of interhemispheric communication preceding the divergent modulation during partial cancellation suggests crossed facilitation prior to successful uncoupling. Furthermore, in this study, the non-dominant hand took on average 75 ms longer than the dominant hand to uncouple on partial cancellation trials. Stimulating at an even later timepoint may illustrate further progressed

uncoupling, indexed by a further divergent modulation of interhemispheric communication. Notwithstanding that, successful partial cancellation still requires a divergent modulation in M1-M1 interhemispheric communication onto each motor representation regardless of the hand used to respond.

During partial cancellation of bimanual movement, transcallosal interactions between M1s also enable the selective re-initiation of unimanual movement to meet task demands. There was a re-engagement of IHI onto the M1 corresponding to the cancelled digit. This increase in IHI was equivalent to that seen in bimanual cancellation trials and provides further evidence that an increase in IHI assists with action cancellation. However, there was a simultaneous release of IHI onto the responding digit representation to enable the required unimanual response. The reversal into interhemispheric facilitation could be serving to enhance other (e.g. thalamocortical) excitatory inputs (Shramm and Kharitonov 1984) for selective movement initiation. The fact that IHI did not increase bi-directionally (i.e. in both hemispheres) 175 ms after the stop cue suggests that IHI is not the mechanism that produces non-selective inhibition seen during partial cancellation (Cowie et al. 2016; Coxon et al. 2007; MacDonald et al. 2014). Instead, the independent modulation of interhemispheric communication mirrors that seen for selected and non-selected responses during unimanual motor preparation and execution (Giovannelli et al. 2009; Hinder et al. 2018; Liang et al. 2014; Perez and Cohen 2008; Tazoe and Perez 2013). Overall, it appears M1-M1 communication is not responsible for non-selective braking of movement but rather enables the selective re-initiation of movement following a partial stop cue.

If our interpretation regarding the roles of M1-M1communication during partial cancellation is correct, there is an interesting prediction that results from this working hypothesis. If interhemispheric communication is responsible for uncoupling response components, increasing/decreasing the degree of coupling between components should

490 increase/decrease the degree of interhemispheric communication bifurcation on Stop
491 Unimanual trials, respectively. Recent behavioural findings from Wadsley and colleagues
492 (Wadsley et al. 2019) may speak to this prediction. The authors found that the delays during
493 Stop Unimanual trials were eliminated when the ARI task required asynchronous bimanual
494 responses. The authors posited that the asynchronous task required less between-hand
495 coupling, which enabled more selective responses. The present findings would predict that
496 the asynchronous (compared to the traditional synchronous) version of the ARI task would
497 therefore show a reduced bifurcation in interhemispheric communication between digits
498 during Stop Unimanual trials, due to a reduced need for neural and functional uncoupling.

499 Combined with previous findings, the current study indicates divergent modulation of
500 CME and IHI for the executed muscle on partial cancellation trials. While CME is suppressed
501 for the continuing component following the stop cue (Cowie et al. 2016; MacDonald et al.
502 2014), IHI onto the corresponding M1 is also decreased. Changes in IHI therefore cannot
503 explain non-selective CME suppression in this context and IHI appears to be modulated
504 independently. Such opposing patterns between short latency IHI and CME have been
505 reported previously during motor preparation (Hinder et al. 2018). However, it is worth
506 noting that single-pulse TMS measures CME that is the result of net facilitation and
507 inhibition onto M1 pyramidal neurons. It is therefore likely that while IHI is released, other
508 inhibitory influences onto pyramidal neurons are increased and/or facilitatory influences are
509 removed, resulting in overall MEP suppression 175 ms after the stop cue. It is also possible
510 that a portion of the non-selective CME suppression observed during partial cancellation
511 might be attributable to the presence of surprising/unexpected stop stimuli (Kenemans 2015).
512 An additional caveat is that suprathreshold TMS lacks the spatial resolution to isolate any
513 possible centre-surround organisation of focal excitatory and surround inhibitory effects of
514 interhemispheric communication (Carson 2020). If a focal excitatory effect is overpowered

by the summative influence of surrounding inhibitory interneurons (Asanuma and Okuda 1962), one would observe only net IHI when using dual-coil TMS.

Conclusion

Interhemispheric communication plays an important role in the preparation and cancellation of bimanual movements. A bilateral increase in inhibition assists simple bimanual movement cancellation. However, M1-M1 interhemispheric inhibition may not be responsible for the non-selective suppression of all movement components that has been observed during partial cancellation. Rather interhemispheric communication enables the neural uncoupling of bimanual response components and facilitates the selective initiation of just the required unimanual movement.

Conflict of interest*:* The authors declare no competing financial interests.

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668 **Figure legends**

669 **Figure 1. Experimental setup for behavioural task and neurophysiological measures.** A)
670 Response inhibition task display (top) and participant response (below) for (from left to right)
671 a Go Bimanual (GG), Stop Bimanual (SS) and Stop Unimanual (GS) trial. Participant has
672 successfully lifted from both switches, kept both switches depressed and lifted from only the
673 left-hand switch, respectively. Other type of Stop Unimanual trial (SG) not shown. B)
674 Orientation of transcranial magnetic stimulation coils delivering test stimulus (TS) and
675 conditioning stimulus (CS) for one participant group. Coil orientations swapped for other
676 group. C) Stimulation times during Go and Stop trials. Stimulation on Go Bimanual (GG)
677 trials delivered at equivalent time points relative to target in experiment 1 (top) and 2
678 (bottom). Stimulation delivered +175 ms relative to the staircased stop cue [S] for all Stop
679 trials in experiment 1 (SS: Stop Left – Stop Right; SG: Stop Left – Go Right; GS: Go Left –
680 Stop Right). GS trials were the main trial type of interest in experiment 2 with stimulation
681 delivered 200, 225 and 250 ms post stop cue. Vertical dashed line denotes target line.

682 **Figure 2. Stop signal reaction time for all Stop trial conditions.** In experiment 1 (N = 27),
683 stop signal reaction time was shorter for Stop Bimanual (SS: Stop Left – Stop Right) trials
684 compared to both types of Stop Unimanual trials (SG: Stop Left – Go Right; GS: Go Left –
685 Stop Right). The inhibitory control process took longer on GS than SG trials, as indexed by
686 the longer stop signal reaction time.

687 **Figure 3. Representative individual EMG traces demonstrating levels of**
688 **interhemispheric inhibition during Go and Stop trials.** All traces are recorded from the
689 right FDI in experiment 1. A) Go Bimanual (GG) trial with stimulation at -600 ms relative to
690 target. The amplitude of the motor evoked potential (MEP) on the conditioned trial (C,
691 bottom) is smaller than the non-conditioned (NC) MEP amplitude (top) illustrating

interhemispheric inhibition (IHI) towards the beginning of the trial, substantially before voluntary EMG burst leading to the (bimanual) lift response. B) Stimulation 175 ms after the stop cue on Stop Bimanual (SS) trials illustrates levels of IHI on a trial when the participant has successfully cancelled the complete bimanual response and no voluntary EMG burst is observed. C) Stimulation 175 ms after the staircased stop cue on a Stop Unimanual trial (SG: Stop Left – Go Right) illustrating the reversal of IHI into facilitation in the responding muscle prior to the unimanual response. All trials show two stimulation artefacts as conditioning stimulus and test stimulus were always applied but order of stimulation determined whether MEP corresponded to a NC or C trial (e.g. test stimulus applied first = NC MEP trial). Calibration bar shows 1 mV.

Figure 4. Excitability and inhibition on Go trials. When collapsed across FDI group, an increase in excitability (A) and decrease in interhemispheric inhibition (C) was observed over the course of Go trials in experiment 1 (N = 20). Changes in excitability (B) and interhemispheric inhibition (D) are also shown separately for left (black circles) and right FDI (white circles). The increase in amplitude of the motor evoked potential (MEP) and decrease of interhemispheric inhibition (IHI) did not differ between digits. Stimulation occurred -600, -225, -175 and -125 ms relative to target.

Figure 5. Interhemispheric inhibition on Stop trials. Values of interhemispheric inhibition (IHI) are displayed as percentages (N = 20). Larger IHI values indicate greater levels of inhibition and negative values reflect facilitation/disinhibition. A) Compared to simple bimanual cancellation on Stop Bimanual trials (SS), IHI increased onto the cancelled (left) digit and was released from the responding (right) digit on SG trials. Only SG trials demonstrated these divergent levels of IHI between digits 175 ms after the stop cue (*$p<0.05$). B) In GS trials of experiment 2, the divergence of IHI between digits was only seen 250 ms after the stop cue. Reversal of IHI into facilitation for both digits at 200 and 225

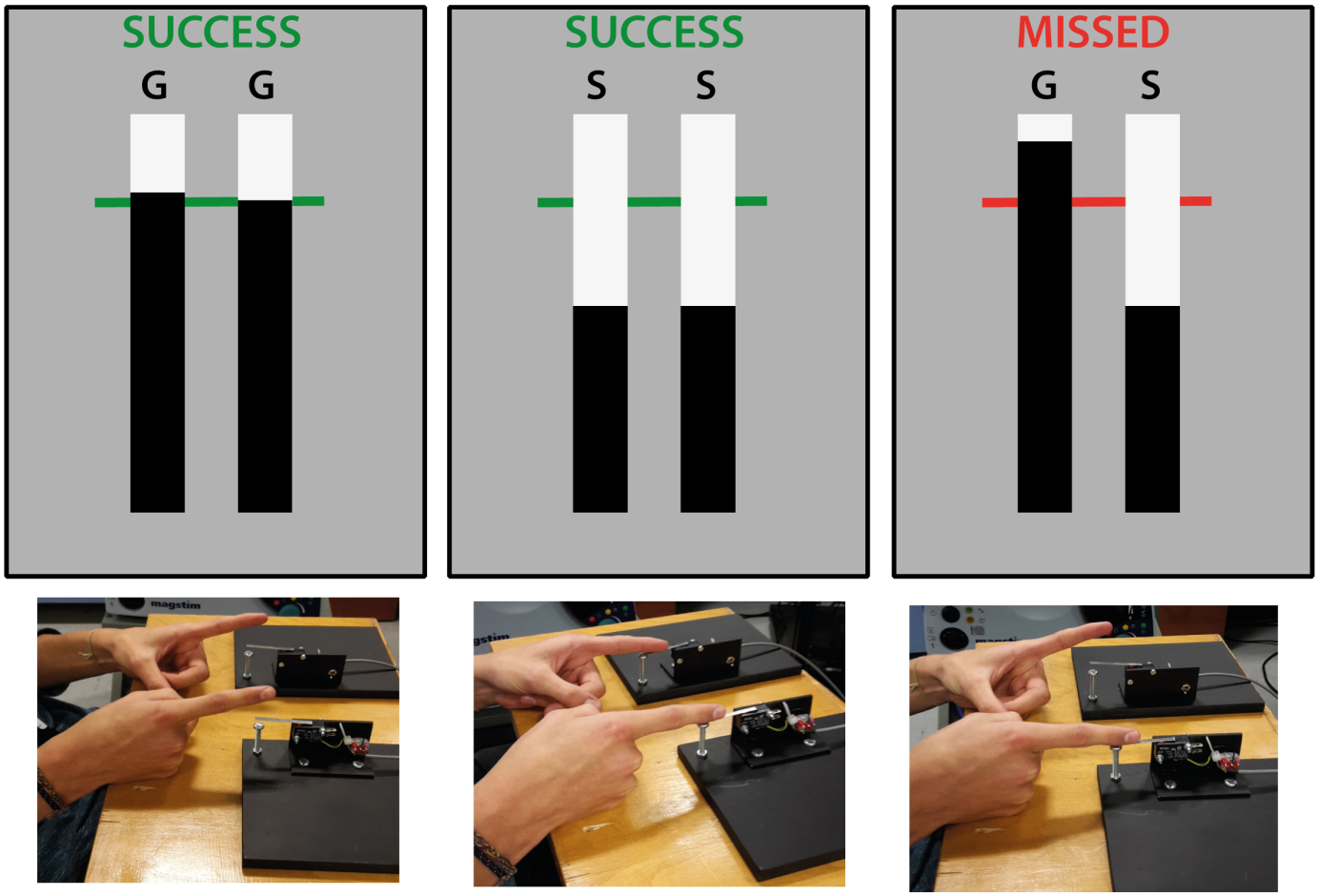
ms may represent crossed facilitation prior to uncoupling. Thick black line denotes digit(s) that successfully stopped.

Figure 6. Relationship between behavioural and neurophysiological measures on GS trials. Participants in experiment 2 (N = 20) who showed a greater release of interhemispheric inhibition (lower %IHI) in the responding (left) digit 250 ms after the stop cue tended to also have a faster stop signal reaction time on these trials. Although despite the visual pattern, the correlation did not reach significance ($R = 0.530$, $p = 0.115$).

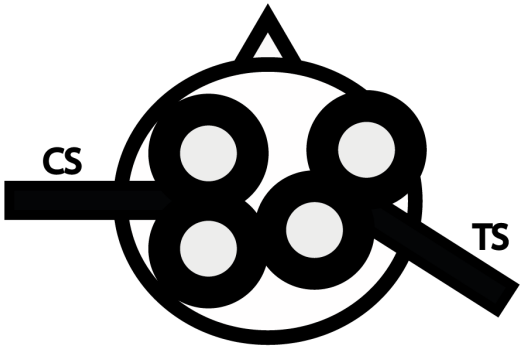
Figure 7. Graphical summary of changes in interhemispheric inhibition during Go and Stop trials. Each panel illustrates neurophysiological findings (right) at snapshots (dashed horizontal lines) preceding successful behaviour in the task (left). Baseline levels of bilateral interhemispheric inhibition (IHI) early on Go trials (-600 ms relative to target) are considered an equivalent starting point for all trial types given the anticipation of a bimanual response on every trial. A) As the bars approach the target (horizontal green line) on Go Bimanual (GG) trials, IHI is release from both primary motor cortices (M1s) into bi-directional facilitation to enable bimanual execution. B) IHI levels are comparable to Go trials at the beginning of Stop Bimanual (SS) trials and initially follow a similar pattern towards facilitation (smaller dashed green lines) prior to the stop cue. However, 175 ms after the non-selective stop cue, IHI is re-engaged onto both M1s to enable bimanual cancellation. C) Initial levels of IHI/facilitation on SG Stop Unimanual (Stop Left – Go Right) trials are comparable to Go trials. However, 175 ms after a selective stop cue, IHI is re-engaged onto the M1 corresponding to the cancelled (left) digit, and further released from the responding M1 (controlling the right digit). The unimanual response comprising the dominant hand is successfully executed after an unavoidable delay. D) The same pattern of IHI/facilitation onto the cancelled/responding M1s is observed during GS (Go Left – Stop Right) as SG Stop Unimanual trials. However, possibly due to the greater difficulty neurally uncoupling and selectively initiating the non-

742 dominant compared to the dominant hand, the distinction between IHI and facilitation is
743 observed 75 ms later (i.e. 250 ms after the selective stop cue). The subsequently delayed
744 unimanual response leads to a longer stop signal reaction time for this condition compared to
745 SG trials.

A



B



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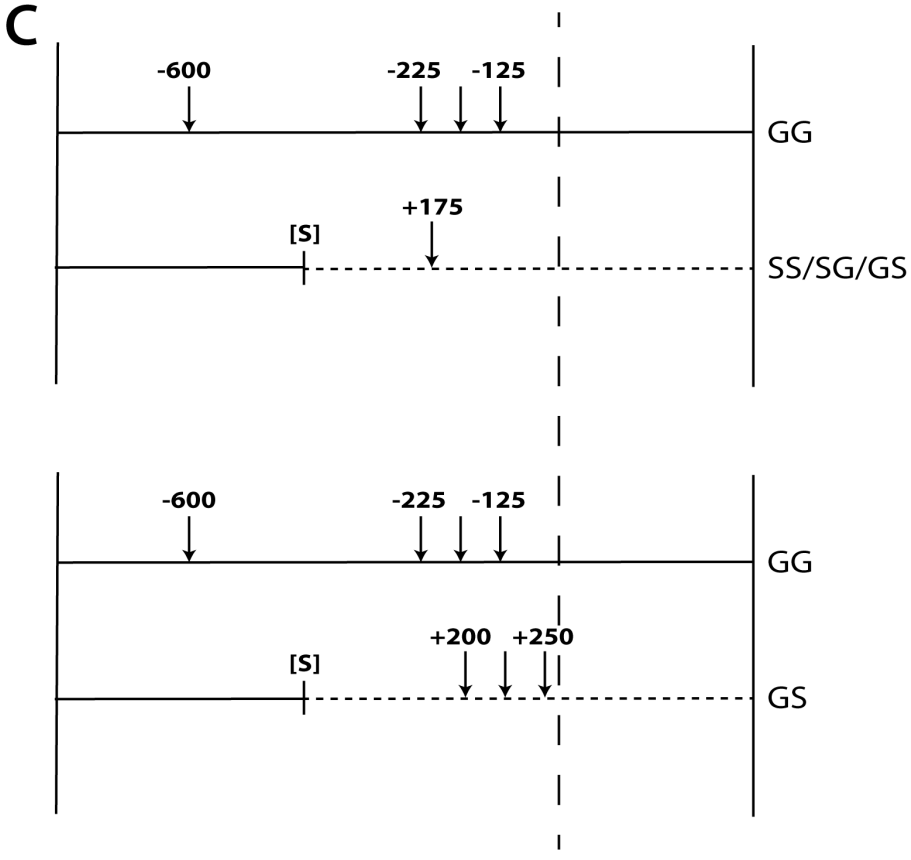

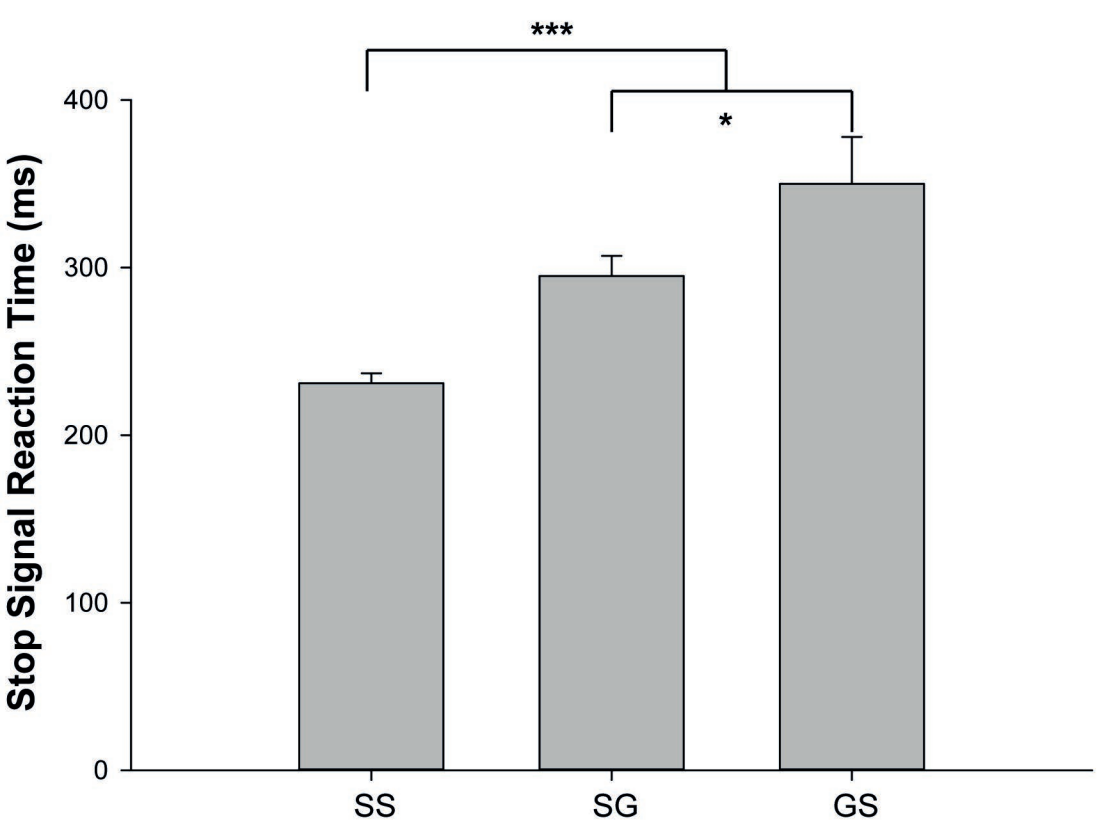

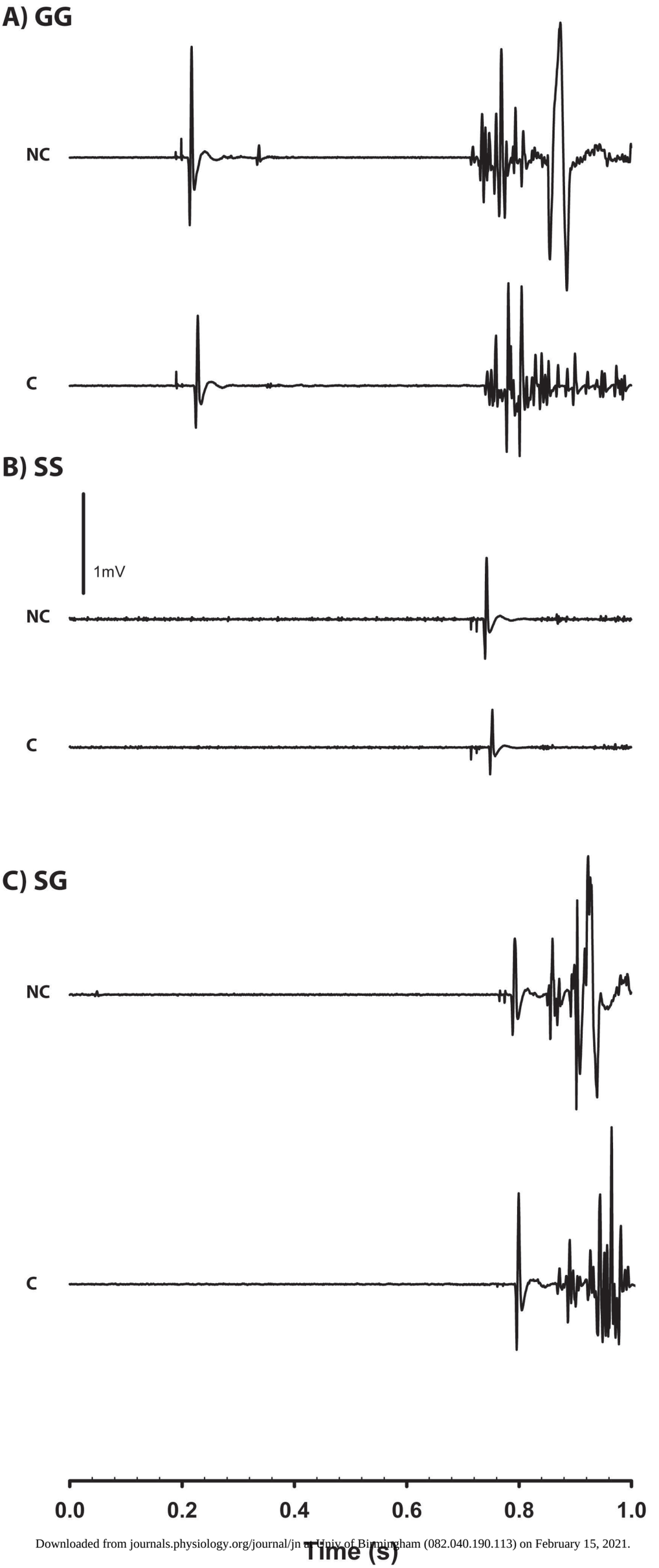

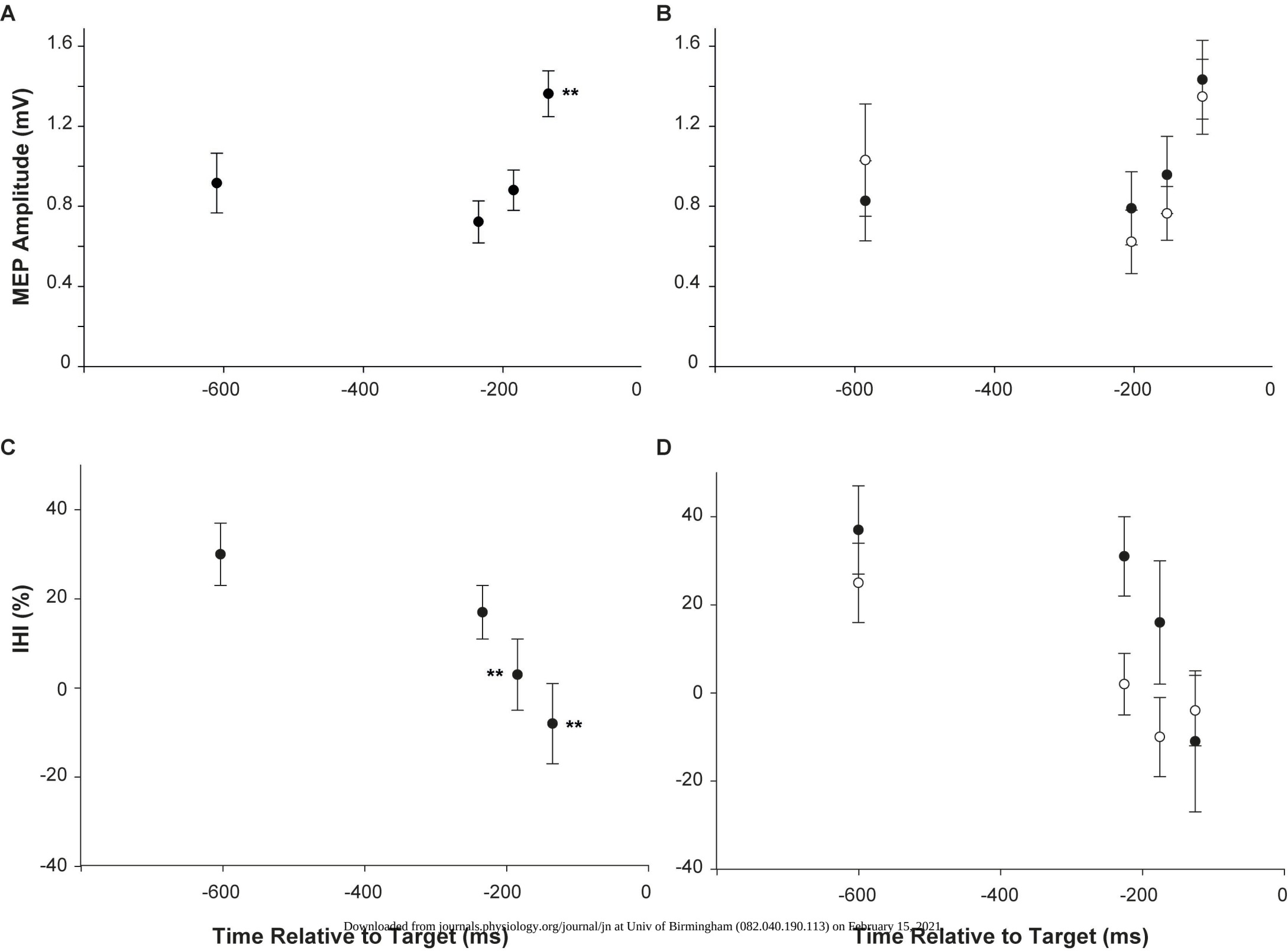

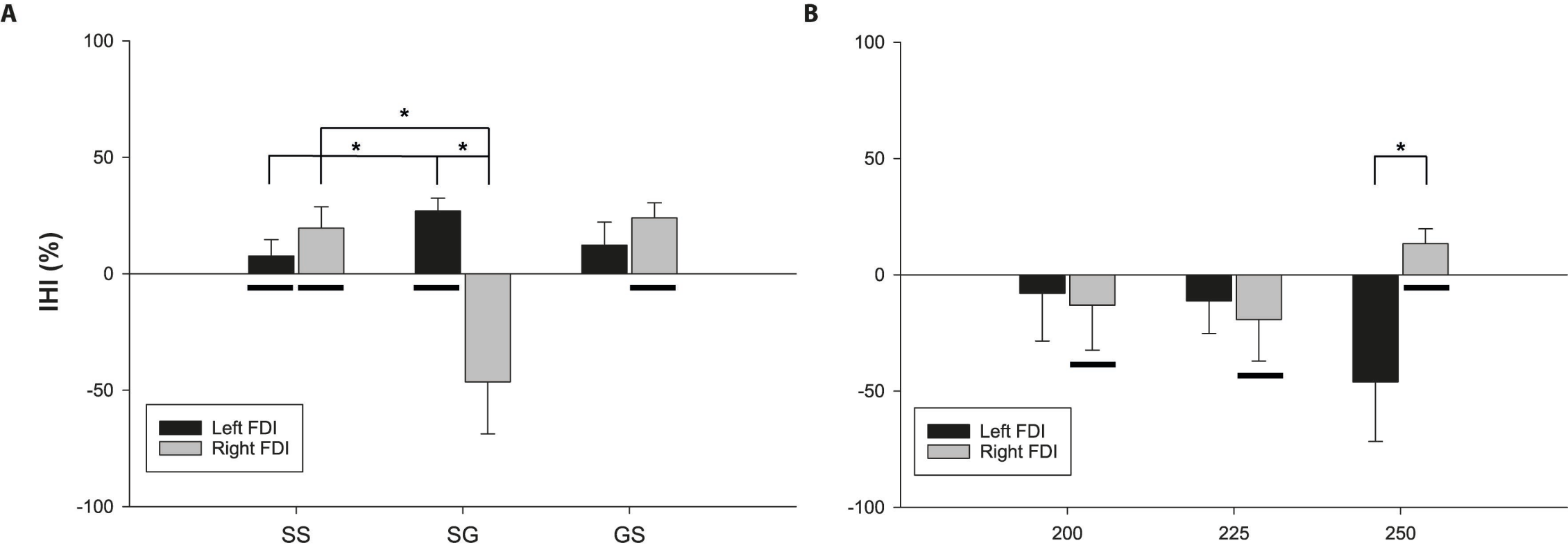

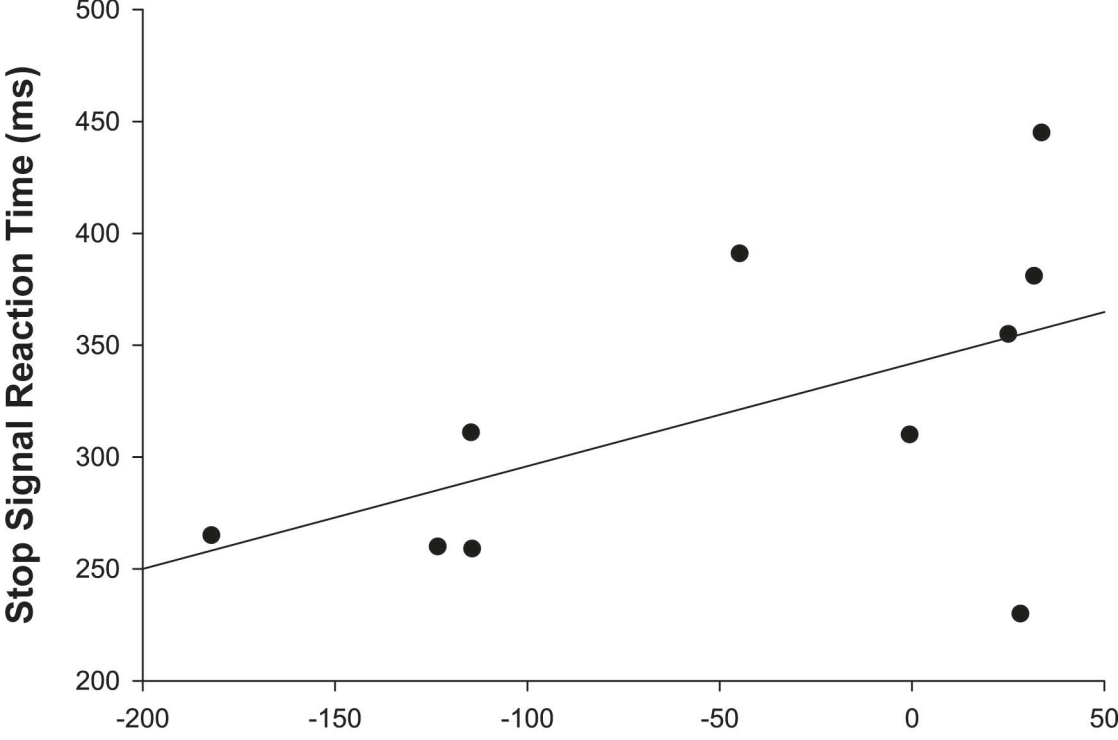

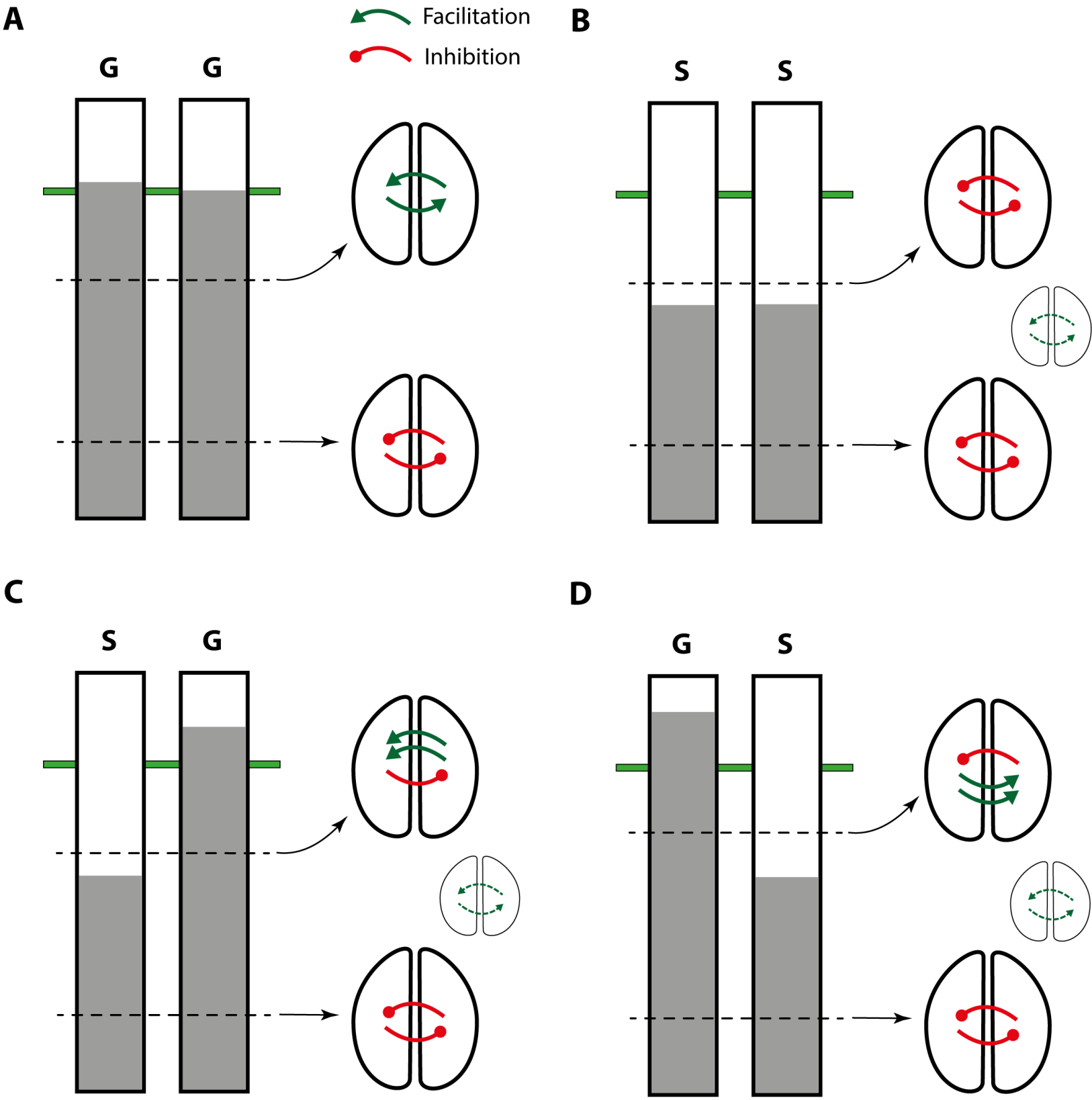

Tables

Participant	Go Bimanual (GG)		Stop Unimanual (GS/SG)	
	Left digit	**Right digit**	**Left digit**	**Right digit**
Left FDI Group				
1	4	13	98	100
2	-6	2	75	37
3	23	10	8	50
4	2	8	85	45
5	29	24	111	87
6	32	05	121	57
7	9	0	47	112
8	31	12	109	-8
9	11	-6	-193	181
10	14	05	-3	46
11	16	15	-60	-62
12	19	02	-23	43
13	11	4	66	3
Average	**15**	**7**	**53**	**52**
SE	**3**	**2**	**14**	**10**

Right FDI Group

1	11	3	94	28
2	23	15	127	96
3	35	8	70	91
4	18	-3	12	71
5	8	4	35	38
6	6	-4	80	58
7	10	11	108	96
8	34	8	106	68
9	6	18	80	-29
10	47	24	136	98
11	9	4	-34	28
12	23	-1	82	38
13	13	10	90	108
Average	**19**	**8**	**76**	**61**
SE	**3**	**2**	**14**	**10**

Table 1. Behavioural lift times in experiment 1

Left and right digit lift times (ms) reported relative to target for both groups. Both digits respond on Go Bimanual trials (GG: Go Left – Go Right), whereas only the left responds on

GS (Go Left – Stop Right) and the right digit on SG (Stop Left – Go Right) Stop Unimanual trials. FDI: first dorsal interosseous; SE: standard error. Negative lift times are possible on Stop Unimanual trials due to the individualised stop cue timing determined via the staircase algorithm for each participant.