Primary Motor Cortex Modulation during Reactive and Proactive Response Inhibition

by

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1 Abstract

A central component of effective motor control is the ability to cancel pre-planned movement, termed response inhibition. When stopping is unexpected, response inhibition is reactive and associated with a non-selective reduction in corticomotor excitability. If forewarned to stop, response inhibition can be proactive and excitability may be selectively decreased. The modulation of GABAergic inhibitory networks within the primary motor cortex during proactive versus reactive response inhibition is unclear. The present study investigated the modulation of long and short-interval intracortical inhibition using paired-pulse TMS in eighteen right-handed participants performing reactive and proactive response inhibition tasks. Measures of long and short interval intracortical inhibition (LICI and SICI respectively) were obtained preceding responses from motor evoked potentials in task-relevant and task-irrelevant intrinsic hand muscles. When one response had to stop, the continued response was delayed to a greater extent in reactive versus proactively cued trials. LICI was reduced in both muscles during all types of response inhibition task compared with “pre-task” baseline. Additionally, on reactive trials, the extent of LICI for task-relevant LICI positively correlated with behavioral response times of the right hand when responses were inhibited on the left side. Task-relevant SICI was reduced when proactive cues indicated responding was highly likely but was unchanged when response conditions were uncertain. These novel findings indicate that $GABA_B$ receptor-mediated pathways may be involved in setting inhibitory tone according to task expectations whereas $GABA_A$ receptor - mediated pathways may be recruited proactively with response certainty.

2 Review of Literature

The cancellation of pre-planned movement, termed response inhibition is important in daily circumstances. Response inhibition can be assessed in tasks that require the reactive suppression of a cued response (Logan and Cowan 1984a; Verbruggen and Logan 2009). The length of the stopping process is a useful biomarker and a hallmark for impairment in a number of motor and impulse control disorders (Lijffijt et al. 2005; MacDonald and Byblow 2015). Response inhibition paradigms have made advances to elucidate a right-lateralized, cortico-subcortical "stopping" network with downstream effects on the primary motor cortex (M1) (Aron and Poldrack 2006; Aron et al. 2014; Coxon et al. 2009; Stinear et al. 2009). When stopping is unexpected, response inhibition is reactive with arguably limited applications to real-world situations (Aron 2011). When a degree of foreknowledge is available, proactive strategies can be employed in advance. The interaction between proactive and reactive inhibition remains unclear. Intracortical inhibitory networks within M1 contribute to movement suppression (Coxon et al. 2006; MacDonald et al. 2014) and can be investigated using transcranial magnetic stimulation (TMS). The role of intracortical networks within M1 during response inhibition is yet to be fully established. This introduction highlights the current knowledge surrounding inhibitory control in both reactive and proactive circumstances. Techniques that can investigate the modulation of the M1 within response inhibition are also discussed.

2.1 Introduction to Response Inhibition

Ever-changing daily circumstances require a motor system that can adapt quickly. Often, anticipated movement needs to be replaced with a more relevant movement, or cancelled completely. Sometimes, circumstantial changes are somewhat expected and can be predicted, such as a car entering an intersection, or elevator doors closing. In these instances, having to brake or stop walking is an outcome that can be *proactively* anticipated. Other situations, such as unseen traffic when crossing a road, are unexpected and require a more *reactive* adjustment to stop movement. Regardless of expectation, whenever a pre-planned response has to be suppressed, the process employed is termed response inhibition (Chambers et al. 2009; Verbruggen and Logan 2008). Recently, a distinction between proactive and reactive response inhibition has been identified (Aron 2011). Proactive response inhibition is associated with time preceding responses where preparatory mechanisms may "set up" the motor system relative to the expected response. Alternatively, reactive response inhibition is associated with the outright stopping process itself, rather than preparation.

Reactive inhibition – The unexpected inhibition of an anticipated response
Network: Hyper-direct pathway of the basal ganglia. Associated with non-selective motor suppression
Timing: Engaged after stop cues are presented

Proactive inhibition – Inhibition of a response under informed circumstances
Network: Associated with the indirect pathway of the basal ganglia. Motor suppression appears to be selective
Timing: Engaged before stop cues are presented

Performance in response inhibition tasks can be indicative of wider impulse control. The stop-signal task is a prominent response inhibition paradigm requiring responses when response cues appear and response inhibition when stop cues are unexpectedly presented (Logan 1994; Logan and Cowan 1984a). Other task variations such as No-Go (Casey et al. 1997; Donders 1969) or anticipatory tasks (Coxon et al. 2006; Slater-Hammel 1960) are also used. While there are variations within these paradigms, imaging studies demonstrate significant structural overlap from a common stopping network (Aron and Poldrack 2006; Coxon et al. 2009; Menon et al. 2001). Impaired inhibitory performance in disorders with known neuro-anatomical degradation can provide information about the response inhibition network. Inhibitory impairments exist in many neurological disorders including Focal Dystonia (Stinear and Byblow 2004), Obsessive Compulsive Disorder (Chamberlain et al. 2006; Lipszyc and Schachar 2010), Attention-Deficit Hyperactivity Disorder (Aron and Poldrack 2005; Lijffijt et al. 2005; Rubia et al. 2007), Schizophrenia (Enticott et al. 2008; Hughes et al. 2012; Kiehl et al. 2000); and in addictive disorders such as substance-use, pathological gambling and internet gaming disorders (Fillmore and Rush 2002; Garavan et al. 2008; Liao et al. 2014; Lim et al. 2016; Stevens et al. 2015). Deficits are also prominent in neuro-degenerative pathologies such as Parkinson's (Gauggel et al. 2004; Rae et al. 2016) and Huntington's (Majid et al. 2013; Rao et al. 2014) disease, and those of old age (Coxon et al. 2012; Smittenaar et al. 2015). These populations tend to demonstrate greater response inhibition latencies, commonly measured as the stop signal reaction time (SSRT); an estimate derived from task response times and stopping success rates (Logan 1994; Verbruggen et al. 2013). Impaired response inhibition is present in a range of motor and cognitive control disorders. An understanding of the neuro-anatomical substrates that mediate response inhibition thus has widespread clinical implications.

A large focus of research has been placed on reactive response inhibition, the processes that rapidly suppress movement when stopping is unexpected. Functional magnetic resonance imaging (fMRI) studies have helped identify key structures and pathways recruited during this rapid suppression (Aron and Poldrack 2006; Chambers et al. 2009; Chikazoe 2010; Wessel and Aron 2017). However, modulation of this network prior to its activation could be just as important as structural and connective integrity. If the brain cannot "set-up" an inhibitory network relative to its current situation, then it will be unlikely to employ it optimally. This notion is supported by results indicating an influence of proactive mechanisms on reactive inhibition (Cai et al. 2011; Chen et al. 2010; Dunovan et al. 2015; Jahfari et al. 2012; Zandbelt and Vink 2010). While imaging studies suggest inhibitory networks engaged in proactive and reactive conditions are similar (Chikazoe et al. 2009b; Jahfari et al. 2010; Zandbelt and Vink 2010), differences also exist (Van Belle et al. 2014; Zandbelt et al. 2013b). Alternative techniques can be used to assess more specific mechanisms underlying response inhibition.

Transcranial magnetic stimulation (TMS) over M1 can investigate the modulation of corticomotor excitability (CME) with temporal precision. The specificity of modulation can be determined by recording electromyography from multiple muscles. During response inhibition tasks, patterns of CME support two types of inhibitory processes. Reactive inhibition is associated with non-selective motor suppression. Reduced CME is observed for muscles after they are cued to stop a pre-planned movement (Coxon et al. 2006; Leocani et al. 2000), continue movement while another is inhibited (Cowie et al. 2016; MacDonald et al. 2014) and even from muscles irrelevant to the task (Badry et al. 2009; Cai et al. 2012b). These results suggest non-selective inhibition is employed when rapid, unexpected stopping is required. Alternatively, when information is provided that a single hand may have to stop a bimanual response, CME is

selectively suppressed for only the cancelled response (Greenhouse et al. 2012; Majid et al. 2012), indicating response information can influence the type of inhibition engaged. Furthermore, reduced CME is observed preceding stop cues for the hand that may have to stop (Cai et al. 2011; Claffey et al. 2010). The extent of CME suppression correlates with response times (Majid et al. 2013), suggesting proactive mechanisms may help optimize the motor system for an anticipated responses. Further investigation is needed to identify the neural substrates responsible for observed reductions in CME. Therefore, TMS can help identify distinct patterns of CME modulation during response inhibition.

Gamma aminobutyric acid (GABA) mediated interneurons within M1 can exert powerful inhibitory effects on corticospinal neurons (Jones 1993; Keller 1993). Paired-pulse TMS can assess the amount of GABAergic intracortical inhibition within M1 associated with certain muscle representations (Kujirai et al. 1993). A limited number of studies have assessed intracortical inhibition within response inhibition tasks. $GABA_A$-mediated short interval intracortical inhibition (SICI) is reduced preceding responses (Duque and Ivry 2009; Reynolds and Ashby 1999; Stinear and Byblow 2003) and remains reduced during movement (Zoghi et al. 2003). After a stop cue is presented, SICI is increased for muscles involved in the cancelled response (MacDonald et al. 2014; Sohn et al. 2002). However, SICI is also increased for nearby muscles not involved in the cancelled response, indicating a non-selective increase in inhibition (Coxon et al. 2006). Response probability does not appear to modulate SICI on a trial-to-trial basis (Sinclair and Hammond 2009). Paired-pulse TMS can also assess $GABA_B$-mediated long interval intracortical inhibition (LICI) (McDonnell et al. 2006). SICI and LICI are both reduced when response cues are pre-warned compared with when they are not (Sinclair and Hammond 2008). Reduced SICI but increased LICI is observed at a "block-level" for reactive stopping blocks compared with Go only blocks (Cowie

et al. 2016; Coxon et al. 2006; MacDonald et al. 2014). Upregulated LICI is associated with response times when one hand has to stop, suggesting LICI may help set response thresholds (Cowie et al. 2016). The functional role of intracortical inhibition within M1 during response inhibition, particularly under proactive conditions, is largely unknown.

2.2 Response Inhibition Paradigms

Numerous types of paradigm have investigated response inhibition. A potential reason for the large number of task variants is the strengths and limitations within paradigms. Until recently, studies have primarily investigated reactive inhibition. Two task types are commonly used: Go/No-Go and stop-signal tasks (Chambers et al. 2009; Logan 1994; Swick et al. 2011). Other tasks such as anticipatory response inhibition tasks also exist (Coxon et al. 2006; Zandbelt and Vink 2010) and may offer advantages. To assess proactive inhibition, adaptations have been made to reactive paradigms, often including informative cues which alter response expectancy before trials (Aron and Verbruggen 2008; Leunissen et al. 2016; Majid et al. 2012). The next sections discuss strengths and limitations of task paradigms commonly used to assess both reactive and proactive response inhibition.

2.2.1 Reactive Inhibition

Both Go/No-Go and stop-signal tasks are extensive within the response inhibition literature. Briefly, the tendency to respond is established by maintaining a higher proportion of Go trials (requiring responses) compared with stop trials; responses are not cued (No-Go), or are signalled to stop (stop-signal) after a response cue is presented (Fig. 1). While both tasks fundamentally demand pre-planned movement to be suppressed, several differences exist. For example, Go/No-Go tasks do not present Go cues on all trials. When Go cues are absent or an

alternative cue is presented, responses are not required (Casey et al. 1997; Donders 1969; Simmonds et al. 2008). It may be argued that response processes are not consistently initiated during these tasks. For example, a strategy to increase stopping success could involve "waiting" until a response cue is presented. The inhibition of a commenced Go processes may not occur. A high proportion of Go trials may discourage this strategy. However, numerous studies have used a low proportion of Go compared with No-Go trials (Chikazoe et al. 2009a; Kolodny et al. 2016; Pornpattananangkul et al. 2016) potentially limiting interpretation. During stop-signal tasks, Go cues are presented on all trials (Logan 1994; Verbruggen and Logan 2008). On a minority (~30%) of trials, the Go cue is followed by a stop cue requiring the initiated Go process to be retracted. The time between Go and stop cue presentation, termed the stop signal delay (SSD) can be adjusted (or "staircased") throughout the task to maintain a certain success rates (Band et al. 2003; Logan et al. 1997). While the presentation of Go cues before stop-signals encourages response initiation, it does not eliminate waiting strategies. A go process may be "paused" or the initiation "stalled" until participants are certain responses are required. Feedback when responses are significantly slowed may discourage this strategy (Aron and Verbruggen 2008; Majid et al. 2012). Presumably, Go/No-Go and stop-signal tasks activate a common response inhibition network with minor regional differences due to task design (Eagle and Baunez 2010). For the sake of this review, it is assumed that results using these tasks apply to a single network. However, there are findings that indicate differences in regional activation between Go/No-Go and stop-signal tasks (see Swick et al. 2011; Zheng et al. 2008). Overall, two prominent types of response inhibition task exist. It is important to consider potential limitations of task designs when interpreting results.

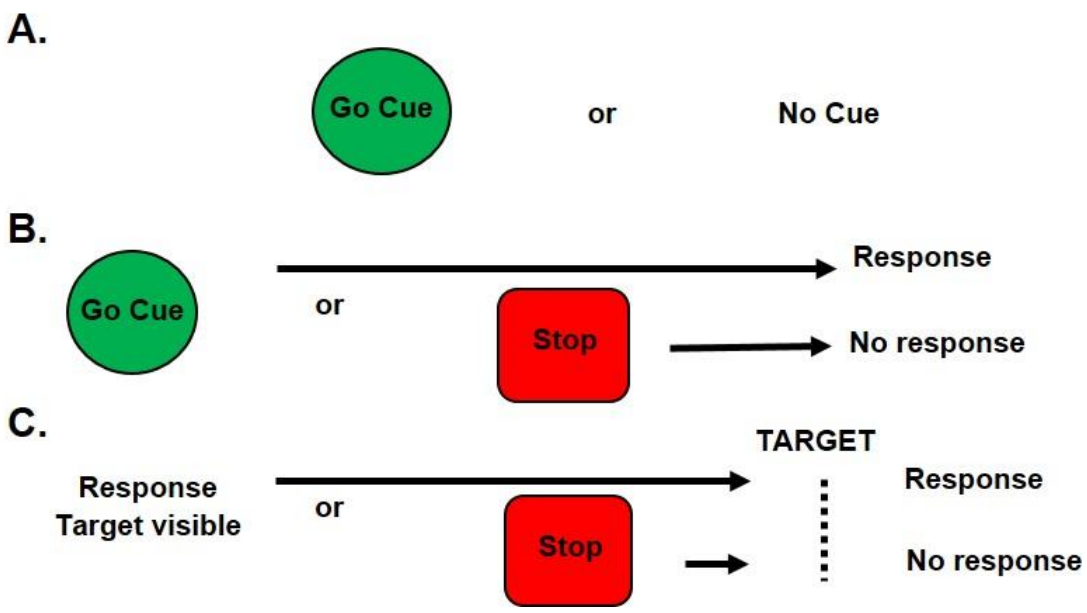

Fig. 1. Prominent response inhibition tasks. A. Go/No-Go task. Go cues require responses. No-Go cues are the absence of a Go cue or sometimes the presentation of an alternative cue. B. Stop-signal task. Go cues require responses. Occasionally a stop-signal is presented after Go cues requiring response inhibition. C. Anticipatory response inhibition task. Trials contain overt response targets (dashed line). On stop trials, the moving component stops before the target, requiring the anticipated response to be suppressed.

Anticipatory response inhibition tasks might offer advantages for the assessment of response inhibition. For these tasks, a response target is displayed at trial onset (Coxon et al. 2006; Slater-Hammel 1960; Zandbelt and Vink 2010). Movement processes can be initiated and executed at a known time. For example, the seminal paradigm by Slater-Hammel (1960) required participants to respond when a rotating "sweep dial" reached a certain target, but not to respond if the dial stopped beforehand. Hence when the moving component of anticipatory tasks (e.g. sweep dial) stops before the target, it is similar to a stop cue in other tasks (Fig. 1). The time between the stop cue and target is the SSD, and can also be "staircased" within anticipatory tasks to increase or decrease stopping difficultly (MacDonald et al. 2012). While participants may still "wait" until they are certain a response is required, the overt response target discourages this strategy,

especially when response times are apparent and feedback provided for each trial (Cowie et al. 2016; MacDonald et al. 2014; MacDonald et al. 2012). Imaging studies have identified similar activation of the response inhibition network for anticipatory tasks compared with other response inhibition tasks (Coxon et al. 2009; Coxon et al. 2012). However, recent models suggest there are differences in Go trial reaction time distributions between stop-signal and anticipatory tasks (MacDonald et al. 2017). In summary, anticipatory response tasks may offer advantages to other commonly used tasks.

2.2.2 Proactive Inhibition

It has been suggested that purely reactive response inhibition may be a limited model for real-world application (Aron 2011). When responses are inhibited in daily life, there is often a certain degree of foreknowledge available. For example, the tendency to rapidly stop crossing a road may increase in areas of high versus low amounts of traffic. Proactive mechanisms likely optimize the motor system relative to current circumstances. To specifically assess proactive response inhibition, stop-signal tasks have presented warning cues before trials (Aron and Verbruggen 2008; Cai et al. 2011; Claffey et al. 2010; Majid et al. 2013; Majid et al. 2012). In these tasks, warning cues such as “Maybe Stop Left” or “Maybe Stop Right” inform the participant to prepare to stop a certain hand. On the majority of trials, Go cues require a bimanual response with both hands. Stop-signals are presented on the minority of trials, requiring the previously specified response to be inhibited while the other continues. Proactive response inhibition can also be assessed at a “block-level” by comparing stop-signal blocks with Go only blocks (Bissett and Logan 2011; Cowie et al. 2016). It is likely that response “waiting” strategies are more prominent in proactive response inhibition tasks than reactive. Response times are slowed when responses may need to be cancelled compared with when they do not (Chikazoe et al. 2009b; Jahfari et al.

2010; Zandbelt and Vink 2010). This may be a limitation of task design; such that proactive mechanisms are not guaranteed to interact with a pre-commenced Go process. Anticipatory response inhibition tasks can investigate proactive response inhibition. Response probability has been modulated on a "trial-to-trial" basis, but only for unimanual responses (Dunovan et al. 2015; Leunissen et al. 2016; Zandbelt et al. 2013b; Zandbelt and Vink 2010). Differences in M1 intracortical inhibition have also been observed between Go only and Stop blocks (Cowie et al. 2016; Coxon et al. 2006; MacDonald et al. 2014), suggesting a proactive modulation. Anticipatory tasks may provoke greater activation of proactive mechanisms. In stop-signal tasks, Go cues cannot be easily expected as there are no "time-referenced" components. When foreperiods are long or of variable length, anticipation may be even more difficult (Lebon et al. 2015). Because anticipatory tasks have response targets, preparatory mechanisms will likely be optimal at a known time, just before responses are initiated. Thus, advantages for investigating proactive response inhibition with anticipatory tasks may exist.

Response preparation during reaction time tasks may also provide insight into proactive response inhibition. While these tasks do not explicitly investigate proactive response inhibition mechanisms (i.e. stop trials do not exist), CME suppression preceding response cue presentation indicates a degree of inhibitory control may be applied (Duque and Ivry 2009; Duque et al. 2010; Greenhouse et al. 2015a; Greenhouse et al. 2015b; Hasbroucq et al. 1997; Hasbroucq et al. 1999b). Reaction time tasks can be "simple" when only one response is possible or "choice" when multiple response alternatives exist. Catch trials are often included to reduce response familiarity, but do not appear to influence the amount of CME suppression preceding response cues (Greenhouse et al. 2015b). Preparatory mechanisms in choice reaction time tasks may be similar to those in proactive response inhibition tasks. Trials require one of either two outcomes. In choice reaction

time tasks either a left or right response is required, whereas proactive response inhibition trials such as “Maybe Stop Left” require a right hand or a bimanual response. In both tasks, uncertainty about the upcoming response exists. Preparatory mechanisms which help resolve conflict between two potential alternatives could be commonly employed. Reaction time tasks provide insight for preparatory mechanisms that may be associated with proactive response inhibition.

2.3 Neuroanatomical Substrates of Reactive Inhibition

2.3.1 Cortical Contributions

Several structures are critical to reactive response inhibition, but the connections and mechanisms they utilize are not completely understood. Reactive inhibition is associated with a right-lateralized network, connected between the right inferior frontal cortex (rIFC), the presupplementary motor area (preSMA), basal ganglia and M1 (Aron and Poldrack 2006; Coxon et al. 2009; Stinear et al. 2009; Wessel and Aron 2017; Zandbelt et al. 2013a). Multiple lines of evidence suggest two cortical structures are essential for response inhibition. Inhibitory performance is impaired when lesions or repetitive TMS cause disruptions to the rIFC or the preSMA (Aron et al. 2003; Cai et al. 2012a; Chambers et al. 2009; Floden and Stuss 2006; Nachev et al. 2007). Recent models portray rIFC as a “brake” which can modulate complete or partial (i.e. pause) response inhibition (Aron et al. 2014; Wessel and Aron 2017). This brake may be implemented through pathways connecting the preSMA to the basal ganglia; specifically, to the subthalamic nucleus (STN)(Duann et al. 2009; Rae et al. 2015; Zandbelt et al. 2013a). Primate studies suggest the preSMA can facilitate voluntary movements to override automatic movement (Isoda and Hikosaka 2007). In humans, activation of the SMA/preSMA is increased during Partial trials, where only one hand has to respond, compared with complete stopping of both hands (Coxon et al. 2009). However, some authors suggest the modulation of rIFC and preSMA is associated

with cognitive control processes more so than initiating response inhibition (Hampshire 2015; Hampshire and Sharp 2015). These studies suggest that both rIFC and preSMA contribute to processes essential for successful response inhibition.

2.3.2 Cortico-Subcortical Contributions

The basal ganglia contain structures that mediate a cortico-subcortical loop, critical for motor control (Parent and Hazrati 1995). When structural integrity is compromised, response inhibition is subsequently impaired. Basal ganglia lesions (Rieger et al. 2003) especially those of the STN (Eagle et al., 2008) are associated with impaired inhibitory performance. Deep brain stimulation of the STN in Parkinson's patients appears to increase inhibitory performance (Limousin and Martinez-Torres 2008; van den Wildenberg et al. 2006). Efficient interception of an initiated Go process relies on intact components of the basal ganglia, in particular, the STN. Go and stop processes are mediated through the basal ganglia via different pathways (Fig. 2). Cortically originating direct and indirect pathways project to the striatum, whereas a "hyperdirect" pathway projects direct to the STN (Chambers et al. 2009; Nambu et al. 2002). The direct pathway can disinhibit motor representations to initiate movement by selectively inhibiting the internal globus pallidus (GPi) and substantia nigra (SNr). The termination of movement can be mediated through the indirect pathway via GPi and SNr to suppress thalamo-cortical output. During reactive response inhibition, the hyperdirect pathway may be activated to rapidly intercept a Go process (Aron et al. 2007b; Aron and Poldrack 2006; Jahfari et al. 2011) associated with non-selective inhibitory effects on the motor system (Badry et al. 2009; Cai et al. 2012b; Coxon et al. 2006; Greenhouse et al. 2012). The integrity of white matter projections to the STN, assessed by diffusion weighted imaging studies, can predict reactive inhibitory performance (Coxon et al. 2012; Rae et al. 2015). Therefore, components of the basal ganglia are essential to reactive response inhibition.

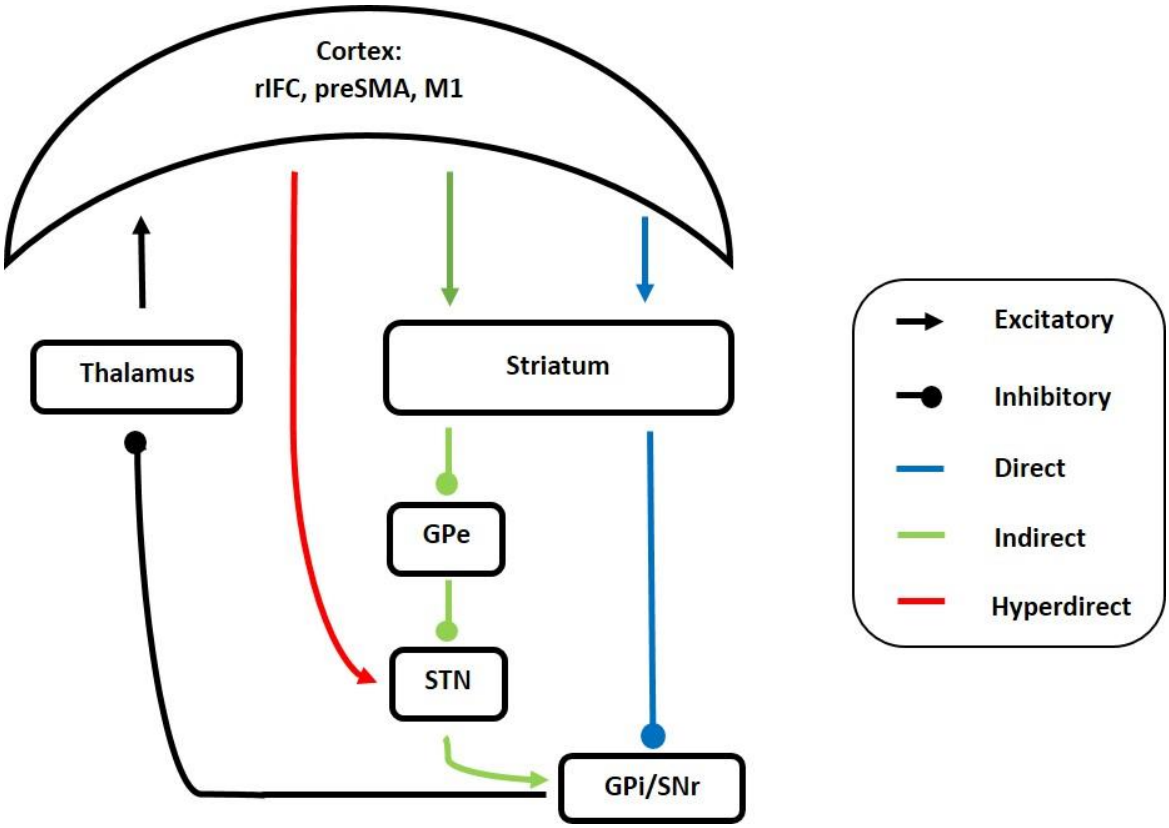

Fig. 2. Cortico-subcortical pathways of the basal ganglia. Reactive response inhibition is associated with the hyperdirect pathway (Red). A cortically originating stop process involving the right inferior parietal cortex (rIFC) and pre supplementary motor area (preSMA, see text for further explanation) is projected to the subthalamic nucleus (STN). Subsequent activation of internal globus pallidus and substantia nigra (GPi/SNr) is associated with widespread suppression of corticomotor excitability, mediated through thalamo-cortical output. Proactive response inhibition is associated with the indirect pathway (green), mediated through the striatum. A reduction in inhibitory input from the external globus pallidus (GPe) can increase STN activity.

2.3.3 Primary Motor Cortex Contributions

M1 is the predominant final processing site before movement signals descend through the spinal cord (Stinear et al. 2009). Converging lines of evidence indicate that GABA mediated intracortical inhibition within M1 contributes to initiation and suppression of movement.

Intracortical interneurons are modulated by cortical and subcortical inputs and can regulate corticospinal neurons through excitatory and inhibitory post-synaptic potentials (Iriki et al. 1991). Neurotransmission occurs within a densely-packed network of interneurons. Selective activation of corticospinal neurons can occur alongside a GABA mediated suppression of adjacent motor representations (Schneider et al. 2002). Pharmacological modulation of TMS elicited responses support intracortical inhibition, signalled via GABA (McDonnell et al. 2006; Werhahn et al. 1999; Ziemann et al. 1996b). The functional role of intracortical inhibition during movement can be assessed using paired-pulse TMS. A reduction in intracortical inhibition precedes movement (Reynolds and Ashby 1999; Stinear and Byblow 2003) and remains reduced during movement (Zoghi et al. 2003). After a stop cue is presented, inhibition is increased in response-relevant (MacDonald et al. 2014; Sohn et al. 2002) and irrelevant muscles (Coxon et al. 2006). One explanation is that increased thalamocortical output may selectively decrease intracortical inhibition to disinhibit corticospinal neurons. However, the exact role of intracortical inhibition and of its connections within the response inhibition network are not clear.

2.4 Neuroanatomical Substrates of Proactive Inhibition

Proactive response inhibition studies have revealed activation of a similar network to reactive inhibition. A common inhibitory network could be proactively engaged before responses occur. In accordance with reactive inhibition, proactive tasks are associated with activation of the rIFC, pre-SMA, STN and striatum (Aron et al. 2014; Chikazoe et al. 2009b; Cunillera et al. 2014; Hester et al. 2004; Swann et al. 2012; Vink et al. 2005; Zandbelt et al. 2008; Zandbelt et al. 2013b). These structures appear to have “downstream” effects on CME (Cai et al. 2011; Claffey et al. 2010; Cowie et al. 2016; Duque and Ivry 2009). Proactive control may be linked with response “caution”. When stop-signal probability is high, Go trial responses are slowed (Jahfari et al. 2010; Ramautar

et al. 2004; Vink et al. 2005; Zandbelt and Vink 2010). Certain substrates may regulate this slowing as part of a speed-accuracy trade off (Wickelgren 1977). The activation of the rIFC is associated with “Maybe Stop” trials (Chikazoe et al. 2009b; Swann et al. 2012). Furthermore, the extent of rIFC activation is correlated with Go response times (Jahfari et al. 2010). Response slowing fits within a proposed spectrum of proactive and reactive processes (Braver 2012). The spectrum is continuous, and increased stop probability is involved with the proactive end of the spectrum. When stopping is not expected, reactive processes are more prominent. A dynamic interaction between proactive-reactive processes is supported by computational modeling at the level of the basal ganglia (Dunovan et al. 2015) and the modulation of reactive responses by proactive information (Cai et al. 2011; Chen et al. 2010; Jahfari et al. 2012; Zandbelt and Vink 2010). These findings suggest that activation of structures under proactive conditions may reflect to a certain extent, the pre-activation of the reactive network.

There are distinctions in structural activation between reactive and proactive inhibition. The laterality of engaged structures differs depending on stop probability. Reactive response inhibition engages a right-lateralized, cortico-subcortical network (Aron et al. 2003; Aron and Poldrack 2006; Coxon et al. 2009; Coxon et al. 2012; Zandbelt et al. 2013a; Zandbelt and Vink 2010). However, activation of a bilaterally organized network appears to be common to reactive and proactive tasks (Leunissen et al. 2016; Li et al. 2006; Van Belle et al. 2014). One explanation for bilateral activation is that proactive inhibition requires additional cognitive processes. Functions such as retaining the given stop probability and optimizing preparatory mechanisms may involve supplementary circuitry. The activation of the dorsolateral pre-frontal cortex (DLPFC) is distinct to proactive tasks. Some authors have presented the DLPFC as an essential location for a reactive-proactive interaction (Van Belle et al. 2014). Others suggest its activation

is circumstantial and may depend more on task requirements than inhibitory processes (Chikazoe et al. 2009a; Jahfari et al. 2010; Swann et al. 2012). The DLPFC has connections with the head of the caudate (Alexander et al. 1986). The head of the caudate may have a role in processing feedback on a trial-to-trial basis (Seger and Cincotta 2005). This supports the interpretation that the DLPFC can keep response goals within working memory during trials (Aron 2011). Tasks which contrast additional cognitive processes may help delineate the importance of DLPFC within response inhibition. Differences appear to exist between reactive and proactive networks. The exact functions of these differences are yet to be established.

Proactive inhibitory control is associated with a selective type of movement suppression. Participants who proactively slow their responses, or are forewarned that they may have to stop a certain hand and continue the other, demonstrate selective suppression of CME during response inhibition (Greenhouse et al. 2012; Majid et al. 2012). This appeals to a separate inhibitory network than that of non-selective reactive inhibition (Badry et al. 2009; Cowie et al. 2016; Greenhouse et al. 2012; MacDonald et al. 2014). Pathways of the basal ganglia can be differentially recruited under different conditions. The hyperdirect pathway results in "widespread" suppression of movement under reactive circumstances, whereas the indirect pathway appears to selectively inhibit movement under more proactive conditions (Aron 2011; Aron et al. 2007b; Hazrati and Parent 1992; Leunissen et al. 2016; Majid et al. 2013; Nambu et al. 2002; Zandbelt et al. 2013b). Investigation of proactive inhibition by Majid et al. (2013) revealed stopping performance relied on striatal-pallidal activation and structural integrity. Additionally, a correlation between these structures and the extent of CME suppression supports a role for the indirect pathway during proactive inhibition (Majid et al. 2013). Other results demonstrate increased activation of the caudate head (associated with the indirect pathway) correlates with increased stop trial probability

(Leunissen et al. 2016; Zandbelt et al. 2013b). Activation of the anterior striatum, involving the caudate appears to also correlate with Go trial response slowing (Zandbelt et al. 2013b). Thus, the indirect pathway may have a degree of control over tonic levels of inhibition that can modulate response thresholds. These results demonstrate the contribution of the indirect pathway to proactive response inhibition. Basal ganglia pathways thus appear to have dynamic roles for reactive and proactive inhibitory processes.

2.5 Proactive Influences on the Corticomotor Pathway

Multiple studies have assessed the excitability of the corticomotor pathway during movement preparation. Reaction time tasks are often used to investigate mechanisms that prepare responses relative to given information. A well-documented suppression of CME exists for task-relevant muscles preceding response cue presentation during reaction time tasks (Davranche et al. 2007; Duque and Ivry 2009; Duque et al. 2010; Hasbroucq et al. 1999a; Hasbroucq et al. 1997; Sinclair and Hammond 2008). Recently, three possible roles have been identified for this suppression of CME. One interpretation is that suppression helps to prevent premature responses. This mechanism termed as “impulse control” is specific to the responding hand (Duque and Ivry 2009; Duque et al. 2012; Duque et al. 2010). Additionally, when informed a hand is no longer required for the upcoming response (or “non-selected”), CME for that hand is also reduced preceding response cues (Duque et al. 2010; Klein et al. 2016; Wilhelm et al. 2016). This explanation has been termed “competitive resolution” and is proposed to act concurrently with impulse control. However, suppression has also been observed in task-irrelevant muscles. MEP amplitude is reduced in the left hand during a simple reaction time task involving only the right hand responses (Greenhouse et al. 2015b). This “irrelevant” reduction in excitability does not particularly align with either of the two proposed mechanisms which target specific muscles.

Instead, it suggests that during response preparation, the motor system may be suppressed in a "widespread" manner. This pattern of suppression is potentially similar to that observed during reactive response inhibition. Overall, the suppression of CME is well established during response preparation, yet the underlying function is unclear.

There are limitations for interpretations of CME suppression during response preparation. The proposal of a sole mechanism which non-selectively suppresses the motor system (Greenhouse et al. 2015b) may be undermined by alternative explanations (Quoilin and Derosiere 2015). First, excitability appears to be reduced to a greater extent in the responding hand than in the non-responding (Greenhouse et al. 2015b). While the authors explain this as global inhibition "centered" on the response, the results also support greater inhibitory effects for impulse control than competitive resolution. Second, task-irrelevant CME suppression may be a result of the higher than normal proportion of catch trials (20%) in the simple reaction time (SRT) task (Greenhouse et al. 2015b). Non-selective inhibitory networks associated with reactive response inhibition may be activated in advance. It is important to understand that interpretations for CME suppression are limited. It cannot be determined if reduced CME is a result of, (1) a withdrawal of facilitatory drive or (2) active inhibition of the corticomotor pathway (Kobayashi and Pascual-Leone 2003). Multiple cortical or subcortical locations could also influence the excitability of the corticomotor pathway. Studies using H-reflex techniques indicate spinal mechanisms could be part of "impulse control" (Duque et al. 2010). However, spinal inhibition appears to account for only part of the CME modulation preceding responses when assessed over time (Hasbroucq et al. 1999a; Touge et al. 1998). In summary, reaction time tasks suggest CME of the motor system is reduced in task-relevant and potentially task-irrelevant effectors during response preparation. Mechanisms which underlie this suppression are unclear but may be closely associated with proactive inhibition.

Alternative techniques may be able to more effectively elucidate the properties of response preparation.

Proactive response inhibition is associated with changes in CME but modulation of intracortical inhibition is unclear. When informed that a certain hand as part of a bimanual response may have to stop (e.g. “Maybe Stop Left”), CME is reduced in that hand (Claffey et al. 2010; Majid et al. 2013) and correlates with Partial trial response times (Cai et al. 2011). These findings suggest that reduced CME may have a proactive function within response preparation. M1 intracortical inhibition is a candidate mechanism for this suppression. Paired-pulse TMS has not been used during these more specific proactive tasks. However, SICI has been investigated preceding response cues in a choice reaction time task (Duque and Ivry 2009). A reduction in SICI is observed for the hand that could or known to be part of an upcoming response, supporting a selective reduction of SICI preceding movement initiation (Coxon et al. 2006; Stinear and Byblow 2003). The modulation of SICI and LICI at a “block level” (Cowie et al. 2016; Coxon et al. 2006; MacDonald et al. 2014), may be explained with a “activation threshold” framework proposed by MacDonald et al. (2014). This model assumes that responses are only made when excitatory processes succeed an inhibitory threshold, maintained by several inhibitory inputs. One input appears to have a role in establishing the level of tonic inhibition relative to task-expectancy (Cowie et al. 2016). A tonic increase in LICI may improve general inhibitory control, while reductions in SICI may support disinhibition of potential responses. Another main inhibitory input within the activation threshold model is the well-documented non-selective suppression associated with reactive inhibition (Badry et al. 2009; Coxon et al. 2006; MacDonald et al. 2014; Majid et al. 2012). Together, these inputs can dynamically modulate thresholds for responding relative to the given circumstances. Therefore, proactive inhibitory control is associated with modulation of CME

which may, in part, be driven by underlying changes in intracortical inhibition. Further evidence is needed to establish the role of M1 intracortical inhibition during response inhibition.

2.6 Transcranial Magnetic Stimulation

Neural circuitry can be externally activated by non-invasive brain stimulation techniques. The strength of elicited responses can be measured using electromyography (EMG) to assay the activity of the corticomotor pathway. During standard TMS protocols, a magnetic coil is usually positioned over M1, targeting pathways associated with intrinsic hand muscles (Rothwell 1997). When a capacitor discharges an electric current through the windings of the coil, an orthogonally orientated magnetic field reaching up to 3 tesla within ~150 microseconds is produced, activating underlying neural tissue via low-strength eddy currents (see Barker et al. 1985; Rossini et al. 2015). While TMS can be used to temporarily alter the excitability of cortical structures (Chen et al. 1997), this overview focuses on TMS as a tool to measure changes in CME and specific intracortical networks. Paired with movement tasks, these techniques provide a useful, non-invasive method of investigating the motor system.

Stimulation over M1 elicits responses from several neural components. At a high enough intensity, TMS or transcranial electric stimulation (TES) can elicit high-frequency (~600 Hz) descending volleys, observed from electrodes positioned in the epidural space of the spinal cord (Boyd et al. 1986; Di Lazzaro et al. 2000; Di Lazzaro et al. 2001). These volleys are observed when electric stimulation over M1 is delivered to humans, cats or monkeys (Day et al. 1989; Kernell and Chien-Ping 1967; Patton and Amassian 1954). Individual volley components have different latencies, indicative of distinct neuron contribution most likely within M1. The shortest latency volley, termed “D-wave”, is thought to result from *direct* pyramidal tract activation.

Anatomically, corticospinal neurons are the closest cortically located neurons in proximity to electrodes of the epidural space. Three to four volleys may also ensue the D-wave. These, termed "I-waves", are likely a result of *indirect* corticospinal neuron activation of the pyramidal tract via trans-synaptic inputs (Rusu et al. 2014; Sakai et al. 1997). A singular model detailing the neural substrates producing these "I-waves" is yet to be established (Esser et al. 2005; Patton and Amassian 1954; Rusu et al. 2014; Ziemann and Rothwell 2000).

2.6.1 Single and Paired-Pulse Stimulation

When single-pulse TMS is delivered over M1 at an intensity above the resting motor threshold (suprathreshold), the corticomotor pathway is activated, resulting in a motor evoked potential (MEP) (Hallett 2007). MEP amplitude recorded using EMG provides a measure of CME, the sum of excitatory and inhibitory inputs influencing the corticomotor pathway (Kobayashi and Pascual-Leone 2003). Modulation of MEP amplitude reflects altered membrane excitability of corticospinal neurons or interneurons that are synaptically connected (Ziemann et al. 1996a). TMS over M1 can result in the activation of several adjacent or overlapping motor representations. Stimulation of a single location can assess the modulation of MEP amplitude from multiple nearby muscles (Coxon et al. 2006; McMillan et al. 2004; Stinear and Byblow 2002). Mechanisms underlying this modulation cannot be directly determined.

Both SICI and LICI are associated with GABAergic inhibition and can be assessed using paired-pulse TMS. The modulation of SICI is associated with precise inhibitory control (Stinear and Byblow 2003; Zoghi et al. 2003). When a subthreshold conditioning stimulus (CS), is delivered 1-5 ms before a suprathreshold test stimulus (TS), the elicited MEP amplitude is supressed (Kujirai et al. 1993). This phenomenon is a result of GABA mediated inhibitory networks. Because inhibitory neurons are activated at low thresholds, subthreshold TMS activates

these inhibitory neurons without eliciting a MEP (Davey et al. 1994; Ilić et al. 2002). SICI is mediated by postsynaptic $GABA_A$ receptors (Di Lazzaro et al. 2006; Hanajima et al. 1998; Ziemann et al. 1996b). Because $GABA_A$ receptors are structurally ionotropic, allowing an almost immediate influx of chloride ions (Bormann 2000), rapid inhibitory effects on the postsynaptic cell are observed. This short-lasting inhibition coincides with the ISI required for assessment of SICI. Investigation of SICI during movement tasks can be performed with high temporal precision (Coxon et al. 2006; MacDonald et al. 2014). In contrast, LICI is associated with more prolonged GABAergic inhibition. When a suprathreshold CS is followed 50-200 ms by a suprathreshold TS, the secondary MEP is suppressed compared with when elicited alone (Valls-Solé et al. 1992). Pharmacological investigations have revealed suppression is mediated by the activation of metabotropic $GABA_B$ receptors (McDonnell et al. 2006; Müller-Dahlhaus et al. 2008). While subthreshold CS pulses during SICI only activate lower threshold interneurons, the suprathreshold CS in LICI produces a MEP, corresponding to the overall level of CME at that point in time. Thus, LICI can produce measures of CME and $GABA_B$ mediated intracortical inhibition simultaneously. Paired-pulse TMS is a useful way to assess the modulation of intracortical inhibition within M1 during movement tasks.

Manipulating TMS intensity and current direction can preferentially activate specific descending volleys. I-waves can be further classified as early (I1) or late (I2, I3, etc) with peaks equally spaced by ~1.5 ms (Patton and Amassian 1954; Rothwell et al. 1991). When TMS intensity is increased, the subsequent order of I-wave recruitment depends on current direction (Day et al. 1989; Di Lazzaro et al. 2001; Sakai et al. 1997). Posterior to anterior (PA) directed currents preferentially activate early I-waves at lower intensities (Di Lazzaro et al. 2012). In contrast, anterior to posterior (AP) directed currents preferentially activate later I-waves and lateral to

medial (LM) currents preferentially activate D-waves (Day et al. 1989; Kaneko et al. 1996; Nakamura et al. 1996; Sakai et al. 1997). Traditionally, protocols investigating intracortical networks have used PA directed TMS currents. While PA stimulation is associated with lower resting motor thresholds (Sakai et al. 1997; Zoghi et al. 2003), recent findings suggest that the assessment of both SICI and to a certain extent, LICI, are more sensitive to stimulation with AP directed currents (Cirillo and Byblow 2016; Sale et al. 2016). The effects of current direction should be considered when investigating intracortical inhibition.

3 Introduction

The ability to cancel a movement when it is no longer required, or is potentially harmful, is critical for daily tasks. Sometimes the decision to stop occurs during movement preparation, and the "would-be" response is suppressed before it can occur. This phenomenon, termed response inhibition, is mediated by a right-lateralized, cortico-subcortical network (Aron et al. 2014; Chikazoe 2010). A conventional approach to studying response inhibition is by unexpectedly presenting "stop" signals to provoke a *reactive* cancellation of planned movement (Verbruggen and Logan 2009). When stopping-goals are provided in advance, it is possible to assess a *proactive* response inhibition process, which also has high behavioral relevance (Aron 2011). Reactive and proactive processes are generally deemed separable (Irlbacher et al. 2014). However, a growing body of literature indicates an interaction, such that proactive cues can alter the effectiveness of reactive inhibition (Cai et al. 2011; Chen et al. 2010; Jahfari et al. 2012; Zandbelt and Vink 2010). However, the mechanisms that dictate this relationship are not clear. Networks within the primary motor cortex (M1) may have a salient role during response inhibition.

Transcranial magnetic stimulation (TMS) of M1 can provide an index of real-time corticomotor excitability (CME) with high temporal resolution (Hallett 2000) through the size of motor evoked potentials (e.g., MEP amplitude). For instance, single-pulse TMS studies have shown MEP size increases before an anticipated movement occurs (Chen et al. 1998; Hoshiyama et al. 1996). Reactive inhibitory processes are implemented after the onset of stop-signals. In these tasks, CME is non-selectively reduced following the unexpected requirement to stop (Badry et al. 2009; Coxon et al. 2006; MacDonald et al. 2014; Majid et al. 2012). Alternatively, proactive inhibitory processes are associated with the time preceding a response or stop imperative, before reactive processes can be employed. During the preparation of an expected response, MEP

amplitude often decreases (Davranche et al. 2007; Duque and Ivry 2009; Duque et al. 2010; Hasbroucq et al. 1997). Furthermore, when response information is provided in advance, proactive strategies can be implemented during preparation. When a cue proactively informs that a subcomponent of a bimanual response may have to be prevented (Cai et al. 2011; Claffey et al. 2010), CME is reduced and correlates with response times (Majid et al. 2013). Suppressing CME to the hand that may have to stop, is likely a result of a proactive processes. However, MEPs elicited by single-pulse TMS demonstrates net inhibition of the corticomotor pathway, not underlying mechanisms. Whether an active inhibition or facilitatory withdrawal exists cannot be determined from single-pulse TMS alone. The present study aimed to assess the modulation of known motor processes during proactive and reactive inhibition using paired-pulse TMS.

Intracortical inhibitory networks within M1 possess regulatory effects on descending pyramidal neurons (Stinear et al. 2009). These networks are comprised of γ-aminobutyric acid (GABA) mediated inhibitory interneurons (Jones 1993; Keller 1993). Two prominent types of intracortical inhibition can be specifically assessed using transcranial magnetic stimulation (TMS): short and long interval intracortical inhibition (SICI and LICI respectively). LICI is mediated by $GABA_B$ receptors (McDonnell et al. 2006) and demonstrates a relatively prolonged suppression of CME. To examine LICI, two suprathreshold stimuli are separated by 50-200 ms. The amplitude of the second motor evoked potential (MEP) is reduced compared with when elicited alone (Valls-Solé et al. 1992; Wassermann et al. 1996). Conversely, SICI is examined using a sub-threshold conditioning stimulus at an interval of 1-5 ms preceding the suprathreshold test stimulus (Kujirai et al. 1993). The conditioning stimulus activates $GABA_A$ receptors and suppresses MEP amplitude generated by the test stimulus (Ilić et al. 2002; Werhahn et al. 1999; Ziemann et al. 1996c). A few studies have assessed SICI during response inhibition with variable results (Coxon et al. 2006;

Duque and Ivry 2009; MacDonald et al. 2014). It may be that these studies under-estimate the modulation of SICI given that all used TMS which induced posterior-anterior current in the brain to elicit and condition MEPs. Recent studies indicate that SICI is more sensitive to anterior-posterior (AP) directed currents than PA (Cirillo and Byblow 2016; Sale et al. 2016). Therefore, while TMS is a useful means of assessing distinct contributions of GABAergic intracortical networks, investigations of these networks during response inhibition is still at a preliminary stage.

Both SICI and LICI have may have important roles within response inhibition. Changes in SICI are associated with movement suppression and initiation. When stopping is required, a non-selective increase in SICI is observed for both task-relevant (MacDonald et al. 2014) and irrelevant muscles (Coxon et al. 2006). Conversely, a selective reduction in SICI precedes single digit movement, indicating a position within the "fine-tuning" of precise movements (Stinear and Byblow 2003). Functional roles of LICI are less clear, but are also associated with motor control. During isometric voluntary contraction, reduced LICI is reported for activated (Kouchtir-Devanne et al. 2012; Opie et al. 2015b) and adjacent muscles at rest (Hammond and Vallence 2007). Recent results also propose a tonic role for LICI within response inhibition. Levels of LICI may be proactively set to inhibitory requirements and appear to associate with response times on trials where just one hand is unexpectedly cued to stop (partial trials) (Cowie et al. 2016). These findings suggest intracortical networks within M1 act with different degrees of selectivity. The activation of these networks within response inhibition, notably proactive control, is not understood.

The present study had three aims. The first aim was to assess both proactive and reactive inhibitory processes within a novel bimanual anticipatory response task. A reduction in Partial trial response times after proactive cues compared with reactive cues was hypothesized, in accordance with stop-signal paradigms (Aron and Verbruggen 2008; Claffey et al. 2010; Majid et al. 2012).

The second was to investigate the modulation of CME and intracortical inhibition at a “cue-level” (Duque and Ivry 2009; Sinclair and Hammond 2009) using a preparation-optimal stimulation time. It was hypothesized that compared with rest cues, 1) left hand CME would be suppressed when cued to respond, and 2) SICI from left first dorsal interosseous (FDI) would decrease when a left hand response was known (or highly likely) but would not change when a response was uncertain. The final aim was to examine the modulation of LICI at a “task-level”. It was hypothesized that compared with pre-task, LICI would decrease non-selectively in both task-relevant and irrelevant muscles.

4 Methods

4.1 Participants

Eighteen participants without neurological impairment participated in the experiment (mean age 26.4 y, range 18-50 y, 8 female) with sixteen participating in both protocols. All were right handed (laterality quotient mean 0.92, range 0.75-1) as determined using the four-item revised Edinburgh handedness inventory (Veale 2014). Written informed consent was obtained before participation and the study was approved by the University of Auckland Human Participants Ethics Committee (Ref. 014398).

4.2 Response Task

The experiment involved a modified bimanual anticipatory response task as reported recently (Cowie et al. 2016; MacDonald et al. 2014; MacDonald et al. 2012). Briefly, participants were seated with forearms in a neutral posture, resting on a table surface, allowing the distal and medial aspect of each index finger to rest on a mechanical switch. A computer display projected

two indicators (as filling bars) (Fig. 3). Switch state was precisely captured with an Arduino and synchronized to the display through an analog-digital interface (NI-DAQmx 9.7; National Instruments). Switch height was adjusted to minimize postural muscle activity. Customized software written in MATLAB (R2011a, version 7.12; The MathWorks) generated the trial order, recorded trial data and controlled the visual output during the task.

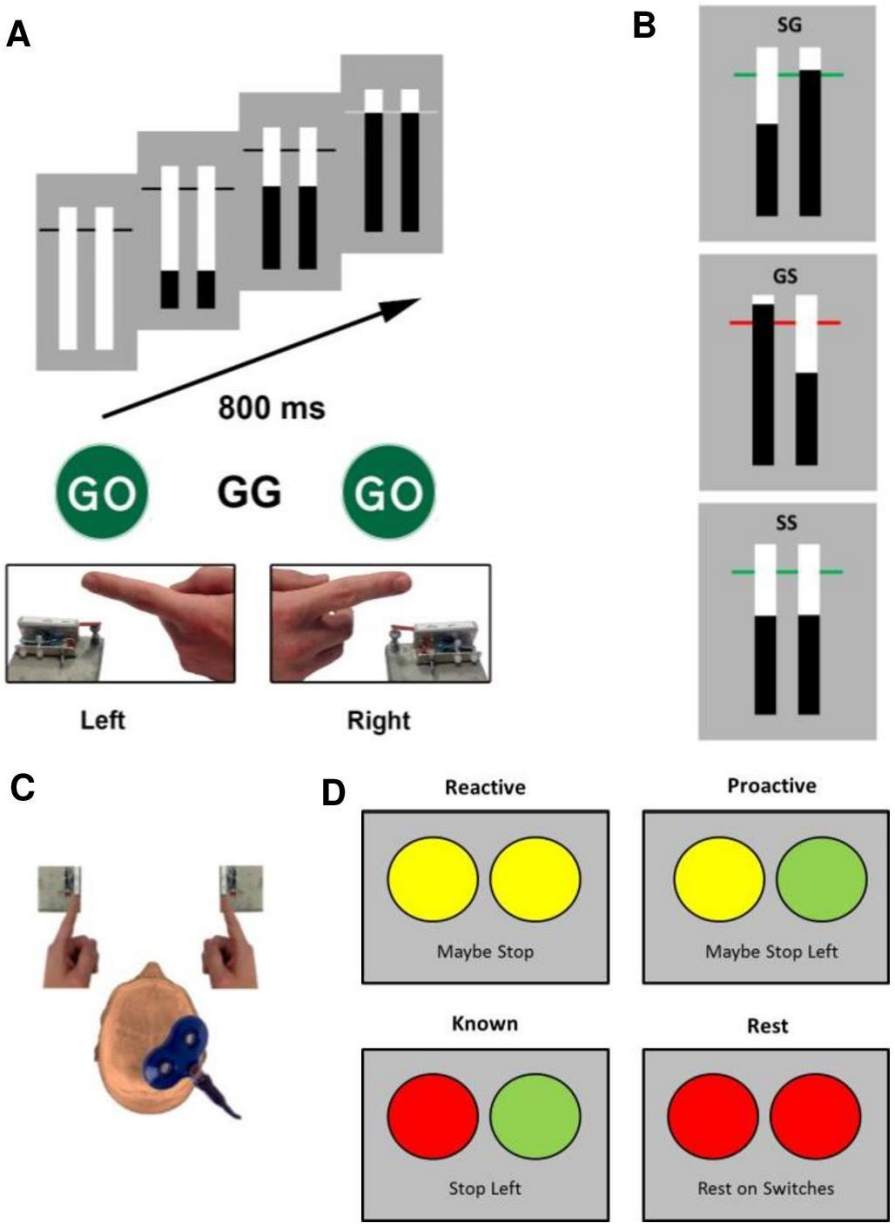

Fig. 3. The anticipatory bimanual response inhibition task. Trials start when both switches are pressed. After 500 ms, indicators (white columns) fill (turn black) at a constant velocity and reach the top after exactly 1 s. Participants are instructed to stop the left, right or both indicators at the target line (800 ms) by abducting the corresponding index finger(s) to release the switches. A. Go trials (GG = Go-Left Go-Right) indicate both switches be released. B. Stop trials were of three types (SG = Stop-Left Go-Right, GS = Go-Left Stop-Right, and SS = Stop-Left Stop-Right). On Partial trials (SG and GS), a single indicator stopped automatically at 550 ms. The response planned on that side must be inhibited, whereas the planned response from the opposite finger should be continued. On stop both trials (SS), both indicators stop after 600 ms

requiring the inhibition of the response on both sides. To indicate success, the target line turned green when lift times were within 30 ms of the target or responses successfully inhibited. If lift times were > 30 ms from the target, or not successfully inhibited, the target line would turn red. C. Transcranial magnetic stimulation was delivered over the right motor cortex to produce motor-evoked potentials in the electromyography recorded from first dorsal interosseous and abductor pollicis brevis of the left hand.D. Four warning cues were combined to produce six task variants. Reactive cues (Maybe Stop, MS) were indicated by two yellow circles. Proactive cues (Maybe Stop left, MSL or Maybe Stop Right, MSR) were indicated by a green circle for the responding hand and a yellow circle for the hand that might be cued to stop. Known cues (Stop Left, SL or Stop Right, SL) were indicated by a green circle for the responding hand and a red circle for the non-responding hand. No response (Rest) cues were indicated by two red circles. Each cue was presented for 1500 ms and followed by one of four trial types (see Table 1).

Participants were instructed to respond by lifting their index fingers (abduction) from the switches to stop the ascending indicators (black) at a horizontal target line (Fig. 3). Go trials [Go-Left Go-Right (GG)] required both indicators to stop at the target (800 ms) by lifting both fingers off the switches. Stop trials required either one or both fingers to remain on the switches. Partial trials [Go-Left Stop-Right (GS) or Stop-Left Go-Right (SG)] occurred when a single indicator stopped (550 ms), requiring only the finger from the other side to respond. Stop both trials [Stop-Left Stop-Right (SS)] required both fingers to remain on the switches as both indicators would stop (600 ms).

Table 1. *Summary of trial type probability relative to warning cue*

Response Type	**Cue**	**P(GG)**	**P(GS)**	**P(SG)**	**P(SS)**
Reactive	MS	0.66	0.11	0.11	0.11
Proactive	MSL	0.66	-	0.23	0.10
	MSR	0.66	0.23	-	0.10
Known	SL	-	-	1.0	-
	SR	-	1.0	-	-
Rest	Rest	-	-	-	1.0

Four warning cues were combined to produce six task variants. Reactive cues (Maybe Stop, MS), Proactive cues (Maybe Stop left, MSL or Maybe Stop Right, MSR), Known cues (Stop Left, SL or Stop Right, SL) and Rest cues. Cues were randomly proceeded by one of four trial types according to a set probability; P(trial occurring). GG = Go-Left Go-Right, SS = Stop-Left Stop-Right, GS = Go-Left Stop-Right, SG = Stop-Left Go-Right

Each trial was preceded by a warning cue of 1.5 s duration. Cues consisted of two coloured circles on the left and right of the screen display, corresponding to each hand. Circle colour provided information about the upcoming response in either a proactive or reactive context (Fig. 3). Because response complexity may affect inhibitory processes (Greenhouse et al. 2015a), 10% of proactive trials were catch trials (Stop Both, SS) to maintain similar complexity with reactive cues. Baseline measures of CME and inhibition were established with "Rest" cues where both fingers rested on switches and no response was required (SS trials). Bar filling occurred 500 ms after fingers were placed on the switches.

4.3 Electromyography

Surface electromyography (EMG) was collected from the first dorsal interosseous (FDI) and abductor pollicis brevis (APB) muscles of the left hand. The left hand was chosen because processes required to successfully cancel a subset of a movement are most pronounced with the non-dominant hand (MacDonald et al. 2012). A belly-tendon electrode montage recorded FDI activity and a belly-belly montage recorded APB activity using 10-mm-diameter Ag-AgCl surface electrodes (Ambu Blue Sensor Paediatric NS, Ballerup, Denmark). For the left hand, a shared ground electrode was positioned on the posterior hand surface (3M Canada). An equivalent belly-tendon montage with a posterior ground electrode configuration recorded FDI activity from the right hand to record behavioral activity. EMG activity was amplified, bandpass-filtered (10–1000 Hz) and digitized at 10 kHz with a CED interface system (MICRO1401mkII; Cambridge Electronic Design Ltd, UK). Data were recorded onto a computer for offline analysis using Signal Software (Version 6.03; Cambridge Electronic Design Ltd, UK).

4.4 Transcranial Magnetic Stimulation

TMS was delivered using a MagPro X100 + option stimulator (MagVenture A/S, Denmark). A figure-of-eight coil (MC-B70) was held tangentially over the right M1 of the participant. The optimal coil position for eliciting MEPs in the left FDI was determined using a slightly suprathreshold intensity and marked on the scalp. The handle was posteriorly positioned and the coil orientated at a 45°angle to the midline, inducing a monophasic, posterior-anterior (PA) directed current for the LICI protocol (Brasil-Neto et al. 1992). For the SICI protocol, the stimulator induced a monophasic anterior-posterior (AP) current (Cirillo and Byblow 2016; Sale et al. 2016).

Motor thresholds were determined using parameter estimation by sequential testing using a TMS motor threshold assessment software (V1.0) (Awiszus and Borckardt 2011). For the LICI protocol, a task motor threshold (TMT) was determined for both FDI and APB of the left hand while the participant rested their index fingers on the switches. TMT was determined as the minimum stimulus intensity required to elicit a MEP in the targeted muscle of at least 50 μV. For the SICI protocol, active motor threshold (AMT) was obtained for left FDI and defined as the minimum stimulus intensity required to elicit a MEP in the FDI muscle of at least 200 μV in amplitude during a low-level voluntary contraction (~10% maximum voluntary contraction).

4.5 LICI Protocol

For the LICI protocol, paired-pulse TMS was delivered with an interstimulus interval of 100 ms (Sanger et al. 2001). Both test and conditioning stimulus (TS and CS respectively) intensities were set to 130% of TMT for FDI. If necessary, conditioning and test stimuli were equivalently adjusted in 1-2% maximum stimulator output (MSO) intervals to produce a conditioned MEP that

was ~50% of test. This intensity remained constant for the LICI protocol to assess modulation of LICI during the task. To adjust for possible changes in corticomotor excitability that may affect LICI estimates (Sanger et al. 2001), 12 rest trials were recorded at two additional stimulation intensities set to 2% above and 2% below the chosen intensity. All three intensities were randomized in a single block of 36 trials. This block of LICI trials provided baseline data that could be used to compare differences in task inhibition relative to any observed increases or decreases in non-conditioned MEP amplitude that occurred.

Participants performed a practice block of 33 trials containing stimulated and non-stimulated trials for each of the possible warning cues. The response task consisted of 396 trials split into 12 blocks of 33 trials with all cue types randomized within blocks. During stimulated trials, the CS-TS were given at 450 and 550 ms respectively. This timing was chosen to precede any response related increases in corticomotor excitability and to coincide with the presentation of stop cues at 550 ms (Cowie et al. 2016; MacDonald et al. 2014). For each cue type (MS, MSR, MSL, SR, SL and Rest) 18 trials were stimulated. Non-stimulated trials had the following Trial Type distributions. For MS cues, 135 non-stimulated trials were collected given that response times can be affected by TMS (Leocani et al. 2000; Ziemann et al. 1997). For each of MSR and MSL cues 51 trials were non-stimulated, whereas for each of SL and SR cues 18 trials were non-stimulated. For Rest cues, 15 trials were non-stimulated to eliminate any effect of TMS expectancy.

4.6 SICI Protocol

For SICI, paired-pulse TMS was delivered with an AP directed current using an ISI of 3 ms (Murase et al. 2015; Peurala et al. 2008). TS intensity was set to produce an average MEP

amplitude of ~0.5 mV, while the participant rested their index fingers on the switches. The intensity of the CS was set to produce ~50% inhibition of the TS (i.e. MEP amplitude of ~0.25 mV). This intensity remained constant for the SICI protocol to assess modulation of SICI during the task. Similar to the LICI protocol, TS intensity was increased and decreased by 2% MSO and 12 trials recorded for conditioned and non-conditioned trials at each of the 3 intensities in a randomized block of 72 trials.

For the SICI protocol the response task consisted of 272 trials split into 8 randomized blocks of 34. In stimulated trials, the CS occurred at 547 ms and TS at 550 ms to match the timing of the TS in the LICI protocol. For each of the 6 cue variations (MS, MSR, MSL, SR, SL and Rest) 18 trials were conditioned and 18 were non-conditioned. For each of MS, MSR, MSL and rest cues, 9 trials were non-stimulated. For each of SL and SR cues, 10 trials were non-stimulated.

4.7 Dependent Measures

To assess task performance, lift times (LTs) were recorded as the time that the switches were released relative to the target line that the filling bars intercepted 800 ms into the trial. Mean LTs from Go and successful Partial trials were calculated after the removal of outliers (± 3 SD; 0.8% removed). Partial trial delays were calculated by subtracting the appropriate (left or right) MS-GG trial LT from the respective Partial trial LT for MSL, MSR (proactive) or MS (reactive) trials. Stop signal reaction time (SSRT) and the percentage of successful trials were determined. SSRT was calculated using the integration method:

$$(\text{SSRT} = \text{SSD} + n\text{th LT})$$

where n is the probability of failing to stop for the given trial multiplied by the number of LTs in the ordered LT distribution, and SSD (stop signal delay) is the bar stop time (550 or 600 ms)

subtracted from target time (800 ms) for the given stop trial (Logan and Cowan 1984b; Verbruggen et al. 2013).

Peak-to-peak MEP amplitude was calculated from EMG 10 to 45 ms after the stimulus. MEPs were excluded when root mean square (RMS) EMG was > 10 μV in the 50 ms before stimulation. One participant had continuous APB EMG activity (> 10 μV) during the SICI protocol and data from this muscle was excluded. Average MEP amplitude from FDI and APB was calculated following trimming of the upper and lower 10 % of trials (Stinear and Byblow 2004; Wilcox 2010). For both SICI and LICI, percent inhibition (%INH) was calculated as:

$$\%INH = [1 - (CS\ MEP\ amplitude / TS\ MEP\ amplitude)] \times 100$$

where CS and TS MEP amplitude were averages for each condition from each participant. To reduce inter-subject variability when assessing the effect of task-context, Rest cue values were normalized to Pre-Task values (1.0). For APB SICI one participant had no pre-task inhibition and another participant's normalized rest-cue inhibition was an outlier (> 3 SD above the mean). Both participants were excluded from the APB SICI analyses.

4.8 Statistical analyses

To assess the effect of Cue Type on LTs, two-way repeated measures (RM) ANOVA with factors Cue Type (Reactive, Proactive, Known) and Hand (Left, Right) were performed for both Partial (one hand response) and Go trial LTs (both hands respond). For Stop trials, one-way RM ANOVAs were performed for stopping success rate and SSRT, using a 5 Trial Type (MS-SR, MS-SL, SS, MSL, MSR) design.

To assess the effect of Cue Type on CME and inhibition, one-way RM ANOVAs with 6 Cue Types (Rest, MS, MSL, SL, MSR, SR) were used to examine both %INH and NC MEP amplitudes

from LICI and SICI protocols. The effect of task-context on inhibition and CME was assessed using one-sampled *t*-tests for Pre-Task and Rest cue average %INH and NC MEP amplitude. To investigate whether the extent of inhibition was associated with the stopping interference effect, linear regression analyses were performed for %INH in both protocols for MS, MSR and MSL cues and the respective Partial trial delays.

Normality was assessed prior to analysis of variance (ANOVA) using the Shapiro-Wilk test. Non-normal data were logarithmically transformed. Statistical tests were performed and reported for the transformed data. The criterion for statistical significance was set to $\alpha = 0.05$. Non-transformed means ± standard error (SE) were reported. Non-spherical data, as determined by Mauchly's Test of Sphericity, were reported using Greenhouse-Geisser corrected *P* values. *Post hoc* comparisons were performed using paired *t*-tests (two-tailed). Bonferroni corrections were applied for multiple comparisons and adjusted *P* values were reported when appropriate.

5 Results

5.1 Lift Times

Lift times are shown in Table 1. Briefly, LTs indicated that participants performed the task accurately, that there was a cost-benefit trade-off with Cue Type, and an interference effect from stopping one side and lifting with the other on Partial trials. For Partial trial LTs (Fig. 4), there was a main effect of Cue Type ($F_{2,34} = 112.9$, $P < 0.001$). LTs were later with Reactive cues (MS, 69 ms ± 5 ms) compared to Proactive (MSL and MSR, 45 ms ± 8 ms, $P < 0.001$) and Known cues (SL and SR, 3 ms ± 5 ms, $P < 0.001$). In addition, Proactive LTs were delayed compared with Known ($P < 0.001$). There was no main effect of Hand ($F_{1,17} = 3.1$, $P = 0.095$) and no Cue Type x Hand interaction ($F_{2,34} = 2.6$, $P = 0.085$). Planned comparisons were undertaken to assess the

hypothesis about Partial trials for each hand. Left hand Partial LTs (Fig. 4) were longer for Reactive cues (78 ± 6 ms) compared with both Proactive (MSR, 49 ± 11 ms; $t_{17} = 4.5$, $P < 0.001$) and Known (SR, 3 ± 5ms; $t_{17} = 15.3$, $P < 0.001$), with Proactive also longer than Known ($t_{17} = 6.0$, $P < 0.001$). For the right hand, Partial LTs were also longer for Reactive cues (59 ± 6 ms) compared with both Proactive (MSL, 41 ± 7 ms; $t_{17} = 3.7$, $P = 0.028$) and Known (SL, 2 ± 5 ms; $t_{17} = 10.5$, $P < 0.001$), with Proactive longer than Known ($t_{17} = 7.8$, $P < 0.001$). Thus, informative proactive cues were associated with reduced Partial trial LT delays.

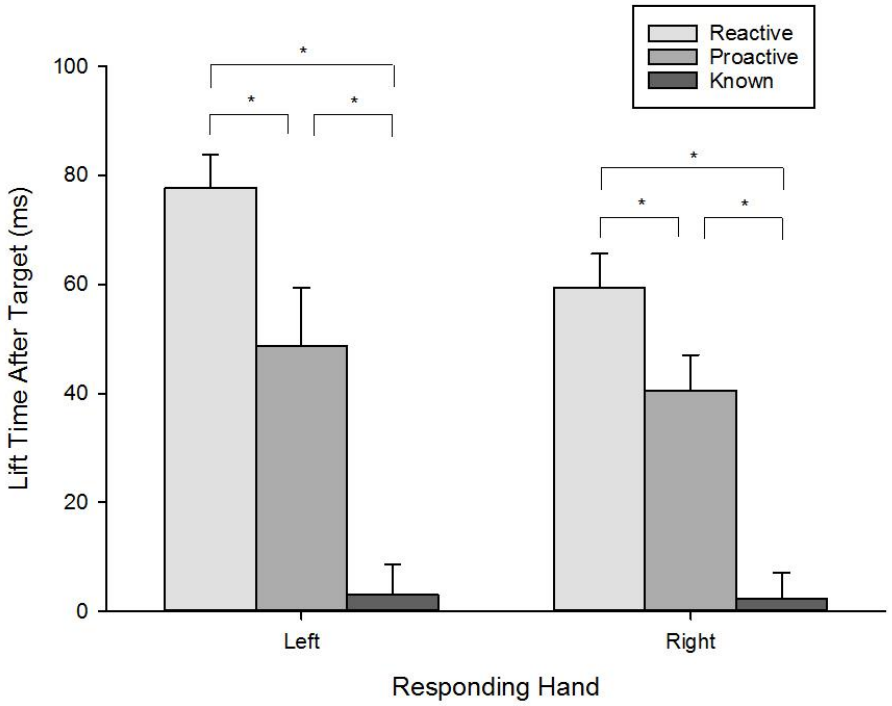

Fig. 4. Partial trial lift times relative to cue. Lift times are defined as the time ellapsed after the target line (800 ms) until a response is made (switch released). Reactive cues (Maybe Stop) required the left, right or both hands to occasionally stop. Proactive cues (Maybe Stop Left and Maybe Stop Right) required only the cued hand to occasionally stop, except on catch trials. Known cues (Stop Left and Stop Right) required the cued hand to always stop. Bars represent the group mean ($n = 18$). Error bars indicate SE. *$P < 0.05$.

For Go trials, there was a main effect of Hand ($F_{1,17}$ = 13.0, P = 0.002) with faster LTs for Right (13 ± 2 ms) than Left (23 ± 3 ms; Fig. 5). There was no main effect of Cue Type ($F_{2,34}$ = 1.2, P = 0.316) but there was a Cue Type x Hand interaction ($F_{2,34}$ = 42.1, P < 0.001). For left hand LTs (Fig. 5), MSR cues (14 ± 3 ms) were shorter than both MS (25 ± 3 ms; t_{17} = 4.3, P = 0.007) and MSL (30 ± 3 ms; t_{17} = 5.2, P < 0.001). For right hand LTs, MSL cues (4 ± 3 ms) were shorter than both MSR (19 ± 3 ms; t_{17} = 4.4, P = 0.006) and MS (15 ± 3 ms; t_{17} = 4.0, P = 0.015). For MS cues (Fig. 5), left LTs were greater than right (t_{17} = 3.4, P = 0.043). For MSL cues, left LTs were also greater than right (t_{17} = 7.0, P < 0.001). These results indicate a proactive "braking" which is expressed more forcefully on the left than right hand.

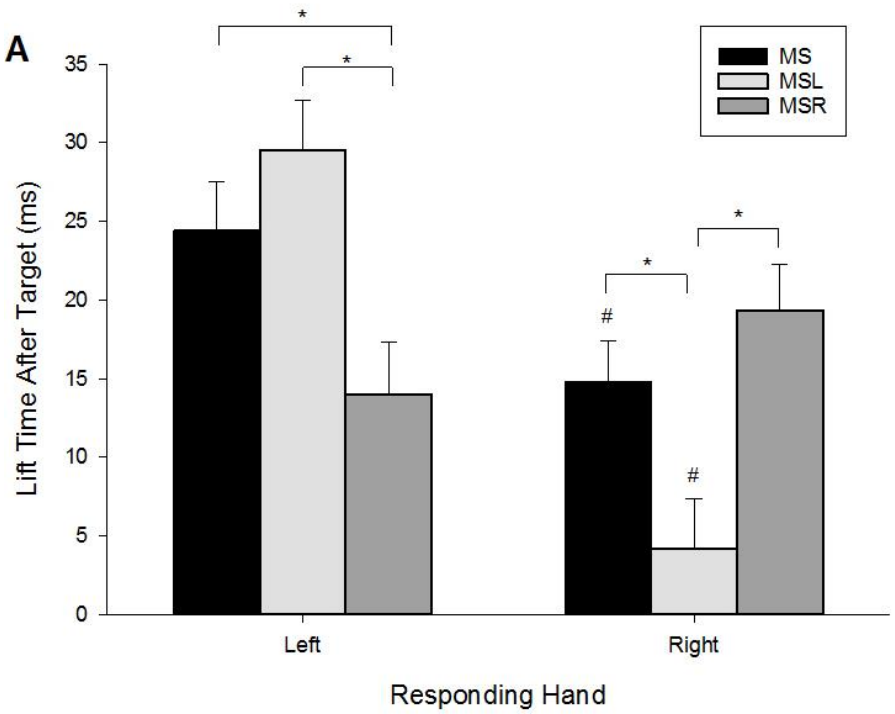

Fig. 5. Go trial lift times relative to cue. MS, Maybe Stop; MSL, Maybe Stop Left; MSR, Maybe Stop Right. Bars represent the group mean (n = 18). Error bars indicate SE. *P < 0.05. #P < 0.05 compared with left for the given cue.

5.2 Success rates and SSRTs

There was no effect of Trial Type ($F_{4,68} = 1.5$, $P = 0.215$) on stopping success rates (Table 1). There was a main effect of Trial Type ($F_{4,68} = 22.6$, $P < 0.001$) on SSRTs with shorter SSRTs for SS trials (202 ± 6 ms) compared with all other Trial Types (SSRTs all > 248.4 ± 6 ms; all $t_{17} > 6.0$, all $P < 0.001$). Therefore, Partial trials were associated with longer stopping processes than when both hands required stopping.

Table 1. *Behavioral results (LICI protocol)*

	Go Trials						
	MS (L)	MS (R)	MSR (L)	MSR (R)	MSL (L)	MSL (R)	
LTs (ms)	24 ± 3	15 ± 3	14 ± 3	19 ± 3	30 ± 3	4 ± 3	
	Stop Trials						
	MS-SR	MS-SL	MS-SS	MSL	MSR	SL	SR
LTs (ms)	78 ± 6	59 ± 6	-	41 ± 6	49 ± 11	2 ± 5	3 ± 5
Success Rate (%)	59 ± 8	66 ± 6	66 ± 6	69 ± 6	57 ± 7	96 ± 2	96 ± 2
Partial Delay (ms)	53 ± 5	45 ± 5	-	26 ± 5	24 ± 10	-	-
SSRTs (ms)	266 ± 10	248 ± 6	202 ± 6	256 ± 6	254 ± 7	-	-

Behavioral values include lift times (LTs) relative to the target (800 ms) for hand (L, Left; R, Right), stopping success rates, Partial trial delays (relative to MS-GG trials) and stop-signal reaction times (SSRTs). MS, Maybe Stop; MSL, Maybe Stop Left; MSR, Maybe Stop Right; SR, Stop Right, SL, Stop Left; SS, Stop Both. Values are reported as mean ($n = 18$) ± SE. * values are also depicted in Fig 4 and 5.

5.3 Stimulation Parameters

For the LICI protocol, TMT was 47 ± 2% MSO for FDI and 51 ± 2% MSO for APB. Task simulation intensity was set at 65 ± 2% MSO (138% TMT for FDI). Average Pre-Task %INH was 64.3 ± 4.8% for FDI and 70.0 ± 5.2% for APB. Average MEP amplitude was 1.9 ± 0.4 mV in FDI and 0.8 ± 0.2 mV in APB.

For the SICI protocol, AMT was 53 ± 2% MSO. Average TS intensity was 76 ± 4% MSO while CS intensity was 39 ± 4% MSO (74% AMT). Average Pre-Task Inhibition was 54.7 ± 3.8% for FDI and 50.3 ± 6.2% for APB. Average MEP amplitude was 0.6 ± 0.1 mV for FDI and 0.5 ± 0.2 mV for APB.

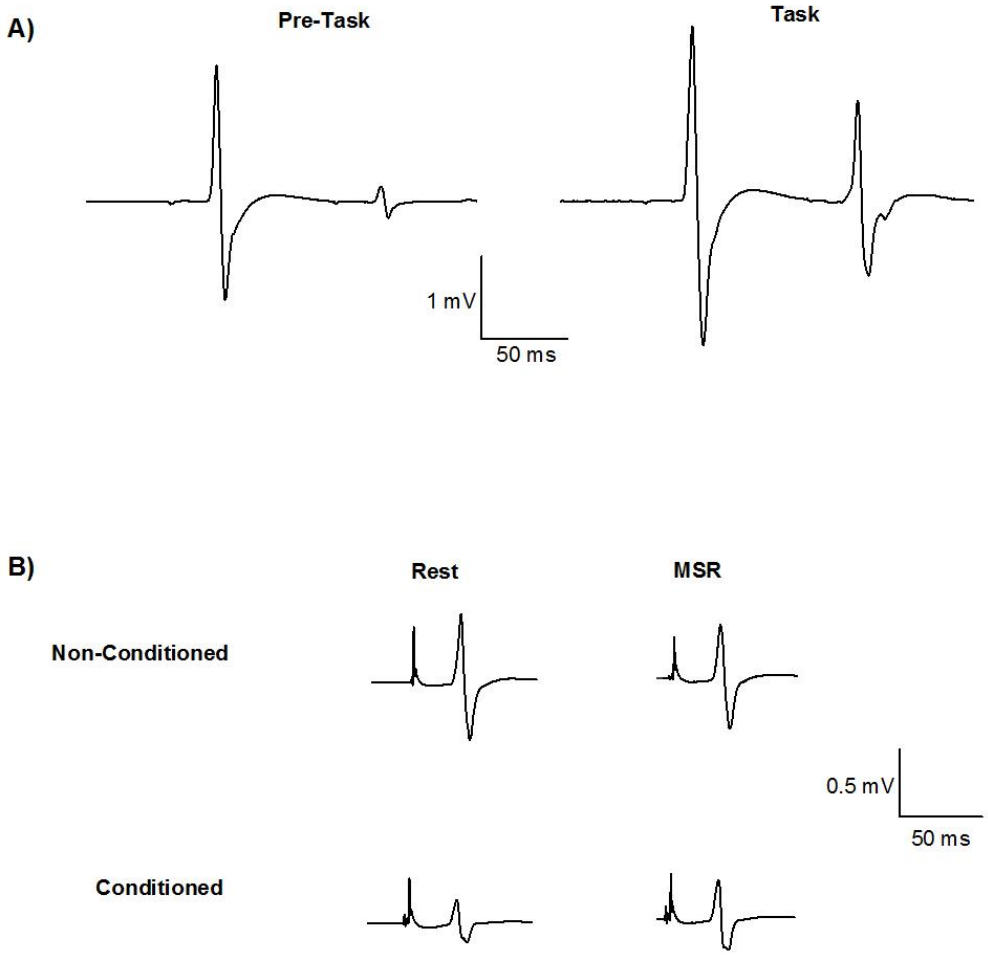

Fig 6. Representative electromyography with motor evoked potentials in left first dorsal interosseous of for a typical participant. A. Long-interval intracortical inhibition (LICI) was weaker during the Task (rest trials) than during Pre-Task as indicated by the larger conditioned (2nd) MEP under Task conditions. B. Short-interval intracortical inhibition (SICI) was reduced for Maybe Stop Right (MSR) trials compared with rest trials. LICI and SICI conditioning stimuli were delivered 450 ms and 547 ms into trials respectively. Test stimuli were delivered at 550 ms.

5.4 Inhibition

For the LICI protocol (n = 17; Fig. 7), there was no main effect of Cue Type for either muscle (FDI: $F_{5,80} = 0.9$, $P = 0.458$; APB: $F_{5,80} = 2.2$, $P = 0.063$). For FDI, %INH decreased during the task by 73.1 ± 22.0% compared with Pre-Task ($t_{16} = 3.3$; $P = 0.004$, Fig. 9B). For APB, %INH also decreased by 70.3 ± 17.6% during the task compared with Pre-Task ($t_{16} = 4.0$, $P = 0.001$), suggesting a non-selective disinhibition within task-context.

For the SICI protocol (FDI n =16, APB n = 14; Fig. 8), there was a main effect of Cue Type ($F_{5,75} = 2.5$, $P = 0.037$) with greater %INH observed in FDI during Rest cues (46.0 ± 5.8 %) compared with MSR (32.7 ± 6.9 %; $t_{15} = 3.5$, $P = 0.003$) and SR (31.9 ± 6.7 %; $t_{15} = 3.5$, $P = 0.003$). No difference was observed between task (Fig. 9D) and Pre-Task (3.7 ± 16.5% decrease; $t_{15} = 0.2$, $P = 0.842$). For APB, there was no main effect of Cue Type ($F_{5,65} = 2.0$, $P = 0.091$) and no difference for %INH between Task and Pre-Task (29.2 ± 32.3% decrease; $t_{13} = 0.9$, $P = 0.382$), indicating no effect of task-context but task-relevant modulation relative to cue.

5.5 Corticomotor Excitability

For the LICI protocol (FDI, n = 17; Fig. 7), there was no main effect of Cue Type for FDI ($F_{5,80} = 2.9$, $P = 0.053$). However, MEP amplitude (2.8 ± 0.5 mV) increased by 58.9 ± 21% during the task compared with Pre-Task ($t_{16} = 2.8$, $P = 0.012$; Fig. 9A). For APB, there was an effect of Cue Type ($F_{5,80} = 5.0$, $P = 0.005$), with greater MEP amplitude for SL cues (0.9 ± 0.2 mV) compared with both Rest (0.8 ± 0.2 mV; $t_{16} = 3.8$, $P = 0.002$) and SR (0.8 ± 0.2 mV; $t_{16} = 4.7$, $P < 0.001$). Task and Pre-Task APB MEP amplitudes did not differ (5.0 ± 14.8 %; $t_{16} = 0.3$, $P = 0.741$). Thus, CME increased for the task-relevant FDI only.

For the SICI protocol (FDI n =16, APB n = 15; Fig. 8), there was no main effect of Cue Type for FDI ($F_{5,75}$ = 0.3, P = 0.857) or APB ($F_{5,70}$ = 2.7, P = 0.084). For FDI, Task MEP amplitude (Fig. 9C) increased by 82.9 ± 27.7% compared with Pre-Task (t_{15} = 3.0, P = 0.009). No difference was observed for APB between Task and Pre-Task (9.3 ± 17.2% increase; t_{14} = 0.5, P = 0.599). Thus, CME increased for the task-relevant FDI only.

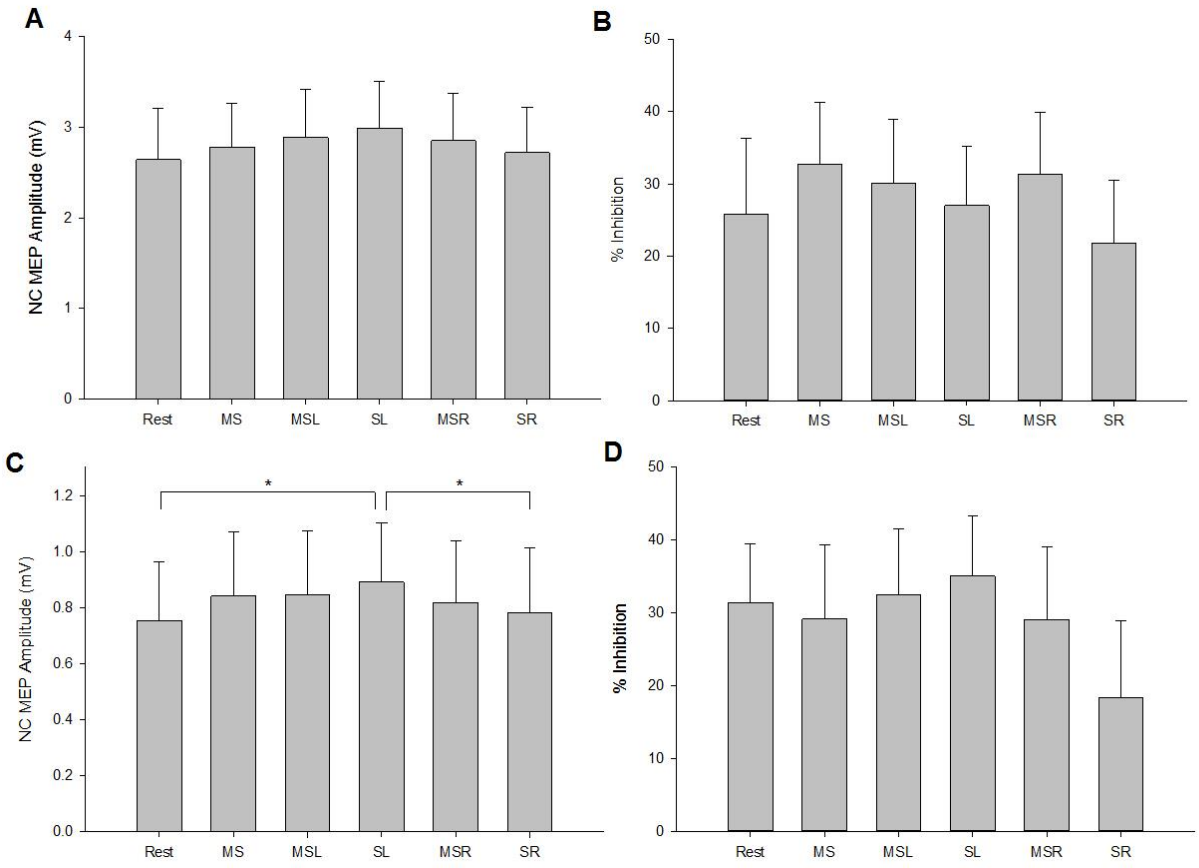

Fig. 7. Modulation of excitability and inhibition relative to warning cue during the long interval intracortical inhibition protocol (n = 17). A. Motor evoked potential (MEP) amplitude of task-relevant (first dorsal interosseous, FDI) muscle from the non-conditioned (NC) stimulation. B. % Inhibition from FDI. C. NC MEP amplitude of task-irrelevant (abductor pollicis brevis, APB) muscle. D. % Inhibition from APB. Means ± SE bars represent non-transformed data. *P < 0.05.

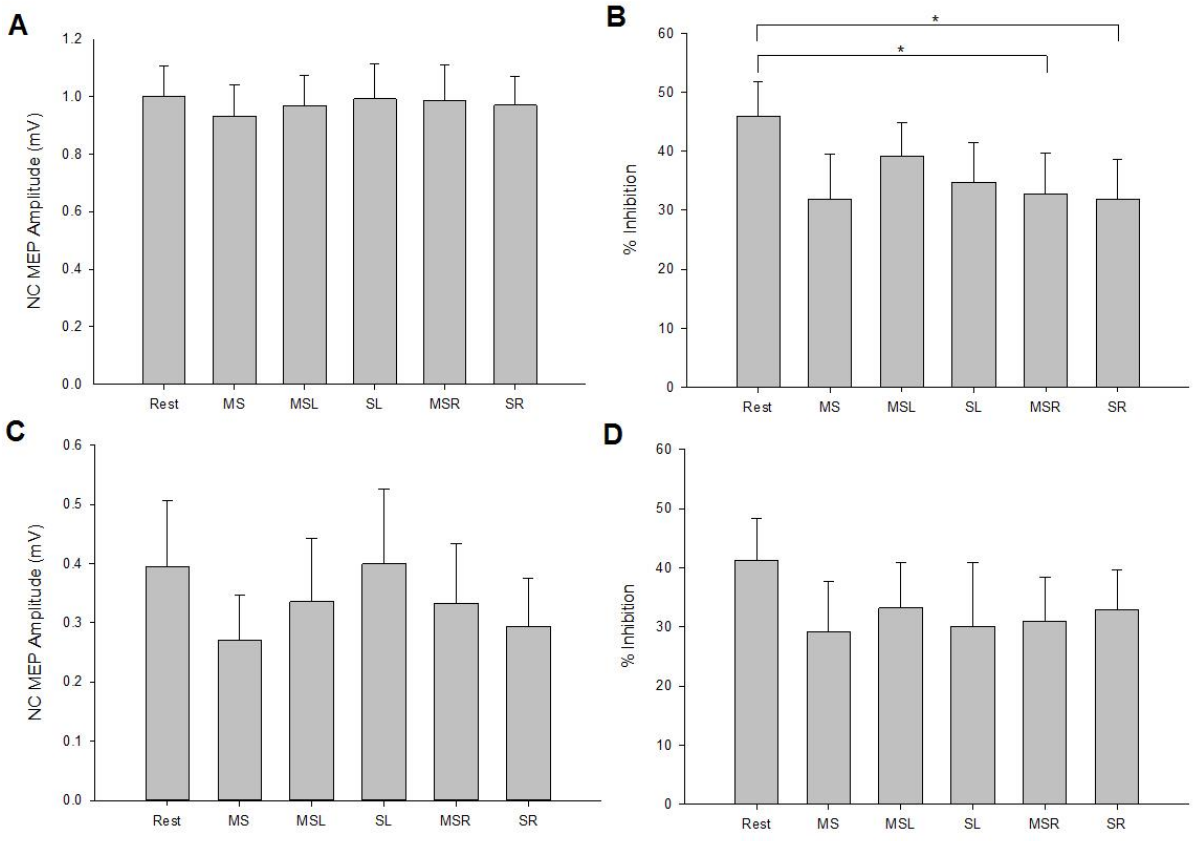

Fig. 8. Modulation of excitability and inhibition relative to warning cue during the short interval intracortical inhibition protocol. A. Motor evoked potential (MEP) amplitude of task-relevant (first dorsal interosseous, FDI; *n* =16) muscle from the non-conditioned (NC) stimulation. B. % Inhibition from FDI. C. NC MEP amplitude of task-irrelevant (abductor pollicis brevis, APB; *n* =14) muscle. D. % Inhibition from APB. Means ± SE bars represent non-transformed data. **P* < 0.05.

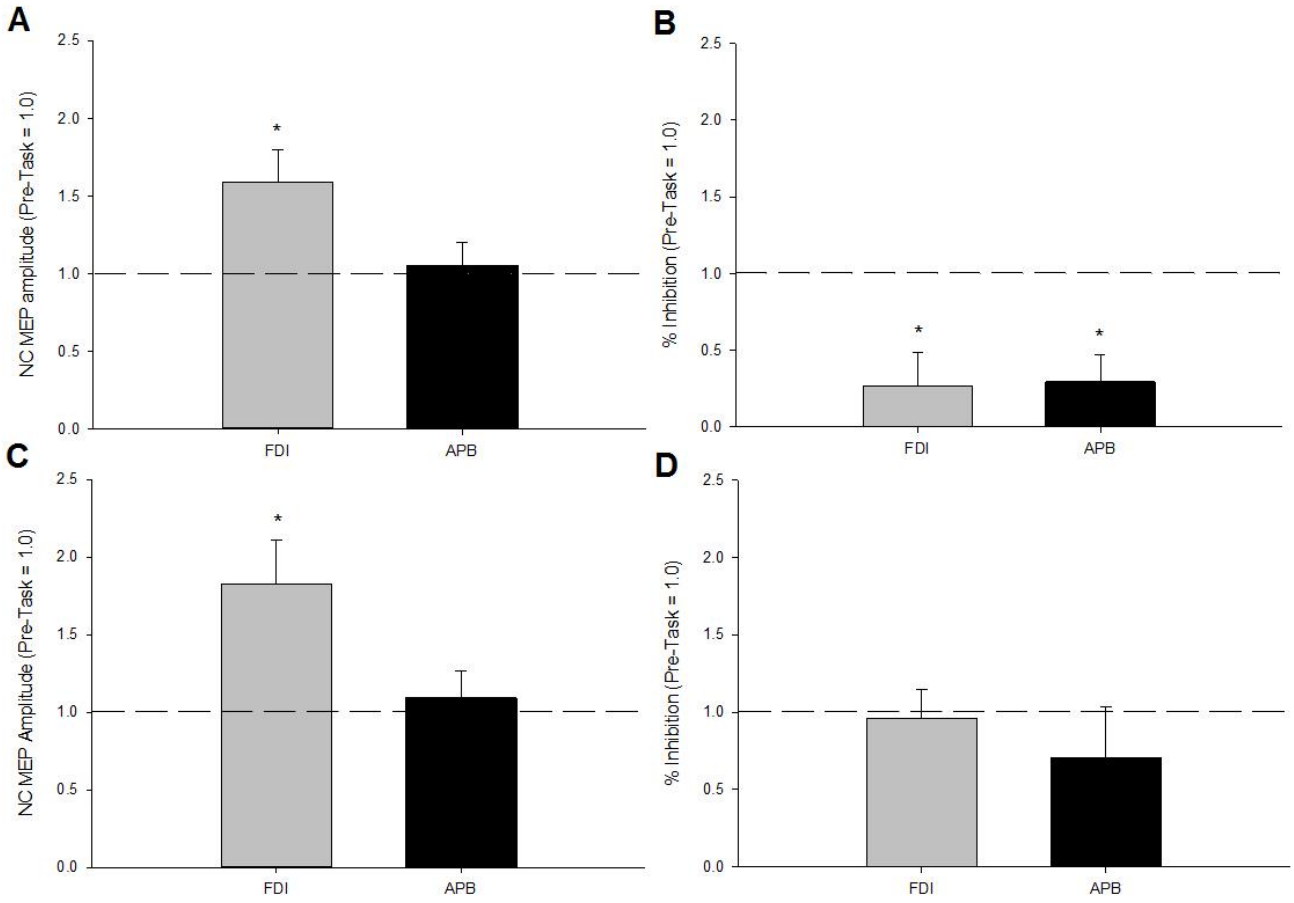

Fig. 9. Effect of response inhibition task context (Rest) on corticomotor excitability and inhibition for FDI and APB. Motor evoked potential (MEP) amplitude reported for the non-conditioned (NC) stimulation during long interval intracortical inhibition (LICI) or short interval intracortical inhibition (SICI). Values are normalized and scaled according to Pre-Task = 1.0 (dashed line). A. Corticomotor excitability for LICI protocol (n = 17). B. LICI. C. Corticomotor excitability for SICI protocol (FDI n = 16, APB n = 15). D. SICI (FDI n = 16, APB n = 14). Bars represent group means. Error bars indicate SE. *P < 0.05.

5.6 Linear regression

There was a positive correlation between LICI during MS cues and MS-SL Partial trial delays for FDI (r = 0.620, P = 0.031, n = 17; Fig. 10A), such that less inhibition was associated with shorter delays. A similar association between LICI during MS cues and MS-SL Partial trial

delays for APB was weak (r = 0.522, P = 0.121, n = 17; Fig. 10B). There were no correlations between FDI SICI or APB SICI and MS-GS, MSL or MSR trial delays (all P > 0.763).

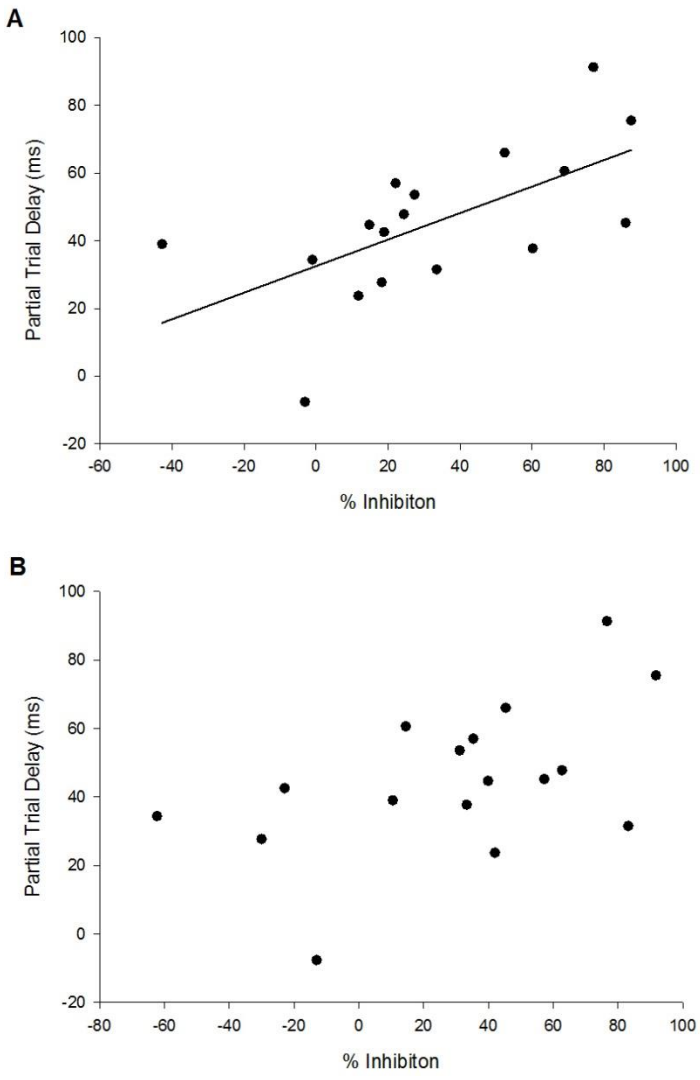

Fig. 10. Correlations between LICI and Partial trial delays of the right hand response for reactive inhibition (Maybe Stop) trials (n = 17). A. Task-relevant first dorsal interosseous (r = 0.620, P = 0.031). B. % Task-irrelevant (abductor pollicis brevis) (r = 0.522, P = 0.121)

6 Discussion

There were several confirmatory and a few novel findings that supported the hypotheses. First, behavioral task performance was in accordance with previous studies. As hypothesized, partial trial responses were delayed for reactive cues, supporting a model of non-selective motor suppression followed by response re-initiation (Cowie et al. 2016; Coxon et al. 2009; MacDonald et al. 2014) When advance information forewarned stopping, Partial trial response times were earlier than during reactive trials, although response delays were not eliminated entirely (Aron and Verbruggen 2008; Claffey et al. 2010; Majid et al. 2012). Neurophysiological studies with paired-pulse TMS indicated that SICI was modulated by cue type, in support of the second hypothesis. Inhibition levels were lower when responses were highly probable or known, similar to previous findings (Duque and Ivry 2009). Interestingly, CME increased during the task but was not modulated by cue type contrary to previous results and our hypothesis (Greenhouse et al. 2015a; Lebon et al. 2015). LICI from left FDI obtained during reactive trials correlated with Partial delays in the responding right hand , such that greater inhibition resulted in longer delays, supporting our hypothesis and previous results (Cowie et al. 2016). In support of our hypothesis of non-selective $GABA_B$-receptor mediated inhibition, LICI was reduced for both task-relevant and irrelevant muscles. These novel findings provide evidence that the networks responsible for LICI may set overall inhibitory tone related to task demands. Conversely, SICI data suggest that $GABA_A$-receptor mediated inhibition may be a mechanism that is used to prevent responses from occurring prematurely and that is reduced immediately prior to voluntary movement in a spatially-specific, task-relevant manner.

6.1 Proactive and Reactive Response Inhibition

The anticipatory task used in the present experiment was derived from the seminal studies of Slater-Hammel (1960). On known trials (SR and SL), LTs were maintained on target, suggesting response preparation was successfully timed relative to the target. Partial trial LTs differed between reactive, proactive and known cues, indicative of divergent preparatory mechanisms. Intracortical inhibition was assessed at the time that stop imperatives were presented. Stop imperatives within anticipatory tasks may be more consistently timed than those presented during a stop-signal task (Lebon et al. 2015), resulting in more notable differences between reactive and proactive cues. This was seen in SICI differences between cue types, but not LICI. Behaviorally, stop signal reaction times (SSRTs) were similar between reactive and proactive Partial trials (~250 ms), which were both longer than reactive cued SS trials (~200 ms). Longer SSRTs support the idea that there is an additional process of response re-initiation after a cancellation of the initially prepared bimanual response during Partial trials (Cowie et al. 2016; MacDonald et al. 2014; MacDonald et al. 2012). Longer SSRTs (~275-300 ms) in Partial trials have also been observed in stop-signal tasks assessing proactive inhibition (Cai et al. 2011; Majid et al. 2012). However, anticipatory tasks minimize response "waiting" strategies.

The present behavioral results provide evidence in support of the idea that there are functional neural constraints on our ability to selectively inhibit responses under reactive conditions. However, under proactive conditions, these constraints appeared to be reduced. For reactive cues, Partial trial LTs were significantly delayed compared with Go trials. This delay, is indicative of an interference effect between stopping and going processes, and is likely due to an inherent inability to selectively inhibit a subcomponent of a well-prepared default bimanual response (Aron and Verbruggen 2008; Coxon et al. 2007; 2009; Greenhouse et al. 2012;

MacDonald et al. 2014). The interference effect indicates that the bimanual movement is cancelled in entirety, and then a subsequent unimanual response is initiated (Coxon et al. 2007; MacDonald et al. 2014). Previous studies have suggested that delays may result from biased estimates and can be reduced with training (Xu et al. 2015). As in our previous study (Cowie et al. 2016), the high success rates observed in the present study (~60%) challenge the notion that delays can be reduced with increased task practice. Even with proactive cues, Partial trial LTs were late compared with Go LTs. Proactive LTs were faster than reactive LTs and support previous findings (Aron and Verbruggen 2008; Claffey et al. 2010; Majid et al. 2012). When the left hand was proactively cued to stop (MSL), left LTs were longer than right LTs on Go trials, indicative of a "braking" mechanism that may temporarily act on the cued hand until a response decision is made (Aron 2011; Jahfari et al. 2010; Majid et al. 2013). It is important to note that there was no difference in left side LTs between proactive (MSL) and reactive (MS) cues. Response slowing may also be employed for some participants, even on reactive trials as part of a speed-accuracy trade off (Wickelgren 1977). Interference effects and slowed LTs accompanied both proactive and reactive inhibition trials.

Contrary to our hypothesis, CME was not modulated by the anticipatory task. Numerous lines of evidence suggest that CME is suppressed during response preparation, before the presentation of response cues (Davranche et al. 2007; Duque and Ivry 2009; Duque et al. 2012; Duque et al. 2010; Greenhouse et al. 2015a; Greenhouse et al. 2015b; Hasbroucq et al. 1999a; Hasbroucq et al. 1997; Labruna et al. 2014; Lebon et al. 2015). It is likely that differences in task design account for a lack of CME suppression observed in the present results. The current task design assessed CME at the time when stop cues (bars stopped filling) occurred (SICI) or 100 ms beforehand (LICI). However, CME was not reduced compared with rest for either of these time

points. One explanation is that premature response suppression does not occur during anticipatory response tasks. If a target is displayed, responses can be initiated at a known time. This interpretation supports a model of "impulse control" for reaction time tasks, in which CME suppression occurs to prevent premature initiation (Duque and Ivry 2009; Duque et al. 2012; Duque et al. 2010; Labruna et al. 2014). To account for uncertainty surrounding the response cue presentation time, motor system excitability may be heightened to react to the first observed stimulus. Suppressive mechanisms are likely required to counter this increase. This interpretation supports why CME attenuation is greatest, closest to response cues (Hasbroucq et al. 1999a; Hasbroucq et al. 1997). As time elapses, response cues become more likely. If heightened motor excitability is widespread, it may also explain why suppression can be observed in task-irrelevant muscles (Greenhouse et al. 2015b). The present results support a model of premature response suppression that is not observed during anticipatory response inhibition tasks.

6.2 Intracortical Inhibition

$GABA_B$ mediated LICI was modulated by task context. While LICI was unaffected by cue type, a reduction compared with pre-task measures occurred. These results engage with a small number of studies that have assessed LICI during movement tasks. Sinclair and Hammond. (2008) used a simple reaction time task in which response cues for unimanual right hand movements were preceded at random, by either a warning cue (auditory signal) or were unwarned. For the warned condition, LICI was reduced compared with unwarned, indicating disinhibition preceded responses at a "cue-level". There are reasons why the current results may not have demonstrated similar "cue-level" modulation of LICI. First, CME also differed between warned and unwarned conditions for Sinclair and Hammond (2008). Changes in underlying CME may confound changes in LICI (Opie and Semmler 2014; Sanger et al. 2001). However, measures of intracortical

inhibition appear to be relatively stable when variance in MEP amplitude is between 1 – 4 mV (Kujirai et al. 1993; Opie and Semmler 2014; Rosenkranz and Rothwell 2003; Sanger et al. 2001). Differences in results be more likely explained by the tasks employed. Sinclair and Hammond (2008) included only two conditions within blocks (warned and unwarned) with occasional rest trials (~15%). However, the present task included six cue variants. It is possible that the increased number of cue types did not allow levels of LICI to be actively adjusted. This interpretation assumes that if blocks contained only a single cue type, LICI may change at a "task-level". This prediction is supported by an increase in LICI when responses may require reactive inhibition, compared with when inhibition is not a possibility (Cowie et al. 2016). To this end, tonic levels of LICI may be adjusted by task-expectations as part of an "activation threshold" model (Cowie et al. 2016; MacDonald et al. 2014; MacDonald et al. 2017). Unfortunately, the current task design does not permit reduced LICI to be directly interpreted as a result of task-expectations. Pre-task measures were assessed in the absence of task components such as visual stimulation. An alternative interpretation is that LICI was reduced as a result of increased attentional demands (Conte et al. 2007). Presumably, attention is increased when responses are warned (Sinclair and Hammond 2008). The presently observed association between task-relevant LICI on reactive trials and right Partial response delays, similar to previous findings (Cowie et al. 2016), lends support to a functional change in inhibition relative to task-requirements. Additionally, increased CME compared with pre-task only existed for task-relevant muscles. Attentional demands would likely affect the excitability of both muscles non-selectively. Further investigation into the modulation of LICI as a result of task-context and stopping requirements is recommended.

The modulation of SICI extends previous findings regarding proactive inhibition. SICI differed between cues types, suggesting an interaction with response expectancy at a "cue-level".

In support of our hypothesis, SICI from left FDI decreased compared with baseline when responding was highly likely (MSR), or required (SR). The amount of SICI did not change when responses were not certain (MSL, MS) or not required (SL). These data are in agreement with a selective release of $GABA_A$ mediated intracortical inhibition observed before movement (Coxon et al. 2006; Sinclair and Hammond 2008; Stinear and Byblow 2003). Duque and Ivry. (2009) assessed SICI 100-400 ms before response cues, investigating response preparation during a choice reaction task providing informative (left or right) and uninformative cues. SICI was reduced for left FDI when cues informed a unimanual left hand response, similar to "Stop Right" cues in the present study. However, some results appear to contrast those from the present experiment. When uninformative cues were presented (i.e. responses were uncertain) SICI was also reduced for the responding hand (Duque and Ivry 2009). Additionally, Sinclair and Hammond (2009) found no difference in SICI between cues that overtly changed the response probability of unimanual responses. These results challenge the currently observed modulation of SICI by cue type. Differences in task design and stimulation time may explain the perceived variance in results. For uninformative cues in Duque and Ivry (2009), either a left or right response was required, but response stopping was not anticipated (except catch trials ~6%). For proactive and reactive cues in the present task, response stopping was a possibility. These results indicate a different response preparation when response inhibition may be required. However, Sinclair and Hammond (2009) found no difference in SICI when cues forewarned the upcoming response probability (83%, 50% or 0%) and thus also the chance of stopping (17%, 50%, 100%). SICI was assessed when imperatives were presented 300 ms after warning cues of 200 ms duration, arguably not providing enough time to process the cue and employ respective preparatory mechanisms. In the present task cues were presented for a period of 1500 ms before trials began, allowing more time for cue

processing and response preparation. Overall, levels of SICI appear to be disinhibited when responses are anticipated with high certainty and proactively maintained when conditions are uncertain.

6.3 Contributions to Response Thresholds

When response inhibition is required, a "race" can be thought to commence between Go and stop processes (Logan and Cowan 1984a). Proactive changes in intracortical inhibition may modulate the position of the "finish line" causing faster or slower responses and increased or decreased stopping success. In the present study, modulation of intracortical inhibition was observed for both LICI and SICI (Fig. 10). A non-selective reduction of LICI occurred within task context, supporting findings from Cowie et al. (2016). SICI was reduced for certain cue types, similar to the results of Duque and Ivry (2009). Recent lines of evidence suggest that competing Go and stop processes during reactive response inhibition may be best explained by an "activation threshold" framework (Cowie et al. 2016; MacDonald et al. 2014; MacDonald et al. 2017). Briefly, a response occurs when facilitatory processes pass a response threshold, maintained by inhibitory processes. Two main inhibitory inputs are associated with this model, yet the underlying mechanism(s) are not confirmed. The contribution of intracortical inhibitory networks to these processes remains unclear.

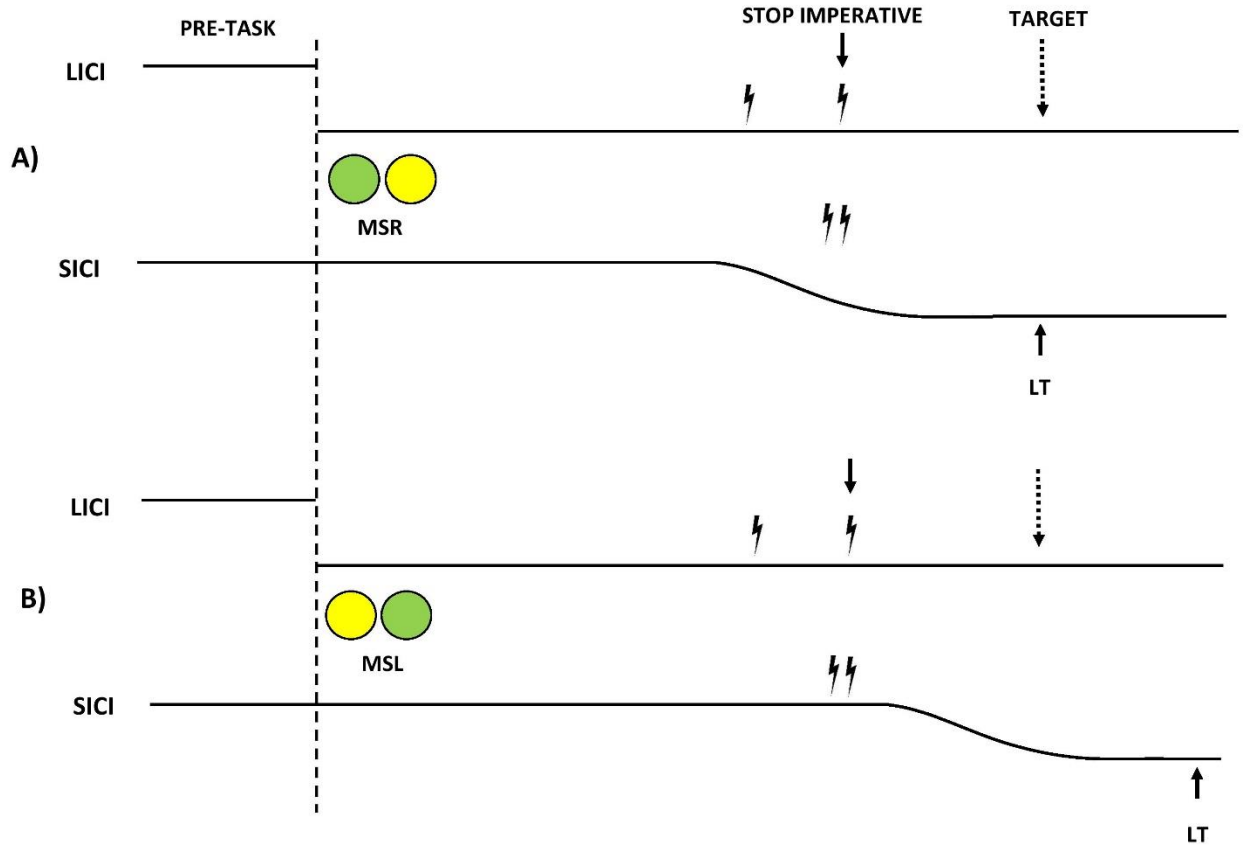

Fig. 11. Predicted modulation of long and short interval intracortical inhibition (LICI and SICI respectively) for the left first dorsal interosseous on proactively cued Go trials. Horizontal lines represent the level of inhibition. Vertical decrements represent a reduction. Dashed line separates pre-task (left) from task measures. From left to right: cues represent the start of trials. Stop imperatives (indicator stopped ascending) did not occur on Go trials but did 550 ms into Stop trials, coinciding with test stimuli for paired-pulse stimulation (lightning bolts). Response target at 800 ms. A. Maybe stop right (MSR) cue. SICI is reduced before stimulation and lift time (LT) is on target. B. Maybe stop left (MSL) cue. SICI is reduced after stimulation and LT is delayed. LICI is reduced for both cues compared with pre-task and remains stable during trials.

The idea that proactive mechanisms can interact with reactive inhibition is supported by present and previous studies (Cai et al. 2011; Chen et al. 2010; Dunovan et al. 2015; Jahfari et al. 2012; Zandbelt and Vink 2010). Task-relevant LICI on reactive trials was positively correlated with MS-SL Partial responses. Moreover, compared with pre-task, LICI was non-selectively reduced in both muscles. One explanation is that reduced LICI helps prepare the motor system for

responding, by decreasing the activation threshold. This interpretation supports an inhibitory input within the activation threshold model that maintains tonic levels of inhibition (Cowie et al. 2016; MacDonald et al. 2014). Presumably, this disinhibition is set to task-expectations and would be greater if stopping was not a potential outcome (for example, only Go trials) (Cowie et al. 2016). As previously interpreted, greater amounts of LICI may strengthen inhibitory control, but concurrently increase the activation threshold for re-initiated movement, resulting in slower response times. The present results add to those of Cowie et al. 2016, demonstrating that under reactive circumstances, the amount of right hemisphere LICI associates with Partial responses from left and right hands. Inhibition within the right hemisphere correlated with response times from the ipsilateral hand. A weak association also existed for task-irrelevant muscles but was non-significant ($P = 0.121$). These results suggest LICI may be a more "widespread" form of inhibition. LICI may help set general inhibitory tone relative to response-expectations, in accordance with an "activation threshold" framework.

SICI was reduced before anticipated responses but unchanged when responses were uncertain. One way to assess the effect of proactive inhibition is by comparing left hand responses on Go trials between MSL and MSR cues (Fig. 11). When responses were of high probability (MSR), a reduction in SICI existed. This reduction may be a proactive mechanism, in which reduced inhibition lowers the activation threshold for the upcoming response. As a result, LTs were on target. In contrast, SICI was unchanged when the hand may have to stop (MSL). Because responses were uncertain, inhibition appeared to be proactively maintained until conditions were more certain. Left hand LTs were slowed, suggesting the activation threshold was not lowered until later, or did not change at all. Because reduced SICI has been consistently shown to precede movement (Reynolds and Ashby 1999; Stinear and Byblow 2003), it is likely that inhibition was

reduced at a later time. These results suggest that when there is a moderate degree of response uncertainty, SICI may proactively "pause" a commenced Go process or "stall" initiation until the response is more certain. The relatively small extent of slowing for the warned response, suggests a temporary "pause" is more plausible. An assessment of CME over time during warned response trials may help elucidate the action of this brake. Other structures have been associated with the proactive slowing of responses. The right inferior frontal cortex (rIFC) is an essential component of both reactive and proactive networks (Aron and Poldrack 2006; Chambers et al. 2009; Chikazoe 2010; Levy and Wagner 2011; Meyer and Bucci 2016; Van Belle et al. 2014). Imaging studies report rIFC activation is associated with maybe stop trials (Chikazoe et al. 2009b; Swann et al. 2012), and the amount of activation correlates with Go trial response slowing (Jahfari et al. 2010). Future studies could assess whether the amount of rIFC activation influences the modulation of intracortical inhibition. The present results suggest SICI can be proactively modulated as part of an incomplete "brake" until response decisions are certain.

7 Limitations and Future Directions

Limitations exist for the present study. In the present results, LICI did not change relative to cue type. Previously, increased LICI has been observed for blocks where reactive stopping is required compared with blocks containing only Go trials (Cowie et al. 2016). In the current task, a similar comparison existed between MS (reactive) and SR (known) trials for the left hand. One explanation is that due to the prolonged inhibitory properties of LICI, there is not enough time for modulation to occur between trials. This may be a limitation of the task. However, $GABA_B$ receptor inhibition has only been observed for up to ~500 ms (Isaacson et al. 1993; Nicoll et al. 1990), allowing time for levels of LICI to be "reset" between trials. Instead, modulation of LICI may have been observed with other paired-pulse parameters. There are differences in the amount

of LICI observed when the inter-stimulus (ISI) interval is either 100 ms or 150 ms (Chu et al. 2008; Opie et al. 2015b; Vallence et al. 2014). Distinct ISIs also demonstrate different patterns of LICI between age (Opie et al. 2015a), and for certain conditions such as ischemic nerve block (Vallence et al. 2012) or theta-burst stimulation of the cerebellum (Koch et al. 2008). Recent evidence suggests underlying inhibitory mechanisms do not differ between ISIs but rather contributions may diverge with time (Opie et al. 2016). Substrates pertaining to response inhibition may not be observed for both ISIs. Time constraints in the present study did not permit investigation of multiple ISIs. For a comprehensive assessment of LICI, it is recommended that both 100 and 150 ms ISIs be assessed.

There are distinctions in LICI when assessed with different TMS current directions. The present study assessed LICI with a posterior to anterior (PA) directed TMS current. When stimulation is delivered in a PA direction, early indirect volleys (I-waves) are preferentially activated (Di Lazzaro et al. 2012). Conversely, anterior to posterior (AP) directed currents appear to preferentially activate later I-waves (Kaneko et al. 1996; Nakamura et al. 1996). Greater inhibition of later I-waves is associated with SICI and LICI (Di Lazzaro et al. 1998; Hanajima et al. 1998; Nakamura et al. 1997). Recent evidence suggests that AP directed currents provide more sensitive measures of SICI and to a certain extent, LICI (Cirillo and Byblow 2016; Sale et al. 2016). Stimulation in the AP direction may therefore reveal the activity of intracortical inhibition with greater resolution. One limitation is that stimulation in the AP direction is associated with higher resting motor thresholds (Cirillo and Byblow 2016; Sakai et al. 1997; Zoghi et al. 2003). It is likely that the required intensity for two suprathreshold pulses may exceed 100% MSO for participants with high thresholds, particularly if 50% inhibition is targeted as in the present experiment. Furthermore, suprathreshold pulses activate multiple neural components, including a

number of later I-waves regardless of AP or PA directed currents (Kaneko et al. 1996). Observed differences in I-wave suppression and hence LICI, are likely minimal with using two suprathreshold pulses. AP directed currents may reveal changes in intracortical inhibition with greater sensitivity, but are not always practical.

Variation within measures from not-target muscles may have influenced the outcome of some results. CME for task-irrelevant APB was greater for SL trials compared with both rest and SR. Modulation of CME did not exist for task-relevant FDI. Previously proposed models cannot easily explain these results. They may lend support to "widespread" inhibition, which is centered on task-relevant muscles (Greenhouse et al. 2015b). However, this model also assumes CME is suppressed preceding responses for task-relevant muscles. The modulation of CME is more likely a result of variability within task-irrelevant APB. Measures from APB were obtained by stimulating an optimal location for FDI. Stimulation intensity was also relative to FDI. Previous results have stimulated individual locations and set intensities for each muscle (Stinear and Byblow 2003). Future studies could minimize the amount of variability by setting stimulation location and parameters relative to individual muscles.

The present results warrant further investigation into the role of the M1 during response inhibition. Only one other study has investigated the modulation of intracortical inhibition (SICI) during proactive response inhibition (Duque and Ivry 2009). With increasing evidence suggesting an important interaction between proactive and reactive inhibition (Dunovan et al. 2015; Jahfari et al. 2012), further research is recommended. Assessment with alternative paired-pulse parameters (including those previously mentioned) could lend further support to the present results. In the present study, LICI was abolished or reversed to facilitation in a small number of participants. Suprathreshold TMS appears to be associated with cortical disinhibition, observed after the effects

of LICI have subsided (Cash et al. 2010; Cash et al. 2011). This phenomenon, termed late cortical disinhibition, appears to depend on task-requirements (Caux-Dedeystère et al. 2014) and may provide additional insight into context-dependent modulation during response inhibition paradigms. While intracortical inhibition is routinely assessed using TMS, further research is still needed to better understand the roles of SICI and particularly LICI within motor control. Connections between M1 intracortical circuits and the surrounding response inhibition network remains poorly understood. Diffusion weighted imaging tractography has helped delineate connections within reactive inhibition networks (Aron et al. 2007a; Coxon et al. 2012). A greater understanding of neuro-anatomical connections to M1 intracortical circuits within a proactive inhibitory network may be useful. Future studies assessing M1 intracortical inhibition during response inhibition could use a range of paired-pulse parameters combined with functional or anatomical imaging techniques.

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