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## Research Report

# Distinct modulation of interhemispheric inhibitory mechanisms during movement preparation reveals the influence of cognition on action control

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ABSTRACT

When selecting actions based on visual warning stimuli (WS), corticospinal excitability (CSE) is initially suppressed, consistent with a neural mechanism to prevent premature release of the competing responses. Despite being implicated in between-hand movement selection and preparation, the role that interhemispheric inhibition (IHI) may play in this 'impulse control' mechanism is not known. Participants performed a warned, between-hand, choice reaction time (RT) task in which the informativeness of the WS (with regards to which hand would be required to respond) was manipulated. Transcranial magnetic stimulation (TMS) assessed CSE of the right primary motor cortex (M1) and IHI from left to right M1 with 10 (IHI10) and 40 (IHI40) msec interstimulus intervals during movement selection and preparation.

Consistent with impulse control, CSE was initially suppressed prior to both left and right hand actions, irrespective of WS informativeness. Subsequent CSE increases occurred in the responding hand which were larger, and occurred earlier, following an informative WS. Importantly, these increases strongly predicted response times. In contrast to the generic CSE suppression, an informative WS permitted a hand-specific release of IHI10 in the responding hand, whereas IHI40 was released in both hands. As *releases* of IHI cannot explain a simultaneous *suppression* of CSE, this suggests several distinct movement preparation mechanisms are at play with IHI modulation occurring independently from impulse control. Notably, the findings support the notion that IHI10 and IHI40 between contralateral motor regions are mediated by discrete transcallosal pathways, and are differently modulated by specific motor and cognitive attributes of a rapid choice task.

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## 1. Introduction

Movement represents the sole means by which we interact with our ever-changing world, and humans possess a hugely complex and adaptable motor repertoire that has undoubtedly been a critical factor in shaping human evolution. A particularly fundamental characteristic of the human sensorimotor system is the ability to execute fast and accurate motor actions in response to external stimuli, especially when faced with a choice between two or more alternatives. Furthermore, the ability to actively suppress, or inhibit, undesired actions (i.e., those actions not selected on the basis of task-related stimuli) is critical in permitting accurate motor interactions with our environment. A number of theories posit how different excitatory and inhibitory mechanisms — which act either globally on the entire motor system or specifically on the cortical representation of muscles within the selected or non-selected limb (e.g., the left arm following a decision to reach with the right arm) — may facilitate fast and accurate responses while simultaneously suppressing undesired actions (Duque, Labruna, Cazares, & Ivry, 2014; Greenhouse, Sias, Labruna, & Ivry, 2015; Labruna et al., 2014; Leocani, Cohen, Wassermann, Ikoma, & Hallett, 2000).

The interplay between cognitive processes and action is critical in human behaviour and is well established in response tasks where participants have to interpret cognitive information pertaining to the task to permit rapid and accurate actions. For example, it is well known that the provision of a warning signal prior to an imperative signal (to which a volitional response is required) has the capacity to shorten reaction times (RTs) in tasks requiring fast-as-possible responses to external visual stimuli (Fecteau & Munoz, 2007). This observation is true for both simple RT tasks, whereby a response has to be issued with a predetermined responding effector (e.g., right index finger), and choice RT tasks, where a selection has to be made between two potential effectors (e.g., right or left index fingers) dependent on the information provided by the cues (Hackley, 2009). While it is understood that this performance benefit occurs as a result of preparatory motor-related processes, rather than attuning sensory processing of the imperative signal (Fecteau & Munoz, 2006; also see Sinclair & Hammond, 2009), our understanding of the specific neural correlates underpinning this behavioural observation is incomplete. Another phenomenon that is well established is that RTs are significantly shorter when the stimulus and the ensuing response are spatially compatible. Despite this stimulus-response compatibility phenomenon being the subject of a significant body of psychological research for over six decades (Fitts & Seeger, 1953; Fitts & Simon, 1952), the neural correlates which mediate this effect are incompletely understood. While work using lateralised readiness potentials derived from electroencephalography suggests stimulus-response compatibility can be observed at the sensorimotor integration stage of a task (De Jong, Liang, & Lauber, 1994; Stürmer, Ouyang, Zhou, Boldt, & Sommer, 2013; Valle-Inclán et al., 1996), the specific processes driving these changes have not been investigated.

Due to its high temporal resolution, transcranial magnetic stimulation (TMS) provides a unique opportunity to assess task-related changes in specific cortical mechanisms during movement selection and preparation, and assess the manner in which specific cognitive attributes of a task may influence specific motor-related preparatory processes. A consistent finding is that during the preparation of a unilateral movement which requires rapid activation of specific muscle groups (e.g., to flex or abduct the index finger or the thumb) in response to an external stimulus, the homologous muscles in the non-selected (or non-target) effector exhibit transient decreases in corticospinal excitability (CSE) prior to onset of muscle activity in the selected limb (Duque et al., 2005; Leocani et al., 2000). This evidence is consistent with the view that the non-selected effector is inhibited to prevent mirror movements (i.e., unwanted muscle activity and movement) that may occur due to the bilateral organisation of the motor system (Davare, Duque, Vandermeeren, Thonnard, & Olivier, 2007; Swinnen, 2002); this concept is known as 'inhibition for deselection' (Duque & Ivry, 2009). However, it is also the case that CSE of the *selected* hand may decrease prior to an ensuing action. Specifically, when a warning signal is provided prior to the imperative signal to which rapid responses are required, CSE is found to decrease in the movement 'foreperiod', i.e., the interval between the warning and imperative signals (Hasbroucq, Kaneko, Akamatsu, & Possamai, 1997; Touge, Taylor, & Rothwell, 1998). This evidence suggests that more generic (i.e., not specific to the selected or non-selected hand) inhibitory mechanisms may be at play during the movement selection and preparation period. Such a mechanism may be important in preventing premature actions (i.e., ensuring that the chosen action is withheld until the imperative signal rather than being released in response to the warning signal) and can be referred to as 'impulse control' (Duque & Ivry, 2009; Duque, Labruna, Verset, Olivier, & Ivry, 2012).

In an attempt to disentangle the role of these two mechanisms during movement selection and preparation, Duque and Ivry (2009) investigated changes in CSE during a between-hand choice RT task where a warning stimulus (WS), which was either *informative* or *uninformative* regarding the nature of the upcoming movement, preceded the imperative stimulus (IS). Intriguingly, CSE suppression in the left hand was greater when an informative WS indicated that limb was selected to respond, compared to when the WS indicated that limb would not respond. Furthermore, when the WS was uninformative, proactive CSE suppression was observed in both hands with no further CSE suppression (in the non-selected hand) following the IS. The results provided strong evidence in favour of an impulse control mechanism (Duque & Ivry, 2009).

While providing valuable insights into the role that corticospinal suppression plays during the selections and preparation of between-hand action choices requiring interaction between the two hemispheres, the work of Duque and Ivry (2009) has focused on assessing net excitability inferred from single pulse TMS; accordingly, it remains to be determined what specific (inhibitory) neural mechanisms might underpin this suppression. Two conceivable explanations would be increased interhemispheric inhibition (IHI) onto the target cortex during the movement selection and preparation period, or due to increased intracortical inhibition within the primary motor cortex. While it is known that IHI is a key mechanism

when selecting between actions with different effectors, the extent to which task-related changes in IHI may underpin impulse control during a delayed choice RT task remains to be determined.

The current study thus aimed to evaluate the degree to which the informativeness of a warning signal (with regard to which hand would respond), and the spatial compatibility of the stimulus-response relationship, affected the extent of the modulation of CSE and IHI during a delayed choice RT task. We were particularly interested to establish the extent to which interhemispheric inhibitory mechanisms underpin the expected suppression of excitability during movement selection and preparation, or whether modulation of IHI occurs independently to impulse control mechanisms. Moreover, we aimed to determine whether the relationship between these neural processes was affected by specific (cognitive) attributes of the task. While previous work has established the existence of two distinct interhemispheric mechanisms (elucidated using dual coil TMS with different interstimulus intervals, Ni et al., 2009), their role in impulse control has not been investigated. If changes in IHI underpin changes in general suppression (impulse control), greater IHI onto both the responding and non-responding hand early in the movement preparation period would be expected. On the basis of the results of Duque and Ivry (2009) these changes would occur prior to information regarding which hand would respond. Alternatively, if IHI was *released* during movement selection (in one or both limbs) while CSE was simultaneously suppressed, this would suggest that impulse control was not mediated by IHI mechanisms. Moreover, this latter scenario would suggest that multiple inhibitory mechanisms were active during the movement selection period underpinning specific aspects of the behaviour.

## 2. Materials and methods

### 2.1. Participants

Thirty-nine right-handed (Oldfield, 1971) young adults — free from any known neurological deficits, and with normal or corrected-to-normal vision — participated in the study. The majority of the cohort were first year psychology students who received course credit for their participation. Other participants received financial compensation ($20) for their time. Experiment 1 ($n = 18$, 9 females; mean age = 25.3 years, range 18—39) and Experiment 2 ($n = 21$, 12 females; mean age = 24.4 years, range 18—39) were both conducted in accordance with the Declaration of Helsinki and approved by the University of Tasmania Human Research Ethics Committee with written informed consent sought from each participant prior to participation. All participants completed pre-experiment screening questionnaires to confirm the absence of any exclusion criteria for participating in TMS studies (Rossi et al., 2009).

### 2.2. Experimental procedure

The experiments were designed to assess CSE and IHI during a *choice RT task* in which participants made a motor response as quickly as possible following visual stimuli. Each experiment consisted of a single session which lasted no more than 2 ½ hours including set-up. The procedure in both experiments only differed in regard to the nature of the warning signal (WS) that was provided: an uninformative WS preceded the imperative (go) signal in Experiment 1, while in Experiment 2 an informative WS was provided. A horizontal array of three light emitting diodes (LEDs) was mounted on a vertical screen positioned at eye level 80 cm in front of participants. Participants were seated with their forearms pronated and resting on a horizontal surface and had to respond as quickly as possible to visual signals by abducting their left, or right, index finger.

In Experiment 1 (uninformative WS task), the central LED was illuminated orange for 500 msec and acted as an uninformative warning signal (i.e., it provided no information regarding whether the subsequent IS would appear on the left or the right of the display). 500 msec after the onset of the WS, the left or right LED was illuminated green (with equal probability and randomly presented within each block of trials) for 500 msec, and acted as an imperative ('go') stimulus. Participants were required to respond as quickly and as accurately (i.e., with the correct hand) as possible following the IS by rapidly abducting their left or right index finger, and make horizontal movements by 'skimming' their finger across the surface of the low-friction table-top. They were instructed to isolate the movements to the second metacarpo-phalangeal joint of the index finger (Hinder, Fujiyama, & Summers, 2012; Hinder, Schmidt, Garry, Carroll, & Summers, 2011). The finger which they were required to move depended on the spatial location of the IS (to the left or right of the central WS) and the task instruction. Specifically, in the spatially 'congruent' task condition, an IS on the left required a left hand response while an IS on the right required a right hand response. In the spatially 'incongruent' stimulus-response condition a left hand response to an IS presented on the right of the visual field, and vice versa, was required. Congruent and incongruent trials were conducted in separate blocks (see below).

An initial block of 66 trials was undertaken in the absence of TMS in order to establish participants' RTs which determined the timing of TMS in subsequent blocks (see *TMS* section, below). This block was conducted under the instruction of either a congruent or incongruent stimulus-response relationship. 32 trials required left hand responses, 32 required right hand responses and 2 were catch trials in which the central WS was not followed by the IS. In these trials participants had to withhold their response; this ensured participants were truly responding to the IS and not guessing the timing and location of the subsequent IS. The inter-trial interval was 5 sec ± 20%, such that the block took ~5.5 min.

The next part of the experiment required participants to sit with their arms and hands relaxed (eyes open and looking straight forward) while baseline (i.e., not during movement selection and preparation) neurophysiological measures using TMS were collected. The purpose of these 'baseline' blocks was twofold; they ensured that TMS stimulation parameters were able to elicit a motor evoked potential (MEP) and interhemispheric inhibitory interactions, and secondly they permitted a baseline reference to which movement-

related changes in CSE and IHI could be related (see *TMS* section, below, for details on stimulation parameters). This block constituted 30 stimulations and lasted 2.5 min.

Subsequently, five blocks of 66 trials were undertaken (in the same stimulus-response relationship as used in the block without TMS) in which TMS was administered during the choice RT task. As with the non-TMS block, 64 trials required a response (32 left hand responses, 32 right hand responses); of these 60 trials involved TMS elicited at various time points relative to the WS, IS and during the RT period (see *TMS* section, below). Two trials were catch trials (no IS) and four trials were response trials (2 left hand, 2 right hand) in which TMS was not elicited; these allowed us to monitor RTs in the absence of TMS. The inter-trial interval was 5 sec ± 20%. Short rest periods between blocks were permitted to prevent fatigue.

Following a break, the above procedure (choice RT block in absence of TMS, baseline TMS measures, 5 blocks of TMS during choice RT) was repeated with the other stimulus-response compatibility condition. The order (congruent/incongruent) was counterbalanced across participants.

In Experiment 2 (informative WS task), the central WS was replaced by *informative* warning signals; in this instance the left or right LED illuminated orange 500 msec prior to turning green (the central LED used in Experiment 1 was not used in this Experiment). The informative WS was always 'valid' with regard to the upcoming IS (i.e., the participant was never given false information by the informative WS, as per Duque & Ivry, 2009). Instead of 66 trials per block there were 68; this was because there were 2 catch trials following a left WS, and 2 catch trials following right WS. In all other respects, the experiment was identical to Experiment 1.

In both experiments a short (500 msec) warning signal foreperiod was used to promote the preparation of actions as much as possible as research has shown that RT is shortened significantly more with a 500 msec compared to a 2500 msec foreperiod (Davranche et al., 2007; Fujiyama, Tandonnet, & Summers, 2011; Hinder et al., 2012) with a corresponding greater change (suppression) of MEP amplitudes with short compared to long foreperiods (Davranche et al., 2007) Here we envisaged that changes in IHI (as well as CSE) during the selection and preparation period would also be most evident with a short, and constant, foreperiod.

### 2.3. Electromyographic recording

Movement related electromyographic activity (EMG) and MEPs evoked by TMS were recorded in all trials from the left and right first dorsal interosseus (FDI), the muscle primarily responsible for the execution of the index finger abductions. A belly-tendon electrode montage (Ag/AgCl disposable electrodes) was used. Data were stored on a computer for offline analysis using custom written CED Signal (Cambridge, UK) scripts.

### 2.4. Transcranial magnetic stimulation

Single pulse and dual coil TMS (Ferbert et al., 1992) were used to assess CSE and IHI from the left to the right primary motor cortex (M1), respectively, and to determine how these were modulated during movement selection and preparation. Following previous work in our lab (Hinder et al. 2012; Hinder, Schmidt, Garry, & Summers, 2010b) and of others (Duque & Ivry, 2009), we evoked MEPs in the left FDI as there is some evidence to suggest that preparation-related modulation of CSE is stronger in the non-dominant hand (Duque et al., 2007; Leocani et al., 2000). Accordingly, we measured CSE of the projections from the M1 representation of left FDI in the right M1, and IHI from the left to the right M1 (i.e., conditioning pulse always applied to the left M1; test pulse always applied to the right M1).

TMS was delivered to the left ('conditioned') and right ('test') cortices using two Magstim 200 units (Magstim Company, Dyfed, UK) and two 'branding iron' style figure of eight coils (with an outside diameter of ~70 mm for each wing). These coils could be placed on each cortex without compromising either coil's positioning relative to the 'motor hotspot' (see below). One experimenter was responsible for maintaining the specific scalp position of each coil throughout the entire experiment. Optimal coil positions for eliciting MEPs from the left and right FDI (with posterior to anterior current direction, i.e., coils at ~45° to the midline), i.e., motor hotspots, were determined prior to the experimental trials, and marked on the scalp. Resting motor thresholds (RMT), from which the stimulation intensities were derived, were determined as the minimum intensities required to elicit MEPs of peak–peak amplitude > 50 μV following TMS stimulation in the right and left FDI muscles in three out of five consecutive trials when stimulating at the motor hotspot (Garry, Loftus, & Summers, 2005; Hinder et al. 2011; Hinder, Schmidt, Garry, & Summers, 2010a; Rogasch, Dartnall, Cirillo, Nordstrom, & Semmler, 2009).

During the TMS trials conducted at baseline and at each time point during the movement preparation trials, we applied three different types of stimulation. One third of the TMS trials involved a single 'test' stimulus (TS) applied to the right cortex at the motor hotspot for the left FDI muscle at 130% left FDI RMT. These trials enabled the excitability of the corticospinal pathways to the left FDI to be determined. In the other TMS trials in each block a conditioning pulse (CS at 130% RMT; Kroeger et al., 2010) was delivered to the motor hotspot for the right FDI muscle (i.e., left M1) to determine the nature of the interhemispheric interaction from the left onto the right M1 (Ferbert et al., 1992). The interstimulus interval between the CS and the TS was either 10 or 40 msec, which allowed assessment of short- and long-interval IHI, respectively (Chen, 2004; Chen, Yung, & Li, 2003; Ni et al., 2009) which are believed to represent different IHI mechanisms which act via distinct interhemispheric pathways and are purportedly mediated by different underlying processes. While IHI40 is believed to be mediated by postsynaptic GABA$_B$ receptors (Chen et al., 2003; Kukaswadia, Wagle-Shukla, Morgante, Gunraj, & Chen, 2005), the mechanism mediating IHI10 is still unclear. With respect to interhemispheric pathways, IHI10 likely occurs via a direct transcallosal pathway, whereas interactions at 40 msec interstimulus interval (ISI) may be a result of indirect pathways which conceivably involve premotor regions in either hemisphere (Chen, 2004; Chen et al., 2003). Indeed, transcallosal pathways upstream of the primary motor cortex are denser than those connecting primary motor regions (Schambra, Sawaki, & Cohen, 2003; see Carson, 2005 for a

review), and thus represent a feasible route for indirect communication between primary motor cortices.

In the baseline TMS blocks, 10 single pulse, and 10 paired pulse trials at each ISI (total of 30 TMS trials per block) were administered. For each of the five blocks in which TMS was applied during movement preparation and selection (of congruent and incongruent task conditions), we administered 10 single pulse and 10 paired pulse trials at each ISI (to measure CSE and IHI in the left hand) at each of the five time points prior to onset of volitional response when the left hand was the responding or non-responding hand (total of 300 TMS trials). Specifically, TMS was applied at the onset of the warning signal (WS), at the onset of the imperative (IS) signal, and at three further time points established on an individual participant basis, as determined by mean response times in the non-TMS movement block conducted prior to the TMS blocks (see *Movement Task* section, above). Specifically, TMS was applied at a delay (with respect to the IS) equivalent to 25, 50 and 80% (IS25, IS50, IS80) of each individual's response time determined for the congruent and incongruent task separately (Fig. 1). In this manner, we were able to relate changes in CSE and IHI to specific points in each participant's movement execution timeframe (e.g., early and late preparation *vs* execution related activity). A number of previous studies have used this methodology to account for inter-individual differences in RT (e.g., Tandonnet et al., 2011), or when RT differences are expected due to group demographics or task manipulations (Fujiyama et al., 2012; Hinder et al., 2012). Because 6—8 trials in each block were non-TMS trials (see above) this gave rise to a total of 5 blocks of 66—68 trials (330—340 trials) for both the congruent and incongruent tasks.

### 2.5. Data analysis

RT was calculated in the 32 left hand and 32 right hand responses in the block conducted *without* TMS for the congruent and incongruent stimulus-response task conditions separately. In this manner RT estimates were unaffected by TMS, with RT being defined as the interval (in msec) between presentation of the imperative signal and onset of muscle activity in the left or right FDI; onset of EMG was defined as the time at which root mean square (rms) EMG first increased above a threshold level equivalent to four times background EMG determined prior to presentation of the warning signal (Hinder et al., 2012). Thus, RTs reported here are comparable to the 'premotor time' described in some studies (Fujiyama et al., 2012). Trials in which RT was less than 100 msec were not included in statistical analysis or determination of TMS timings, as these responses likely represent instances of premature responses (i.e., responding to the warning signal or pre-empting the imperative signal) (Hinder et al., 2012). Furthermore, trials in which responses were made with the incorrect hand (see below) were not included in RT calculations.

Occurrence of errors was also determined in the blocks without TMS in those of the 64 trials (32 left and 32 right hand responses) where a valid RT was observed (i.e., >100 msec). Errors were classified as trials in which participants exhibited EMG bursts (with burst onset as defined above) with the incorrect hand prior to a burst in the correct hand, or simply an incorrect hand response in the absence of a correct hand response. RT (msec) and errors (proportion of trials with incorrect hand responses) from both experiments were analysed together using analysis of variance (ANOVA) with the within-group factors of congruency (congruent, incongruent) and hand (left and right hand responses) and the between-groups factor of WS type (uninformative, informative). We also determined that participants were able to successfully withhold responses on the majority of catch trials; this ensured that participants did not pre-empt the IS and respond too early, especially when provided with an informative WS. Inferential statistics were not undertaken on this parameter as it does not represent a measure of particular importance for the interpretation of the current task.

For TMS (at baseline and during the movement task), any trial with excessive EMG in a 40 msec time window immediately prior to TMS (Carson et al., 2004) was excluded from analysis. CSE was determined at baseline, and at each time point (WS, IS, IS25, IS50, IS80) during movement selection and preparation. For the purposes of assessing changes in CSE during movement selection and preparation, MEP values at IS, IS25, IS50 and IS80 were normalised to the MEP at WS to yield nMEP values; nMEPs greater than 1 indicate increased CSE relative to that CSE at WS (facilitation), while values less than 1 indicate suppression (reduced CSE relative to excitability at the WS). While differences between CSE at baseline and WS represent generic task-related changes in CSE (e.g., heightened arousal and attention), we were specifically interested in the temporal changes of CSE during the task, and thus normalised CSE to WS rather than normalising CSE during movement to CSE at rest.

IHI between the left and right M1 at each ISI (10 and 40 msec) was determined as the average MEP amplitude (determined as described above) following paired-pulse stimulation (determined for 10 msec and 40 msec paired pulse trials, separately) at baseline and at each time point, relative to the average MEP amplitude in response to single pulse TMS at the corresponding time point (i.e., ratio). IHI ratios for each ISI (referred to as IHI10 and IHI40) less than 1 represent inhibitory interactions (which are expected at rest), while IHI greater than 1 represent a facilitatory interaction. As with CSE, IHI10 and IHI40 ratios during movement preparation were qualitatively compared to values at baseline before values at IS, IS25, IS50 and IS80 were normalised to the comparable IHI ratio determined at WS; these are referred to as nIHI10 and nIHI40 (Hinder et al., 2010b). nIHI values greater than 1 represent facilitatory changes (i.e., release of inhibition) during movement preparation (relative to that inhibition exhibited at WS), while values less than 1 represent inhibitory changes (stronger inhibition) during movement preparation (relative to that IHI exhibited at WS). Normalisation of CSE and IHI precludes the data from being biased by any particular participant with particular high/low values at warning signal onset.

To fully assess the temporal changes in CSE and IHI (at long and short ISI) during movement selection and preparation, we conducted ANOVA on nMEP, nIHI10 and nIHI40, with congruency (congruent, incongruent), hand (responding, non-

A) Experiment 1

Uninformative warning signal

Imperative signal

500ms

500ms

ITI = 5 s (± 20%)

Congruent trials

Incongruent trials

B) Experiment 2

Informative warning signal

Imperative signal

500ms

500ms

ITI = 5s (± 20%)

Congruent trials

Incongruent trials

C) TMS timing

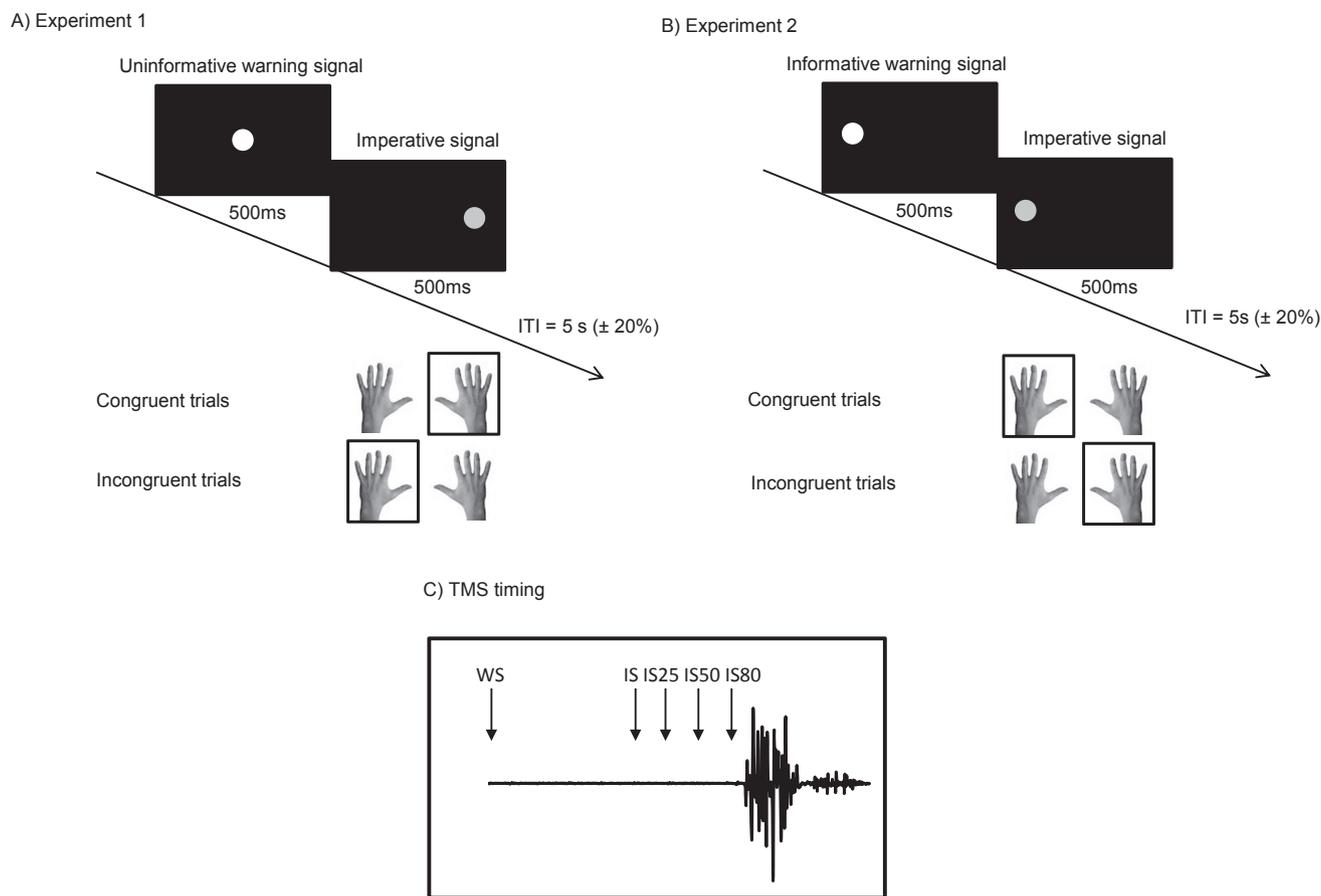WS                    IS IS25 IS50 IS80

Fig. 1 – Schematic of choice reaction time task with an A) uninformative and B) informative warning signal. C) Timing of TMS during movement selection and preparation. In both experiments an orange warning signal (WS, here depicted by a white circle) was provided prior to a green imperative signal (IS; depicted by a grey circle). The participant was instructed to respond as quickly as possible to the IS by abducting the left or right index finger depending on the location of the IS and task instruction (congruent or incongruent spatial stimulus-response relationship; conducted in separate blocks). Panel A) shows an informative WS followed by IS on the right. Panel B) shows an informative WS followed by IS on the left. The response hand for congruent and incongruent trials is shown by a black border. The presentation of left and right IS was randomised within each block and occurred with equal probability. C) Motor evoked potentials following single and dual coil TMS (see *Transcranial Magnetic Stimulation* section) were recorded in the left hand at five time points between the WS and movement onset (represented by the EMG burst in the panel) when the left hand was the responding (selected) or non-responding (non-selected) hand.

responding) and time (IS, IS25, IS50 and IS80) as within-subject's factors for each WS group separately (as per Duque & Ivry, 2009). nIHI10 and nIHI40 were analysed separately as they represent distinct neural mechanisms (Hinder et al., 2012; Ni et al., 2009) rather than the same mechanism assessed with different ISIs.

Subsequently, a direct comparison of CSE and IHI changes between the groups provided with informative or uninformative WS was conducted. In this case, we were specifically interested in comparing CSE and IHI at two specific time points, namely IS and IS50 (c.f., Duque & Ivry, 2009). Changes in excitability and inhibition at IS represent changes (in the responding and/or non-responding hand) that may have occurred as a result of the WS (presented 500 msec prior to the IS). At IS, hand-specific information regarding the upcoming

movement was available following an informative WS, whereas in the case of the uninformative WS, only general preparatory (i.e., timing) information was available. IS50 represents a time 50% of the average RT (calculated for each participant and each congruency condition separately) following the IS. Accordingly, with average RTs of between 184 msec (informative WS) and 254 msec (uninformative WS) IS50 is, on average, 92–127 msec following the IS (see Results for more details); this latency should provide sufficient time for the IS to have been visually processed and hand-specific modifications made to cortical excitability and inhibition in the responding and non-responding hand. Importantly, while being late enough to permit processing of the IS, changes in CSE and inhibitory mechanisms at IS50 are primarily affected by *movement preparation* processes, and not processes related

to movement execution *per se*. In contrast, changes at IS80 — which based on the average RT data would occur on average 36—50 msec (for informative and uninformative WS trials), but conceivably as little as a few msec,[1] prior to EMG onset — would involve contributions from both preparatory and (predominantly) execution-related processes. Because in this analysis we are primarily interested in the effect of WS type on movement *preparation*, we selected the IS50 time point to directly compare between the WS types. Accordingly, we undertook ANOVA with the within-subject factors of congruency (congruent, incongruent), hand (responding, non-responding) and time (IS, IS50) and the between-subject factor WS type (uninformative, informative); the dependent variables were nMEP, nIHI10 and nIHI40.

We predicted that if hand-specific information affects the modulation of CSE and IHI, differences between responding and non-responding hands at IS would be expected following an informative, but not following an uninformative, WS. Furthermore, hand-specific cue information was available by IS50 in both WS conditions, so differences between responding and non-responding hands could be apparent in both informative and uninformative conditions if CSE and IHI are indeed regulated in a hand-specific manner during movement selection and preparation.

Finally, we conducted linear regression analyses to determine relationships between changes in CSE and IHI at specific time points during movement selection and preparation and RT. These analyses were undertaken on a post-hoc basis founded on the interpretation of CSE and IHI findings. Specifically, we were interested in whether hand-specific modification of CSE or IHI (in the responding left hand) made possible by either the informative warning signal or, in the case of the uninformative warning signal, by the subsequent imperative signal, could predict the speed of responses. When a number of potential predictors of RT were identified, these predictors were entered into a multiple linear regression (Hinder et al., 2012; Liuzzi, Horniss, Zimerman, Gerloff, & Hummel, 2011) using a backward stepwise method (with an F probability of .1 used as an exclusion criterion) to minimise the suppressive effects (i.e., when a predictor has a significant effect but only when another variable is invariant) which can otherwise occur and increases the risk of type II errors (Field, 2009). When a single potential predictor was identified, a simple linear regression was undertaken. In both cases, average left hand RTs in the baseline (non-TMS) trials was used as the outcome (behavioural) variable because all predictors were based on CSE of projections from the right (responding) M1 (i.e., excitability of the left hand), or inhibitory processes from the left onto the right (responding) M1 (left

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[1] With mean RT of 184 msec (informative WS)—254 msec (uninformative WS), and the substantial intra-individual variability that is present in many choice RT experiments, it is likely that RT was substantially shorter in some trials. While the criteria for inclusion of trials in statistical analysis was that volitional EMG was not present prior to TMS, it is conceivable that EMG onset may have occurred immediately after the TMS pulse, i.e., TMS was administered very late in the movement execution period (and conceivably *after* release of the motor command from M1). Accordingly, changes in MEP at this time represent execution-related, rather than preparatory, processes.

hand). Furthermore, using the non-TMS trials as our behavioural measure of response speed ensured that that this variable was not affected in any way by TMS pulses used to assess CSE or IHI.

For all ANOVA, if the sphericity assumption was violated ($\varepsilon < .7$), Greenhouse-Geisser degrees of freedom adjustment was applied (Quinn & Keough, 2003). Tukey HSD post-hoc procedures were used to explore significant main effects and interactions. The critical *p*-value was set at .05.

## 3. Results

TMS was well tolerated by all participants with no adverse effects. The choice RT task was well executed by all participants. Results are reported as mean ± 95% confidence intervals (CI) around the mean.

### 3.1. RT

RT in trials in which a correct response was made was significantly faster when the warning signal was informative (184 ± 18 msec) compared to when it was uninformative (254 ± 19 msec) [$F_{(1,37)} = 29.055$, $p < .001$, $\eta_p^2 = .440$] and significantly faster in the congruent (195 ± 14 msec) compared to the incongruent (244 ± 18 msec) condition [$F_{(1,37)} = 30.538$, $p < .001$, $\eta_p^2 = .452$] (Fig. 2). These main effects are best described by the statistically significant congruency × WS type interaction [$F_{(1,37)} = 10.907$, $p = .002$, $\eta_p^2 = .228$]. Post-hoc comparisons revealed that RT was significantly faster when an informative WS was provided, compared to when an uninformative WS was provided in both the congruent ($p = .004$) and incongruent conditions ($p < .001$). For the uninformative WS, congruent RT (216 ± 22 msec) was significantly faster than incongruent RT (293 ± 30 msec) ($p < .001$); for the informative WS, while congruent RT (174 ± 17 msec) was faster than incongruent RT (194 ± 23 msec), the difference was smaller than that observed for the uninformative WS, and did not reach statistical significance ($p = .110$) (Fig. 2). All other main effects and interactions were not significant ($p > .405$).
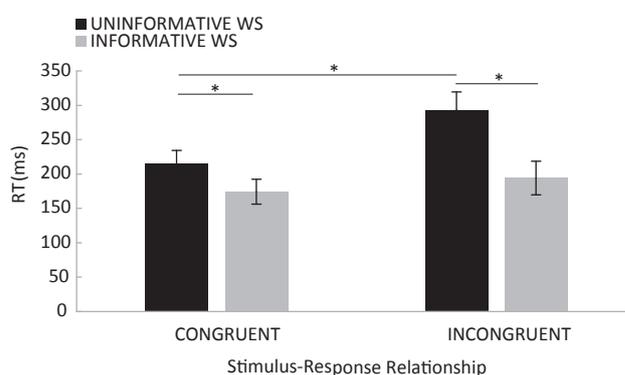


Fig. 2 — **Reaction times in the congruent and incongruent conditions in which uninformative or informative warning signals were provided. Error bars represent 95% CI. * indicates statistically significant differences ($p < .05$) in the interaction term (for full statistical details, see text).**

## 3.2. Errors

Averaged over all conditions, errors occurred infrequently, being exhibited on $3.3 \pm .7\%$ of trials (i.e., an average of ~2.1 errors per 66−68 trial block). Error rates were significantly lower when the warning signal was informative ($1.4 \pm 1.0\%$) compared to when it was uninformative ($5.1 \pm 1.0\%$) [WS type main effect: $F_{(1,37)} = 26.599, p < .001, \eta_p^2 = .418$] and significantly lower in the congruent ($1.5 \pm .7\%$) compared to the incongruent ($5.0 \pm 1.2\%$) condition [$F_{(1,37)} = 29.299, p < .001, \eta_p^2 = .442$]. Somewhat lower error rates were observed when the left ($3.0 \pm .7\%$) compared to the right ($3.6 \pm .8\%$) hand should have been the responding hand, although this did not reach the a-priori significance level [$F_{(1,37)} = 3.344, p = .076, \eta_p^2 = .083$]. These effects are best described by the statistically significant three-way interaction of congruency $\times$ hand $\times$ WS type [$F_{(1,37)} = 4.364, p = .044, \eta_p^2 = .106$]. Post-hoc comparisons of this interaction revealed that error rates were significantly lower for congruent compared to incongruent trials (for both left and right hand responses) when an uninformative WS was provided (both $p < .001$). No significant differences were observed in error rates between congruent and incongruent trials (for both left and right hand responses) when an informative WS was provided (both $p > .666$). Error rates did not differ significantly between hands in both congruent and incongruent trials when an informative WS was provided (both $p > .432$), or in the congruent trials when an uninformative WS was provided ($p = .396$). However, error rates were higher ($p = .008$) when the correct response should have been made by the left hand ($9.9 \pm 2.0\%$) compared to the right hand ($7.6 \pm 1.8\%$) during incongruent trials with an uninformative WS.

## 3.3. RMT

Average RMT (as a percentage of maximum stimulator output) in the left (conditioned) and right (test) hemisphere was $41.3 \pm 2.8\%$ and $41.9 \pm 2.8\%$, respectively, in Experiment 1 (uninformative WS). This resulted in stimulation intensities of $53.5 \pm 3.6\%$ (left hemisphere, conditioning pulse, 130% RMT) and $54.3 \pm 3.7\%$ (right hemisphere, test pulse, 130% RMT). In Experiment 2 (where an informative WS was utilized), average RMT in the left (conditioned) and right (test) hemisphere was $42.9 \pm 2.5\%$ and $41.1 \pm 3.0\%$, respectively, resulting in stimulation intensities of $55.9 \pm 3.3\%$ and $53.2 \pm 4.3\%$ corresponding to 130% RMT in the left (conditioning) and right (test) hemispheres.

## 3.4. CSE

MEPs elicited by single pulse TMS in the baseline blocks were $1.97 \pm .69$ mV and $1.76 \pm .56$ mV (prior to the congruent and incongruent movement blocks, respectively) in Experiment 1. In Experiment 2 the comparable values were $2.03 \pm .53$ mV and $1.97 \pm .51$ mV. Paired $t$-tests revealed no significant differences in CSE prior to congruent and incongruent trials in either experiment (both $p > .500$). Accordingly, for the purpose of (qualitative) comparisons of CSE during movement preparation and selection to baseline, CSE at baseline was expressed as the average MEP size in the two baseline blocks in each experiment (Experiment 1: $1.86 \pm .55$ mV; Experiment 2: $2.00 \pm .46$ mV).

The pattern of (raw) MEP amplitudes is shown in Fig. 3A−B. ANOVA was conducted on CSE normalised to that excitability observed at WS, for the uninformative, and informative, WS conditions separately (Fig. 3C and D). For the uninformative WS, ANOVA revealed statistically significant effects of Time [$F_{(3,51)} = 30.376, p < .001, \eta_p^2 = .641$] and Hand $\times$ Time [$F_{(3,51)} = 3.991, p = .013, \eta_p^2 = .190$]. All other main effects and interactions were not statistically significant (all $p > .238$). Exploration of the two-way interaction (Fig. 3C) revealed that for both the responding and non-responding hands, excitability at IS, IS25 and IS50 was suppressed relative to WS (all values < 1 with CI not encapsulating 1 with CSE suppression of 20−30% relative to WS). Furthermore, post-hoc analysis revealed that there was no significant difference in CSE at the IS, IS25 and IS50 time points for either hand (all $p > .137$). At IS80, CSE of both hands increased relative to all preceding time points (all $p < .003$ for both hands), indicative of a release of suppression. This increase was larger for the responding hand such that CSE at IS80 was significantly greater than that at WS for the responding hand (nMEP = 1.28, 28% facilitation of CSE relative to WS), but not for the non-responding hand (nMEP = 1.03). The difference in CSE between the responding and non-responding hand at IS80 was not, however, statistically significance ($p = .100$).

For the informative WS, ANOVA again revealed statistically significant effects of Hand [$F_{(1,20)} = 12.011, p = .002, \eta_p^2 = .375$], Time [$F_{(3,60)} = 23.834, p < .001, \eta_p^2 = .544$] and Hand $\times$ Time [$F_{(3,60)} = 15.675, p < .001, \eta_p^2 = .439$], with all other main effects and interactions not statistically significant (all $p > .420$). Post-hoc comparisons on the two-way interaction (Fig. 3D) revealed significant differences in CSE between hands at IS25, IS50 and IS80 (all $p < .05$). While both hands showed significant suppression (nMEP < 1) at IS (nMEP = .77 for both hands; 23% suppression of CSE relative to WS), the responding hand showed progressive increases in CSE following IS (indicating a reduction/release of the early suppression) between successive time points that were statistically significant between IS and IS25 ($p = .015$) and between IS50 and IS80 ($p = .006$), such that CSE at IS25 (nMEP = .89; 11% suppression) and IS50 (nMEP = 1.01; 1% facilitation) was not significantly different to that at WS, and CSE at IS80 (nMEP = 1.53; 53% facilitation) was significantly *greater* than CSE at WS. In contrast, for the non-responding hand, no statistically significant temporal changes in CSE were observed between IS, IS25 and IS50, such that excitability at all these points (nMEP = .77, .80, .84) remained significantly suppressed relative to CSE at WS. A late increase in non-responding hand CSE occurred following IS50 (IS50 to IS80: $p = .005$; nMEP at IS80 = 1.01). However, this was less pronounced than that increase observed in the responding hand, such that non-responding hand CSE at IS80 was not significantly different to CSE at WS.

A direct comparison between CSE following informative and uninformative warning signals was subsequently undertaken at IS and IS50 (see Data analysis section). Four-way ANOVA revealed statistically significant effects of Time [$F_{(1,37)} = 16.426, p < .001, \eta_p^2 = .307$] and Hand $\times$ Time [$F_{(1,37)} = 9.249, p = .004, \eta_p^2 = .200$]. Moreover, of particular theoretical importance are the statistically significant interactions involving WS type, namely Hand $\times$ WS type [$F_{(1,37)} = 4.201, p = .048, \eta_p^2 = .102$], and Time $\times$ WS type
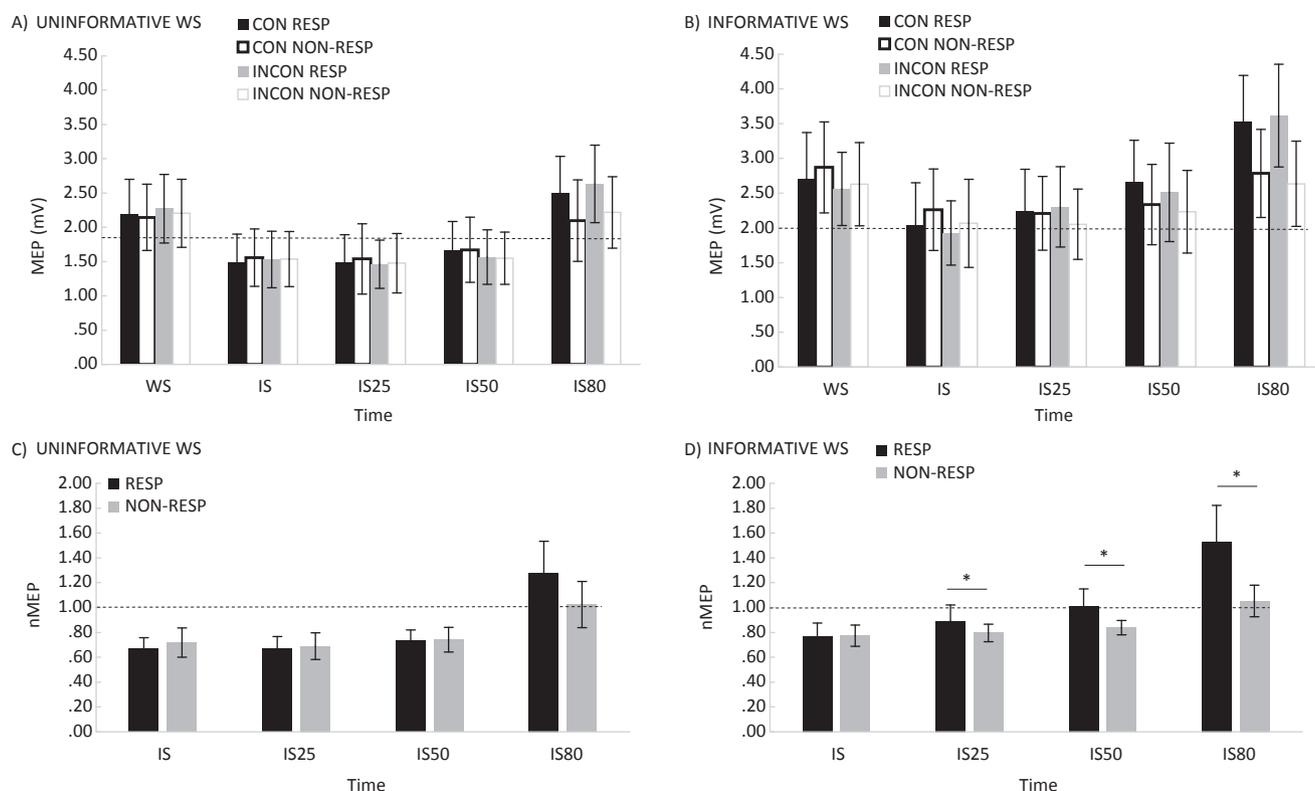
Fig. 3 — A–B): Raw MEP amplitude (mV) in the responding and non-responding hands during the choice reaction time task in which an uninformative (panel A) or informative (panel B) WS was provided. Horizontal lines represent MEP amplitude (i.e., CSE) in the baseline (rest) trials and error bars represent 95% CI. C–D): Normalised CSE (relative to WS) in the responding and non-responding hands during the choice reaction time task with uninformative (panel C) or informative (panel D) WS. Dotted horizontal lines represent CSE at WS (i.e., nMEP = 1). Error bars represent 95% CI. Statistically significant differences between hands are signified by * (p < .05). (Statistically significant differences as a function of time are described in the main text.). CON_RESP: congruent task, responding hand; CON_NONRESP: congruent task, non-responding hand INCON_RESP: incongruent task, responding hand INCON_NONRESP: incongruent task, non-responding hand. RESP: responding hand (averaged over congruent and incongruent conditions). NON-RESP: non-responding hand (averaged over congruent and incongruent conditions).

$[F_{(1,37)} = 5.076, p = .030, \eta_p^2 = .121]$, which are best described with reference to the three-way interaction of Hand × Time × WS type $[F_{(1,37)} = 3.495, p = .069, \eta_p^2 = .086]$ which, while not reaching the a-priori level of significance, was associated with a medium effect size (Sink & Stroh, 2006). Due to the theoretical significance of the three-way interaction, and its importance in understanding the two statistically significant two-way interactions involving WS type, post-hoc comparisons were undertaken (Fig. 4). These post-hocs, together with interpretation of CI to assess the extent of changes in excitability relative to WS, indicate that for the uninformative WS condition, CSE was suppressed at both IS and IS50 for both responding and non-responding hands (25–30% suppression relative to WS), and did not vary between hands at either time point or between time points for either hand (all p > .21). In contrast, in the informative WS condition, while excitability was suppressed to a similar extent for the responding and non-responding hand at IS (23% suppression in both hands), excitability in both hands increased between IS and IS50 (both p < .045). This increase was larger for the responding hand

such that at IS50 there was a significant difference in excitability between responding and non-responding hands (p < .01); the suppression of CSE in the responding hand had been completely released (nMEP = 1.01; 1% facilitation relative to WS) while the non-responding hand remained somewhat suppressed (nMEP = .84; 16% suppression) relative to WS. Finally, there was a significant difference in nMEP for the responding hand at IS50 between the informative (nMEP = 1.010) and uninformative (nMEP = .73) conditions (p = .002); for the non-responding hand at IS50, the difference in normalised CSE between informative (nMEP = .84) and uninformative (nMEP = .74) did not reach the a-priori level of significance (p = .072).

The current CSE results are consistent with previous research (Duque & Ivry, 2009) whereby CSE is suppressed proactively in both hands when the warning signal was uninformative, but also when an informative WS allowed early determination of which hand will be required to move. To ascertain whether the subsequent release of CSE suppression in the responding hand was related to RTs, we conducted
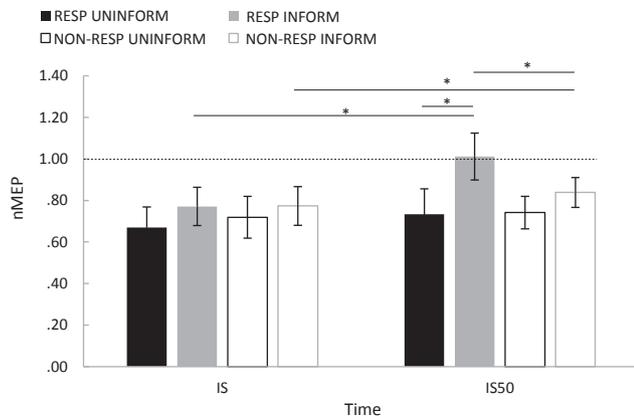
**Fig. 4** – Comparison of normalised CSE in the responding and non-responding hands at IS and IS50 when provided with an uninformative or informative WS (all data are averaged over congruent and incongruent task conditions). Horizontal line represents CSE at WS, and error bars represent 95% CI. * indicates statistically significant differences (*p* < .05). RESP UNINFORM: responding hand, uninformative WS; RESP INFORM: responding hand, informative WS; NON-RESP UNINFORM: non-responding hand, uninformative WS; NON-RESP INFORM: non-responding hand, informative WS.

regression analyses (see Methods). To disentangle the early suppression of CSE from the later increases in CSE (i.e., releases of this suppression) which may represent mechanisms associated with preparation for action, we computed the change in excitability between IS and later time points. For the uninformative WS, we did not observe any hand-specific differences in CSE that could be hypothesised to predict RT; thus regression was not conducted in this instance. With respect to the informative WS task, differences in CSE between the responding and non-responding hands were apparent at all time points following IS (but which varied in magnitude at each time point) due to incremental increases in CSE of the responding hand (Fig. 3D and associated Hand × Time interaction); accordingly, we determined whether these increases in the responding hand (relative to IS) predicted RT using multiple linear regression (see Data analysis). The model revealed that the early increase in CSE between IS and IS25 (but not the later changes in CSE at IS50 and IS80) significantly predicted RT ($R = -.521$, $p = .015$); specifically, a larger increase in excitability (representing a release of the early suppression observed at IS) was associated with faster RTs.

### 3.5.    Interhemispheric inhibition – 10 msec ISI

In Experiment 1, baseline IHI10 (prior to the congruent and incongruent movement blocks) was .78 ± .14 and .83 ± .26, respectively. In Experiment 2, baseline IHI10 was .64 ± .10 and .61 ± .10 prior to the congruent and incongruent movement blocks, respectively. There was no significant difference in inhibition between the two baseline blocks in each experiment (both $p > .620$); as such, for the purposes of qualitative comparison of IHI10 during movement preparation to IHI at

baseline, we calculated an average baseline IHI10 ratio for Experiment 1 (.80 ± .15) and Experiment 2 (.62 ± .07). The fact that these ratios are significantly less than 1 (i.e., CI do not include 1), indicates that the TMS parameters adequately captured IHI at rest (i.e., not during movement selection/preparation).

Changes in baseline IHI10 values during movement selections and preparation are shown in Fig. 5 (panels A and B); these values were normalised to IHI10 at WS (to yield nIHI10) for statistical analyses (Fig. 5C and D). For the task involving an uninformative WS, the release of IHI in the congruent task (nIHI10 = 1.418; 42% release of that inhibition exhibited at WS) was greater than that release of IHI in the incongruent task (nIHI10 = 1.239; 24% release of inhibition) although this did not reach the a-priori level of significance [effect of congruency $F_{(1,17)} = 3.513$, $p = .078$, $\eta_p^2 = .171$]. The effect of time [$F_{(3,51)} = 2.623$, $p = .060$, $\eta_p^2 = .089$] and the Hand × Time interaction [$F_{(3,51)} = 2.730$, $p = .053$, $\eta_p^2 = .138$] both failed to reach the a-priori level significance level. There was a statistically significant three-way interaction of Congruency × Hand × Time [$F_{(3,51)} = 3.622$, $p = .019$, $\eta_p^2 = .176$] (Fig. 5C); Post-hoc comparisons revealed a significant difference in nIHI10 between responding and non-responding hands at IS80 in the congruent task ($p = .037$), driven by the fact that nIHI10 increased (release of inhibition) between IS and IS80 for the responding hand in the congruent task ($p = .019$).

For the informative WS condition, ANOVA revealed a significant main effect of hand [$F_{(1,20)} = 6.042$, $p = .023$, $\eta_p^2 = .232$] with the responding hand exhibiting a release of that inhibition present at WS (apparent at all times following WS), but no change in the level of inhibition (relative to WS) for the non-responding hand (Fig. 5D) at any time point. All other main effects and interactions were not statistically significant (all $p > .200$). Notably, the absence of any effects involving congruency suggests the informative WS nullified the congruency-related effects observed when an uninformative WS was provided.

We next compared nIHI10 at the two particular time points of interest (IS, IS50) between the two WS types. ANOVA revealed a significant effect of Hand [$F_{(1,37)} = 5.106$, $p = .030$, $\eta_p^2 = .121$] but the effect of Time failed to reach statistical significance [$F_{(1,37)} = 3.314$, $p = .077$, $\eta_p^2 = .082$]. The Time × WS type interaction was statistically significant [$F_{(1,37)} = 4.536$, $p = .040$, $\eta_p^2 = .109$] where-as the Hand × WS type interaction failed to reach the a-priori level of significance [$F_{(1,37)} = 3.546$, $p = .068$, $\eta_p^2 = .082$]. These interactions were further explored by post-hoc comparisons due to their theoretical importance in explaining differences due to the nature of the WS and the fact they were associated with medium effect sizes (Cohen, 1988; Sink & Stroh, 2006). With respect to the Hand × WS type interaction (Fig. 6A), there were no statistically significant differences in nIHI10 for the responding ($p = .322$) or non-responding ($p = .113$) hands between WS type. Furthermore, while there was no significant difference in nIHI10 between the responding and non-responding hands in the uninformative WS condition ($p = .799$), there was a greater release of IHI in the responding, compared to the non-responding hand, in the informative WS condition ($p = .004$). In regard to the TIME × WS type interaction (Fig. 6B), while there were no significant differences in nIHI10 between WS types at IS
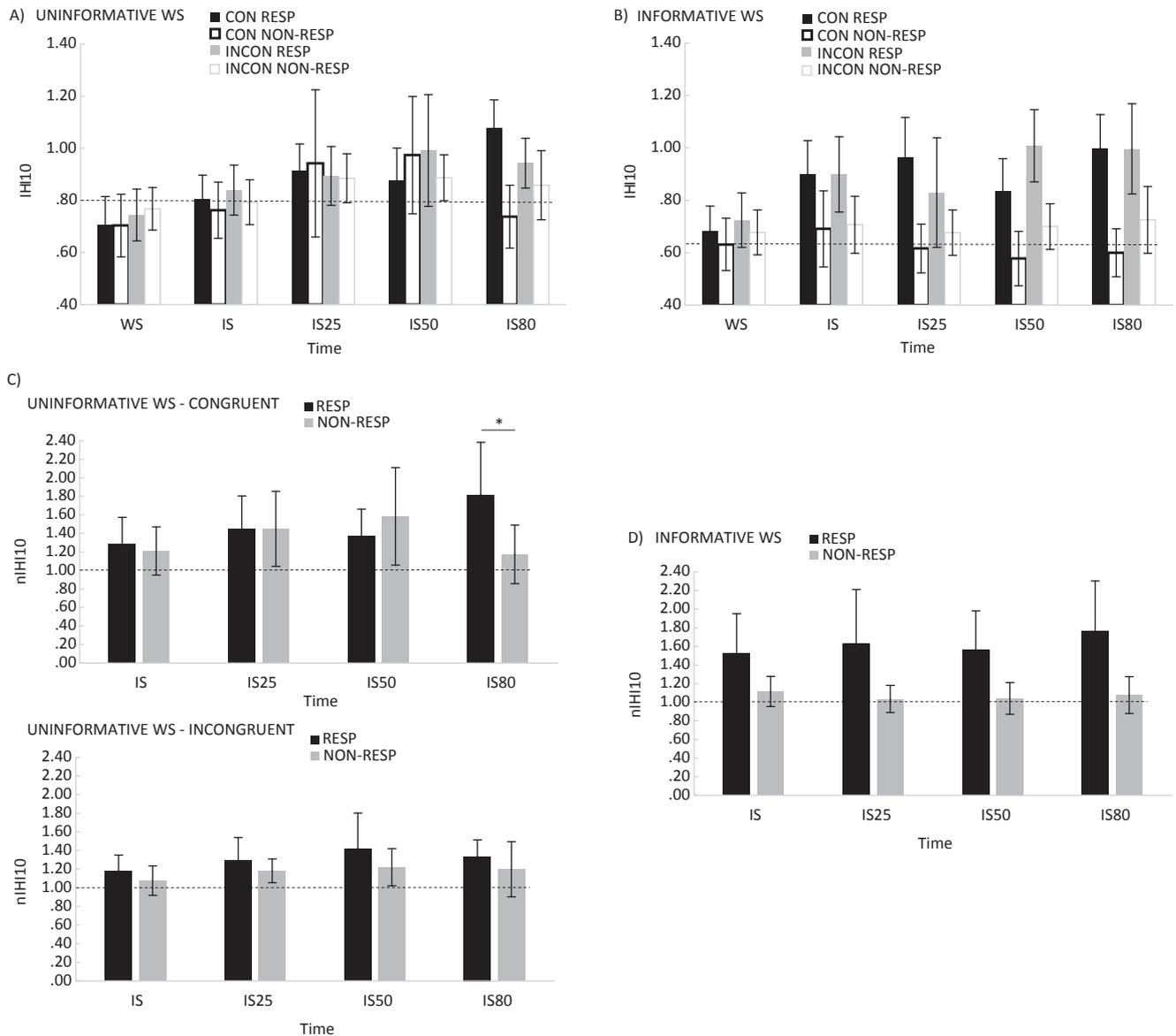
Fig. 5 — A—B): IHI10 ratios (i.e., IHI measured with 10 msec ISI) in the congruent and incongruent tasks and responding and non-responding hands during a choice reaction time in which an uninformative (panel A) or informative (panel B) WS was provided. Horizontal lines represent IHI10 ratios in the baseline trials and error bars represent 95% CI. C—D): IHI10 normalised to WS (nIHI10) in the responding and non-responding hands in the uninformative (panel C; upper graph: congruent task; lower graph: incongruent task) and informative (panel D) WS. Horizontal dotted lines represent IHI10 at WS, and error bars show 95% CI. * indicates statistically significant differences (p < .05). CON RESP: congruent task, responding hand; CON NON-RESP: congruent task, non-responding hand; INCON RESP: incongruent task, responding hand; INCON NON-RESP: incongruent task, non-responding hand. NB: data is presented for CON and INCON conditions separately in panel C) but not in panel D) as a main effect of congruency was only observed during the uninformative WS task — thus panel D data are averaged over CON and INCON conditions.

($p = .401$) or IS50 ($p = .527$), a significant release of inhibition was exhibited between IS and IS50 in the uninformative WS condition ($p = .011$). In contrast, when an informative WS was provided, nIHI10 was not significantly different between the two time points ($p = .821$). This suggests that when an informative WS was provided, IHI10 was released early (i.e., by the time of the IS nIHI10 was already > 1) with no further release of inhibition observed between IS and IS50.

Regression analyses were undertaken to determine whether hand-specific modifications of IHI10 observed in the responding hand predicted RT when either an uninformative, or informative, warning signal was provided. For the uninformative WS, only during the congruent task, at the IS80 time point, did nIHI10 vary between hands (Fig. 5C, top panel). However, linear regression revealed that the extent of the release of inhibition at this time point was not associated with
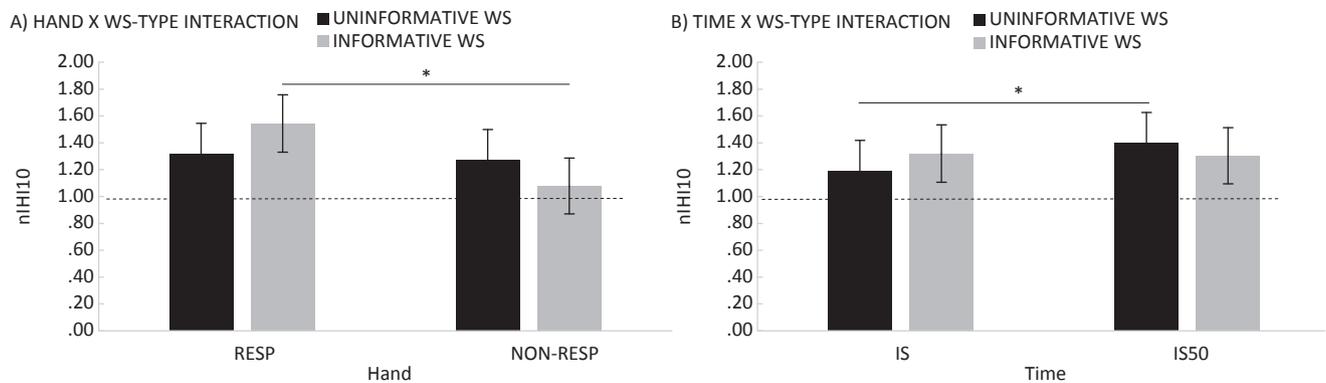
**Fig. 6 — Direct comparison of nIHI10 at IS and IS50 when provided with uninformative or informative warning signals. A) Hand × WS type interaction B) Time × WS type interaction. Horizontal lines represent IHI10 at WS, and error bars represent 95% CI. * indicates statistically significant differences ($p < .05$).**

RT ($R < .001, p = .901$). With respect to the informative WS task, the release of IHI10 (relative to WS) in the responding hand was greater than in the non-responding hand at all time points following WS (across both task congruency conditions); the extent of this difference did not vary as a function of task congruency or time (Fig. 5D). As such, we used the averaged nIHI10 value across both congruency conditions and across all four time points as a sole predictor of RT in a linear regression. The regression revealed that the release of inhibition did not predict RT ($R = .165, p = .477$).

### 3.6. Interhemispheric inhibition — 40 msec ISI

In Experiment 1, baseline IHI40 — measured prior to the congruent and incongruent movement blocks — was $.84 \pm .10$ and $.91 \pm .23$, respectively. In Experiment 2, baseline IHI40 was $.83 \pm .11$ and $.76 \pm .12$ prior to the congruent and incongruent movement blocks, respectively. There was no significant difference in inhibition between the two baseline blocks in each experiment (both $p > .310$); accordingly, IHI40 at baseline was represented by the average baseline IHI40 ratio across the two blocks in Experiment 1 ($.87 \pm .12$) and Experiment 2 ($.80 \pm .08$). As with IHI10, these ratios are <1, and thus indicate TMS parameters adequately measured IHI interactions at rest.

Changes in IHI40 during movement preparation are shown in Fig. 7 (panels A and B); for statistical analyses, these IHI40 values were normalised to IHI40 at WS (nIHI40, Fig. 7C and D). For the uninformative WS task, ANOVA revealed that all main effects and interactions failed to reach the a-priori level of significance (all $p > .115$, all $\eta_p^2 = .109$). nIHI values were all significantly greater than 1 (i.e., IHI was significantly released relative to the extent of inhibition exhibited at WS) at all time points from IS onwards, but the extent of this release of inhibition did not vary significantly as a function of congruency, hand or time (Fig. 7C).

ANOVA conducted on nIHI40 for the informative task revealed that the generalised release of inhibition exhibited at IS (i.e., nIHI40 > 1 and CI do not encompass 1 for both hands at all time points) did not vary as a function of Hand [$F_{(1,20)} = 3.941, p = .061, \eta_p^2 = .165$] or Time [$F_{(3,60)} = 2.624$,

$p = .059, \eta_p^2 = .116$]. All other main effects and interactions were not statistical (all $p > .322$).

The influence of WS type on nIHI40 (in responding and non-responding hands, and in congruent and incongruent task conditions) was assessed at the IS and IS50 time points, as previously described for CSE and nIHI10. There was a significant main effect of Hand, with a greater release of IHI40 in the responding compared to the non-responding hand [$F_{(1,37)} = 5.291, p = .027, \eta_p^2 = .125$], but this *was not* moderated by WS type. The effect of Time was not significant [$F_{(1,37)} = .126, p = .724, \eta_p^2 = .003$] but there was a significant interaction of Time × WS type [$F_{(1,37)} = 5.287, p = .027, \eta_p^2 = .125$]. This interaction was driven by increases in the release of inhibition from IS to IS50 in the uninformative WS, and decreases in the release of inhibition in the informative warning signal (Fig. 8). Post-hoc comparisons revealed that these time-related changes did not, however, meet the a-priori level of significance in the uninformative ($p = .193$) or uninformative ($p = .058$) warning signal condition.

In contrast to the hand-specific changes in CSE and IHI10 described previously, task-related releases in IHI40 did not vary significantly as a function of hand (nor across time points or congruency conditions) in either the uninformative or informative conditions (Fig. 7C and D and associated analyses). Accordingly, regression was not undertaken as a change in IHI40 in both the responding and non-responding hands would not be predicted to underpin the behavioural response of the responding limb (see Methods).

## 4. Discussion

This study investigated how CSE and interhemispheric inhibitory processes were modulated during a choice RT task requiring a between-hand selection based on visual stimuli. As expected, congruency of the stimulus-response relationship and the degree of information provided by a warning signal prior to the imperative (go) stimulus both affected behavioural performance — as indicated by the speed and accuracy of the motor response. However, the effect these
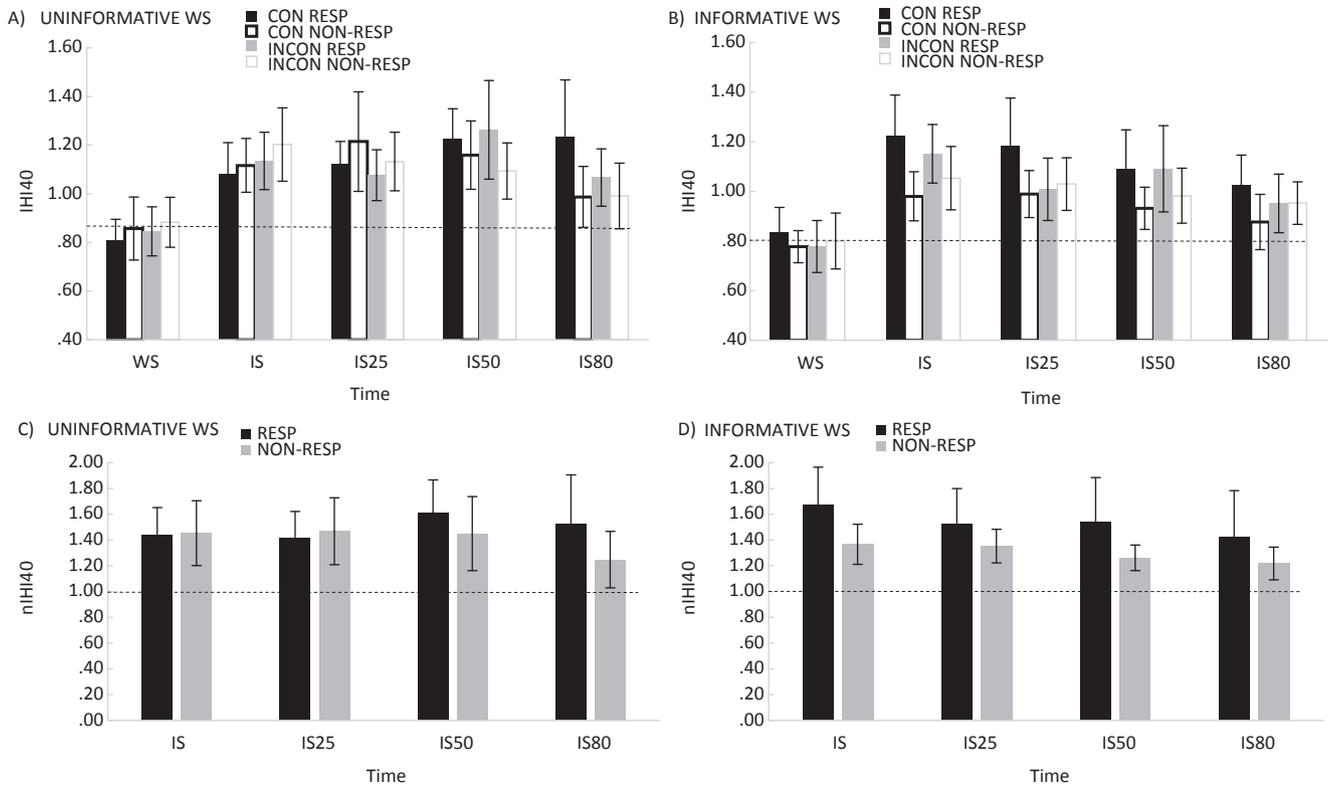
Fig. 7 — A—B): IHI40 ratios (i.e., IHI measured with 40 msec ISI) in the congruent and incongruent tasks and responding and non-responding hands (See legend) during a choice reaction time in which an uninformative (panel A) or informative (panel B) WS was provided. Horizontal lines represent IHI40 ratios in the baseline trials and error bars represent 95% CI. C—D): Normalised IHI40 (nIHI40) in the responding and non-responding hands following an uninformative (panel C) or informative (panel D) WS, averaged over congruency conditions. Horizontal dotted lines represent IHI40 at WS, and error bars show 95% CI. CON RESP: congruent task, responding hand; CON NON-RESP: congruent task, non-responding hand; INCON RESP: incongruent task, responding hand; INCON NON-RESP: incongruent task, non-responding hand; RESP: responding hand (averaged over congruent and incongruent conditions); NON-RESP: non-responding hand (averaged over congruent and incongruent conditions).

manipulations had on CSE and IHI mechanisms differed. The findings are consistent with the notion that an impulse control mechanism acts early in response selection, but that the modulation of interhemispheric inhibitory mechanisms occurs independently of this impulse control.
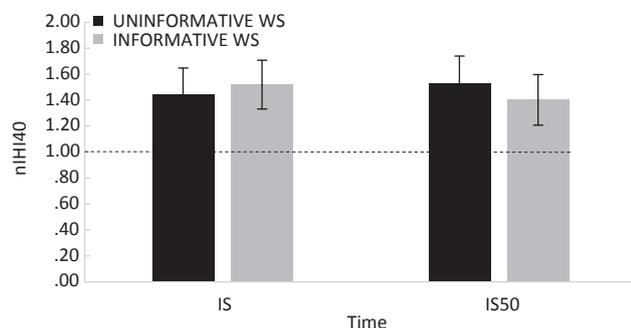


Fig. 8 — Direct comparison of nIHI40 between the uninformative (black) and informative (grey) WS conditions at IS and IS50: Time × WS type interaction. Horizontal dotted line represents IHI40 at WS, and error bars show 95% CI.

## 4.1. Informative warning signals facilitate earlier hand-specific modulation of CSE

Analysis of CSE in the uninformative warning signal condition revealed a suppression of excitability that was apparent in both responding and non-responding hands at IS (500 msec following the uninformative WS), and which was maintained at IS25 and IS50. That is, provision of task-specific information (by way of the IS in this case) regarding which hand would respond did not result in any release of suppression in the responding hand until very late in the movement generation period (IS80). Moreover, the fact that the degree of CSE suppression in the non-responding hand was not increased (i.e., suppressed to a greater extent) following the IS is further evidence to suggest that CSE was suppressed proactively in both limbs and not additionally moderated by hand-specific cues.

Even when an informative WS was provided, a generic (i.e., evident in both hands) suppression of CSE was observed at IS (Fig. 3D), when ample time had passed such that hand-specific alterations to CSE in response to the WS could have been made. Overall, the current findings in regard to CSE suppression are consistent with those previously reported by Duque and Ivry

(2009) and strongly suggests that the suppression of excitability during movement preparation *does not* represent a mechanism related to deselection of the non-selected hand. Rather, the suppression likely represents an impulse control mechanism which (proactively) down-regulates the CSE of *both* potential responding limbs to minimise the likelihood of responding prior to the IS. It is interesting to note, however, that some recent research (Duque et al., 2012; Lebon et al., 2016) has suggested that, rather than a single generic inhibitory mechanism being active during response preparation, two distinct inhibitory mechanisms might be acting concurrently on the selected and non-selected limbs (see also Bestmann and Duque, 2016, for discussion). That is, following an informative warning signal, CSE in the non-responding hand is reduced as a result of being the non-selection action (inhibition for deselection), while the responding hand CSE is also reduced but to prevent a premature response (i.e., impulse control). However, the fact that we observed suppression of CSE in the non-responding limb that was indistinguishable following an uninformative versus informative warning signal suggest a generic impulse control mechanism is operating in both limbs in this instance.

A novel finding of the current study was that hand-specific differences in CSE were found to occur *earlier* in the movement preparation period when an informative WS was provided compared to an uninformative WS (Fig. 3C and D; Fig. 4). Specifically, when provided with an informative WS, the responding hand exhibited incremental reductions in the extent of the early suppression (i.e., increases in excitability, or release of suppression) from IS25 onwards while CSE of the non-responding hand remained suppressed until just prior to onset of the response. Moreover, an important finding was that multiple regression revealed that the increase in CSE at IS25 relative to IS was a significant predictor of RT: those participants who were able to utilise the informative warning signal to release the early suppression in the responding hand to the greatest degree exhibited the fastest responses. Accordingly, while only correlational in nature, it is likely that the ability to release the early suppression (thought to represent impulse control) in the responding hand represents a neurophysiological correlate that underpins the behavioural observation that informative warning signals can significantly speed up RTs.

The release of the early suppression of CSE in the responding hand (followed by significant facilitation of CSE at IS80) in the informative WS condition resulted in statistically-significant differences in CSE between the responding and non-responding hands that were evident from IS25 onwards; no such between-hand difference was only observed in the uninformative WS condition. The direct comparison of CSE between the two tasks — undertaken with either an uninformative or informative warning signal — confirmed these findings: from IS (early preparation) to IS50 (late preparation), the most pronounced increases in CSE were observed for the responding hand in the informative WS condition, where-as no changes in CSE were observed over this time period for the responding hand in the uninformative condition (Fig. 4).

Interestingly, for neither the informative nor the uninformative WS conditions, did we observe that stimulus-response congruency overtly affected CSE. Accordingly, it can be concluded that although RTs were, on average, faster in the congruent compared to incongruent tasks, CSE at comparatively the same time during the movement preparation period (i.e., 25, 50, or 80% of the task-specific RT) was not dissimilar between the different stimulus-response conditions. That is, the measure of CSE of projections from primary motor cortex appears insensitive to the cognitive processes associated with deciphering between simple (congruent) and more 'complex' (incongruent) stimulus-response relationships.

### 4.2. Modulation of IHI occurs independently of changes in CSE

Whether interhemispheric inhibitory mechanisms play a role in the generic suppression of CSE (impulse control) during movement selection and preparation was investigated by assessing IHI with 10 msec and 40 msec ISIs at the same time points (relative to the external stimuli) at which CSE was measured. IHI between contralateral primary motor areas assessed at 10 msec ISI (i.e., IHI10) occurs via the direct transcallosal pathways of the corpus callosum (Ferbert et al., 1992; Ni et al., 2009). For IHI10, the inhibition that was present at baseline was maintained at onset of the WS, suggesting that the nonspecific attention or arousal effects that were at play during the task, and which resulted in increased levels of CSE at WS relative to baseline, did not overtly affect IHI10. The subsequent temporal changes in IHI10 varied between the tasks where uninformative and informative WS were provided. For the uninformative WS task, a release of inhibition was observed in *both* the responding and non-responding hands. The fact that inhibition from left to right M1 was released *prior* to the time where information regarding whether the left hand would be required to respond or not, is a novel and intriguing finding. Firstly, it suggests that even though CSE of the descending pathways from the right primary motor cortex is *suppressed* prior to movement selection irrespective of whether the left hand is selected or not selected to respond (presumably as an impulse control mechanism), there is a concurrent *reduction* in the extent of IHI which occurs prior to knowledge regarding which hand will be required to move. The release of IHI10 may therefore represent a generic mechanism related to movement 'readiness'. Indeed, consistent with our previous work in a simple RT task (Hinder et al., 2012), we did not find any association between changes in inhibition and RT, lending weight to the postulation that changes in inhibition are not specifically related to rapid responses in simple or choice tasks.

For the informative WS task, a release of inhibition (relative to IHI at WS) was observed at all time points following the WS for the responding hand. No significant change in the level of IHI was observed at any of the time points following WS for the non-responding hand (Fig. 5D), suggesting that when a WS indicates a hand is not required to move, IHI onto that hand is maintained. This hand-specific modulation of IHI10 was invariant across time, where-as the concurrent changes in CSE varied significantly as a function of hand and time (Figs. 3 and 4, and associated analyses). Importantly, this finding again strongly suggests that IHI10 modulation occurs *independently* of changes in CSE and thus represents a distinct neural process associated with movement selection and preparation which is not underpinned by, or underpinning,

the concurrent changes in CSE. As such, this finding clearly indicates that the informative WS enabled hand-specific modulation of IHI10 as soon as the information contained within the WS had been processed (i.e., 500 msec after the WS, at IS); this early release of IHI10 in the responding hand (together with no changes in the non-responding hand) persisted throughout the rest of the movement selection/preparation period with no further changes in the degree of the inhibition exhibited.

The direct statistical comparison of IHI10 between the two different WS types provide confirmation of the interpretation that only information provided within the informative WS enabled early hand-specific modulation of IHI10 (Fig. 6). Specifically, this analysis confirmed the early release of inhibition (at IS) in the responding (but not in the non-responding) hand was maintained at IS50 for the informative WS task (Fig. 6A) together with a release of inhibition that increased over time for *both* the responding and non-responding hand in the uninformative WS task (Fig. 6B). These findings indicate that the generic (i.e., in both the responding and non-responding hands) suppression of CSE early during the movement selection period (as indicated by reduction in MEP amplitude) *is not* mediated by changes in short-interval (10 msec) IHI interactions between primary motor cortices. Specifically, a suppression of CSE of the pathways innervating a particular hand would be expected if IHI onto that hand was increased (greater inhibition). To the contrary, we observed early *releases* of IHI onto both the responding and non-responding hand following an uninformative WS, and early *releases* of IHI onto only the responding hand following an informative WS. The data are thus consistent with the notion that CSE suppression and IHI modulation (specifically releases of inhibition during movement preparation which vary according to the informativeness of the warning signal) act as independent neural mechanisms (Fujiyama et al., 2016; Hinder et al., 2012).

In contrast to the findings for single pulse TMS, where stimulus-response congruency didn't alter the temporal modulation of CSE, here we observed that the release of IHI10 appeared to be mediated by task congruency in the uninformative condition. These findings suggest that cognition (i.e., interpretation of a visual stimulus — both in terms of its informativeness and in relation to the imposed stimulus-response relationship) can directly influence action control via modification of specific inhibitory mechanisms. Interestingly, congruency effects on IHI10 were not observed when an informative WS was provided, suggesting that early knowledge of which hand would be required to respond negates any congruency effects. That is, when the motor system can plan its response, direct inhibitory pathways between primary motor cortices (as assessed by dual coil TMS at 10 msec ISI) are regulated in a similar manner irrespective of whether the planned response is congruent or incongruent with the visual stimulus. Indeed, this early knowledge permitted a release of inhibition in the responding hand, with no change observed in the non-responding hand; in contrast, when an uninformative WS was provided release of inhibition was observed in *both* hands (Fig. 6C—D). The current data suggest that in the incongruent condition — in which a 'conflict' between the stimulus and required response is induced — the 'direct response' pathway is not initially activated as proposed in earlier work (Ridderinkhof, 2002). That is, in incongruent trials IHI in the non-responding limb (i.e., left limb when presented with a right side IS or right side informative WS) is maintained, rather than being released as would be predicted under the Ridderinkhof's activation-suppression model for conflict tasks (Ridderinkhof, 2002). Rather, the single and dual coil TMS approach in the current task suggest that a 'suppression-activation' model of responses would provide a parsimonious explanation of the data in the current conflict paradigm. This postulation is also consistent with some of our previous work (Fujiyama et al., 2012) in which no increases in intracortical inhibition (SICI) was observed in no-go trials relative to the degree of SICI observed prior to a go or no-go stimulus. That is, the level of inhibition exhibited early in movement preparation (before a go or no-go stimulus was presented) was sufficient to prevent movement, and was only 'released' when a go stimulus was presented.

The hand-specific release of inhibition during movement selection and preparation assessed at 10 msec ISI *was not* observed when inhibition was probed at 40 msec ISI. Indeed, IHI40 was released in both hands during movement selection and preparation irrespective of either warning signal informativeness or stimulus-response compatibility. It is conceivable, therefore, that the interhemispheric mechanism assessed via IHI40 is more influenced by top-down processes — which are more global in nature and thus affect both limbs — than the interhemispheric mechanism assessed by IHI10. Indeed, IHI40 appears to be pre-set prior to any cognitive processing related to which limb will respond.

## 5. Summary and conclusion

In summary, the current data support previous research suggesting that during a task requiring a rapid choice between possible actions, corticospinal suppression acts as a generic mechanism most likely to prevent premature motor responses (i.e., impulse control). We extend previous work to show that the ability to quickly release this early suppression, based on interpretation of an informative warning signal, was associated with faster response times. Moreover, we observed that concurrent with the corticospinal suppression, a hand-specific release of IHI assessed using paired pulse TMS with a short (10 msec), but not long (40 msec) ISI, was observed, suggesting multiple preparatory processes are at play during a delayed choice task. The fact that this short interval IHI varied according to task congruency and warning signal information suggests a direct influence of cognitive task attributes on an action control pathway directly connecting primary motor regions (Chen, 2004; Chen et al., 2003).

## Acknowledgements

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