# The role of primary motor cortex in manual inhibition of return: A transcranial magnetic stimulation study

**Abstract**

Inhibition of return (IOR) is a behavioural phenomenon characterised by longer response times (RTs) to stimuli presented at previously cued versus uncued locations. The neural mechanisms underlying IOR effects are not fully understood. Previous neurophysiological studies have identified a role of frontoparietal areas including posterior parietal cortex (PPC) in the generation of IOR, but the contribution of primary motor cortex (M1) has not been directly tested.

The present study investigated the effects of single-pulse transcranial magnetic stimulation (TMS) over M1 on manual IOR in a key-press task where peripheral (left or right) targets followed a cue at the same or opposite location at different SOAs (100/300/600/1000ms). In Experiment 1, TMS was applied over right M1 on a randomised 50% of trials. In Experiment 2, active or sham stimulation was provided in separate blocks.

In the absence of TMS (non-TMS trials in Experiment 1 and Sham trials in Experiment 2), IOR was observed in RTs at longer SOAs. In both experiments, IOR effects differed between TMS and non-TMS/sham conditions, but the effects of TMS were greater and statistically significant in Experiment 1 when TMS and non-TMS trials were randomly interspersed. The magnitude of motor-evoked potentials was not altered by the cue-target relationship in either experiment.

These findings do not support a key role of M1 in the mechanisms of IOR but suggest the need for further research to elucidate the role of the motor system in manual IOR effects.

**Keywords:** Inhibition of return; inhibitory control; transcranial magnetic stimulation; primary motor cortex; M1.

## 1. Introduction

Inhibition of return (IOR) is a phenomenon that is thought to reflect mechanisms involved in facilitating efficient search (typically in the visual modality) by discouraging resampling of previously sampled locations [1–4]. The majority of studies examining mechanisms of IOR have used variations of the cue-target paradigm [5], in which a stimulus that does not require a response (the cue) appears in a location peripheral to a central fixation point, followed by a stimulus that does require a response (the target). The target randomly appears at the same location as the cue (cued target) or at a different location from the cue (uncued target). Typically, a facilitatory effect is found at stimulus onset asynchronies (SOAs) of < 200 ms, such that response times (RTs) are shorter to cued than uncued targets. At longer SOAs (> 300 ms), RTs are longer to cued than uncued targets, which is the canonical sign of IOR [6].

Despite more than 35 years of research, the mechanisms and neural bases of this IOR phenomenon remain unclear [7,8]. In addition to numerous behavioural studies (for reviews see [9–11]), IOR has been investigated using a range of neuroscience methodologies including studies of neurological patients [12–14], neuroimaging [15,16], electrophysiology (e.g., [17,18]; see [19] for review), and neurostimulation [20–24]. Although there is an established role of the superior colliculus, a midbrain structure implicated in attention and oculomotor control ([25–27], evidence has accumulated that suggests frontoparietal regions also have a role in producing inhibitory effects in both attention and oculomotor control (implicated in manual and saccadic IOR, respectively). This frontoparietal network includes the frontal eye fields (FEF) as well as structures within the posterior parietal cortex (PPC), particularly the temporoparietal junction (TPJ) and intraparietal sulcus (IPS), which connect to ventral and dorsal visual pathways respectively (e.g., [20]).

Evidence for a role of PPC regions in manual IOR is consistent with the proposal that visual salience or priority maps of the environment are coded in intraparietal cortex [24,28,29]. These parietal maps may subsequently influence facilitatory or inhibitory activity in oculomotor control centres [23] and in premotor and primary motor (M1) cortex [8,30]. It has been suggested that IOR effects on manual responses are less robust than effects on saccadic responses, involving a less direct route from IPS via frontoparietal networks to premotor and motor areas, compared to the more direct saccadic route from FEF to oculomotor control regions [8].

A small number of studies have used transcranial magnetic stimulation (TMS) to investigate the neural basis of IOR. TMS is a technique with high temporal and spatial resolution that can be used to transiently disrupt the function of a particular cortical area, such that the resulting effect on behaviour reflects the involvement of the stimulated area in producing the target behaviour [31]. In one study employing a manual cue-target task [23], single-pulse TMS delivered to the right FEF shortly before the appearance of the target stimulus eliminated IOR on the side ipsilateral to stimulation. In comparison, an active control condition in which TMS was delivered to the superior parietal lobule did not alter IOR. Although the task required a key press response while the eyes remained centrally fixated, the involvement of the FEF was suggested to reflect inhibitory effects related to the suppression of a stimulus-driven saccade and the programming of a new saccade towards the contralateral location. In another study using dual-pulse TMS during a manual cue-target task [22], stimulation was applied to the right IPS or right TPJ between cue and target onset, which was compared with a sham stimulation condition. Although RTs showed the expected pattern of facilitatory and inhibitory cueing effects on the ipsilateral (right) side in all conditions, inhibitory cueing effects on RTs for contralateral targets were found in the sham condition but not with active TMS. Additionally, stimulation of right, but not left, parietal cortex has been found to disrupt manual IOR in target-target tasks (in which participants respond to consecutively presented targets; [20,21]) and a spatial remapping task [24]. In sum, the findings of previous research using TMS provide converging evidence that the FEF and PPC contribute to the expression of manual IOR effects.

Given the proposed route of inhibitory activity from PPC to motor areas in the production of manual IOR effects (e.g.,[8]), neurophysiological investigation of the involvement of the motor cortex could further elucidate the neural pathway of IOR. Although neurophysiological studies of motor contributions to manual IOR have not previously been conducted, evidence from behavioural studies points to the involvement of motor representations in manual IOR. For example, further to examining RTs as indices of facilitation and inhibition, Welsh and Elliott [32] (see also [30,33,34]) examined the potential expression of IOR mechanisms in manual aiming trajectories towards a target stimulus. Aiming trajectories were examined because deviations towards or away from cued locations are assumed to reflect the activation or inhibition of competing response codes associated with the cues [35–38]. Welsh and Elliott [32] (see also [34]) demonstrated facilitatory and inhibitory effects on reach trajectories in the form of (i) a bias in movement trajectories toward the cued location at 100 ms SOA, where no facilitation was found in RTs, and (ii) a bias in movement trajectories away from the cued location at 850 ms, which was later than IOR was observed in RTs. These findings suggest that further inhibitory processes may operate downstream of the perceptual-attentional mechanisms involved in initiating the response, such as by influencing the activation of the reach trajectory in M1 and/or premotor regions [8,30].

The two experiments reported in the present paper were designed to investigate the role of the motor system in manual IOR, by testing the effects of administering TMS to M1 during a cue-target task with a key-press localization (left vs. right) response. TMS was applied to right M1 only, because the left hemisphere may be involved in coding movements of both right and left limbs (e.g., [39]) which could result in an over-generalised effect of stimulation to left M1. Based on the evidence from aiming trajectories indicating facilitatory and inhibitory effects on motor programming [32,34], it was predicted that stimulation of M1 would disrupt IOR in manual RTs on the side contralateral to stimulation. However, if facilitatory and inhibitory cueing effects result solely from spatial mapping mechanisms in neural regions that have reciprocal connections with M1 (e.g., areas of PPC) and are not further influenced by activity in M1, then TMS would not be expected to alter the pattern of facilitatory and inhibitory cueing effects.

To further explore whether mechanisms of IOR are represented in M1, motor-evoked potentials (MEPs) generated by TMS of M1 were also examined in a left index finger muscle. If the facilitatory and inhibitory mechanisms that influence RTs to cued and uncued targets are represented in M1 activity, then the amplitude of MEPs recorded from the hand contralateral to stimulation should be larger following left cues than right cues at shorter (facilitatory) SOAs, and smaller following left cues than right cues at longer (inhibitory) SOAs. If facilitatory and inhibitory mechanisms are not reflected in M1 activity, then no differences in MEP amplitudes should be observed.

## 2. Experiment 1

### 2.1. Methods

#### *2.1.1. Participants*

Based on sample sizes in previous studies using TMS to investigate cortical contributions to IOR effects and other studies exploring corticospinal excitation [22,23,40,41], 15 healthy volunteers were recruited from the University of Toronto community. Technical issues led to incomplete data collection from one participant, resulting in a sample size of 14 (8 females). Participants had a mean age of 23.9 ± 3.4 years, were right-hand dominant according to a screening questionnaire (based on [42]) and had normal or corrected-to-normal vision. Prior to inclusion in the study, participants completed a medical history screening questionnaire to

ensure that the use of TMS was not contraindicated [43,44]. All procedures were approved by the University of Toronto Ethics Review Office and participants provided written informed consent.

### *2.1.2. TMS*

TMS was administered using a single-pulse monophasic stimulator (MagStim 200; The MagStim Company, Whitland, UK) with a 70 mm figure-of-eight coil. An image-guided neuronavigation TMS system (Brainsight 2; Rogue Research, Montreal, Canada) was used during the mapping of the target location for stimulation of the left first dorsal interosseous (FDI) muscle. This system enabled accurate re-positioning of the TMS coil between trials, following registration of anatomical landmarks from each participant to a template MRI scan. The Brainsight 2 software was also used to record EMG data at 3000 Hz via surface electrodes attached to the FDI muscle of the left index finger.

Prior to the experiment, a mapping procedure was completed for each participant to determine the optimal scalp location and coil position to maximally stimulate the neurons representing the target left FDI muscle. First, an approximate location of the representation of the left hand in right M1 was determined by marking a point on the scalp that was 6 cm lateral (on the right side of the scalp) and 2 cm anterior from the intersection of the nasion-inion line and the interaural line. Using this location as a starting point, the optimal location was then identified via an iterative process in which the TMS coil was moved around the scalp in 1 cm steps in concentric circles while pulses were administered until a repeatable MEP was elicited in the left FDI. The coil was placed tangentially to the scalp and angled with the handle oriented posteriorly at an angle of approximately 45° to the interaural line. Stimulation began at 30 % intensity; if no MEP was observed after 1 mapping sequence, the output was increased in 5 % increments and the mapping cycle was repeated.

Once the target area was established, this location was recorded in the Brainsight 2 software to provide a reference point for consistent coil positioning and orientation during the experiment. The stimulation intensity was then adjusted up and down in small increments until the resting motor threshold (rMT) was identified, defined as the minimum stimulus intensity to evoke 5 out of 10 MEPs of at least 50 µV peak-to-peak amplitude from the left FDI [45]. The test stimulation intensity was then set at 130 % of the individual's rMT for the data collection phase.

### *2.1.3. Cue-target task*

Participants were seated in an armchair with an adjustable brace that supported the upper neck and base of the skull. Stimuli were presented on a monitor (Dell REV A00) at a distance of approximately 70 cm, with a keyboard positioned on the table within comfortable reaching distance. During the experiment, participants were asked to rest their left and right index fingers over the left and right "shift" keys, and to return their fingers to these "home" positions after each response in preparation for the next trial.

Each trial began with the word "READY" appearing in the centre of the screen, prompting participants to place their fingers in the "home" positions and to relax their muscles in both arms. This preparation period also allowed the experimenter to position the TMS coil over the identified scalp location using Brainsight. A second experimenter then initiated the trial via a mouse click, which replaced the word "READY" with a blank screen for 1000 ms, followed by a grey central fixation cross and two open grey boxes (2.5 cm x 2.5 cm) at 10.5 cm to the right and left of the fixation cross (8.5 degrees of visual angle), which is similar to previous studies of IOR (e.g., [46–48]). After 1500 ms, one of these two peripheral target locations was cued for 50 ms by an increase in the thickness of the border of the grey square.

Following the cue, at a stimulus onset asynchrony (SOA) of 100, 300, 600, or 1000 ms, a target was presented in the form of a white square that filled one of the grey target boxes. Participants were asked to respond as quickly and accurately as possible, by lifting their index finger from the "home" key, then abducting it to press the adjacent key ("Z" for left targets or "?" for right targets). Participants were also instructed to ignore the cue, which they were told was irrelevant and non-predictive, and to maintain fixation on the central cross. A custom E-Prime program (Psychology Software Tools, Pittsburgh, PA) was used to control experimental stimuli and record responses and RTs.

On 50 % of trials, a single TMS pulse was administered over the target area of M1 50 ms prior to the onset of the target (i.e., 50, 250, 550, or 950 ms after the cue for trials with SOAs of 100, 300, 600, or 1000 ms, respectively). The other 50 % of trials were performed without TMS. Throughout testing, EMG data from the left FDI was recorded for 200 ms, from 50 ms prior to TMS onset to 150 ms after TMS onset. Participants completed a practice/familiarisation block (including both TMS and non-TMS trials) followed by a further 10 test blocks, each consisting of 32 trials, with rest breaks provided between blocks. Within each block, trials were randomized for Cue location (left/right), Target location (left/right), SOA (100 ms/300 ms/600 ms/1000 ms) and TMS condition (TMS/non-TMS). At the beginning and end of each block, two additional TMS pulses at the test stimulation level (130 % of the individual's rMT) were administered to provide resting "baseline" measurements of MEP amplitude (corticospinal excitability) for use in normalization calculations.

### *2.1.4. Data processing and analysis*

Behavioural responses were extracted from E-Prime and RTs exceeding 2 standard deviations from the participant's mean for each cue/target/SOA combination were identified as outliers and removed. RTs were also removed from trials in which the incorrect key was pressed or the RT was shorter than 100 ms (indicating an anticipatory error). These criteria resulted in the removal of 3 % of non-TMS trials (range 1–11 % per participant) and 3 % of TMS trials (range 1-8 % per participant). The mean number of remaining trials per participant per condition (cue location x target location x SOA x TMS condition) was 9.31 out of 10 (SD = .90); see Supplementary Data for a breakdown of the number of trials per condition for each participant.

Raw EMG data from TMS trials were extracted from Brainsight 2 and MEP amplitude was calculated for each trial as the absolute µV difference between the highest and lowest voltages recorded after the TMS pulse. MEP outliers were identified in two steps. First, background EMG amplitude was calculated as the mean absolute value for the 50 ms window prior to the TMS pulse. Any trials in which the pre-stimulus average EMG exceeded 3 standard deviations of the total mean (across all trials) for that participant were excluded [45]. Second, for each participant, the mean peak-to-peak MEP amplitude was calculated for each trial on which TMS was delivered (as the difference between the largest positive and negative values during the MEP). Peak-to-peak amplitudes exceeding 3 standard deviations of the participant's mean MEP for a specific cue/target/SOA condition were excluded. These criteria resulted in the removal of a total of 4 % of trials (range 3 - 12 % per participant).

Following outlier removal, normalization was performed by dividing raw MEP amplitude for each trial by the mean peak-to-peak amplitude from the two pre-block and two post-block baseline MEPs. This normalization procedure was conducted to accommodate any within- and between-block changes in corticospinal excitability and any slight changes in the placement and orientation of the coil.

RT data were analysed in a 4-way repeated-measures ANOVA with the factors Cue (left, right), Target (left, right), SOA (100 ms, 300 ms, 600 ms, 1000 ms), and Condition (TMS, non-TMS). Where sphericity was

violated, the Greenhouse-Geisser correction was applied (indicated by degrees of freedom reported with decimals). To test specific *a priori* predictions and examine cueing effects more closely, two sets of planned comparisons were conducted using paired t-tests. First, for each stimulation condition (i.e., separately for TMS and non-TMS trials), RTs were compared for left vs. right cues on each target side at the four different SOAs. Second, to directly examine the effects of TMS, "cueing effects" for each target side were calculated as the difference in RTs for left vs. right cues, which were then compared between stimulation conditions (TMS vs. non-TMS) at each SOA on each target side. Normalized MEPs from the TMS trials were analysed in a 2-way repeated measures ANOVA with the factors Cue and SOA. Analyses were conducted in R [49] using the packages "afex" and "emmeans". Finally, to evaluate the evidence for null effects in the MEP data, Bayesian analysis was conducted using JASP (version 0.16; JASP Team, 2021). Bayes Factor statistics are reported alongside the ANOVA results, where BF01 values above 1 indicate evidence in favour of the null hypothesis over the alternative hypothesis with BF01 values above 3 indicating strong evidence in favour of the null hypothesis [50]. For interaction terms, the Bayes exclusion factor across matched models (BFexcl) is reported, which can be interpreted similarly to BF01 [51].

Plots showing individual participants' mean RTs and MEPs are provided in the Supplementary Figures.

## 2.2. Results

### *2.2.1. Response times*

The 4-way ANOVA showed a significant main effect of SOA ($F(1.87, 24.27) = 42.52$; $p < .001$; $\eta^2_G = .066$), reflecting a general decrease in RTs with increasing SOAs. The following interactions were also significant: Condition x Target ($F(1, 13) = 31.45$; $p < .001$; $\eta^2_G = .012$), Condition x Cue x Target ($F(1, 13) = 7.37$; $p = .018$; $\eta^2_G = .003$), Condition x Target x SOA ($F(1.85, 23.99) = 5.56$; $p = .012$; $\eta^2_G = .0026$), and Cue x Target x SOA ($F(2.26, 29.2) = 13.98$; $p < .001$; $\eta^2_G = .013$). Finally, there was a significant Condition x Cue x Target x SOA interaction ($F(2.66, 34.63) = 8.54$; $p < .001$; $\eta^2_G = .0038$). To provide insight into this 4-way interaction, t-tests were conducted to examine cueing effects on each target side at each SOA in the TMS and non-TMS trials separately (see Figure 1), as well as differences in cueing effects between stimulation conditions.

*2.2.1.1. Non-TMS trials:* Cueing effects were examined for each target side (left, right) using paired t-tests to compare mean RTs following left and right cues at each SOA. For both left side (Figure 1A) and right side targets (Figure 1B), the only significant cueing effects occurred at 600 ms. RTs to left targets at 600 ms were longer in cued trials (left cue; M = 437.07 ms, SD = 59.86 ms) than uncued trials (right cue; M = 413.96 ms, SD = 60.85 ms, $t(13) = 4.20$; $p = .001$; $d = .39$). RTs to right targets at 600 ms were also longer in cued trials (right cue; M = 439.41 ms, SD = 56.33 ms) than uncued trials (left cue; M = 418.92 ms, SD = 61.91 ms, $t(13) = -3.11$; $p = .0082$; $d = .34$). All other comparisons were non- significant ($t < 1.8$; $p > .1$).

*2.2.1.2. TMS trials:* For targets on the left side (Figure 1C), there was a significant facilitatory effect at 100 ms, whereby RTs were shorter on cued trials (left cue; M = 443.77, SD = 57.07) than uncued trials (right cue; M = 472.26 ms, SD = 65.53 ms, $t(13) = -6.37$; $p < .001$; $d = .58$). This early facilitatory effect at 100 ms was also found for right side targets (Figure 1D), with shorter RTs in cued trials (right cue; M = 423.26 ms, SD = 62.21 ms) than uncued trials (left cue; M = 458.06 ms, SD = 66.97 ms, $t(13) = 5.12$; $p < .001$; $d = .40$). Additionally, for targets on the right side a significant inhibitory effect was present at 1000 ms, whereby RTs were longer on cued trials (right cue; M = 411.62 ms, SD = 71.44 ms) than on uncued trials (left cue; 385.49 ms, SD = 65.18 ms, $t(13) = -3.22$; $p = .0068$; $d = .54$). All other comparisons were non-significant ($t < 2.1$; $p > 0.05$).

*2.2.1.3. Comparing TMS vs. non-TMS trials*

For targets on the left side, significant differences in cueing effects (left cue RT – right cue RT) between TMS and non-TMS trials were found at 100 ms (TMS M = -33.14 ms, SD = 19.46 ms; non-TMS M = -7.44 ms, SD = 29.39 ms; $t(13) = 2.50$; $p = .013$; $d = 1.03$), 300 ms (TMS M = -11.84 ms, SD = 28.74 ms; non-TMS M = 12.09 ms, SD = 26.44 ms; $t(13) = 2.88$; $p = .013$; $d = .87$), and 600 ms (TMS M = -.66 ms, SD = 24.22 ms; non-TMS M = 23.83 ms, SD = 21.23 ms; $t(13) = 2.56$; $p = .024$; $d = 1.08$). For targets on the right side, a significant difference in cueing effects (right cue RT – left cue RT) between TMS and non-TMS trials was only found at 100 ms (TMS M = -34.43 ms, SD = 25.17 ms; non-TMS M = 4.64 ms, SD = 44.91 ms; $t(13) = 3.48$; $p = .004$; $d = 1.07$). All other comparisons were non-significant ($t < 1.8$; $p > .1$).

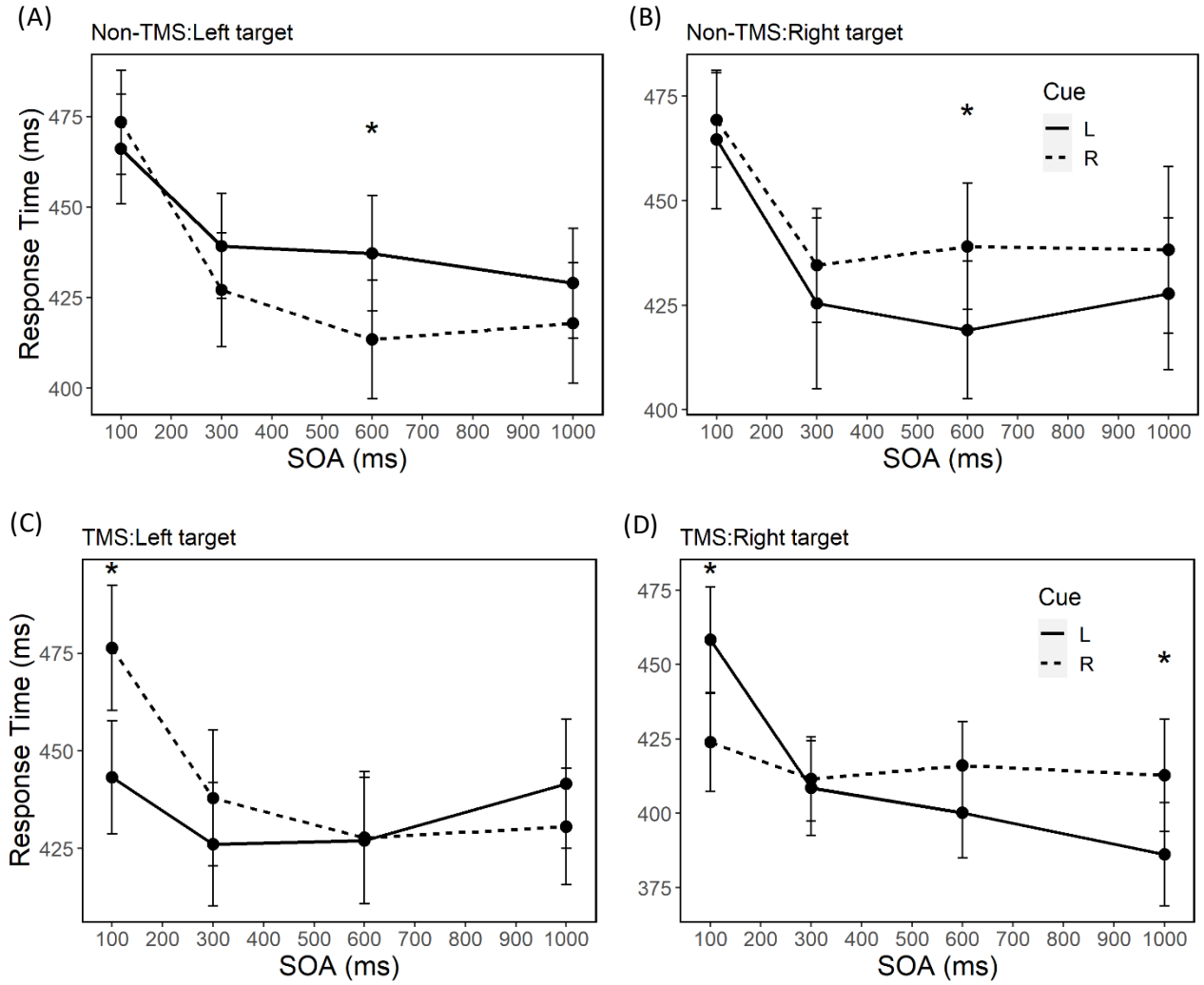


*Figure 1. Mean response times (RT) in Experiment 1 for non-TMS trials (panels A and B) and TMS trials (panels C and D) at each stimulus onset asynchrony (SOA) for cued and uncued targets on left and right sides (*p < .05). Note that for left side targets, cued trials were those in which the cue appeared on the left side prior to the target, while for right side targets, cued trials were those in which the cue appeared on the right. In TMS trials, stimulation was applied to the right hemisphere, corresponding to responses to targets on the left side. Error bars represent SEM.*

*2.2.2. Motor-evoked potentials*

Results of the MEP analysis are illustrated in Figure 2. There were no statistically significant effects of Cue ($F(1,12) = .10$; $p = .75$; $\eta^2_G < .001$; $BF01 = 4.55$) or SOA ($F(1.65,19.79) = 1.00$; $p = .37$; $\eta^2_G = .01$; $BF01 = 5.10$), and no significant interaction between Cue and SOA ($F(3,36) = .35$; $p = .79$; $\eta^2_G = .002$; $BFexcl = 7.85$).

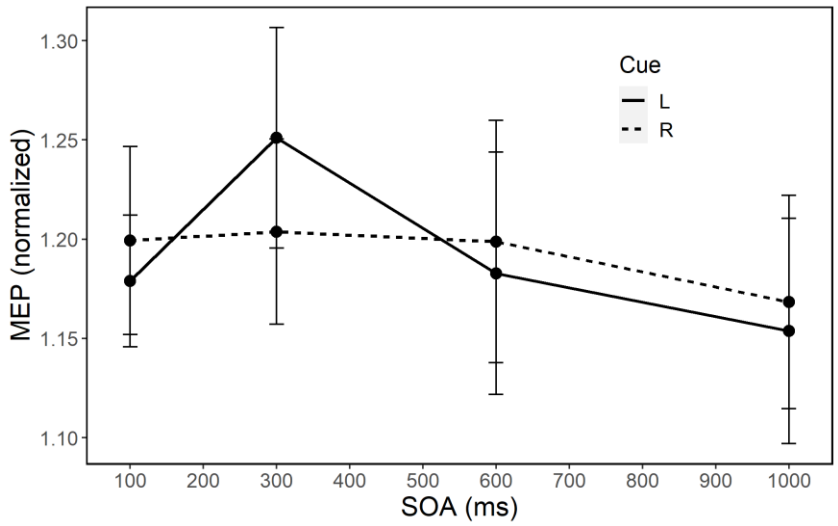


*Figure 2. Mean normalized motor evoked potentials (MEPs) recorded from the left FDI muscle during TMS trials in Experiment 1 at each stimulus onset asynchrony (SOA) for cues on the left and right sides. Error bars represent SEM.*

2.3. Discussion

In trials without TMS, longer RTs to cued than uncued targets at the 600 ms SOA on both sides indicated the presence of IOR [9,52]. In TMS trials, the pattern of effects for each target side was less straightforward. First, facilitatory effects occurred at the shortest SOA (100 ms) for targets on both sides, which were not found in non-TMS trials. Second, although IOR was present in responses to targets on the right side of space (ipsilateral to the side of stimulation), this inhibitory effect appeared at the later SOA of 1000 ms, compared to 600 ms in non-TMS trials. Finally, IOR was not observed for targets on the left side in TMS trials at any SOA. Direct comparison of cueing effects under TMS and non-TMS conditions further indicated a reduction in IOR effects when TMS was applied, particularly on the left side (contralateral to stimulation).

This pattern of effects may reflect some involvement of M1 in the expression of IOR in manual tasks, as suggested by Welsh et al. [30]. Alternatively, because TMS trials were randomly interspersed with non-TMS trials, the results may represent an over-generalised effect of TMS, potentially attributable to neural noise in the motor system induced by stimulation (e.g., [46]) leading to an overall increase in activation [arousal?]. Another possibility is that the differences in the cueing effects between the TMS and non-TMS conditions

reflect differences in the sensory experience between the trials, such as an alerting effect caused by the sound and/or cutaneous stimulation generated by the TMS pulse.

Despite the disruption to RTs, there were no statistically significant changes in MEPs corresponding to cueing effects. The absence of MEP modulation is not consistent with the prediction that facilitatory and inhibitory mechanisms activated by the cue might be represented in M1. Thus, the finding that cueing effects were not reflected in MEPs suggests that the mechanisms leading to IOR do not influence corticospinal excitability, and therefore may not alter motor programming in M1.

To further explore the potential involvement of M1 in the expression of IOR in manual responses, a second experiment was conducted using the same cueing task. In Experiment 2, blocks of active TMS trials were compared to a sham stimulation condition designed to control for incidental effects associated with the experience of receiving TMS. Sham conditions are widely used in TMS studies as a means of controlling for the characteristics of the active stimulation condition, such as the auditory and tactile experience and psychological factors such as expectation [54], but without providing any neural stimulation. Therefore, by presenting active TMS and sham conditions in separate blocks, it was expected that this design would more clearly reveal the effects of stimulation to M1 while controlling for aspects of the sensory experience.

## 3. Experiment 2

### 3.1. Methods

#### *3.1.1. Participants*

A new sample of 16 participants was recruited from the University of Toronto. Three participants were excluded because of technical issues, resulting in a sample size of 13 (9 females) in the final analysis. Participants had a mean age of 22.5 ± 3.9 years, were right-hand dominant and had normal or corrected-to-normal vision. All procedures were approved by the Research Ethics Board at the University of Toronto and participants provided written informed consent.

#### *3.1.2. Design and procedure*

The cue-target task was the same as in Experiment 1 (as described above). The main difference between experiments was that instead of TMS and non-TMS trials being interspersed randomly within each block, active TMS of M1 and sham stimulation were performed in separate blocks (5 blocks of 32 trials per condition). The order of the two conditions (TMS blocks first or sham blocks first) was counterbalanced between participants. The same TMS calibration and administration procedure was performed as described in Experiment 1 for the TMS blocks, with EMG recordings measured from the left FDI muscle. In the sham condition, the coil was positioned in the same location as in the TMS trials but was rotated by 90 °, such that one edge of the coil was in contact with the participant's scalp, but the generated magnetic field was oriented perpendicular to the scalp. Hence, participants received a similar auditory experience to the TMS condition and a tactile experience from the scalp contact, but no magnetic stimulation was applied directly to the scalp and underlying neurons.

#### *3.1.3. Data processing and analysis*

Technical issues in data collection resulted in the loss of data from one sham block from two participants and one TMS block for one participant. For the remaining trials, processing of RT outliers and identification of

anticipatory responses resulted in the removal of 6.1 % of trials in the TMS condition (1.3 – 20.6 % per participant) and 4.2 % trials in the Sham condition (.6 to 10.6 % per participant). The mean number of remaining trials per participant per condition (cue location x target location x SOA x TMS condition) was 9.27 out of 10 (SD = .99). Outliers based on pre-activation EMG data and peak-to-peak MEPs were removed in the same way as for Experiment 1, resulting in the elimination of .9 % trials in total (0 - 3.8 % per participant). See Supplementary Data and Figures for a breakdown of individual participants' trials and data.

Initial statistical analysis found no significant influence of the between-subjects factor of condition order (TMS first vs. Sham first) on the key results of interest for RT or MEPs; i.e., there was no interaction between Order, Cue, Target, and SOA. Order was therefore not included in the subsequent analyses, which were otherwise the same as described in Experiment 1.

## 3.2. Results

### *3.2.1. Response times*

The 4-way ANOVA showed significant main effects of Condition ($F(1, 12) = 19.08$; $p < .001$; $\eta^2_G = .32$), Target ($F(1, 12) = 6.26$; $p = .028$; $\eta^2_G = .025$), and SOA ($F(2.34, 28.03) = 24.81$; $p < .001$; $\eta^2_G = .088$). RTs were generally longer in the TMS condition (M = 398.68 ms, SD = 69.83 ms) than the sham condition (M = 333.63 ms, SD = 40.36 ms) and for targets appearing on the left side (M = 373.67 ms, SD = 59.15 ms) than the right side (M = 358.64, SD = 51.04 ms), as well as generally decreasing with longer SOAs. The following interactions were also significant: Condition x Target ($F(1, 12) = 11.74$; $p = .005$; $\eta^2_G = .017$), Condition x SOA ($F(1.58, 19.01) = 12.68$; $p < .001$; $\eta^2_G = .022$), Target x SOA ($F(2.32, 27.79) = 10.68$; $p < .001$; $\eta^2_G = .0095$), Condition x Target x SOA ($F(2.62, 31.43) = 3.39$; $p = .035$; $\eta^2_G = .0036$), Target x Cue x SOA ($F(1.91, 22.92) = 13.0$; $p < .001$; $\eta^2_G = .029$). Although the 4-way interaction between Condition, Target, Cue, and SOA was not statistically significant ($F(1.88, 22.52) = .28$; $p = .74$; $\eta^2_G < .001$), post hoc analyses consistent with Experiment 1 were conducted.

*3.2.1.1. Sham trials:* Paired t-tests assessing cueing effects at each SOA in the Sham condition revealed a significant inhibitory effect for targets on the left side (Figure 3A) at 300 ms, with longer RTs in cued trials (left cue M = 328.18 ms, SD = 28.30 ms) than uncued trials (right cue; M = 320.50 ms, SD = 34.84 ms; $t(12) = 2.26$; $p = .043$; $d = .48$). Significant inhibitory effects were also found at 600 ms (left cue M = 345.77 ms, SD = 24.39 ms; right cue M = 307.08 ms, SD = 29.47 ms; $t(12) = 9.27$; $p < .001$; $d = 1.61$) and 1000 ms (left cue M = 334.61 ms, SD = 41.44 ms; right cue M = 303.3 ms, SD = 28.77 ms; $t(12) = 3.44$; $p = .0049$; $d = 1.01$). Inhibitory effects of the cue were also observed for targets on the right side (Figure 3B) at 600 ms, with longer RTs in cued trials (right cue; M = 330.73 ms, SD = 26.91 ms) than uncued trials (left cue; M = 309.49 ms, SD = 37.77 ms; $t(12) = 4.02$; $p = .0017$; $d = .78$), as well as at 1000 ms (right cue M = 315.38 ms, SD = 30.78 ms; left cue M = 309.13 ms, SD = 45.37 ms; $t(12) = -2.45$; $p = .03$; $d = .48$). All other comparisons were non-significant ($t < 1.4$; $p > .1$).

*3.2.1.2. TMS trials:* In the TMS condition, a significant inhibitory effect was found for the left target (Figure 3C) only at 600 ms, where RTs were longer in cued trials (left cue, M = 425.38 ms, SD = 71.02 ms) than uncued trials (right cue, M = 403.37 ms, SD = 104.56 ms; $t(12) = 3.95$; $p = .0019$; $d = .45$). For right side targets (Figure 3D), significant inhibitory effects were again found at 600 ms ($t(12) = -2.20$; $p = .048$; $d = .25$), with longer RTs in cued trials (right cue; M = 382.87 ms, SD = 55.56 ms) than uncued trials (left cue; M = 366.68 ms, SD = 57.08 ms), and at 1000 ms (right cue M = 381.71 ms, SD = 51.24 ms; left cue M = 360.07 ms, SD = 69.88 ms; $t(12) = -2.28$; $p = .042$; $d = .32$). All other comparisons were non-significant ($t < 2.0$; $p > .05$).

*3.2.1.3. Comparing TMS vs. Sham trials*

There were no significant differences between stimulation conditions on either target side. Nonetheless, consistent with the pattern of RTs reported above, a non-significant trend indicated a reduction in the inhibitory cueing effect on the left side at 1000 ms in the TMS condition (M = 5.56 ms, SD = 33.20 ms) compared to the Sham condition (M = 26.01 ms, SD = 27.24 ms; t(12) = 1.87; p = .087; d = 67).

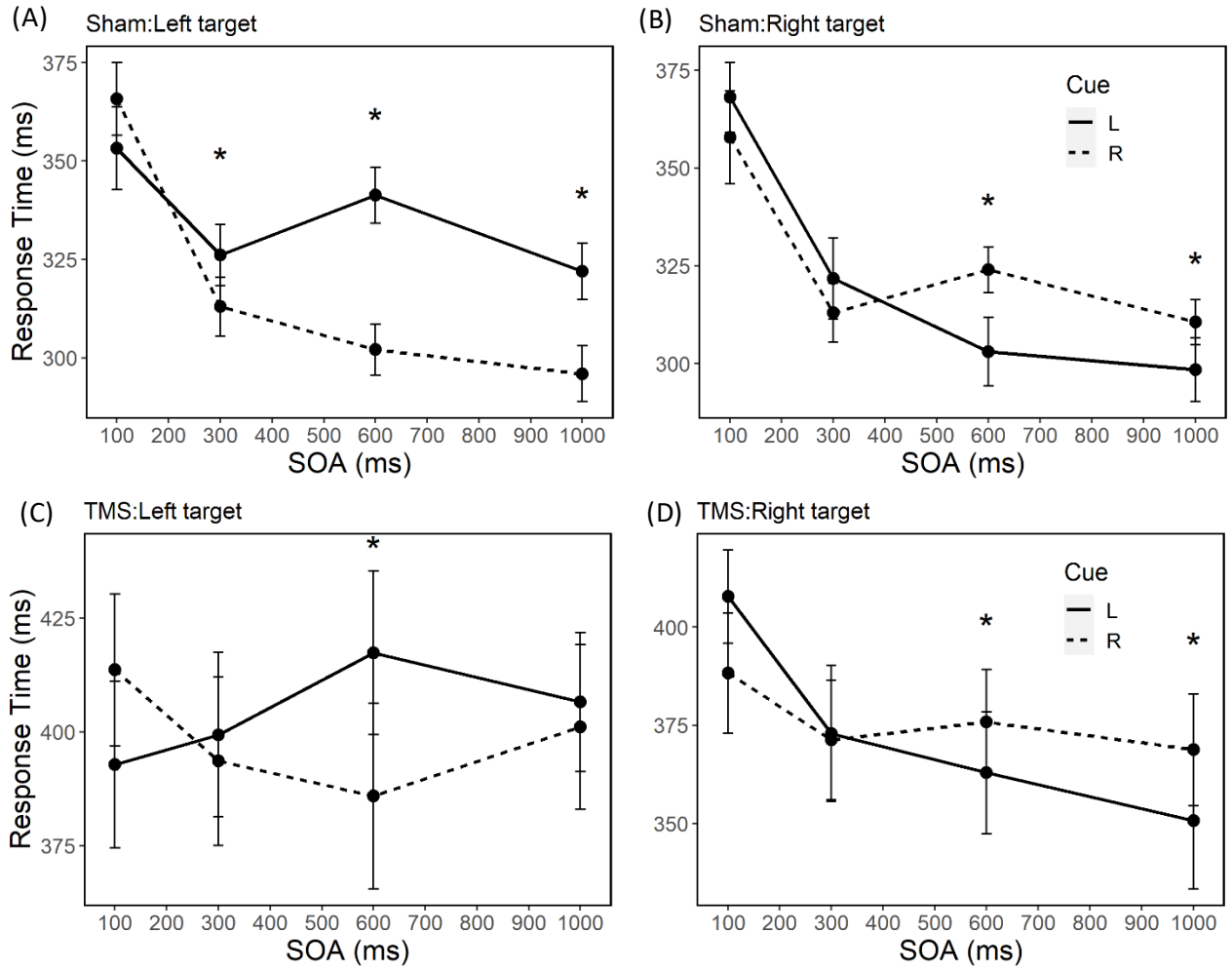


*Figure 3. Mean response times (RT) in Experiment 2 for Sham trials (panels A and B) and TMS trials (panels C and D) at each stimulus onset asynchrony (SOA) for cued and uncued targets on left and right sides (*p < .05). Note that for left side targets, cued trials were those in which the cue appeared on the left side prior to the target, while for right side targets, cued trials were those in which the cue appeared on the right. In TMS trials, stimulation was applied to the right hemisphere, corresponding to responses to targets on the left side. Error bars represent SEM. Note that the values on the y-axes are different between plots, reflecting longer overall RTs in the TMS condition.*

*3.2.2. Motor-evoked potentials*

As illustrated in Figure 4, the MEP results were consistent with Experiment 1. There were no significant effects of Cue ($F(1,12) = .65$; $p = .44$; $\eta^2_G < .001$; $BF01 = 4.17$) or SOA ($F(3,36) = 1.28$; $p = .30$; $\eta^2_G = .009$; $BF01 = 2.82$) on normalized MEPs during TMS trials. The interaction between Cue and SOA was also non-significant ($F(3,36) = .43$; $p = .73$; $\eta^2_G < .002$ $BFexcl = 6.59$).

Finally, an additional analysis was conducted in which the MEP data from the two experiments were combined in a mixed ANOVA with the repeated-measures factors of Cue and SOA, and the between-subjects factor of Experiment. The results of this combined analysis of MEPs across Experiments 1 and 2 showed no significant effects of Cue, SOA, or Experiment (all $F < 2.0$; $p > .2$; $BF01 > 1.3$)[1].

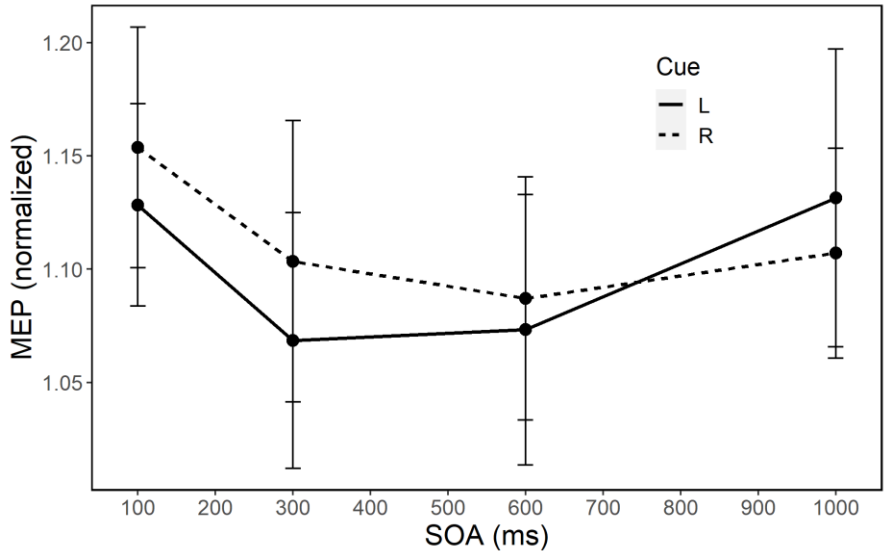


*Figure 4. Mean normalized motor evoked potentials (MEPs) recorded from the left FDI muscle during TMS trials in Experiment 2 at each stimulus onset asynchrony (SOA) for cues on the left and right sides. Error bars represent SEM.*

## 3.3. Discussion

Similar to the non-TMS trials of Experiment 1, the expected pattern of inhibitory effects was observed in the sham stimulation condition, although IOR occurred over a longer timeframe for targets on the left side than in Experiment 1, with evidence of inhibition emerging at 300 ms and persisting to 1000 ms. In the TMS condition, inhibitory effects appeared to be reduced on the left side (contralateral to stimulation), but not on the right side (ipsilateral to stimulation). Unlike in Experiment 1, the direct comparison of TMS and Sham conditions did not reveal significant differences in cueing effects, but only a non-significant trend indicating

[1]The absence of meaningful cueing effects on MEPs was further confirmed by equivalence testing using the two one-sided tests (TOST) procedure, which indicated that effects at all SOAs were significantly within the equivalence bounds for a large effect size (dz -.57 to .57).

some reduction of IOR at 1000 ms on the side contralateral to stimulation. Additionally, there was no evidence of increased facilitation at the 100 ms SOA in the TMS condition. Finally, cueing effects were not evident in MEPs, further indicating that IOR is not reflected in corticospinal excitability.

## 4. General Discussion

The role of M1 in manual IOR was explored in two experiments by examining the effects of TMS during a cue-target task. The application of single-pulse TMS to right M1 was associated with altered patterns of RTs in both experiments. In conditions without TMS (non-TMS trials in Experiment 1 and sham trials in Experiment 2), IOR was evident at longer SOAs, with increased RTs when targets were presented at the same location as a non-predictive cue than when presented at the uncued location, consistent with previous findings (e.g., [9,52]). The effects of cueing on RTs were altered when TMS was administered over M1, although the pattern of effects differed somewhat between experiments, possibly reflecting artefactual effects caused by randomising TMS and non-TMS trials in Experiment 1. The magnitude of the MEPs generated by stimulation of M1 did not change according to the location and timing of cues in either experiment, indicating that there was no effect of the cue on corticospinal excitability. The overall pattern of results is not consistent with the proposal that the mechanisms of IOR are represented in M1. That is, the present results provide some evidence that stimulation of M1 can disrupt the expression of IOR, but that the mechanisms responsible for IOR might not be reflected in the activity of M1 or the corticospinal tract more broadly. This overall conclusion is discussed below through further consideration of the RT and MEP data.

In Experiment 1, IOR consistently emerged in RTs at the 600 ms SOA in non-TMS trials. In TMS trials, IOR for targets on the left side (contralateral to stimulation) was absent, whereas for targets on the right (ipsilateral) side the inhibitory effect was observed at the later SOA of 1000 ms. An unexpected finding of Experiment 1 was that facilitatory effects at the shortest SOA (100 ms) were observed for targets on both sides when TMS was administered. This enhanced facilitation effect at short SOAs, as well as the disruption to IOR effects, may have arisen as a by-product of the alerting experience of receiving TMS when stimulation was unpredictable (i.e., when randomly interspersed with non-TMS trials). For example, through processes of multisensory integration [55,56], attention to the auditory or tactile stimulus could heighten visual attention to the cue (which appeared shortly before the TMS pulse) or to the target (which appeared quickly following the TMS pulse), resulting in faster orienting to the target and a delay in subsequent inhibition.

The sham condition in Experiment 2 replicated auditory and tactile aspects of the experience of receiving TMS but without the active stimulation. This sham condition was included to control for incidental sensory/alerting effects arising from the TMS condition that may have been present in Experiment 1, and to assess whether such incidental effects - rather than the direct effects of cortical stimulation - may explain the altered pattern of RTs on TMS trials of Experiment 1. Evidence of IOR was present in sham trials of Experiment 2, although this was found across a greater range of SOAs than in Experiment 1. Moreover, no significant early facilitation effects were found in TMS trials in Experiment 2, suggesting that the facilitatory effects in Experiment 1 may have been due to a heightened alerting caused by the randomised TMS presentation. Additionally, there was a significant overall difference in RTs between conditions in Experiment 2 but not Experiment 1, further indicating that performance in the non-TMS trials of Experiment 1 may have been disrupted by being randomly interspersed with TMS trials.

It should be noted that, although the sham condition in Experiment 2 controlled for aspects of the TMS experience (see also [22]), it did not control for potential broader neuromodulatory effects that may have

resulted from TMS to M1. Future studies could instead compare stimulation of M1 against an "active" control condition, where TMS is applied to an alternative brain region (e.g., [23]).

In sum, across Experiments 1 and 2, RTs in trials without stimulation to M1 demonstrated a relatively consistent pattern, whereby no facilitatory cueing effects occurred at short SOAs and inhibitory cueing effects occurred at later SOAs. TMS appeared to disrupt the expression of cueing effects on the side contralateral to stimulation, but the effect of TMS was attenuated when a sham-controlled, blocked design was used in Experiment 2.

Although there was some evidence that TMS to M1 can affect the expression of IOR in RTs, the absence of any cueing effect on MEPs does not support a *direct* role of M1 in producing IOR in manual responses. Based on the hypothesis that IOR effects might be represented in M1, it was expected that MEPs recorded from the left hand would be increased when the cue was presented on the left side relative to the right at short SOAs (reflecting a facilitation of responses in the corticospinal tract of the right hemisphere/left hand system), and decreased following cues on the left relative to the right at longer SOAs (reflecting inhibition of responses in the corticospinal tract). The data from both experiments (analysed separately as well as combined) are not consistent with these predictions because MEP amplitude did not vary significantly according to cue location or SOA. Although it can be challenging to base conclusions on null effects because of several factors (including lack of statistical power due to low sample size), this is not likely the case here, given that: (1) the combined analysis (with a larger sample size) did not yield any statistically significant effects; and (2) Bayesian analysis provided evidence in favour of the null hypothesis. Thus, it seems that rather than being represented in M1, the mechanisms of IOR may be represented in areas that have reciprocal connections with and receive inputs from M1, such as PPC and premotor cortex (e.g., [8,30]). That is, the findings are consistent with the hypothesis that the mechanisms of IOR are coded in areas of the frontoparietal network that have reciprocal connections with M1, and that the activity of these regions was affected by orthodromic or even antidromic action potential "noise" generated by the stimulation of M1. In this way, M1 may have a role in the expression of IOR rather than a causal role in producing IOR effects.

The potential involvement of the motor system at some level in IOR effects was previously indicated by behavioural findings that demonstrated deviations in the trajectories of aiming movements corresponding to facilitatory and inhibitory cue-target pairings [32,34]. Although these behavioural studies did not implicate specific cortical areas in representing the aiming trajectories, evidence from neural recordings in non-human primates has indicated that multiple reach responses can be simultaneously represented in premotor and parietal regions (e.g., [57]; see [58] for review). Thus, it is possible that the representations leading to the trajectory deviations observed in previous work [32,34] are located in premotor and parietal cortices, rather than M1. It should also be noted that the present experiments involved discrete key press responses instead of the dynamic and more continuous aiming movements in the previous work [34], so it is possible that the different manual actions are differently represented in the motor system. Additionally, the nature of the manual response used in the present study (lifting and moving the finger to another key before pressing) could have resulted in different effects than if a simple downward key-press response was used. This type of response was selected so that the activity of the FDI muscle (which is an abductor and flexor of the index finger) could be more effectively isolated. Although this response may have had an unintended influence on RTs because the abduction component involved motion that was in the opposite direction to the side of space on which the target was presented, it is likely that this influence would have been negligible given that cuing effects were still generally observed.

Taken together, the present findings suggest that instead of disrupting performance at the level of motor response coding in M1, TMS may have interfered with the expression of inhibitory mechanisms originating

in areas with reciprocal connections to M1 that are involved in attention and motor response selection, such as the PPC or premotor cortex [8,30]. This explanation is consistent with previous TMS studies demonstrating evidence of the involvement of PPC in manual IOR [20,22]. Future neurophysiological studies should further elucidate the role of the motor system in the expression of manual IOR, such as by investigating the effects of stimulation to the premotor cortex, examining the effects of TMS at different time intervals in relation to the target, or investigating effects of TMS on RTs and corticospinal excitability for different types of manual response such as simple key presses and aiming movements.

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