The role of interhemispheric inhibition mechanisms during partial response inhibition of prepared motor actions

by

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Abstract

One aspect of impulse control in human motor behaviour is the cancellation of part of an action without warning, while the remaining parts continue. Previous research has highlighted a distinct pattern of corticomotor excitability modulation, whereby excitability increases with the anticipation of movement, then is inhibited when required actions are suddenly altered, and finally reinitiated with the required response. The present study aimed to investigate interhemispheric inhibitory mechanisms between the two primary motor cortices as a possible method of partial response inhibition modulation. Transcranial magnetic stimulation was given to participants while they performed an anticipatory response inhibition task in the form of a bimanual index finger abduction task, intercepting a target line with two rising bars on a screen. Occasionally, participants were required to inhibit the finger abduction response of either one or both index fingers. When inhibiting the left-hand response and continuing the right, there was a dissociation in interhemispheric inhibition post stop cue, with interhemispheric inhibition being released onto the responding hand and increased for the cancelled hand. This dissociation suggests interhemispheric inhibition allows for the uncoupling of motor actions before the subsequent reinitiation of required responses. Interhemispheric inhibition is therefore fundamental to partially inhibiting movement responses.

Acknowledgements

I would like to thank my supervisors, Dr Hayley MacDonald and Dr Ned Jenkinson, for their knowledge, patience and encouragement throughout my Master of Science degree. Thank you also to Alison Hall and Matt Weightman for their support and technical assistance.

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INTRODUCTION

Chapter 1

Defining response inhibition

Most of us take our ability to inhibit unwanted movements for granted. The act of preventing a pre-planned movement or action is known as response inhibition (RI): abolishing a movement, usually because of environmental happenings (Fuster, 1997, cited in Coxon, Stinear and Byblow, 2007). Suppressing a movement rendered redundant can aid goal-orientated behaviour in fluid environments (Verbruggen & Logan, 2008).

Reactive and proactive RI

Without the aid of foreknowledge, RI is reactive (Aron, 2011) and movements are hard to inhibit (MacDonald et al., 2014; Aron and Verbruggen, 2008). Real life examples of reactive RI included avoiding a road traffic collision or starting to walk across a road but seeing an oncoming car and having to stop. Conversely, proactive RI is where an individual is already aware of, or cued to, the approaching behavioural tendency they will need to inhibit (Aron, 2011). Proactive RI often involves preventing a potential response before it occurs, rather than after the movement process has begun (Meyer and Bucci, 2016). Proactive RI is easier to execute than reactive RI (Aron and Verbruggen, 2008), however is slower due to the proposed pathways involved (see *Neural mechanisms of RI*). The current study focuses on reactive RI.

Testing RI (behaviourally)

Widely-used methods of testing RI include the Go/No-Go task (*fig. 1*), which requires responding to a Go cue (normally by pressing a button or key) and withholding that response

when presented with a No-Go cue (Donders 1868, 1969, cited in Gomez, Ratcliff and Perea, 2007). Despite appearing to engage the need for inhibition of a response, participants were rather not responding at all when presented with a No-Go cue. Instead, participants were likely to simply discriminate between the two types of stimuli, Go and No-Go cues (Coxon et al., 2007) and perform a choice reaction time task.

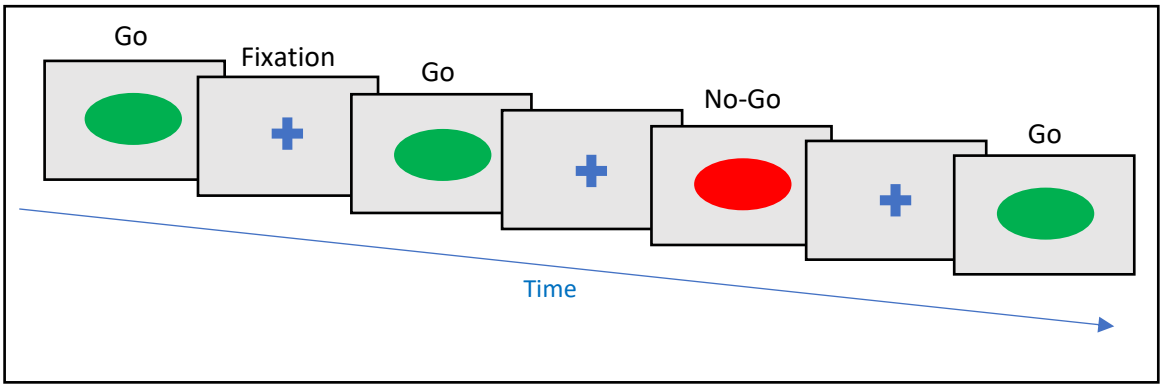

Fig. 1. An example of the Go/No-Go task. Participants correctly respond to a Go signal (green oval) within 500ms of presentation, by pressing a button. When a No-Go signal is presented (red oval) participants correctly responds by not pressing the button. A blue fixation cross is displayed in between signals for 1000ms.

Another mechanism for testing RI is the Stop Signal task (SST) (Logan and Cowan, 1984). Participants expect to respond to a Go signal, usually by pressing a button or switch with their index or middle digits. However, on some trials the Go signal would quickly be followed by a Stop signal, indicating that the participant should withhold the corresponding response (*fig.2*). The longer the length of time between the Go signal and the Stop signal (stop signal delay, SSD), the more difficult it is to inhibit the Go response because the likelihood of the movement in response to the Go signal increases with time. The SST is a popular method for testing reactive RI, both in humans (Aron and Poldrack, 2006; Kenner et al., 2010; Mars et al., 2009; Sharp et al., 2010) and animals (Eagle and Robbins, 2003). Analysis of SST uses

stop signal reaction time (SSRT), an estimation of the latency of the RI process that takes place after a given stop cue (Logan and Cowan, 1984; Verbruggen and Logan, 2008).

One issue with SST raised by some studies (Verbruggen and Logan, 2008; Verbruggen and Logan, 2009; MacDonald, Stinear and Byblow, 2012) is the potential that individuals purposefully delay their response to the Go stimulus 'just in case' the Stop signal appears, rather than reacting to the Go stimulus immediately (in order to increase their likelihood stopping success). The use of this strategy would give a false impression of RI alone being responsible for successful trial completion, rather than a more complex cognitive strategy. In general, studies do try to counteract the use of strategy by instructing participants not to wait for the stop signal and react as soon as they see the Go cue, however Verbruggen and Logan (2008) suggest that past studies that have included such instructions still observed increased RTs to Go cues, as the urge to delay responses in order to be successful is hard to resist.

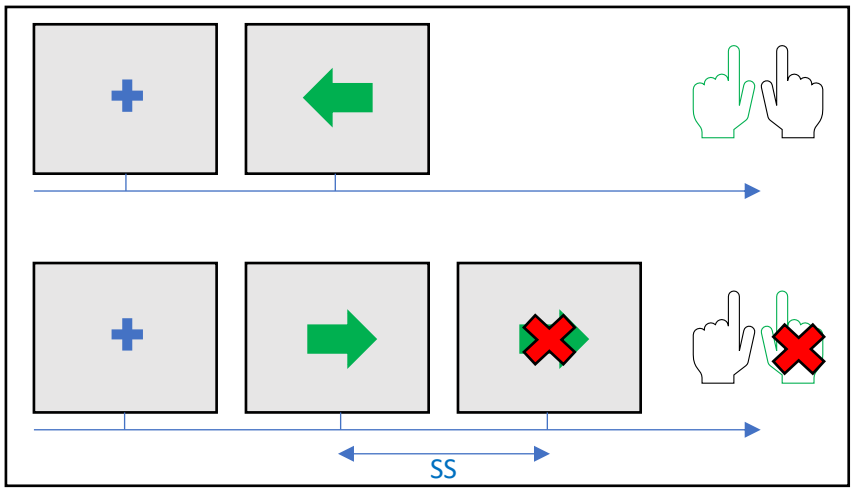

Fig. 2. An example of a Stop Signal task. When a Go cue is presented (in this case, a green arrow pointing left to cue the left hand or pointing right to cue the right hand) participants respond by pressing a button or key with the corresponding finger. However, on some trials, the Go signal may be followed by a Stop signal (the red cross over the arrow), cueing the participant to withhold the response they had initially been cued to perform. The time between Go and Stop signal (stop signal delay, SSD).

The anticipatory response inhibition task (ARI, Slater-Hammel, *fig.3*) is less prominent in the literature but has still been used by a number of studies. MacDonald et al. (2014) argued that, unlike the SST, the ARI task ensures participants have prepared a motor plan for executing the task response on every trial, rather than being tempted to withhold any response. In Slater-Hammel's original ARI task, participants had to stop a revolving pointer by depressing keys or switches; occasionally the pointer would stop revolving before it reached the pre-determined stop angle, in which case the participant would have to inhibit their already-planned response of stopping the pointer. This task was adapted by Coxon et al. (2007) to include two rising bar indicators, each controlled by a separate hand/digit, thus creating a bimanual task. When participants depressed keys/switches, the bars would start to rise (typically after a very brief delay period), and they would stop rising when the keys/switches were released. The same stopping principal was applied in that participants were required to stop the rising bar indicators when they intercepted a target, in this case a horizontal line. However, occasionally one or both indicators would stop rising before reaching the target, cueing the participant to not release the corresponding key/switch. Versions of the ARI task have since been used to study selective RI (MacDonald et al., 2012; 2014). The current study takes this line of experimentation one step further to investigate the phenomenon of interhemispheric inhibition (see *Interhemispheric inhibition (IHI) section below*) using the ARI task.

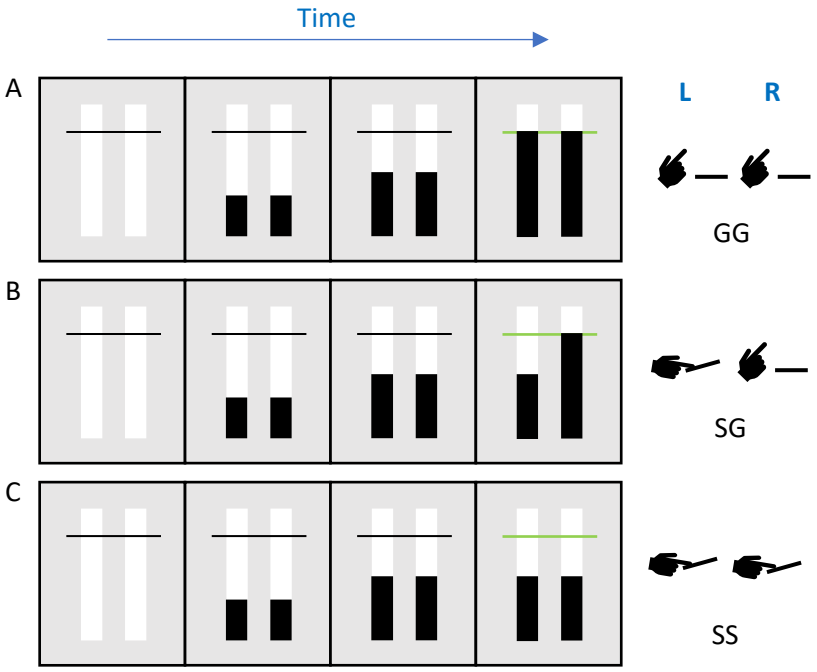

Fig. 3. Examples of trials in the Anticipatory Response Inhibition task. When participants depress switches with their index fingers, black bars rise towards a target line, intercepting the line 800ms after trial onset. Participants control this interception by lifting their index fingers off the corresponding switches. Participants are given visual feedback (written or a line colour change) on whether the line was intercepted correctly with the correct bar(s). **A**) Go trial. Participants execute the lift response on both hands. **B**) Stop-left, Go-right trial. The left bar automatically stops before reaching the target line, so participants inhibit the lift response of the left hand but intercept the line with the right bar. **C**) Stop-both trial. Both bars stop before reaching the target line, so inhibition of both hands' lift responses is required.
If, on any trial, participants lift a finger that was cued to be inhibited, or they miss interception of the target line, this is considered an unsuccessful trial.

Neural mechanisms and pathways of RI

Comprehensive evidence from many studies using transcranial magnetic stimulation (TMS) magnetic resonance imaging (MRI), intracranial and electroencephalography (EEG) and

recordings from the basal ganglia consistently demonstrated that a number of interconnected areas of the human brain are involved in RI.

Experiments have identified that cortical areas in the right inferior frontal cortex (rIFC) and pre-supplementary motor area (preSMA) play major roles in the network of RI (Aron, 2004; Aron and Poldrack, 2006; Coxon, Stinear and Byblow, 2006; Verbruggen and Logan, 2008; Majid et al., 2012; Aron, Robbins and Poldrack, 2014; Erika-Florence, Leech and Hampshire, 2014; Meyer and Bucci, 2016). Reports that TMS of the pre-SMA and lesions to the rIFC affect an individuals' ability to inhibit responses implicate that these are areas of control in RI (Aron et al., 2003; Rieger, Gauggel and Burmeister, 2003).

The basal ganglia (BG) and associated fronto-BG circuits are also thought to be crucial in RI (Aron and Poldrack, 2006; Stinear, Coxon and Byblow, 2009). The BG receives input from the rIFC and preSMA, with connections to the primary motor area (M1) forming a pathway for final motor output (Aron and Poldrack, 2006; Coxon, Stinear and Byblow, 2009; Meyer and Bucci, 2016). There are known to be three pathways originating in the cortex that travel through the BG. These have been called the direct, indirect and hyperdirect pathways, the names arising from the number of connections each pathway makes through the BG on its way back to the thalamus (see Fig. 8.1, Watkins and Jenkinson, 2016).

In broad terms, activation of the direct pathway leads to an increase in the activity of thalamus inputs to the cortical areas responsible for increasing motor behaviour, whereas the indirect pathway has the opposite effect on the same thalamic inputs and therefore an opposing influence on motor behaviour (Calabresi et al. 2014; Heckman et al. 2018). Normal movement is thought to be sub served by a balance between the pro-kinetic direct pathway and the anti-kinetic indirect pathway. The hyperdirect pathway also has an inhibitory effect on

the motor system and crucially has the capability to do so at very short latencies, due to its very direct pathway though the basal ganglia with less synapses than the indirect pathway (Aron and Verbruggen, 2008). It is thought that the neural mechanism that drives the fast action cancellation required for reactive RI is the activation of the hyperdirect pathway.

Selective vs global stopping

There are thought to be two possible mechanisms under which RI operates; selective or global stopping. Selective stopping is the ability to selectively inhibit particular responses whilst continuing other movements (Coxon et al., 2007), whereas preventing all movement with no differentiation is global stopping. Selective RI is prominent in everyday life, for example you can stop walking upon reaching a road crossing whilst continuing to have a conversation on the phone. Reactively stopping one behaviour whilst concurrently performing another makes stopping more difficult/less likely (Aron and Verbruggen, 2008), and continued execution of the other action is delayed (Coxon et al. 2007; Aron and Verbruggen, 2008). On the other hand, proactive, selective RI (where foreknowledge gives an indication of which part of a movement needs to be inhibited) does not come at such a cost to behaviour (Aron and Verbruggen, 2008; Claffey et al., 2010) because not all aspects of behaviour performed at that point in time have to be stopped.

It is important to understand that the selective or global RI presented at the behavioural level is different to selective and global neural mechanisms used to produce the RI (Aron and Verbruggen, 2008; Aron, 2011). Whilst studies (Coxon et al., 2007; Aron and Verbruggen, 2008; Ko and Miller, 2011; MacDonald et al., 2012, 2014) have shown the ability to be behaviourally selective when rapidly reacting to a ‘stop’ cue in an ARI task, it is suggested

that the need for rapid stopping in reactive RI constrains the neural mechanisms to producing a global RI, rather than the slower (but less interfering overall) mechanistically selective stopping seen with foreknowledge (Aron and Verbruggen, 2008).

Coupling and uncoupling

MacDonald et al. (2012, 2014) raised the suggestion that movement plans are comprised of sets of actions coupled together to make one plan. These movement parts must be 'uncoupled' before selective reinitiation of the necessary parts can go ahead (MacDonald et al., 2014; Ko and Miller, 2012; Coxon et al., 2007). The theory of coupling adds to the argument that reactive RI is achieved through a non-selective mechanism, because all movement components have to be stopped (MacDonald et al., 2012) before the selected components can be reactivated. MacDonald et al. (2012) found that uncoupling homologous pairs of muscles (required to activate simultaneously) was harder than uncoupling heterogenous pairs of muscles, because homologous pairs are more tightly coupled, and a greater amount of inhibition was required.

Race model

Coxon et al. (2006) replicated findings by Slater-Hammel (1960) that the further into a trial a participant gets, the harder it is for them to inhibit part of a response, with the likelihood of falsely responding increasing the later into a trial the stop cue came. A well-known explanation for this phenomenon is the 'race model' (Logan and Cowan, 1984). This framework states that the brain command process for responding and the command process for stopping are 'racing' against each other when a person is faced the possibility of going or

stopping, such as in the ARI task or stop-signal paradigm. Whichever process finishes first in 'the race' is the command that gets executed.

Transcranial magnetic stimulation (neural testing)

MacDonald et al. (2014), like many other studies investigating RI, used transcranial magnetic stimulation (TMS), to probe the activity of neurons whilst completing the RI task. Magnetic stimulation uses a coil (held parallel to the cortex) through which a capacitator is discharged, changing the magnetic field, which induces an electric current in the brain tissue underlying the coil (Barker, Jalinous and Freeston, 1985; Tofts, 1990), which flows in the opposite direction to the flow of the current in the coil. When held over the motor cortex, the magnetic stimulation of neurons leads to movement twitches in target muscles corresponding to the stimulated area of the motor cortex (Barker et al., 1985). Penfield and Boldrey's (1937) 'map' of the motor cortex, depicting where movement control for each body part is represented and the amount of control the brain has over those limbs/muscles, allows one to pinpoint specific areas of the M1 for TMS.

With the production of muscle twitches, TMS probes levels of excitability (likelihood of neurons to fire) of the corticospinal motor system. The measurement is known as corticomotor excitability (CME), identified by the amplitude of the muscle action potential, or motor evoked potential (MEP), produced by a given TMS pulse (Barker et al. 1985; Wasserman et al. 2008). It is important for the target muscle to be resting and not voluntarily contracted before and during the TMS pulse as a larger muscle twitch is elicited when the muscle is engaged. MEP amplitude is also influenced by thinking about a movement (Kiers, Fernando and Tomkins, 1997), which would occur when participants engage in a RI task and

need to be taken into account when comparing between MEPs from stimulation during the task and MEPs at rest.

There are various coil types to be used for TMS, as described by Wasserman et al. (2008). Circular TMS coils, which were used in Barker et al.'s (1985) original experiment, is the most basic coil type, forming a single circle. The secondary current is around the edge of the coil, with the magnetic field in the centre underneath the circle. Circular coils can stimulate deep into the cortex, however accuracy/focality is compromised because a large area of the cortex is covered by the coil circumference (where the secondary current runs) (Wasserman et al., 2008). Figure-eight TMS coils have two coils placed side by side, with each coil's secondary current running in the same direction at the 'junction' point of the figure-eight. The combined secondary electric currents at the figure-eight junction create a much more accurate stimulation focal point than the circular coil, but slightly weaker and therefore superficial (Roth, Zangen and Hallet, 2002; Wasserman et al. 2008; Klomjai, Katz and Lackmy-Vallee, 2015). Figure-eight coils vary in diameter and can be 'flat' (the coil handle lies at a parallel angle to the coil) or 'branding' (handle lies perpendicular to the coil). Flat, figure-eight coils were used in the current study to allow focal stimulation of the hand muscles.

Single pulse TMS causes a single, unconditioned MEP (Klomjai et al., 2015). Paired pulse TMS consists of two consecutive pulses either from the same coil or one pulse each from separate coils, with the latency between the first and second pulse labelled the inter-stimulus interval (ISI). The first pulse is called the conditioning stimulus (CS), as it has an effect on the amplitude of the second pulse, the test stimulus (TS). Pulses from the CS are non-conditioned, pulses from the TS are conditioned. Increasing or decreasing the ISI allows for the study of inhibitory and facilitatory mechanisms of intracortical (Klomjai et al., 2015; MacDonald et al., 2014) and interhemispheric (Ferbert et al., 1992; Tsutsumi et al., 2012; Rothwell, 2011;

Daskalakis et al., 2002) networks. Paired pulse TMS can be administered concurrently to performing RI tasks to study potential RI mechanisms. Paired-pulse ISIs of longer latencies (roughly 50ms) can investigate long-interval intracortical inhibition (LICI) (McDonnell, Orekhov and Ziemann, 2006), whereas ISI latencies as little as 1-3ms can investigate short-interval intracortical inhibition (SICI) (Fisher et al., 2002). Neurotransmitter gamma-amino butyric acid (GABA) is thought to be the mediator of SICI and LICI (Wasserman et al., 2008; Cirillo et al., 2018), with SICI reflecting GABAa mediation (Coxon et al., 2006) and LICI reflecting GABAb mediation of intracortical networks (Werhahn et al., 1999; Wasserman et al., 2008). The same mechanisms are considered to underlie interhemispheric inhibition networks (Chen, 2004).

IHI

The phenomenon of IHI describes a conditioning TMS stimulus (the pulse that arrives first) onto one M1 to decrease the MEP from a test stimulus (pulse arriving second) on the contralateral M1 (Ferbert et al., 1992; Chen, Yung and Li, 2003). First investigated by Ferbert et al. (1992), it has since been used to study the potential mechanisms of RI, how the hemispheres interact and ways in which IHI can affect and assist movement (Fling and Seidler, 2012; Daskalakis et al., 2002; Chen et al., 2003; Chen, 2004; Vassiliadis et al., 2018; Hiraoka et al., 2014; Hinder et al., 2018, to name a few publications). As with intracortical inhibition, there are thought to be mechanisms of short-latency IHI (SIHI) and long-latency (LIHI) (Puri et al., 2018; Tsutsumi et al., 2012; Chen et al., 2003), again being mediated by GABAa and GABAb respectively (Chen, 2004). These are suggested to operate via direct and

indirect transcallosal pathways (see *Neural mechanisms and pathways of RI* section), respectively (Puri et al., 2018). As these BG pathways receive input from the preSMA and rIFC (Aron and Poldrack, 2006; Coxon et al., 2009; Meyer and Bucci, 2016), this suggests these brain areas are also influential in IHI.

Welniarz et al. (2019) advocates for the involvement of the SMA over IHI during movement preparation, too. Hinder, Fujiyama and Summers (2012), Fujiyama et al. (2016) and Hinder et al. (2018) suggested that the modulation of IHI during movement preparation was crucial to the success of subsequent movement execution. More specifically, Hinder, Fujiyama and Summers (2012) and Hinder et al. (2018) suggested decreased IHI was seen when the required movement was revealed to participants. Similarly to reactive RI instigating a global suppression of movement but proactive RI allowing for selective suppression because of the knowledge provided, Hinder et al. (2018) found that an informative warning signal allowed for hand-specific changes to IHI.

IHI can be influenced by TS intensities, with a higher TS intensity decreasing IHI (Daskalakis et al., 2002) and increased with a higher CS intensity (Chen et al., 2003). It is common to use stimulation intensities for IHI around 90-120% of a participant's resting motor threshold. IHI is also increased by voluntary contraction of the target muscle (Mochizuki, Huang and Rothwell, 2004). Damage to the areas of the brain thought to house IHI mechanisms, caused by disease such as Parkinson's disease or stroke can negatively affect these areas' functionally activity, in turn affecting the functionality of IHI (Murase et al., 2004; Li et al., 2007).

As aforementioned, there are thought to be longer and shorter latency IHI pathways that can be probed through varying IHI latencies. Short-latency IHI (SIHI) can be investigated using around 10ms ISI and long-interval IHI (LIHI) at roughly 40ms ISI (Ferbert et al., 1992; Chen

et al., 2003). SIHI has been shown to require higher CS intensities than LIHI (Ni et al., 2009), while Uehara et al. (2013) promotes functional differences between SIHI and LIHI observed in unilateral muscle contractions. Both these characteristics could be linked to the latencies relying on different neuronal mechanisms (Chen et al., 2004; Ni et al., 2009).

The current study uses an ISI of 10ms, to investigate the SIHI mechanisms during partial RI, in an ARI task. Rationale for this comes from MacDonald et al. (2014), who studied SICI during in bimanual ARI task using dual-pulse TMS, with results suggesting partial reactive RI utilised short-latency pathways involving GABAa-mediated mechanisms (note, the same neurotransmitter thought to mediate SIHI (Chen et al., 2004)). However, crucially, MacDonald and colleagues also wrote that SICI alone could not fully explain their results of CME suppression 175ms after the stop cue was presented in Partial trials of an ARI task, because SICI did not increase at this timepoint. Cirillo et al. (2018), took this further to suggest that when requiring the need for proactive inhibition, SICI was decreased substantially, indicating GABA-ergic mechanisms play a crucial role in RI. When taking into account that a bimanual task involves input and output to and from both left and right M1, there is the possibility that structures from both hemispheres interact via transcallosal pathways (Puri, Nikitenko and Kemp, 2018), which can be studied via interhemispheric inhibition TMS techniques explained below. It is possible that interhemispheric inhibitory mechanisms are contributing to the suppression of corticomotor excitability that MacDonald et al. (2014) demonstrated 175ms after the stop cue on partial RI trials (*fig. 4*, white circles). Importantly, this MEP suppression was observed in the executed hand that was never cued to stop on partial RI trials. The current study tests whether this timepoint for MEP suppression coincides with an increase in interhemispheric inhibition onto the M1 controlling the executed hand.

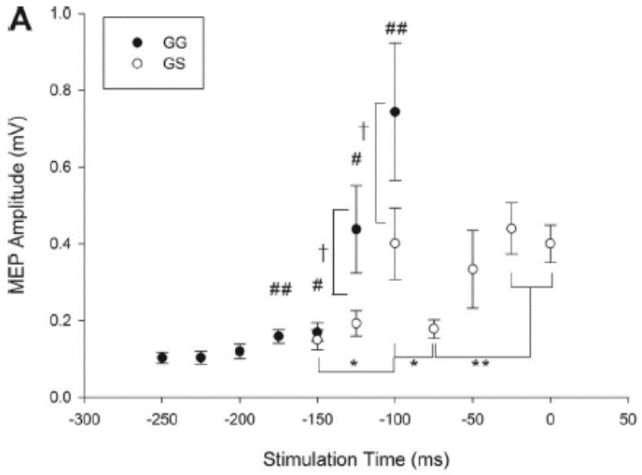

Fig 4. Modulation of corticomotor excitability relative to target, taken from MacDonald et al. (2014). Left FDI motor evoked potential (MEP) amplitudes are reported relative to the target at 800 ms during Go trials (GG) and partial RI trials (GS). The stop cue was presented at -250 ms on GS trials. Notice the decrease in MEP amplitude at -75 ms, which is 175 ms after the (irrelevant) stop cue.

IHF

Another, less well studied, example of interhemispheric interaction is interhemispheric facilitation (IHF). In their original study on IHI, Ferbert (1992) also reported seeing IHF, though the phenomenon was “capricious” in nature and difficult to replicate between stimulation blocks. Further studies have demonstrated that IHF can be elicited with a similar CS to that used in IHI but at shorter inter-stimulus intervals. For example, IHI is typically seen if the TS is given around 10ms after a CS in the opposite hemisphere (which is the chosen ISI in this study). IHF is seen if the test stimulus is given around 4-5ms after the conditioning stimulus (Hanajima et al., 2001). It appears that IHF is a less robust phenomenon that IHI, and though we will not be assessing it directly in this study, it is of note that there appears to be both inhibitory and facilitative processes.

Aims and Hypotheses

Aim

To investigate whether interhemispheric inhibitory mechanisms contribute to behaviour and the modulation of the CME during partial RI.

Hypotheses

1) We will replicate previous results that excitability will increase during Go trials when participants are expecting to intercept the target through simple bimanual movement execution.
2) During partial RI trials, there will be an increase in IHI 175ms after the stop cue onto the hemisphere controlling the delayed response.

Chapter 2

Protocol development

Coil orientations

Figure-eight coils can be orientated so that the current flow in the brain is going in different directions. Orientations include posterior-anterior (PA), lateral-medial (LM), and anterior-posterior (AP), with the letter abbreviations reflecting the direction of the current through the brain, not through the coil itself. Research has suggested PA at a 45 degree angle to the parasagittal plane to be the optimal figure-eight coil orientation for eliciting the largest responses from small hand muscles (Brasil-Neto et al., 1992; Rothwell et al., 1999; Weber and Eisen, 2002) whilst requiring low thresholds for eliciting the MEPs (a steep stimulus-response curve) compared to other orientations (Chen et al., 2003). Concurrently, Chen et al. (2003) stated IHI showed no directional coil preference.

In the current study, pilot studies revealed a difficulty in fitting a figure-eight coil over each M1 in the optimal orientation, despite using the smallest figure-eight available to the laboratory (7.7cm diameter). It was decided to TS coil would remain in PA orientation, but the CS coil would be laterally rotated 45 degrees from the PA orientation so that the coil arm was perpendicular to the parasagittal plane of the skull (*fig. 5*) and the current flowed LM in the brain. The altered orientation would be as close to the PA orientation as possible without interfering with or compromising the position of the TS coil and allowed for consistency in coil placement between participants. This CS compromise was deemed acceptable as no specific MEP amplitude was required from the CS, as explained in the *TMS* section of *Methods* below. The rotation of the CS coil would occur after the most appropriate position

on the scalp for stimulating the first dorsal interosseous (FDI) muscle, the target muscle in the current study, had been identified.

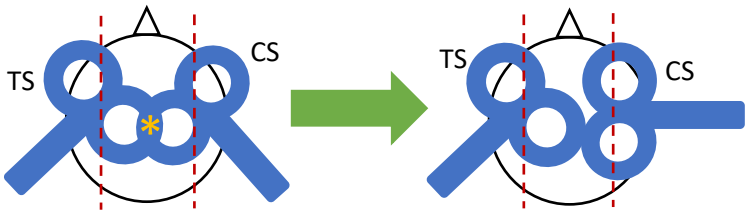

Fig. 5. Keeping both coils in the optimal orientation for the lowest threshold intensity when hotspotting the M1 area would often result in an overlap of the coils (*). After piloting, the decision was made to orientate the CS coil to 90 degrees to the parasagittal plane for all participants, enabling the CS coil to lay flat and the TS coil to remain at optimal orientation (45 degrees to parasagittal plane) without interference. Parasagittal planes for each brain hemisphere are represented by red vertical dashed lines.

METHODS

Participants

A total of 27 healthy adults between 18-50 years old and with no known neurological impairment (mean age 24.6 ±6 years, 10 male) took part in this study. All self-reported as being right-handed. Participants received monetary compensation for taking part in the experiment. Ethical approval was obtained from the University of Birmingham Ethics Committee (ERN_15-1573).

The task

Equipment and setup

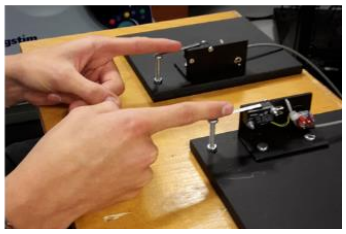

Fig. 6. Photograph displaying the resting hand position during the task.

The task was displayed on a computer monitor (47.8 x 27 cm) at eye-level, approximately 1.3m in front of the participants, who were seated upright in a comfortable chair with head and footrests. Two custom-made microswitches were situated on a table in front of participants, on which they were able to rest their wrists/forearms (see *fig. 6*). Participants would rest the tips of their index fingers (medial edge) onto the switches, depressing the weight-sensitive switches with the relaxed weight of their hands. Two clamps attached either side of the head rest held the two TMS coils in place throughout the task. Each M1 was stimulated by a flat, figure-eight (wing diameter 7.7cm) taped TMS coil and Magstim200 unit. Surface electrodes using a belly-tendon montage were placed on the first-dorsal interosseous (FDI) muscle of each hand, with a ground electrode placed on the bony prominence of the left elbow. Electrode signals were filtered (20-1000

Hz), amplified and recorded for offline analysis with Signal Software (Cambridge Electronic Designs, version 6.04).

The task was controlled using custom software written in MATLAB (the MathWorks; MacDonald et al., 2014). The microswitches were monitored by an arduino (Arduino, 2019), which in turn communicated with MATLAB via an analogue-to-digital USB interface (NI-DAQmx; National Instruments, 2019) to display the task on the computer monitor. The arduino also triggered the TMS machines and Signal during the task.

Anticipatory Response Inhibition Task

An ARI (Slater-Hammel, 1960; Coxon et al., 2007; MacDonald et al., 2012, 2014) task was used to investigate RI. The monitor displayed two white vertical narrow rectangles (1.8cm x 21.6 cm) at the start of each trial; the right rectangle corresponded to the participants' right switch and the left rectangle corresponded to the left switch (*fig. 7*). Participants depressed both switches with the medial (to keep the hand in a posture that ensured finger abduction using the FDI) tips of their index fingers to begin each trial. After a variable delay of 400-900ms the two black bars would rise within the rectangles at the same rate towards a fixed horizontal target line, intercepting the line 1s after trial onset. (*fig. 7*). On most trials, known as **Go** (GG) trials, the aim was to stop both bars as close to this target line as possible, by using index finger abduction to lift both fingers simultaneously off the switches. If both bars were stopped within 30ms of the target, the target line went green and "Success" was displayed on-screen; otherwise, the bar turned red and "Miss" was displayed (*fig. 7*). Occasionally, one of the two or both bars would cease rising before reaching the target line (Stop trials, *fig. 9*). **On 'Stop Both'** (SS) trials, both bars would automatically stop rising and

participants would have to inhibit both fingers. The trials in which one finger was inhibited were Stop Partial trials, split into two types: **'Stop-Left, Go-Right'** (SG) trials, requiring the participant to inhibit the left finger-abduction response but still stop the right bar at the target line by lifting the right finger, and **'Go-Left, Stop-Right'** (GS) trials, requiring the participant to prevent the right-hand finger-abduction response but still stop the left bar at the target line. The pairing of letters denotes the spatial mapping of index fingers, for example SG: the letter on the left represents the action of the left finger (Stop), and the letter on the right represents the action of the right finger (Go).

As on Go trials, feedback was displayed similarly on Stop trials (*fig. 9*). On SS trials, only if both switches remained depressed when the bars stopped was 'Success' displayed on-screen. On GS and SG trials, if a participant failed to keep one finger on the switch, the feedback 'Failed Stop' was shown. If the participant successfully inhibited the corresponding lift response, but missed the target with the other bar, the screen would display 'Successful stop but missed target'. If the participant performed both elements of the trial correctly, i.e. inhibiting their response and intercepting the target line with the other bar, the feedback would read 'Success'.

All participants completed on average two-to-three practice blocks, each comprised of 35 Go trials. Practice blocks ensured participant familiarization and were used to set TMS stimulation intensities (see TMS section). For the first practice block, the first five trials were unstimulated, then followed 30 stimulated practice trials; any practice block(s) thereafter had stimulation on all trials. The task proper was comprised of 600 trials total split into 10 blocks of which 420 were Go trials (120 stimulated) and 180 were Stop trials (all stimulated), split equally between the three Stop trial types.

Staircase procedure

Participants were kept to a 50% trial success rate by varying the task difficulty. Presenting the Stop trial cue later after trial onset (increasing Stop Signal Delay, SSD), made the task harder as participants had less time to react, and vice versa when presenting the cue earlier in the trial (increasing SSD). The stop cue was set to 600ms after trial onset (200ms before target) for each participant and was altered in increments of 25ms. Differences in ability made it necessary to tailor task difficulty to each participant, to standardise the experience of each participant, as is standard with most stop-signal tasks (Logan and Cowan, 1984).

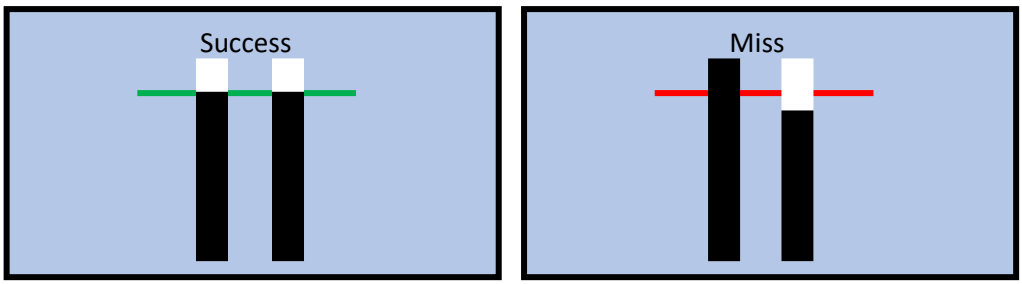

Fig. 7. Examples of the monitor display at the end of a successful (A) and unsuccessful (B) Go trial (GG). The bars could be stopped within 30ms of the target line before being considered a miss.

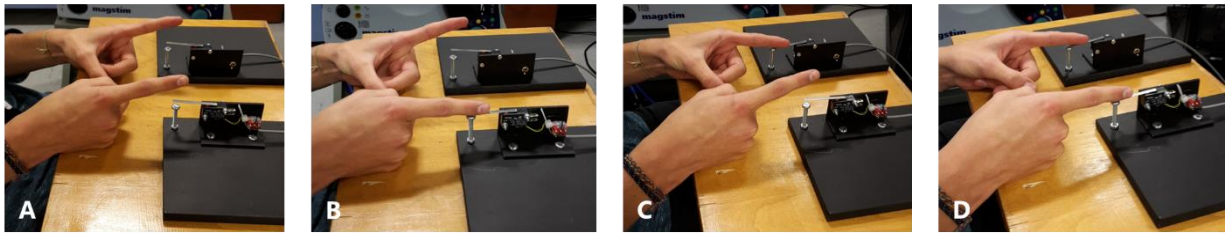

Fig. 8. Desired hand positions of each trial type. A) ‘Go’ trial; both fingers lift (abduction) off the switches when bars reach the target line. B) ‘GS’ trial; right bar has stopped early, serving as the cue for the right finger-abduction to be inhibited, instead remaining on the switch. C) ‘SG’ trial; left finger-abduction is inhibited. D) ‘SS’ trial; both lifts inhibited.

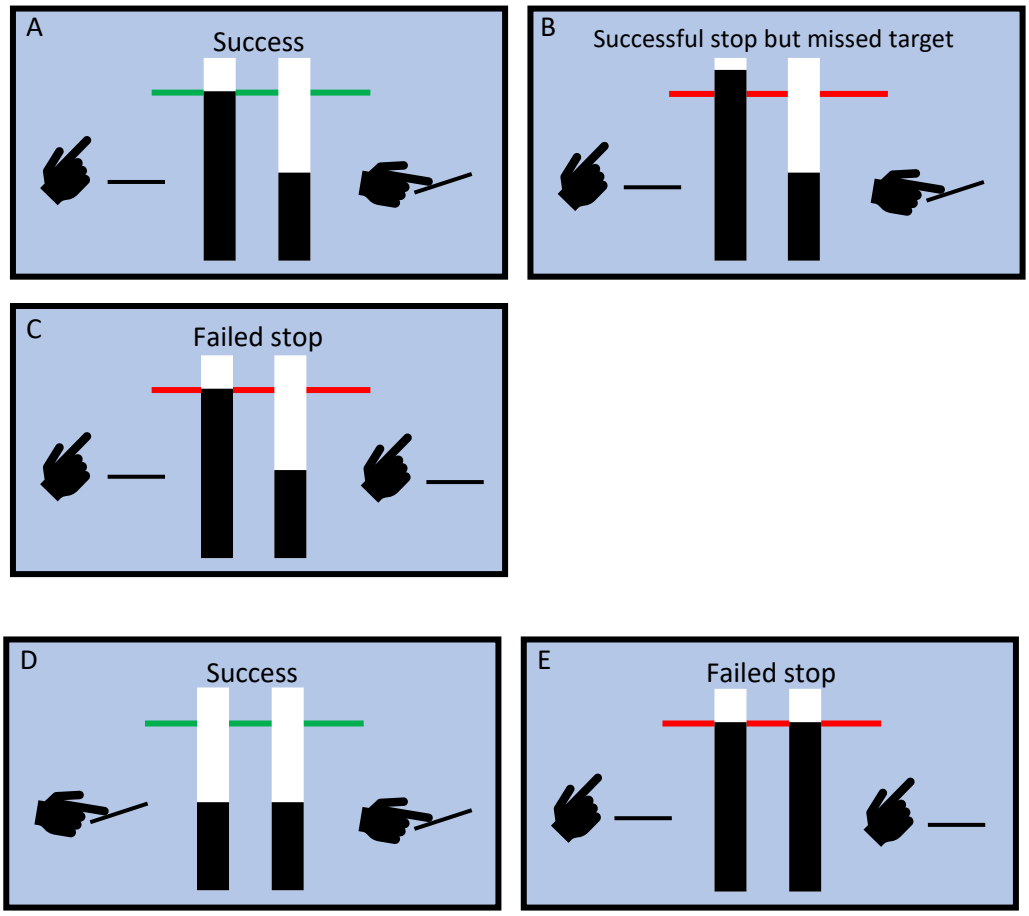

Fig. 9. Examples of potential finger-abduction behaviours and the consequent monitor displays at the end of different types of Stop trials. **A)** a successful GS trial (a Stop Partial trial: Go-Left, Stop-Right). **B)** a partly successful GS trial, where the participant successfully withheld their right-hand finger abduction response but failed to intercept the target line with the left-hand bar. **C)** an unsuccessful GS trial; the participant failed to withhold their right-hand abduction response. **D)** a successful SS trial; the participant withheld both finger-abduction responses. **E)** an unsuccessful SS trial; the participant failed to withhold finger-abduction responses in both hands.

TMS

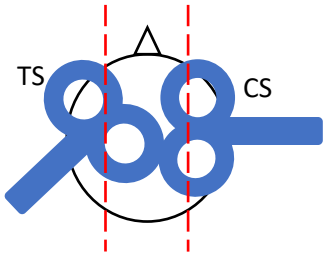

Fig. 10. Coil orientation for a participant in the Right FDI group. TS coil was kept in the optimal (45 degrees from the parasagittal plane) position for hotspotting FDI. CS coil was hotspotted at 45 degrees then rotated to 90 degree from the parasagittal plane for the remainder of the testing session.

The TMS coils were positioned tangentially to the head with the test stimulus (TS) coil orientated at 45 degrees and the conditioning stimulus (CS) coil at 90 degrees to the parasagittal plane of the skull, inducing a PA or LM current respectively (*fig. 10*). Coil orientation is important, in that different coil orientations are known to stimulate different subpopulation of neurones. However, in the context of supplying a CS for IHI orientation is not a factor for two reason: i) no specific MEP amplitude was required from the CS, as the CS was deemed to be the amplitude of stimulation of the ipsilateral M1 that provided a 50% decrease in the TS and so could be adjusted until this criterion was fit (see methods). ii) Previous work has shown that the CS for IHI show no preference for coil orientation (Chen et al., 2003). To locate the FDI hot spot, the optimal position of each coil (that caused the biggest visible muscular twitch in the FDI muscle of each hand) over each brain hemisphere was identified and marked on the scalp. Participants in the Left FDI group (n = 13, 5 male, 23.8 ±4.4 years) received the TS over the right M1 (stimulating left FDI), and participants in the Right FDI group (n = 14, 5 male, 25.4 ±7.1 years) received the TS over the left M1. The protocol for obtaining appropriate stimulation intensities for the task proper was as follows: **1)** Task motor threshold (TMT) was determined one hemisphere at a time and was taken as the minimum percentage Maximum Stimulator Output (%MSO) required to obtain a MEP of 0.05mV four out of eight consecutive stimulations. This was labelled as TMT and not resting motor threshold (RMT) because participants' FDIs were completely at rest, but their hands were resting on the switches in the trial starting position. **2)** Through single-coil stimulation,

%MSO of the TS coil was altered in 1-5% increments from TMT until an average of 1.5mV was obtained. **3)** Using dual-coil stimulation, with an inter-stimulus internal (ISI) of 10ms, intensity of the CS coil (having been re-orientated to 90 degrees from parasagittal plane, see *fig. 10*) was then increased in 2% increments to achieve a roughly 50% inhibition of the non-conditioned (NC) MEPs of the TS hemisphere. Although previous studies (MacDonald et al., 2014) set out to obtain equal TS MEPs in the region of 1 or 1.5mV in each hemisphere at this stage of TMS set up, due to the difficulty of positioning the TS coil at the best (90 degrees) orientation to elicit MEPs, we allowed the CS MEP to be smaller as long as the CS coil consistently produced a 50% inhibition onto the TS. Participants were instructed to rest their hands on the task switches throughout setting the stimulation levels. **4)** The same dual coil set up was used during practice trials, where stimulation came 200ms after trial onset, to obtain an average NC MEP on the TS hemisphere of 1mV, and 50% inhibition of the TS when conditioned.

Once practice trials were complete with satisfactory IHI measurements, the task proper was started using the %MSO obtained from Practice trials. Half of the task trials were stimulated; **non-conditioned** (NC) MEPs were recorded from trials when the **TS** pulse fired **first**, whereas **conditioned** (C) MEPs were recorded from trials when the **TS** pulse fired 10ms **after** the CS pulse. For the current study, on Go trials (*fig. 11*), NC MEPs were recorded at 190, 565, 615 and 665ms after trial onset, and C MEPs at 200, 575, 625 and 675ms after trial onset, with these stimulation timepoints being pseudorandomized for each task. A 10ms inter-stimulus interval (ISI) was chosen to investigate the short-latency mechanisms of IHI (Ferbert et al., 1992). The 190ms NC / 200ms C MEP timepoint was included in the task proper to use as a baseline comparison to the Practice trials, which allowed for the assurance that brain activity was 'starting on the same page' each trial regardless of the possibility of Stop trials.

On Stop trials, NC MEPs were recorded 165ms after the stop cue and C MEPs 175ms after the cue. These stimulation times for Stop and Go trials were designed with the knowledge that response time sees a delay of roughly 100ms on Stop trials compared to Go trials (Coxon et al., 2007; MacDonald et al., 2012, 2014, Duque et al., 2017).

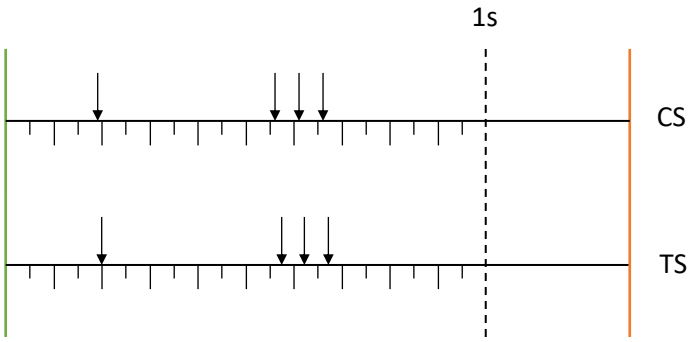

Fig. 11. The various stimulation pulse timepoints for CS and TS during Go trials, when C MEPs were recorded, represented by vertical, down-facing arrows. Vertical dashed line represents the timepoint in the trial where the bars would reach the target line, 1s post trial onset. CS timepoints were 190, 565, 615 and 665 ms post trial onset. TS timepoints were 200, 575, 625 and 675 ms post trial onset. When NC MEPs were recorded, CS and TS timepoints were swapped.

Data analysis

Dependent measures – behavioural data

Average lift times (LTs) relative to stop target, reported in seconds to three decimal places, were determined for all Go trials, and successful Stop Partial trials (LT from the responding finger). LTs were removed if they were three standard deviations (SD) above or below the mean LT, to exclude outliers (roughly the top and bottom 10%). LTs on unstimulated Go trials were compared with stimulated Go trials to confirm that the TMS pulse did not influence behaviour. Stop trial success rates were recorded to check that a 50% success rate was achieved. Stop signal reaction time (SSRT) was calculated using the integration method

(Logan and Cowan, 1984). LTs for SS, GS and SG trials were rank ordered within trial type and the *n*th number selected, *n* obtained by multiplying the number SS, SG or GS trials by the probability of stop signal response.

Dependent measures – TMS data

Average peak-to-peak amplitudes for NC and C MEPs were calculated for each participant by trimming the top and bottom 10% of MEPs for each trial type and stimulation time. Percentage inhibition (%IHI) was calculated as 100 – ((C MEP / NC MEP) * 100). Root-mean-squared (RMS) EMG was calculated over a 50ms window from 12-62ms before the TMS pulse. If the RMS value was above 15μV, the trial was excluded from analysis. This value was based on previously used RMS cut-off points from at-rest MEPs of 10μV (MacDonald et al., 2014), therefore 15μV was decided as appropriate for an FDI preparing to be activated.

Statistical analysis

Mixed effects (ME), repeated measures (RM) analysis of variance (ANOVA) were used on dependent measures. LT was subjected to a two-group (L and R) × two-digit (left FDI and right FDI) × two trial type (Go and Partial) ME RM ANOVA. The success of the staircase to achieve 50% success for Stop trials of each stop type were confirmed using a within-group t-test, with $\alpha \leq 0.05$ indicating statistical significance. SSRT was subjected to a three-trial type (Stop Both, Stop Left, Stop Right) × two-group (L and R) ME RM ANOVA.

A two-group (L and R) × six stimulation time ME RM ANOVA tested for differences in Go trial excitability (NC MEPs), with the same design used to compare % inhibition (C MEPs). Root mean squared (RMS) comparison also used a two-group (L and R) × six stimulation time ME RM ANOVA, again with NC MEPs used to investigate excitability and C MEPs for % inhibition. A two-group (L and R) × three trial type (Stop Both, Stop Left, Stop Right) ME RM ANOVA was used to compare excitability and % inhibition for Stop trials. Go and Stop trials MEPs were compared for excitability and % inhibition using a between groups ANOVA.

The conservative Greenhouse-Geisser *P* value is reported for non-spherical data, with $\alpha \leq 0.05$ the criterion for significance. Post hoc paired *t*-tests were used to test interactions and main effects. All results are shown as mean ± standard error (SE).

RESULTS

Behavioural data are presented for n = 14 for Right FDI Group, n = 13 for Left FDI Group. TMS data are presented for n = 10 for Right FDI Group and n = 10 for Left FDI Group. The difference in group size is due to the fact that TMS data could not be collected or reliably analysed for some participants who had a TS that required more than 70% maximal stimulator output (%MSO). Confirmation that the TMS pulses themselves had no influence on participant behaviour was assessed through paired *t*-test comparison of LTs on stimulated and unstimulated Go trials, for both Right and Left FDI Groups. This comparison revealed there were no significant differences between stimulated and unstimulated Go trials for either Group (all $p > 0.079$).

Behavioural data: percentage maximal stimulator output, lift times, success rate, bar stop time

Average stimulation intensity in the task for the TS of the R FDI Group was 52 ± 3 %, with CS at 57 ± 1 %MSO. As expected, this is above the average TMT of 44 ± 2 %MSO and 47 ± 2 %MSO for the TS and CS respectively. For the Left FDI Group, TS was 58 ± 2 %MSO, and CS at 58 ± 2 %. TMT for the Left FDI Group were 49 ± 2 %MSO for the TS and 47 ± 3 %MSO for the CS. Differences between the Left and Right FDI Group are expected as a consequence of dominant and non-dominant brain hemispheres. CS intensity for both groups were ~120% of TMT.

The RM ANOVA produced a main effect on lift time (LT) of Trial Type ($F_{1,25} = 61.81$, $p < 0.001$; *fig. 12*). With the target interception at 800ms from trial onset, there was an average LT (relative to trial onset) of 813 ± 2 ms on Go trials collapsed across digit, compared with an

average of 861 ± 7 ms on Stop Partial trials, a significant difference of 48 ± 6 ms, (t_{13} = -7.675, $p < 0.001$). There were no other significant main effects or interactions (all p > 0.272). Both groups showed the expected lift time delay on Stop Partial compared to Go trials, and this delay was comparable between the left and right fingers.

For SSRT (*fig. 13*), a RM ANOVA produced a main effect of Trial Type ($F_{1.4,33.4}$ = 15.177, $p < 0.001$). There was a significant difference of 64 ± 14 ms (t_{25} = -5.202, $p < 0.001$) between SSRT of SS (231 ± 6 ms) and SG (295 ± 12 ms) trials, a significant difference of 118 ± 28 ms (t_{25} = -4.829, $p < 0.001$) between SS and GS (350 ± 28 ms) trials, and a significant difference of 54 ± 24 ms between SG and GS trials (t_{25} = -2.246, $p = 0.034$). There were no other main effects or interactions (all $p > 0.312$). Replicating previous studies (Coxon et al., 2007), stopping all components of the prepared response was faster than stopping either component individually.

Success rate for each Stop trial type (*fig. 14*) of each group was calculated and compared to a 50% success rate. In the Right FDI group, SS success (49.2 ± 0.6 %) was not different from 50% (t_{13} = -1.321, $p = 0.209$). However, the SG trial success rate of 48.5 ± 0.6 % (t_{13} = -2.793, $p = 0.015$) and GS success rate of 46.9 ± 0.9 % were significantly different from 50% (t_{13} = -3.538, $p = 0.004$). For the Left FDI group, SS success rate of 49.6 ± 0.6 % (t_{12} = -0.686, $p = 0.506$) was not different from 50%. However, SG success rate of 46.9 ± 1 % (t_{12} = -3.164, $p = 0.008$) and GS success rate of 46.3 ± 0.7 % (t_{12} = -5.557, $p < 0.001$) were significantly different from 50%. Participants found partial stopping much harder than inhibiting all responses. It is also worth noting that the difference in success rate between SG and GS trials was significant in the Right FDI Group (t_{13} = 2.303, $p = 0.038$), but not the Left FDI Group ($p = 0.587$). Participants had the highest Partial trial success rate with the trial that required continuation of the finger-abduction response from the *dominant* hand (SG). The deviation

from 50% success for Partial trials confirms the appropriate use of the integration method for calculating SSRT because the alternative 'mean' method assumes a success rate of 50%, which in this case would have provided inaccurate data analysis.

Comparing between average bar stop times (from trial onset) on Stop trials (*fig. 15*) produced a main effect of Trial Type ($F_{2,50} = 16.085$, $p < 0.001$). There was also a significant difference between the SS bar stop time (0.577 ± 0.006 s) and SG (0.479 ± 0.025; $t_{26} = 4.133$, $p < 0.001$), and between SS and GS (0.438 ± 0.033 s; $t_{26} = 4.709$, $p < 0.001$). There were no other main effects or interactions (all $p > 0.086$).

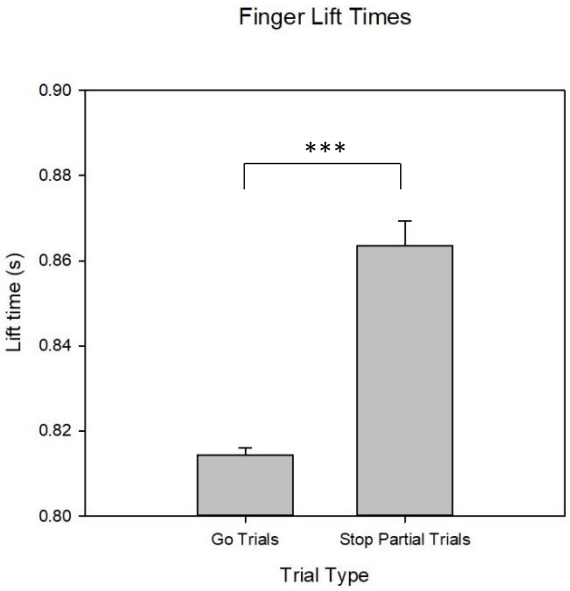

Fig. 12. Average finger lift response times for Go trials and Stop Partial trials (SG and GS collapsed across trial type). *** = $p < 0.001$.

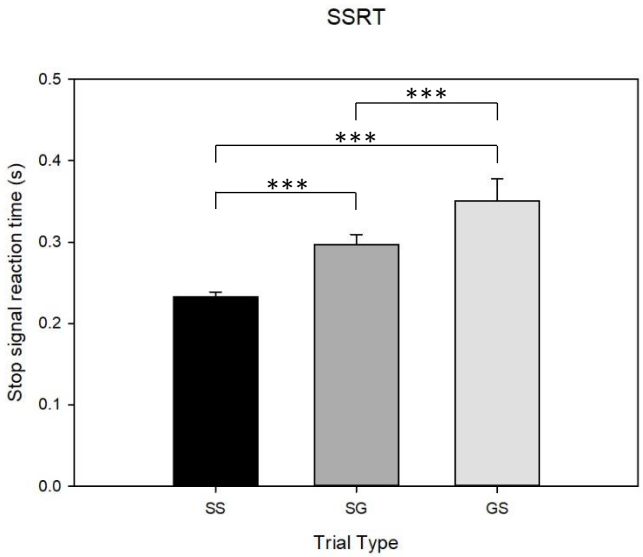

Fig. 13. Stop Signal Reaction Time. *** = $p < 0.001$.

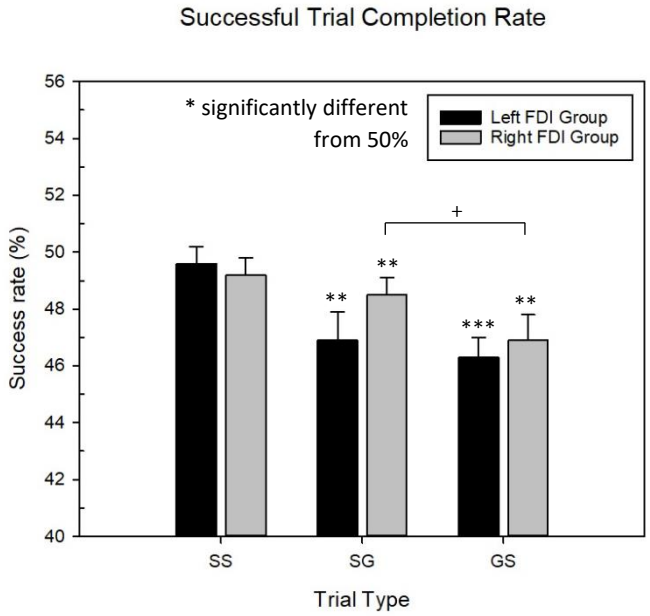

Fig. 14. Success rate, for each group, of each Stop trial type. ** = $p \leq 0.01$. *** = $p < 0.001$. + represents a significant difference in success rate between SG and GS trials of the Right FDI Group ($t_{13} = 2.303$, $p = 0.038$).

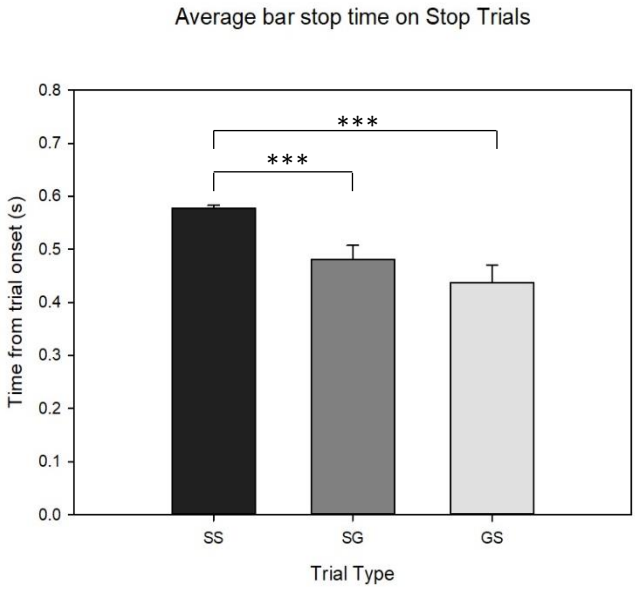

Fig. 15. Average bar stop time for each Stop trial type, collapsed across groups. *** = $p < 0.001$.

TMS data: root mean squared, motor excitatory potential and %IHI on Go and Stop trials

An RM ANOVA on Go trial Excitability (*fig. 16*) produced a main effect of Stimulation Timepoint ($F_{3.3,62.2} = 6.82$, $p < 0.001$), with no other significant main effects or interactions ($p > 0.165$). There was no significant difference in MEP amplitude between Rest (1.15 ± 0.10 mV) and Practice (1.05 ± 0.07 mV; $p = 0.203$) or between Practice and Go190 (0.92 ± 0.15 mV; $p = 0.414$). Comparable MEP amplitudes confirm no change to overall excitability when the possibility of RI (Stop trials) was introduced following the practice blocks and affirms the use of the 190ms timepoint as an appropriate baseline to compare with later timepoints on Go trials. There were no significant differences between the Go190 baseline timepoint and later into the trial at Go565 (0.72 ± 0.11 mV; $p = 0.083$) or Go615 (0.88 ± 0.10 mV; $p = 0.810$). However, there was a significant increase of 0.45 ± 0.12 mV ($t_{20} = 3.747$, $p = 0.001$) from Go190 to the last timepoint, Go665 (1.4 ± 0.12 mV). Excitability on Go trials 'ramped up'

when the bars were close to the target line. For RMS, there was a Stimulation Time x Group interaction on Go NC trials ($p = 0.020$). *T*-tests revealed no significant differences between groups at each timepoint ($p > 0.061$), but a significant decrease from rest to practice timepoints in the Right FDI Group ($t_{10} = -2.956$, $p = 0.014$). These significant differences in RMS do not directionally coincide with significant differences in MEP value.

For % IHI on Go trials (*fig. 17*), an RM ANOVA produced a main effect of Stimulation Timepoint ($F_{2.9,51.7} = 15.336$, $p < 0.001$), with no other significant main effects or interactions ($p > 0.383$). There was no significant difference between Rest (52 ± 4 %) and Practice (48 ± 4 %). However, there was a significant decrease of 17 ± 5 % ($t_{19} = 3.382$, $p = 0.004$) from Practice to Go200 (30 ± 7 %). There was no significant difference ($p = 0.091$) between timepoints Go200 and Go575 (17 ± 6 %). Conversely, there was a significant decrease of 28 ± 7 % ($t_{19} = 4.115$, $p = 0.001$) from Go200 to Go625 (3 ± 8 %), and a significant decrease of 39 ± 12 % ($t_{19} = 3.220$, $p = 0.005$) from Go200 to Go675 (-8 ± 9 %). Both groups showed a decrease in % IHI the later into a Go trial they were stimulated. When participants had the knowledge that inhibiting responses would be a possibility, IHI mechanism activity decreased. For RMS, there was a main effect of Stimulation Time ($p = 0.004$) and a Group x Stimulation Timepoint interaction ($p = 0.036$). However, post-hocs revealed no significant differences at timepoints collapsed across groups (all $p > 0.377$), between groups (all $p > 0.120$), or within groups (all $p > 0.337$).

An ANOVA revealed no significant main effects or interactions for Excitability on SS (0.91 ± 0.11 mV), SG (0.72 ± 0.08 mV) or GS trials (0.89 ± 0.09 mV), for Trial Type ($F_{2,38} = 2.433$, $p = 0.101$) or group ($F_{2,38} = 0.963$, $p = 0.391$). At 175ms after the stop signal, excitability is comparable between all stop trial types, suggesting there are comparable levels of excitability between partial and complete behavioural stopping, as well as between the responding and

cancelled fingers on Partial trials (as shown by a lack of Group effect), collectively provides further evidence for the same non-selective inhibitory mechanism being engaged across all types of RI. There were no significant differences in RMS (all $p > 0.156$).

For %IHI on Stop trials (*fig. 18*), there was significant Trial Type x Group interaction ($F_{1.5,27.6} = 9.963$, $p = 0.001$). Within the Right FDI group, %IHI was significantly greater ($t_9 = 2.680$, $p = 0.025$) for SS trials (20 ± 9 %) than SG trials (-46 ± 21 %). GS trials (24 ± 5 %) also had significantly greater %IHI than SG trials ($t_9 = -3.271$, $p = 0.010$). Within the Left FDI group, the only significant difference came in %IHI of SS trials (8 ± 7 %) being less than that of SG trials (27 ± 7 %; $t_9 = -2.466$, $p = 0.037$). There was no significant difference in %IHI between Left FDI Group and Right FDI Group in both SS and GS trials (both $p > 0.268$). In SG trials, The Left FDI Group's %IHI of 27 ± 7 % was significantly greater than the Right FDI Group's -46 ± 21 %, a mean difference of 73 ± 22% ($t_{10.9} = -3.310$, $p = 0.007$). Whilst SS and GS trials had no difference in IHI onto responding and inhibited fingers, the SG trials did show a dissociation between the two fingers and a release of IHI onto the responding finger. For RMS, there was a main effect of Trial Type ($p = 0.002$) and a main effect of Group ($p = 0.031$). Collapsed across Trial Type, Right FDI Group RMS (3.1 ± 0.2 μV) was significantly greater than Left FDI Group RMS (2.4 ± 0.2 μV; $t_{32} = 2.532$, $p = 0.016$). Collapsed across Group, SS RMS (3.3 ± 0.3 μV) was significantly greater than SG RMS (2.6 ± 0.2 μV; $t_{23} = 2.850$, $p = 0.009$) and GS RMS (2.3 ± 0.2 μV; $t_{23} = 3.448$, $p = 0.002$). Importantly, there was no Group x Trial Type interaction ($F_{1.5,33.5} = 0.391$, $p = 0.632$) that mirrored the pattern of IHI results. Background muscle activity before the TMS pulse in the task was unlikely to influence our IHI results.

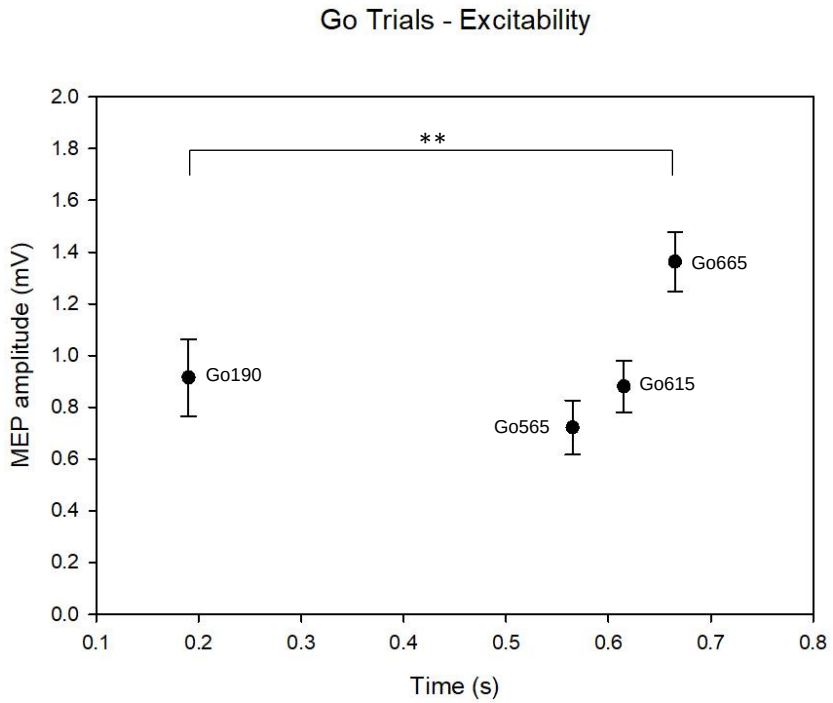

Fig. 16. Amplitude for NC MEPs (excitability) at each stimulation timepoint during Go trials, collapsed across groups. ** = $p \leq 0.01$. Practice trial excitability not included as non-significant when compared to equivalent timepoint in the task proper ($p = 0.203$).

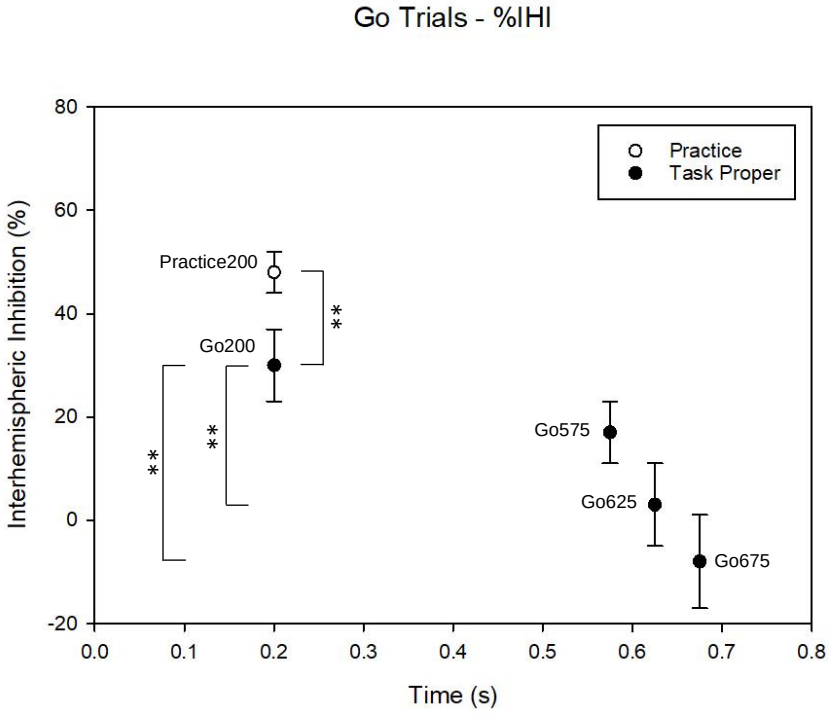

Fig. 17. %IHI taken for Practice Trials (clear plot) and the four stimulation timepoints of Go trials in the task proper (filled plots). ** = $p \leq 0.01$.

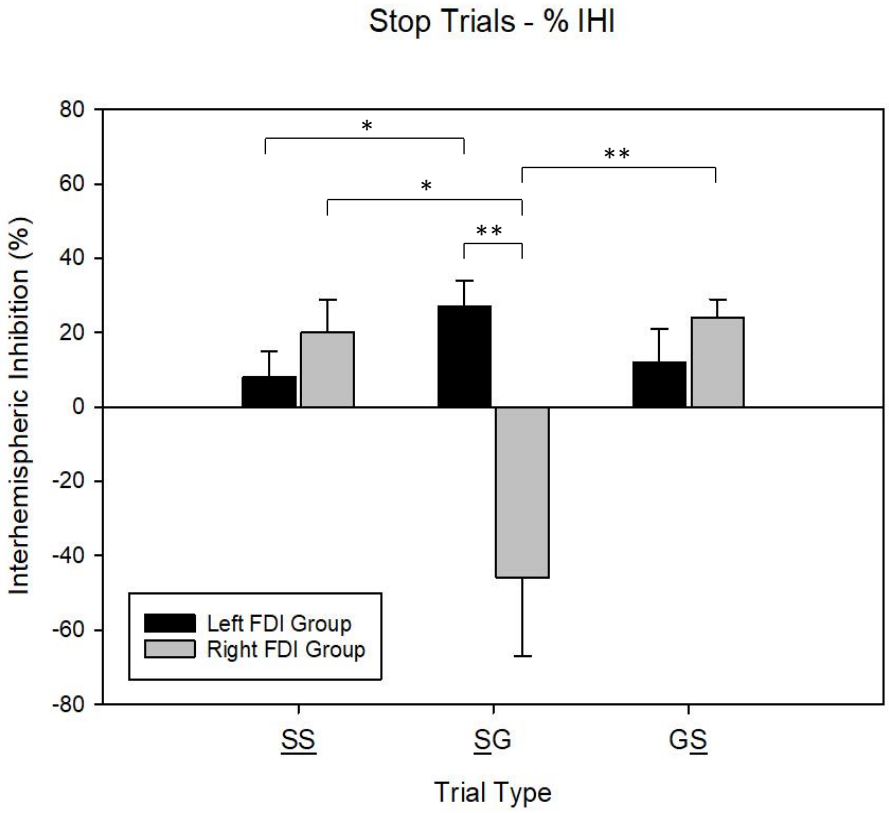

Fig. 18. %IHI on each Stop type, for each group. * = $p \leq 0.05$, ** = $p \leq 0.01$. The FDI(s) finger-abduction response being inhibited is underlined for each χ axis label.

DISCUSSION

Summary and novel findings

The present study replicates the previous finding from MacDonald et al. (2014) that CME of the FDI increases during a Go trial when no inhibition is required. It was also more difficult to inhibit part of a planned response whilst continuing execution of other movements (as opposed to inhibiting the whole prepared response), judging by decreased success rate and longer stop signal reaction times for Stop Partial trials compared to Stop Both Trials. CME rose throughout standard Go trials prior to responses, and IHI decreased over the same time period. Contrary to our hypothesis, IHI was not responsible for global suppression during partial IHI. After the stop cue on SG trials, IHI was increased onto the inhibited FDI and decreased onto the responding FDI compared to Stop-Both Trials. From this final finding, we suggest IHI is instead the mechanism used to uncouple motor responses when only partial cancellation of a movement is required. We predict that the dissociation in IHI between hemispheres occurs at a slightly later time point on the more difficult GS trials compared to SG trials, corresponding to the longer SSRT in the GS condition.

Lift Times

Participants performed as expected, not delaying their responses to increase the probability of responding to a stop cue, as demonstrated by the group average Go LT being only 13ms after the target line. Furthermore, Stop Partial trial LTs were significantly delayed by around 50ms compared to Go trial LTs, replicating previous studies that used the ARI task (Coxon et al., 2007, 2009; Stinear et al., 2009; MacDonald et al., 2012, 2014). The neurological processes

required to respond during partial movement cancellation (Stop Partial trials) appear more complex and therefore take longer to execute compared to simple movement execution (Go trials). Behaviour on SS trials was also as expected and can be explained by the race model, whereby successful stopping would have required the stop process to finish before the Go process in the 'race' (Logan and Cowan, 1984). The race model is also an accepted explanation of successful vs unsuccessful RI in the SST (Hughes, Fulham and Michie, 2016).

Stop Signal Reaction Times

The current study found that the response to a stop cue was faster when all components of the response (SS trials) were inhibited, replicating findings by Coxon et al. (2007). Combining this finding with both SG and GS stop types having success rates significantly less than the 50% target (whereas SS did not), it can be concluded that participants found Stop Partial trials significantly harder than Stop Both. This inference further supports the theory by MacDonald et al. (2012) that behaviour on partial RI trials requires global stopping, uncoupling and reinitiating motor plans, because responses to SS trials don't require uncoupling or reinitiation of movement so should technically be faster to execute than Partial trials.

SSRT was longer for GS trials than SG trials, indicating GS was a more difficult task condition. SG trials requires a continuation of the finger-abduction response from the participants' right hand, crucially their dominant hand (all participants were right-handed). Bar stop times were not significantly different between SG and GS trials, so the stop cue was coming at comparable timepoints in the two types of trials. Findings by MacDonald et al. (2014) indicate the suppression as a result of seeing the stop cue is non-selective and should thereby occur in both trial types at the same time. Therefore, only the process following non-

selective inhibition (namely the uncouple-reinitiate process) takes longer when the non-dominant FDI still needs to respond to task demands.

TMS data: Go Trials

As with the results of MacDonald et al. (2014), excitability on Go trials was seen to 'ramp up' the closer the bars got to the target line. This pattern of CME during anticipation of action has been seen in several studies (Chen et al., 1998; Duque et al., 2010; Marinovic et al., 2013). The increase in CME in a temporally expected manner supports the use of the ARI task, as participants were in a state of higher excitability for movement anticipation and preparation at the time of the stop cue, enforcing reactive RI without allowing participants to use a waiting strategy to increase the probability of responding to the stop cue. Although crucially, pretrigger rmsEMG remained at resting levels throughout the task and for all the analysis, indicating participants had not started to initiate muscle activation at the time of stimulation. This implies any modulations observed in MEP amplitude reflects modulation at a cortical level.

Concurrently to CME, participants showed a decrease in %IHI the further into the Go trial, and closer to response execution, they got. Interestingly, %IHI was significantly lower at the beginning of Go trials (stimulation timepoint Go200) than at the same timepoint in Practice Trials (200ms after trial onset). When the knowledge of the possibility of RI was introduced, IHI reduced in Go trials. This kind of reduction in inhibitory control of around 20% has been show previously in relation to intracortical mechanisms (Coxon et al., 2006; MacDonald et al., 2014) and is suspected to result from an increased state of attention during the more difficult task conditions when Stop trials are introduced.

TMS data: Stop trials

The absence of differences in CME 175ms after the stop cue between each Stop type (SS, SG or GS), supports the theory that a global suppression mechanism is required to reactively inhibit part of a response, and that the mechanism is the same for each Stop Type, even when the desired behavioural outcome is selective inhibition (Majid et al., 2012; MacDonald et al., 2012, 2014). Research by Majid et al. (2012) further demonstrated that this global suppression mechanism extends to limbs not used in the performed action, when speed is crucial to the behavioural outcome (such as in the current study task). If the neural mechanisms of reactive RI were able to be selective in process rather than just outcome, we may have expected to see higher CME on SG and GS trials compared to SS trials, as no suppression would be seen in the responding muscle on Stop Partial trials.

The novel finding of the current study is that a release of IHI appears to be beneficial in behaviourally selective RI. The current study showed no difference in IHI between digits in SS and GS trials, where the left (non-dominant) digit was required to stop. Conversely, SG trials did show a dissociation in IHI between the left and right digits, with a release of IHI onto the dominant hemisphere controlling the responding right digit. Studies looking at movement preparation (Hinder et al., 2012, 2018) and force production (Fling and Seidler, 2012) found that similarly to the current study, too high a level IHI is unfavourable to task performance. This hints similarity to the current study finding of a reduction in IHI onto the responding digit being associated with a shorter SSRT on Stop Partial trials, despite the studies cited and the current study testing different aspects of impulse control. Furthermore, Hinder et al., (2012, 2018) demonstrated that during movement preparation, when required to rapidly choose between responses after being presented with an informative warning cue about which hand would respond, a release of IHI for the responding hand was also seen

following the cue. The ability to release IHI quickly led to quicker response times (Hinder et al., 2018). Even though direct comparisons cannot be made to the current study findings as these studies were investigating movement preparation rather than RI (and foreknowledge on the required movement was provided) the similarities in findings with the current study suggest the act of releasing IHI is crucial in multiple aspects of impulse control.

The fact that a clear dissociation in IHI between hemispheres leads to a faster response during partial movement cancellation implies that IHI is the main mechanism responsible for uncoupling of motor plans in the uncouple-reinitiation of movement proposed by MacDonald et al. (2012). The dissociation also implies IHI is not the mechanism responsible for global RI in this paradigm, as initially hypothesised. Importantly, the current study found that SS trials did not show any IHI release, thought to be because no uncoupling of motor plans was needed (both finger abduction responses were inhibited). IHI is only modulated if uncoupling of the bimanual response is required to allow selective reinitiation of a unimanual movement.

A crucial observation in the current study findings is that the IHI release and faster SSRT is only seen in the trial type where the right (dominant) index digit was required to continue movement execution. Research such as Serrien, Ivry and Swinnen (2006) has shown the dominant hand to be better at performing tasks, potentially due to larger a M1 with stronger interconnections (Hammond, 2002), so it is credible that IHI onto the dominant hemisphere would respond more quickly in the current study task. Whereas it is more difficult and takes longer to uncouple the non-dominant hand from the dominant one (Byblow et al., 2000; MacDonald et al., 2012), which might relate to the lack of an IHI release at the time point investigated and a longer SSRT when the non-dominant hand was still required to respond during partial RI.

In the Right FDI Group, there was a significantly higher success rate for SG trials than GS trials. The trial type with the greatest IHI release (Right FDI Group SG) also showed the most significant difference in success rate compared to the opposing Stop Partial trial type (GS). Whereas, this difference was not significant in the Left FDI Group. This discrepancy further supports the working hypothesis that rapid uncoupling to release the dominant hand in a right-handed population is more successful than releasing the non-dominant hand, in the time frame studied.

Collectively, the current study findings suggest that IHI is involved in the uncoupling process required during behaviourally selective RI and that this mechanism appears to be more efficient in right-handed participants when IHI needs to be increased onto the hemisphere controlling the non-dominant hand but released onto the dominant brain hemisphere. The lack of differences in CME across Stop trial types when IHI variations were observed adds weight to the suggestion that IHI and CME are separate mechanisms working independently (Hinder et al., 2012; Fujiyama et al., 2016 and Hinder et al., 2018), whilst both appearing to contribute to the behavioural outcomes of RI.

Limitations, clinical implications and future research directions

A potential limitation of this study was the task length. Participants had to concentrate on the task screen for roughly 1.5 hours to accommodate the number of trials needed to collect generalisable and valid data. This may have induced some mental fatigue. However, short breaks were given every 10 or so minutes, minimising any possible fatigue effects. Additionally, the staircase procedure means the study task differed slightly from person to person in terms of stop cue timing and stimulation times on Stop trials. Yet if the stop cue was

set a one timepoint for all participants, the task would be too hard for some participants and too easy for others, potentially leading to big discrepancies in success rate. The staircase procedure was therefore necessary.

Investigating the role of IHI of RI is proving valuable to the research filed of impulse control and how this is affected by neurological deficits seen in diseases such as Parkinson's disease, or in stroke patients (Murase et al., 2004; Li et al., 2007). Understanding the functional mechanisms of IHI could also have implications for the recovery of stroke patients (Murase et al., 2004).

We hypothesise that the IHI decrease seen in unimanual Stop trials was greater in the right FDI in SG trials than the left FDI in GS trials because the dominant hemisphere could release IHI quicker than the non-dominant hemisphere. In the case of this study, all participants were right-handed (left-hemisphere dominant). Two valuable follow-up studies to lead from this hypothesis would be to investigate IHI at later timepoints in unimanual Stop trials, and to recruit left-handed participants to test dominant right hemispheres. These potential research pathways would enable us to build on the current study results that point to a difference in IHI release based on dominant and non-dominant hemispheres. Stimulating later into the trial than the current study's stimulation timepoints would tell us if a release of IHI happens later for the non-dominant finger when it is still required to respond during partial RI. A further follow-up study could investigate whether training people to increase the use of their non-dominant hand would have any effect on the potential release of IHI on GS trials, if the current study speculations on the influence of hand-dominance on IHI release are correct. The current study hypothesises the results of a future experiment with left-handed participants to mirror those of the right-handed participants (i.e. the dominant left FDI to show greater IHI release and faster SSRT when responding during GS trials). Interestingly, other research has

suggested left-handed people do not have such big asymmetries in digit performance compared to right-handers (Pool et al., 2014). This finding further fuels such investigation into hand dominance and IHI.

Conclusion

The present study aimed to investigate IHI mechanisms during partial RI. The present study results suggested that IHI is the mechanism responsible for uncoupling motor responses following global suppression, to enable the necessary responses to be selectively re-initiated. However, further investigation with left-handed participants would help solidify this theory. We confirmed our first hypothesis that CME would increase over the duration of a Go trial. However, contrary to our second hypothesis, IHI did not increase 175ms the stop cue on Partial trials. Instead, there was a significant release of IHI at this timepoint onto the dominant hemisphere when the dominant hand was required to continue during partial RI. The release of IHI was associated with a faster behavioural response during partial RI. Further research is needed to solidify the working hypothesis that dissociations in IHI are required to uncouple motor responses by investigating the pattern of IHI at later time points during the more difficult partial RI condition when the non-dominant hand responds. If an equivalent increase in IHI onto the hemisphere controlling the cancelled hand and release of IHI onto the hemisphere controlling the non-dominant hand is seen, this would further support that IHI is responsible for uncoupling and a release in IHI is beneficial for behaviourally selective RI performance.

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