Using transcranial magnetic stimulation to investigate the neural mechanisms of inhibitory control

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Running head

Transcranial magnetic stimulation and inhibitory control

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Abstract

Many everyday situations necessitate inhibition of motor responses, specifically the non-selective cancellation of all movement or the cancellation of specific components of a multicomponent action. Successful and timely application of response inhibition often depends on the availability of prior information regarding stopping demands. Using paired-pulse transcranial magnetic stimulation, Cirillo and colleagues (2017) provide novel neurophysiological evidence for distinct roles of $GABA_A$-ergic and $GABA_B$-ergic mechanisms underlying response inhibition in the presence and absence of prior information.

Hallmark features of human motor control include the ability to make quick and accurate responses when faced with multiple alternatives as well as adapting to constant sensory changes within our environment. Such adaptability often requires that a planned movement be cancelled prior to execution, a concept referred to as 'response inhibition' or 'inhibitory control'.

In a laboratory setting, inhibitory control has been commonly investigated using the stop signal task or the anticipated response inhibition task, where infrequent stop signals are presented either after the go signal or prior to a time-locked anticipated movement, respectively. Inhibitory performance is assessed by determining the interval between the go and the stop signal that yields ~ 50% successful stopping. Using this information and the average reaction time on go trials, psychological models such as the 'horse-race' model are able to estimate the time taken to successfully inhibit the response. This quantitative measure of the covert stop process, known as the stop signal reaction time, has proven to be particularly useful and is widely utilized as a research and clinical tool. On a neurophysiological level, applying transcranial magnetic stimulation (TMS) over the primary motor cortex – thereby eliciting motor evoked potentials (MEPs) from task-relevant and task-irrelevant muscles – has proven insightful in assessing the state of the motor system and furthering our understanding of the neural correlates of response inhibition. Extensive research has reported a robust suppression of corticospinal excitability shortly after stop signal onset ('reactive inhibition'), not only in task-relevant effectors but also in task-*irrelevant* effectors including other muscles of the responding hand, homologous muscles of the non-responding hand, and leg muscles, suggesting that the mechanism subserving inhibition acts in a non-selective manner (Duque et al., 2017).

More recently, researchers have utilized variations of these response inhibition tasks, whereby only one component of a bimanual movement requires inhibiting (e.g., one hand's response is cancelled while the other hand continues to execute a response). Such tasks allow researchers to investigate the *selectivity* of response inhibition as opposed to the global, non-selective, mechanism elicited in the aforementioned tasks. Selective inhibition tasks could be considered more relevant to many everyday activities which often require only one part of a multicomponent action to be inhibited. However, a robust finding is that reaction time delays of ~100 ms occur in the non-cancelled component of selective stop trials (Duque et al., 2017), suggesting that the mechanisms recruited in these tasks are not optimised for selective inhibition. Indeed, recent research has revealed that selective inhibition tasks may actually rely upon a 'generic' global stopping mechanism that inhibits *both* hands prior to re-initiation of movement in the hand not required to stop (MacDonald et al., 2014; Raud & Huster, 2017). Under more ecologically valid conditions where prior information about stopping demands is available, it has been suggested that individuals are able to *proactively* recruit selective inhibitory processes (Aron, 2011). Indeed, when participants are provided with prior information about which hand may be required to stop, conceivably facilitating selective stopping mechanisms, the stopping interference cost is reduced (Duque et al., 2017). Moreover, electrophysiological data indicates that motor activity of the unstopped hand is less

susceptible to inhibitory interference, experiencing only a transitory pause in movement-related excitability compared to the greater suppression observed following uninformative cues (Raud & Huster, 2017).

Surprisingly, there exists a paucity of research in regards to the underlying neurophysiological mechanisms of selective inhibition, regardless of whether prior information is provided or not during these tasks. Does the observed suppression of corticospinal excitability prior to a stop signal being presented relate to a reduction in faciliatory drive, greater engagement of inhibitory processes, or perhaps both? To this end, a paper published by Cirillo and colleagues (2017) aimed to address this gap in knowledge by investigating intracortical inhibitory networks within the primary motor cortex using an anticipated response inhibition task. Participants were required to respond bimanually on the majority of trials (~ 67%) with the remaining trials (~33%) requiring cancellation of either one (left or right) or both hands following a stop signal. On every trial, participants were provided with warning cues, which provided varying degrees of information regarding upcoming stopping demands. Greater levels of informativeness led to more substantial reductions in selective stopping delays, thereby indicating that the cue was utilized to improve task performance.

Of particular interest though, was the utilization of short-interval intra-cortical inhibition (SICI) and long-interval intra-cortical inhibition (LICI) TMS protocols to probe $GABA_A$- and $GABA_B$-ergic inhibition in task-relevant and task-irrelevant muscles during the selective stop task. While a generic reduction in $GABA_B$-ergic inhibition was observed during the task in both muscles compared to a baseline (non-task) condition, this was not affected by the nature of the cues provided. Given that LICI is associated with tonic inhibition, this is interpreted as the $GABA_B$-ergic system setting an overall inhibitory tone based on task engagement. Unlike LICI, cue-specific modulations of $GABA_A$-ergic inhibitory mechanisms were observed in the task-relevant muscle only. SICI was significantly reduced when cues indicated that stopping would either be definitely not or highly unlikely to be required, with this release of inhibition likely facilitating rapid responses. Overall, Cirillo and colleagues demonstrate distinct roles of intracortical inhibitory networks within the primary motor cortex underlying unique aspects of response inhibition.

However, the observed suppression in the primary motor cortex is likely to be influenced not only by intracortical *inhibitory* mechanisms but also by variations in *faciliatory* drive to this region. In this regard, new TMS methodology offers the opportunity to understand the intricacies of underlying neurophysiological changes during response inhibition. It is well-established that a single TMS pulse activates separate excitatory synaptic inputs. These inputs arrive at the corticospinal neurons at slightly different times resulting in distinct activations of the corticospinal tract. However, until recently, technological constraints limited researchers in their ability to selectively investigate the varying contributions of these excitatory inputs. Hannah and colleagues (2017) utilized a novel controllable pulse parameter TMS device that enabled these excitatory inputs to be selectively recruited by manipulating coil current direction and TMS pulse width. Results indicated that late, compared to early, excitatory inputs were selectively supressed during preparatory inhibition

(between warning and go signals) across a wide range of tasks (simple and choice reaction time tasks; go/no go task). Thus, in addition to modulations of active inhibitory processes, varying contributions of different excitatory inputs may also underlie selective stopping mechanisms and as such these novel methodologies could further our understanding.

Besides intracortical variations in inhibitory and excitatory mechanisms discussed above, the primary motor cortex is likely to be influenced by other cortical regions implicated in response inhibition. Given the bimanual nature of the selective stopping task, it seems plausible that task performance is influenced by the extent of communication between the two primary motor cortices. Dual-coil TMS allows the investigation of interhemispheric inhibition between the two primary motor cortices during response inhibition. It is thought that there are two distinct mechanisms subserving interhemispheric inhibition that act via distinct interhemispheric pathways, mediated by unique underlying processes. Short-interval interhemispheric inhibition is likely to occur via a direct transcallosal pathway, whereas long-interval interhemispheric inhibition via an indirect pathway which is likely to involve premotor regions. Importantly, distinct modulation of these interhemispheric inhibitory mechanisms has recently been reported during movement preparation during a choice reaction time task in response to informative and uninformative cues (Hinder et al., 2018), suggesting a conceivable role in selective inhibition as well. Similarly, this utility of the dual-coil TMS procedure could be applied to investigate the functional connectivity between the primary motor cortex and other cortical regions implicated in response inhibition, such as the pre-supplementary motor area and the right inferior frontal cortex (Neubert, Mars, & Rushworth, 2013). Therefore, dual-coil TMS would prove immensely valuable in investigations of selective response inhibition, both in the presence and absence of warning cues that provide information regarding stopping demands. Furthermore, an important consideration is the *temporal* nature of the observed changes. Utilizing these diverse TMS protocols at multiple time-points before and after stop signal presentation has the potential to highlight the temporal progression of the mechanisms underlying inhibitory control.

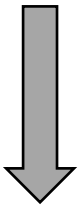
In addition to using the aforementioned TMS protocols to investigate the nature of task-related functional connectivity between the different brain regions, repetitive forms of TMS can be utilized to temporarily *disrupt* task-relevant brain regions. For instance, the critical role of the pre-supplementary motor area has been demonstrated using ‘excitatory’ and ‘inhibitory’ forms of repetitive TMS resulting in an improvement and impairment in response inhibition, respectively (Watanabe et al., 2015). Similarly, administering inhibitory repetitive TMS over the right inferior frontal cortex impairs response inhibition as well (Obeso et al., 2013). Hence, using the various forms of repetitive TMS could provide direct *causal* evidence for the role of the various brain regions in mediating selective stopping, of which currently little is known.

Finally, considering the ubiquitous nature of response inhibition, it is important to discuss the terms ‘reactive’ and ‘proactive’ that are used to categorize response inhibition. These terms have been characterised *temporally*, i.e., reactive inhibition being stimulus driven, evident after a stop signal is presented, and proactive

inhibition being mediated by a stopping goal, apparent before stop signal presentation (Meyer and Bucci 2016). Response inhibition has also been categorised *contextually* as by Cirillo and colleagues, where reactive inhibition occurs when stop signals appear unexpectedly (uninformative cues) and proactive inhibition occurs when stop signals appear with some degree of anticipation (informative cues). These categorisations have the potential to create ambiguities, such as when TMS-induced inhibitory processes are measured a) before the stop signal (temporal classification: 'proactive' inhibition) in the presence of an uninformative cue (contextual classification: 'reactive' inhibition), or b) after the stop signal (temporal classification: 'reactive' inhibition) in the presence of an informative cue (contextual classification: 'proactive' inhibition). Rather than utilizing a generic, broad-based, temporal or contextual classification, we suggest inference of response inhibition processes based on the amalgamation of the aforementioned criteria, i.e., the time-point of TMS delivery relative to the presentation of the stop signal (before: anticipation phase; after: stopping phase) as well as the degree of information provided by a prior cue (lying on a spectrum from 'uninformative/no foreknowledge' to 'fully informative/complete foreknowledge') as detailed in Table 1. Therefore, TMS-induced measurements during the anticipation phase would relate to proactive inhibitory processes, ranging from little cue-specific proactive inhibition following uninformative cues (generalised task-related proactive inhibition may be evident) to maximal cue-specific proactive inhibition following fully informative cues. Likewise, TMS-induced measurements following uninformative cues during the stopping phase would mainly reflect reactive inhibitory processes. Warning cues providing any information regarding stopping demands would result in the TMS-induced measurements during the stopping phase to reflect an interaction between proactive and reactive inhibitory mechanisms. Consequently, we urge future studies to be particular in their utilization of terms relating to 'reactive' and 'proactive' inhibition and to consider both the warning cue type, as well as the timing of TMS-induced measurements when referring to these terms. Readers may benefit from explicit consistent statements in this regard to infer the extent of proactive and reactive inhibitory engagement.

Future research on the advancement of computational control frameworks specific to selective inhibition, such as the activation threshold model, is highly relevant, particularly given recent research indicating traditional models are unable to account for interference effects observed during selective stopping (MacDonald et al. 2017). Moreover, further studies should investigate how response inhibitory processes may vary due to structural and functional brain changes resulting from disease or ageing.

Table 1 - Matrix outlining the extent of quantifiable proactive and reactive inhibition based on TMS timing (anticipation phase: before stop signal; stopping phase: after stop signal) and warning cue type (lying on a spectrum, as indicated by a grey arrow, between uninformative cues and fully informative cues).

		TMS timing	
		Anticipation phase (before stop signal)	**Stopping phase (after stop signal)**
Warning cue type	**Uninformative**  **Fully informative**	Minimal proactive inhibition	Maximal reactive inhibition
		Maximal proactive inhibition	Interaction between proactive and reactive inhibition

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