Informative Cues Affect Proactive Modulation of Corticospinal Excitability During a Selective vs. Global Stop Signal Task.

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A report submitted as a partial requirement for the degree of Bachelor of Psychological Science with Honours in Psychology at the University of Tasmania, 2017.

Statement of Sources

I declare that this report is my own original work and that contributions of others have been duly acknowledged.

Signed…… Date: ……

Abbey Lack

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List of Abbreviations

ADHD: Attention Deficit Hyperactive Disorder

ANOVA: Analysis of Variance

ATM: Activation Threshold Model

BiGo: Bimanual Go

BiGoRT: Bimanual Go Reaction Time

CI: Confidence Interval

CNS: Central Nervous System

CSE: Corticospinal Excitability

CST: Corticospinal Tract

CUE: TMS stimulation Time Point 1 (at cue onset)

CUE750: TMS stimulation Time Point 2 (750ms after cue onset)

DV: Dependent Variable

EEG: Electroencephalography

EMG: Electromyography

FDI: First Dorsal Interosseous

fMRI: Functional Magnetic Resonance Imaging

IHI: Interhemispheric Inhibition

IS: Imperative Signal, stimulation Time point 3 (at IS onset)

IS100: Stimulation Time Point 4 (100ms after IS onset)

M: Mean

M1: Primary Motor Cortex

MEP: Motor Evoked Potential

ms: Milliseconds

MSB: Maybe Stop Both

MSL: Maybe Stop Left

MSR: Maybe Stop Right

mV: Millivolt

NoCue: Uncued trials

PMC: Pre-Motor Cortex

rTMS: Repetitive Transcranial Magnetic Stimulation

RMT: Resting Motor Threshold

RMS: Root Mean Square

SD: Standard Deviation

SMC: Supplementary Motor Cortex

SS: Stop Signal

SSC: Selective Stop Cost

SSD: Stop Signal Delay

SSRT: Stop Signal Reaction Time

SST: Stop Signal Task

TMS: Transcranial Magnetic Stimulation

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Abstract

The ability to inhibit and reprogram movement in response to changing goals is fundamental to successful engagement with the world (Bestmann & Duque, 2016). The current study utilised single pulse transcranial magnetic stimulation (TMS) to explore modulation of corticospinal excitability (CSE) in 23 (12 female) young adults during movement preparation in a task that required unimanual (selective) or bimanual (global) stopping of a bimanual button press. On some trials a cue informed participants of the stop type that *might* be required. Overall, CSE in the non-stopping hand was greater than in the hand that was cued to stop, which supports a facilitation model of CSE modulation. Behaviourally, there was a significantly reduced selective stopping cost (SSC) and improved stopping performance during cued trials. However, no significant differences in CSE modulation or stopping performance were observed between selective and global stopping. These findings support a flexible and generic mechanism for inhibition, rather than independent mechanisms for global and selective stopping. This research contributes to a body of literature aiming to elucidate the neural underpinnings of inhibition, which is essential for understanding how it is impaired in healthy ageing or conditions like Attention Deficit Hyperactive Disorder (ADHD), Schizophrenia, or Tourette's Syndrome.

The ability to inhibit and reprogram movement in response to continuously changing goals is central to effective engagement with the environment (Bestmann & Duque, 2016). Inhibitory control is a widely utilised and adaptive function that pervades everyday life, with many situations requiring termination of a planned response because of new, or updated, sensory information. For example, a person may engage inhibitory control processes to refrain from eating an item of unhealthy food, saying something inappropriate, or pressing the accelerator when the traffic light turns green if a child runs into the road.

The current research focused on inhibitory control in relation to terminating a prepared motor action. Specifically, measurements of corticospinal excitability (CSE) in response to a visual stop signal task (SST) were used to infer the neural correlates of inhibitory control underlying behavioural changes in stopping ability in a sample of healthy young adults. This introduction will provide the reader with information pertaining to the techniques and concepts addressed in the study, including aspects of human motor control, inhibitory control, transcranial magnetic stimulation (TMS), electromyography (EMG) and SSTs. It will then offer an overview of the relevant literature and briefly outline the aims and hypotheses of the current experiment.

Human Motor Control

The human motor system is adept at executing rapid responses to external stimuli and relies upon several cortical processes including visual encoding of stimuli, perceptual/cognitive decision-making, and preparation and execution of required actions. The primary motor cortex (M1) is considered the forefront of the human motor system (Kandel, Schwartz, Jessell, Siegelbaum, & Hudsbeth, 2013)

and consists of a strip of cortex that runs in a medial-to-lateral direction along the dorsal section of the frontal cortex in both the left and right hemispheres of the brain. It is structured topographically with respect to the contralateral body, and is where all corresponding motor outputs converge and depart from (Kandel et al., 2013, Stinear, Coxon, & Byblow, 2009). Voluntary action encompasses a broad cortical and sub-cortical network (Kandel et al., 2013); prior to signals converging at M1, frontal cortical regions are closely involved in the planning of voluntary actions. The initiation of voluntary movement is said to begin in the prefrontal cortex with commands sent to M1 via the premotor cortex (PMC) and supplementary motor cortex (SMC, Kandel et al., 2013). The PMC and SMC are located directly anterior to the central sulcus on the same gyri as M1. The PMC exerts control over motor behaviour by aiding perceptual decision making about movement goals and has been implicated in the decision-making component of motor activity (Crammond & Kalaska, 2000; Wallis & Miller, 2003). In contrast, the SMC contributes contextual control over voluntary movement, selecting and executing actions that are appropriate for a task or situation. Moreover, lesions to the SMC are associated with impaired ability to suppress or initiate movements (Kandel et al., 2013).

Communication between the central nervous system (CNS) and peripheral muscles is achieved via descending and ascending neurons (Lawrence & Kuypers, 1968). These neurons have long axons that amass to form tracts that carry specific information to and from the cortex. The corticospinal tract (CST) is the principle motor pathway; it is via this tract that M1 controls the limbs and torso to execute planned actions (Luo, 2016). In fact, the discharge of individual corticospinal neurons is associated with movement of specific parts of the body (Evarts, 1968). Ninety-five-98% of the CST axons cross at the medulla such that the left hemisphere

controls the right side of the body and vice versa (contralateral control). This is an important implication for the investigation of CSE as researchers must focus on the behaviour of limbs contralateral to the hemisphere of concern. The cell bodies of CST neurons are predominantly located in M1 and constitute the pyramidal cells of layer V (Kandel et al., 2013). Evidence of this comes from single cell recording in primates that showed the activity of neurons in M1 is associated with changes in the direction and amplitude of muscle activity during wrist movements (Evarts, 1968). Techniques such as TMS are often used to investigate the CST as they are very effective at stimulating these neurons; moreover, an observable response can be elicited in peripheral muscles which can provide a measure of the input-output characteristics of the pathway.

Researchers are interested in how individuals can modulate the excitability of the CST to inhibit planned responses in tasks requiring dextrous control. Understanding how the CNS activates and integrates fine muscles to respond to visual stimuli is important in many activities of daily functioning. For example, pouring a cup of tea, writing, and using a knife and fork all require fine motor skills and interplay between inhibitory and facilitatory mechanisms. TMS allows the excitability of the CST to be measured using EMG, which records motor evoked potentials (MEPs) in peripheral muscles (Rothwell, 2011). Measurement of MEP modulation allows inferences to be made about the structure or function of a neural pathway (Coxon et al., 2009). Combining TMS with behavioural responses can determine how CSE changes because of an intervention, or during a task. For example, the neural processes related to the temporal modulation of CSE have been explored by administering TMS at various time points during delayed reaction time (RT) tasks. The comparison of MEP amplitudes in the time between a cue and an

imperative ‘go’ signal (IS) allows researchers to infer about the temporal evolution of CSE during movement preparation (Hinder et al., in press).

Transcranial Magnetic Stimulation

TMS is a non-invasive cortical stimulation technique that is used to investigate brain function in humans (Rothwell, 1997). It is a safe and well-established procedure, which is used not only to investigate brain function, but has been producing consistent results in a range of clinical interventions, including for treatment-resistant depression (George et al., 2000; Loo & Mitchell, 2005). The technique involves placing a coil of copper windings over a participant’s cortex, tangentially to the scalp, and discharging a magnetic pulse. A brief 200ms electrical current of up to 5kA is induced in the coil and results in a perpendicular magnetic field that penetrates through the cortical tissue, which in turn generates a weaker current in the cortex. If the pulse is of sufficient intensity, the neurons in layer V, where intra-cortical neurons synapse on to corticospinal neurons, depolarise and fire. When M1 is appropriately stimulated, TMS can evoke action potentials that propagate along the CST resulting in MEPs in peripheral muscles that can be recorded using EMG in the contralateral side of the body. These MEPs are representative of the excitability of the CST at the exact time of stimulation, with larger amplitudes reflecting greater CSE (Coxon, Stinear, & Byblow, 2009, Kandel et al., 2013). Accordingly, the temporally precise nature of TMS allows researchers to investigate the excitability of different brain regions at specific time points during the planning and subsequent cancellation of volitional movement.

Inhibitory Control

Inhibition is a pervasive aspect of cognition and voluntary movement control, implicated in cell firing, cortical circuitry, and the subsequent volitional control of behavioural output (Aron, 2007). As an executive function of the cognitive system, inhibitory control involves a collaboration of mental processes including, encoding, recognition and retrieval that function to supress natural or stimulus driven response tendencies and ignore irrelevant information, facilitating effective engagement with the environment (Logan & Cowan, 1984). Accordingly, inhibitory control is engaged when planning and executing strategies for optimal task performance (Schachar, Tannock, & Logan, 1993), which can be related to the control of many aspects of cognition, emotion and behaviour (Aron et al., 2007).

Both excitatory and inhibitory neurons are intimately involved in shaping motor output and the ability to use these two independent systems in a precise and adaptive manner is fundamental to control of movement (Kandel et al., 2013). Behavioural and electrophysiological studies aim to elucidate the specific contribution of these mechanisms to the control of voluntary movement. For example, during the preparation of voluntary responses, inhibition of CSE is apparent. This inhibition has been suggested to function as a conflict resolution mechanism, whereby the correct response is chosen from a number of competing responses, and then to prevent premature execution of the selected response (Labruna et al., 2014). In support of this theory, Duque, Labruna, Verset, Olivier, and Ivry (2012) implicated independent pre-frontal projections to M1 in inhibitory control mechanisms. In this study, repetitive TMS (rTMS) was administered over the frontal cortex preceding single pulse TMS over M1. While rTMS over the lateral prefrontal cortex was associated with the competition resolution process, rTMS over the dorsal

prefrontal cortex corresponded to the impulse control process. Supporting evidence from TMS research found CSE was reduced immediately following a cue in a SST, regardless of whether the cue was informative about the nature of the inhibition. This suggested that inhibition occurred to prevent the known response from being elicited too quickly (Duque & Ivry, 2009).

This research has been extended using paired pulse/ dual coil techniques, as single pulse TMS can only show changes in net excitability. These techniques allow researchers to ascertain whether changes in MEPs are due to changes in inhibitory or facilitatory mechanisms. For example, Hinder et al. (in press) conducted a delayed choice RT task in which cues were provided prior to an IS that were either informative or uninformative about the hand that would be required to respond. TMS was administered to the right M1 to assess CSE, while a conditioning pulse from left to right M1 with 10 (IHI10) or 40 (IHI40) ms interstimulus intervals was administered to assess interhemispheric inhibition (IHI) during the selection and preparation of movement. The findings of this study were consistent with an impulse control mechanism, with suppression of CSE evident in the left and right hands prior to movement execution irrespective of whether the cue was informative about the upcoming response. This suppression was followed by an increase in CSE in the responding hand that was larger when the cue was informative than when it was uninformative, with greater CSE corresponding to faster RTs. Contrary to the view that there is a single generic CSE suppression mechanism during movement preparation, IHI10 was simultaneously released in the responding hand alone whereas IHI40 was released in both hands in response to an informative cue. This suggests, in addition to impulse control, there are multiple mechanisms that

contribute to the preparation of various aspects of voluntary movement, as one mechanism cannot simultaneously release and engage inhibition.

This research highlights a key distinction in inhibitory control, which is that of global and selective inhibition. Regarding motor actions, global inhibition is a broad 'braking' of action that occurs in response to a stimulus (Badry et al., 2009). For example, if a car pulled out as a person began to cross the road, they would withhold the step they planned to take. In addition to halting the relevant movement, they might stop the conversation they were having with their friend, or stop chewing the gum in their mouth. It is suggested this brief, widespread inhibition is produced by a hyper-direct basal ganglia output that bypasses the striatum in order to respond quickly (Badry et al., 2009; Majid, Cai, George, Verbruggen, & Aron, 2012). Furthermore, evidence from neural imaging, lesion and stimulation studies have implicated the sub-thalamic nucleus of the basal ganglia in rapid stopping in humans (Wessel & Aron, 2017). Fast inhibition is useful from an evolutionary point of view; however, most instances requiring response prevention do not demand such speed, therefore afford a more complex and accurate form of inhibition. To ride a bike, play a musical instrument, or partake in a game of football the ability to inhibit only part of an ongoing action is required. Selective inhibition is therefore inhibition of one aspect of a response while continuing with another (Aron & Verbruggen, 2008; Coxon, Stinear, & Byblow, 2007). This inhibition is said to occur via an indirect basal ganglia pathway that incorporates the striatum and subsequent additional synapses (Majid et al., 2012, Kandel et al., 2013).

Further research into the contribution of the basal ganglia in motor inhibition proposed preparation of movement comprises separate stages. First, thalamocortical projections to M1 are inhibited by widespread output from the basal ganglia,

producing brief and expansive motor suppression (i.e., global inhibition). Second, internal projections within the basal ganglia release inhibition from a division of the output cells to facilitate the required action (Kandel et al., 2013, Mink & Thach, 1993). This argument forms the basis for the re-start hypothesis (Claffey, Sheldon, Stinear, Verbruggen, & Aron, 2010), which suggests global inhibition is obligatory in all situations requiring the abortion of action, and selective inhibition involves the subsequent initiation of a selected movement. However, research by Duque et al. (2012) suggested a more complex explanation and implicated prefrontal projections as mediators of the basal ganglia network. This line of inquiry is supported by research in preparatory inhibition using SSTs, which propose a prefrontal –sub thalamic network of inhibitory control (Aron et al., 2007). Despite this research, it remains unclear whether selective and global inhibition employ independent mechanisms or, whether they are varying aspects of a generic mechanism of inhibition.

Deficient inhibitory control can manifest as impulsive behaviour and speech, perseveration, mania, obsessions, and failed extinction in post-traumatic stress disorder (Aron, 2007). Impairment of the inhibitory control network is implicated in several conditions such as Tourette's Syndrome (Ziemann, 1997), Attention Deficit Hyperactive Disorder (ADHD, Schachar et al., 1993; Schachar, Mota, Logan, Tannock, & Klim, 2000), and focal dystonia (Beck, Schubert, Richardson, & Hallett, 2009), as well as in ageing (Williams, Ponesse, Schachar, Logan, & Tannock, 1999). As such, it is important the underlying mechanisms of inhibition are investigated to understand and subsequently treat disorders in which impulse control breakdown is a major underlying manifestation. It is also important to discover how inhibitory control changes as a function of healthy ageing, which is characterised by a decrease

in cognitive functioning, including deficits in memory, attention and decision-making, as well as various aspects of motor control (Fujiyama et al., 2012). Older adults exhibit deficits in response inhibition during motor preparation and planning; however, the underlying biological causes for these deficits are unclear (Coxon, Van Impe, Wenderoth, & Swinnen, 2012). While it is consistently reported that older adults exhibit significantly slower RT and stop signal RT (SSRT) compared to younger adults (Williams et al., 1999) the neural correlates underlying these changes are largely unknown, as comparative studies involving neurophysiological techniques remain sparse and inconclusive. Increased understanding of how inhibitory control declines across the lifespan will allow researchers to develop interventions that can curb such degeneration, thus helping to maintain movement dexterity late in life. In turn, this will mitigate the economic burden of aged care and provide the means for older adults to continue to live fulfilling and independent lives.

Stop Signal Tasks

TMS has been used in conjunction with laboratory-based behavioural paradigms to assess the neurophysiological correlates of inhibitory control in relation to action stopping (Duque, Greenhouse, Labruna, & Ivry, 2017). The use of RT tasks is crucial for determining causal relationships between neurophysiology and behaviour, knowledge of which is essential for investigating disorders of inhibitory control and ageing (Duque, Petitjean, & Swinnen, 2016). SSTs used in conjunction with some neuroimaging and stimulation techniques can determine additional relationships regarding the neurophysiology of inhibitory control (Badry et al., 2009; Duque et al., 2012; Majid et al., 2013). The standard SST, outlined by Verbruggen and Logan (2009) comprises a choice RT task that involves responding to an

imperative ‘go’ stimulus (IS) with a key press (e.g. left hand for image of a circle, right for image of a square). Occasionally the IS precedes a stop signal (SS), an auditory or visual stimulus that requires the participant to withhold the selected response. Findings show that successful inhibition is more likely if the SS occurs closer to the IS and less likely if it occurs closer to the time of response. The dominant theoretical basis for SST performance is the horse race model, whereby response inhibition depends on the respective completion of stop and go processes, triggered by the SS and IS respectively (Logan & Cowan, 1984). The assumption that independent processes facilitate stopping and going forms the basis for the measurement of SSRT, which represents the speed of the inhibition process (Aron et al., 2007). Stop signal delay (SSD; the delay between IS onset and the appearance of the SS) is subtracted from RT to calculate SSRT. To obtain an accurate measure of SSRT, SSD is manipulated depending on stopping success to result in 50% response accuracy. This delay can be increased or decreased in fixed increments, or varied dynamically (Verbruggen & Logan, 2009).

Literature Review – Neural Correlates of Stop Signal Behaviour

Currently, little is known about the neural processes engaged when stopping and going occur simultaneously (Coxon et al., 2009). An SST that involves cancellation of both unilateral and bilateral actions is considered an effective index of inhibitory control that can differentiate between inhibition that acts globally (i.e., affects all motor processes), or specifically onto the limb that is required to be inhibited (Coxon et al., 2007; Williams et al., 1999). Behaviourally, selective stopping has elicited SSRTs of ~100ms slower than global stopping, which suggests additional neural circuitry is employed to facilitate this response (Coxon et al.,

2009). However, it is unknown whether this RT cost is due to the recruitment of an independent mechanism or whether a generic process exists that can be elaborated to inhibit selectively.

In a study that investigated whether providing a cue resulted in employment of an independent selective neural mechanism, Majid et al. (2012) conducted a series of three experiments using a variation of the SST that required a bimanual response following an IS on the majority of trials. On some trials a visual SS indicated for the participant to cancel one aspect of the bimanual movement (e.g., either the left or right hand). CSE was measured in the leg (task irrelevant) by administering TMS during the SST. Experiment one showed that when there was no information provided about which hand might have to stop (i.e., no informative cues), CSE in the leg was suppressed. In contrast, experiment two showed that when informative cues were provided there was no suppression in the leg. Experiment three compared CSE in cued and uncued conditions directly and leg suppression was only apparent in the uncued condition. Thus, global and selective inhibition processes were suggested to be dissociable and employing different neural networks.

The selective stop cost (SSC) is the difference in RT between a bimanual go response and a unilateral go response that occurs following a selective SS (Coxon et al., 2007). The occurrence of this effect in selective stopping *without* cues (e.g., in a reactive control scenario) points to a mechanism whereby the selected response is initiated following global inhibition of all responses (Aron & Verbruggen, 2008). In contrast, this effect is found to be smaller in tasks that utilise informative cues, which is suggested to be indicative of a selective mechanism that can inhibit part of a response without affecting the ongoing aspects of the movement (Claffey et al., 2010).

Considering these findings, recent literature has sought to isolate a selective mechanism of inhibition that is recruited when information is provided about the upcoming trial. For example, Claffey et al. (2010) used TMS to assess whether informative cueing created a control that is imposed on the response that may be required to stop. In the period of their task between a cue and the IS, MEPs were significantly suppressed in trials where the right hand was cued as maybe being required to stop relative to when the cue indicated the right hand would not be required to stop, indicating proactive modulation of CSE. Consistent with prior research (Aron & Verbruggen, 2008; Stinear et al., 2009), they found that the SSC was reduced when informative cues were provided, however SSRT was increased. This research provided further support for the 're-start hypothesis' in reactive stopping, but proposed that participants set up a control to respond proactively and selectively to visual stimuli when they had knowledge about the upcoming response.

To further investigate proactive selective inhibition, Cai et al. (2011) used an SST to show that MEPs in the hand that might need to stop were significantly smaller in amplitude than when that hand was at rest. Their findings support an active mechanism for suppression that is applied in accordance to the participant's goals, prior to the execution of action. However, a limitation of this study was that comparison to a baseline where the participant was at rest did not allow the dissociation between suppression that occurred because of the cue, from that which occurred to stop a premature response in the task (impulse control; Hinder et al., in press). This suggests the significant suppression observed in this study may not have been active modulation in response to the cue. The current study compared CSE in conditions whereby the left/right hands were cued to maybe stop to conditions where

there was no informative cue. This allowed the dissociation of CSE modulation due to the cue, to that occurring as impulse control.

In addition to single pulse TMS research, Majid et al. (2013) showed that activation of striatal, pallidal, and frontal areas, as observed using functional magnetic resonance imaging (fMRI), was associated with increased proactive motor suppression during preparation for selective stopping, as measured by TMS-evoked MEPs. Furthermore, increased striatal activation correlated with increased selectivity in behaviour, which supports an indirect basal-ganglia-pathway model of selective inhibition and explains why people with reduced striatal and pallidal cortical tissue (e.g., evident in Huntington's disease) cannot engage proactive motor suppression, thus exhibit impaired selective stopping ability in behavioural tasks. The authors proposed that selective inhibition was implemented by basal ganglia channels that were set up in accordance with participant's goals.

These studies support the view that selective and global inhibition are underpinned by different neural mechanisms, with the former being successfully investigated using proactive stop signal tasks that utilise informative cues. However, according to Xu, Westrick and Ivry (2015), the behavioural and neurophysiological differences between global and selective stopping are not indicative of independent neural networks. Instead, these authors propose a more generic and flexible inhibitory mechanism. Using a model-based approach, they showed that with adequate training participants could selectively inhibit a response without a SSC. They suggested differences in behaviour and CSE between selective and global stopping were reflective of an overlap between selected and not-selected aspects of a multicomponent response. Minimising the overlap through training eliminated the cost associated with making a selective cancellation of an aspect of the movement. It

was subsequently proposed that inhibition employs a generic mechanism that can be modified according to context or training.

In another study, MacDonald, McMorland, Stinear, Coxon, and Byblow (2017) combined TMS with a reactive SST that required the subsequent cancellation of bimanual (global) or unimanual (selective) aspects of a bimanual go response. Using an activation threshold model (ATM) of response inhibition, they showed that CSE modulation during selective stopping is facilitated by nonselective inhibition. These authors suggest global inhibition in response to the stop signal elevates the activation threshold to a point that cannot be achieved by the initial (go) response. Following this increase, an obligatory facilitation process occurs so the new inhibition threshold can be met and the responding aspect of the movement subsequently initiated.

It remains unclear whether what is behaviourally observed as inhibition is due to active suppression, or by the amplification of mechanisms that facilitate the task relevant response (Cai et al., 2011; Coxon et al., 2009). The latter suggests the best response is selected out of a range of competing options, which include not responding. When it comes to voluntarily withholding a planned response this means, as opposed to actively suppressing the planned response, an alternative response (stopping) is chosen and amplified (Nieuwenhuis & Yeung, 2005), this is termed the facilitation model (Cai et al., 2011). However, studies have shown that suppression of CSE occurs in the stopping hand prior to excitation in the responding hand during selective SSTs, suggesting active suppression is key to the facilitation of correct selective responses (Coxon et al., 2009). It is unclear how both systems are implicated in the voluntary termination of prepared motor actions, and how they are modified depending on contextual changes such as cueing and task design.

A limitation of aforementioned studies is they utilised a design whereby all stop types were intermingled (Cai et al., 2011; Claffey et al., 2010; Majid et al., 2013, 2012). This limitation revealed a need to investigate designs whereby participants are required to employ proactive control on a response for a block of trials. It would be expected that more modulation of CSE and better performance would occur in blocked designs where there is no trial to trial variation. Precise examination of how the networks of inhibition generalise is key to understanding their involvement in overlapping circuits, thus providing a more thorough understanding of how cognition, emotion and behaviour are controlled by inhibitory mechanisms (Aron et al., 2007). In addition, further research is required to determine whether selective inhibition is accomplished via active suppression, selective facilitation, or both.

Current Study

The current research employed a variation of the well-established SST (Verbruggen & Logan, 2009) in which a bimanual response was selectively or globally inhibited. In addition, TMS was used to investigate the neural correlates of stopping in a sample of young adults. We aimed to investigate claims by previous researchers relating to the dissociation of global and selective mechanisms of inhibition, with the use of left, right (selective) and bimanual (global) stops in conditions requiring proactive and/or reactive stopping. We also investigated whether selective inhibition was due to active suppression or selective facilitation, with the comparison of CSE in maybe stopping and non-stopping hands to when there was no informative cue. We aimed to explore whether the use of a proactive cue influenced stopping performance (indexed by SSRT) and SSC, and whether this

was contextually dependent on block design. Specifically, we were interested in whether enabling the application of advance control to all responses in a block would result in better stopping performance and reduced SSC, compared to blocks with intermingled selective and global stops that were either cued or uncued. We also aimed to discover how blocked conditions might change the way participants modulated CSE, as measured by MEP amplitude. However, due to the exploratory nature of the blocked vs. mixed design, there were no specific hypotheses.

Method

Participants and Screening

Twenty-three young adults (12 female) with an average age of 25 years (*SD*=5, range: 20-40) participated in a single session experiment (~ 2.5 hr) that had received ethics approval from the Tasmanian Human Research Ethics Committee (Appendix A). Most participants were university students who received course credit or a $20 gift voucher for their participation. Participants met standard TMS criteria (Rossi et al., 2009) and were right handed (*M*=83, *SD*=20, range=30 - 100) as per the Edinburgh Handedness Inventory (Appendix B), whereby laterality quotient was measured on a continuum from -100 to +100 with numbers over zero being associated with a degree of right handedness (Oldfield, 1971). Exclusion criteria included, but not limited to, a history of seizures, migraines or concussion, previous adverse reactions to TMS, metal implants above the shoulders, and the use of some psychotropic medications. Participants were screened online for contraindications to TMS prior to attending the laboratory and again upon arrival (Appendix B, Rossi et al., 2009). Before undertaking the experiment, they were briefed and given an

information sheet (Appendix C) and informed consent was obtained (Appendix D). As the SST used in the experiment involved the presentation of red and green coloured stimuli, participants were screened for colour-blindness prior to completing the experiment (Appendix E). The Ishihara test (Ishihara, 1971) is the most prevalent and accepted screening test for congenital protan and deutan effects (i.e., inherited red /green effects) and is considered the most efficient test for colour blindness (Birch, 1985). A simplified version of this test was developed for the current experiment and involved six of the plates used in the 38-plate edition. In the instructions for administration of the simplified version, Ishihara (1971) stated 6 plates comprising a demonstration plate (plate 1) plus one plate from numbers 2,3,4,5, one from 6,7,8,9, one from 10,11,12,13, one from 14,15,16,17, and one from 18,19,20,21 should be used. As such, plates 1,2,6,10, 14 and 18 were chosen. The images were presented and participants wrote their answers in a space provided on the pre-screening form.

Materials and Procedure

Stop Signal Task

The experiment comprised nine blocks of 100 trials of a stop signal task (SST). Visual stimuli were developed and presented using PsychoPy (Peirce, 2009). Each trial began with a visual cue presented for 500 milliseconds (ms) that was either informative about which hand may have to stop: Maybe Stop Both (MSB), Maybe Stop Left (MSL), or Maybe Stop Right (MSR), or an uninformative fixation cross (NoCue). The IS began 1500ms after the onset of the cue and consisted of two green arrows (presented for 500ms) that required a simultaneous bimanual button press using the index fingers of the right and left hand (Figure 1, Figure 2). On 30% of

trials this stimulus was followed by a SS indicated by either the left, right or both arrow/s turning red. The SSD was dynamically manipulated for each stop type independently according to whether the participant stopped successfully on the previous iteration of that stop type, thus enabling the calculation of SSRT. For each stop type, SSD was initially set at 130 ms after the IS and decreased or increased in 50 ms increments.

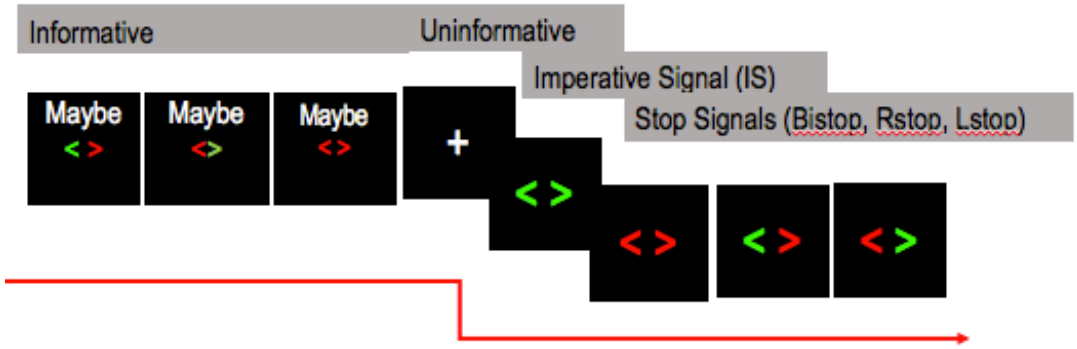

Figure 1: Visual stimuli as presented using PsychoPy (Peirce, 2009). Each trial began with a 500 ms cue that was either informative or uninformative. The uninformative cue was a fixation cross, whereas the informative cues comprised red/green arrows that corresponded to the SS that might occur. A red arrow indicated that if a stop signal occurred then the corresponding hand/s would have to stop. Following a 1000 ms blank screen the IS was presented (for 500 ms), indicated by two green arrows. On 30% of trials, after a variable delay, a SS replaced the IS, indicated by one or both arrows turning red.

Initially, participants engaged in a practice block of the SST. This block included all four cue conditions with no TMS. Verbal instructions were given as well

as presented on the screen and participants were reminded to respond as quickly and accurately as possible to the IS. They were told it wouldn't be possible to stop on all stop trials but it was important they should try. Participants then engaged in nine blocks of 100 trials comprising two 'no cue' blocks, one block of each 'MSL', 'MSR', and 'MSB' and four mixed blocks (Table 1). The block design was constructed to ensure adequate numbers of trials in each condition for both behavioural and TMS analyses (see below). Block order was randomised among participants to control for learning and fatigue effects using a number generator in excel.

Table 1

Configuration of stop and go trials in each of the 9 blocks: There was one block of trials whereby all cues were maybe stop left (MSL), one block of maybe stop right (MSR), one block of maybe stop both (MSB), two blocks with no cue (NoCue), whereby either of the three stop types could occur, and four mixed blocks whereby all stop and cue types were possible. There were 100 trials in each block, with 30% (i.e., 30) valid stop trials.

Block	Left stops	Right Stops	Bimanual stops	Go trials
MSL	30	-	-	70
MSR	-	30	-	70
MSB	-	-	30	70
NoCue	10	10	10	70
Mixed	10 (4NC, 6MSL)	10 (4NC, 6MSR)	10 (4NC, 6MSB)	70 42 cued, 28 uncued

Electromyography and Transcranial Magnetic Stimulation

Ag/AgCI electrodes were placed on the left and right hands over the first dorsal interosseous (FDI) muscle in the belly tendon montage, with a third grounding electrode on the ulnar styloid process (Claffey et al., 2010). This is an appropriate muscle to investigate CSE changes during a button presses as it contributes to flexion of the index finger and is easily accessed with surface EMG. In addition, it has a cortical representation that is easily accessed with TMS with minimal side effects (i.e., superficial motor map). EMG was used to record the muscle activity evoked when participants made volitional motor response, and MEPs when TMS was administered. EMG data was recorded at 2kHz amplified (x1000) and notch filtered (50Hz) using CED amplifier and data acquisition hardware before being stored on a computer for offline analysis. During EMG set up, participants were asked to observe their EMG activity and relax their arms and hands as much as possible. This allowed them to practise actively relaxing so throughout the experiment they could respond to bio-feedback about their muscle activity, ensuring clear and reliable data. TMS was applied using a MagStim 200^2 stimulator and figure of eight "branding iron" coil with a diameter of 70mm. Utilising a figure eight style TMS coil offers focal stimulation and was therefore a spatially precise way to stimulate neurons corresponding to the FDI muscle (Rothwell, 1997). As a starting point for locating the FDI 'motor hotspot', the coil was placed over the right motor cortex, 5cm lateral to the vertex and oriented ~45 degrees from the midline (Rothwell, 1997). As everyone has a slightly different topographical map, the experimenter located the hotspot by moving the coil in a consistent manner, using a conceptual grid to cover the surrounding cortical area (approx. $5cm^2$). The motor hotspot was located as the M1 site whereby the largest MEP was elicited in the FDI muscle. Resting motor

threshold (RMT) was identified as the stimulator intensity required to elicit an MEP of 1 mV amplitude in three out of five consecutive trials (Hinder et al., in press). TMS intensity was set at 130% of RMT for the experiment, except in one participant where MEPs at this intensity were too large, causing saturation of MEPs on the A/D converter, thus 120% RMT was used. A baseline TMS block was recorded before and after the task blocks comprising 12 trials of MEP pulses while subjects were at rest. This ensured stability of the baseline across the experiment (Labruna et al., 2014), and provided a measure of resting-state CSE. During some trials within the nine SS blocks, TMS was administered at one of four time points. CUE, CUE750, IS, and IS100 (Figure 2). TMS administered at the onset of CUE was not intended to measure trial by trial CSE modulation as participants had not had time to process the cue. Instead, its purpose was a baseline for CSE modulation within the trial. Stimulation at CUE750 was intended to capture preparatory modulation of CSE in response to the cue. At this time-point, the participant had visually processed the cue and may have modulated CSE accordingly. At IS, participants had not processed the 'go signal', therefore MEP amplitudes remained indicative of preparatory processes immediately before IS processing. Last, the IS100 time-point was included as there is some evidence that MEP amplitudes at this stage reflect late preparatory modulation of CSE. However, it may be excluded from analysis if it cannot be reliably dissociated from processes related to execution of action.

As the current study was interested in CSE modulation during the preparatory period (i.e., proactive modulation), TMS was only administered on go (and not stop) trials to ensure adequate CSE data for analysis. Although both hands were required to respond simultaneously in the SST, MEPs were only measured in the left hand (TMS to the right M1), which is usual practise in motor control research.

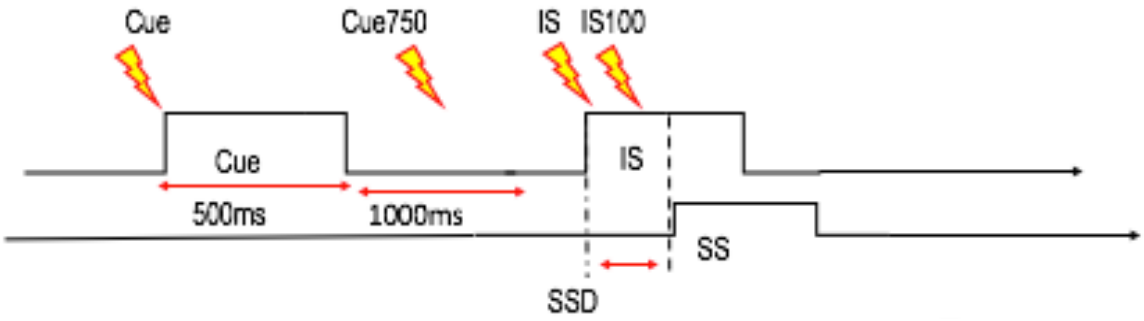

Figure 2: Timeline of visual stimuli presentation and TMS administration. On some go trials at one of four 4 time points (CUE, CUE750, IS, IS100) a TMS pulse was administered. Note that on go trials (i.e., TMS trials) a stop signal (SS) did *not* appear following the IS.

Design and Data Analysis

A within-subject design examined differences in behaviour and neurophysiological correlates (CSE) of action stopping in a sample of young adults. Dependent variables (DVs) included bimanual go RT (BiGoRT), SSC, which was calculated by subtracting RT of the non-stopping hand during a selective stop from BiGoRT, and SSRT, which was calculated using the mean method, i.e., subtracting SSD from BiGoRT (Verbruggen & Logan, 2009). BiGoRT was investigated with a 2 (Block Type: Blocked vs. Mixed) X 4 (Cue Type: NC, MSB, MSR, MSL) repeated measures (RM) ANOVA. SSC was investigated with a 2 (Cue Type: Cue, NoCue) X 2 (Hand: Left, Right) X 2 (Block Type: Mixed, Blocked) RM ANOVA. SSRT was investigated with a 2 (Cue Type: Cue, NoCue) X 2 (Block Type: Mixed, Blocked) x 3 (Stop Type: Left, Right, Bimanual) RM ANOVA and a 2 (Cue Type: Cue, NoCue) X 3 (Stop Type: Left, Right, Bimanual) RM ANOVA using data from only blocked conditions.

The neurophysiological DV was MEP amplitude. MEP analysis was conducted using the first three time points to ensure all modulatory effects were preparation-related and not execution related (i.e., not in response to the IS). That is, the fourth time-point (IS100) was excluded from the current analyses as it occurred too late in the preparation process to be reliably distinguished from the execution related changes in CSE. To investigate proactive changes in CSE in global vs selective stopping a 2 (Block Type: Mixed, Blocked) x 3 (Cue Type: MSB, MSL MSR) X3 (Time: CUE, CUE750, IS) RM ANOVA was conducted. NoCue was excluded from this analysis because it did not provide information as to whether the participant was required to prepare a selective or global stop, thus it was irrelevant to the question. To address whether CSE modulation during action preparation for selective movement was associated with facilitation of the responding hand or suppression of the non-responding hand, a 2 (Block Type: Mixed, Blocked) x 3 (Cue Type: MSL, MSR, NoCue) X3 (Time: CUE, CUE750, IS) RM ANOVA was conducted. MSB was excluded as it was not cueing a selective stop, thus it was irrelevant to the question. In this analysis, NoCue was used as a baseline to compare CSE in the maybe stopping (MSL) and non-stopping (MSR) hands. Prior to analysis MEP data was filtered and trials were excluded if root mean square (RMS) EMG in the 100ms prior to TMS stimulus exceeded 10uV.

All analyses were conducted using IBM SPSS statistics with an *a* priori alpha level set at .05 (IBM Corp., 2012). A Greenhouse-Geisser correction was applied to all comparisons whereby the assumption of sphericity was violated ($\varepsilon<.70$). Where necessary, significant main effects and interactions were followed up using Sidak-corrected pairwise comparisons. Results were reported as mean (*M*), standard deviation (*SD*) +95%CI. Partial eta squared (η_p^2) was provided as an effect size for

main effects and interactions and Cohen's *d* was used to interpret effect sizes in follow up pairwise comparisons. In both instances effect sizes were interpreted as 0.2=small, .5=medium and .8=large (Cohen, 1992).

Results

Behavioural Measures

Participants performed well in the task, with 98% of go trials correctly executed. The SSD staircases were successful at manipulating stopping performance, with an average convergence rate of 60% stop success.

Reaction Time

Participants responded significantly faster to the bimanual go (BiGo) signal in the blocked conditions (*M*=472ms, *SD*=80ms, 95%CI[437,506]) compared the mixed conditions (*M*=493ms, *SD*=83ms, 95%CI[458,529]), F(1,22)= 38.604, *p<.001,* ηp^2 =.637. No significant differences in BiGoRT were observed across cue type, F(3,66)=1.191, *p=.136,* η_p^2=.080, and the interaction between block type and cue type was not statistically significant, F(3,66)=1.151, *p=.335,* η_p^2=.050.

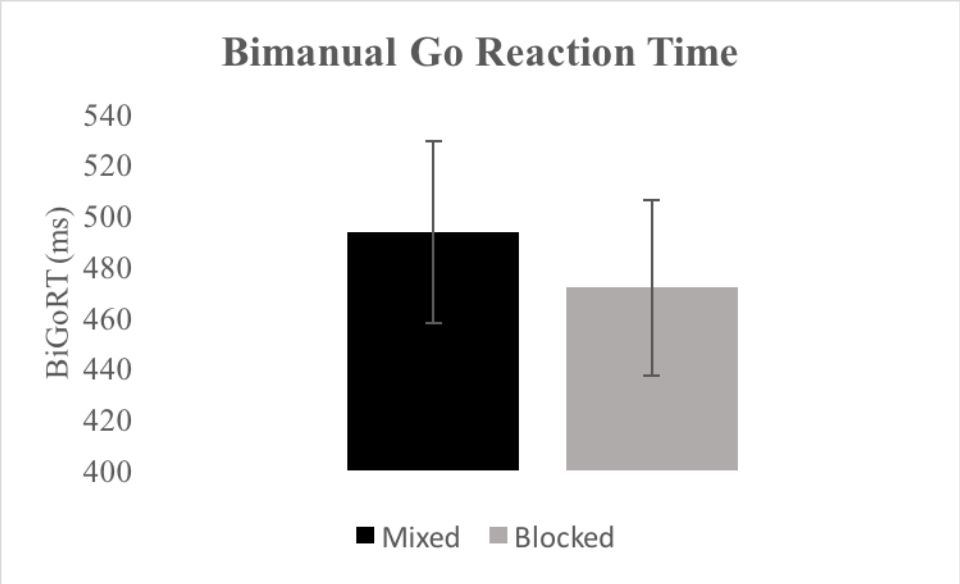

Figure 3: Comparison of bimanual go reaction time (ms) in the blocked and mixed trials. Data are averaged across cue types. Error bars represent 95% CI

Selective Stop Cost

SSC was significantly reduced in the cued conditions (*M*=101ms, *SD*=47ms, 95%CI[81,122]) relative to uncued conditions (*M*=126ms, *SD*=39ms, 95%CI[110,43]), F(1.22)=9.950, *p=.005,* η_p^2=.311. This suggested that providing information about which hand may have to stop permitted a faster response in the non-stopping hand. There was no significant difference in SSC between the left and right hand, F(1,22)=.843, *p=.368,* η_p^2=.037, or between mixed and blocked conditions, F(1,22)= .194, *p*=.664, η_p^2=.009, and no significant interactions (all p> .093, all $\eta_p^2 < .123$).

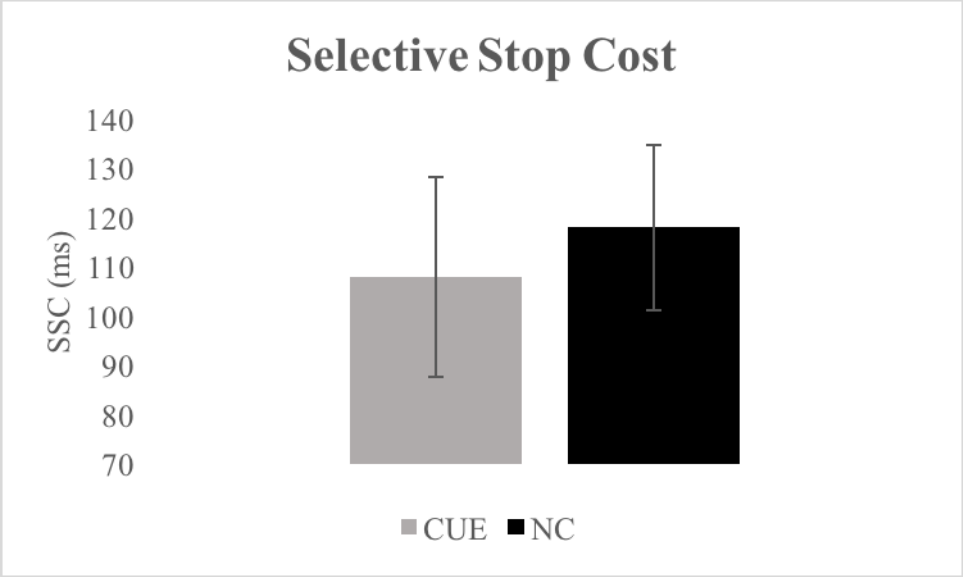

Figure 4: Comparison of SSC (ms) in the cued and uncued trials. Data are averaged across block type and hand. Error bars represent 95% CI.

Stop Signal Reaction Time

SSRT could not be reliably interpreted for the Cue vs. NoCue comparison in mixed conditions due to a limitation in the design – while stop type staircases were independently assigned, the staircases were not independently assigned for the different cue types for each stop type. Accordingly, the omnibus ANOVA to compare mixed and blocked trials did not include cue type as a factor. This ANOVA (stop type x block type) yielded a significant main effect of block type, $F(1,22)=10.779$, $p=.003$, $\eta_p^2=.329$, with significantly better stopping performance (across all stop types) in blocked conditions (M=265ms, SD=27ms, 95%CI[253,277]), than mixed conditions (M=289ms, SD=40ms, 95%CI[272,306]). There was no significant main effect of stop type, $F(2,44)=1.659$, $p=.202$, $\eta_p^2=.070$, and no significant interaction between stop type and block type ($p=.545$, $\eta_p^2=.027$) When blocked conditions were analysed separately (with cue type included as an additional factor), participants required significantly less time to correctly respond to

the stop signal (and countermand the planned action) in the cued conditions (*M*=251ms, *SD*=34ms, 95% CI[236, 265]) compared to the uncued condition (*M*=279ms, *SD*= 31ms, 95%CI[266, 293]), F(1,22)=13.859, *p=.001,* η_p^2=.386, indicating that provision of a cue improved stopping performance. The main effect of stop type was not statistically significant, F(2,22)=1.181, *p=.312,* η_p^2=.051 with bimanual SSRT (*M*=261ms, *SD*=29ms, 95%CI[249,273]) not significantly shorter than left (*M*=263ms, *SD*=34ms, 95%CI[249,278]) and right (*M*=270ms, *SD*=32ms, 95%CI[256,284]) SSRT. There was no significant interaction between stop type and cue, F(2,22)=.718, *p=.410,* η_p^2=.032, suggesting there was no behavioural difference between selective and global stopping ability, regardless of cue.

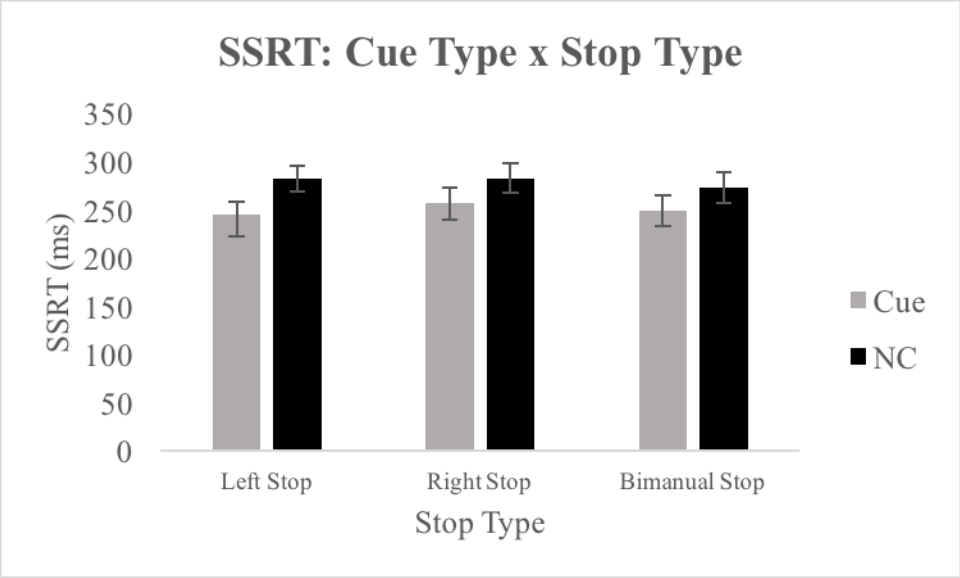

Figure 5: Comparison of SSRT (ms) in left, right and bimanual stops in cued and uncued conditions in blocked trials. Error bars represent 95%CI

Neurophysiological Measures

The average RMT for participants was 42% of maximum stimulator output (MSO) (*SD*=8% MSO, range: 28-60% MSO) and average testing intensity was 54% MSO (*SD*=10% MSO, range: 36-78% MSO).

MEP Amplitude

A paired samples *t*-test of MEP amplitudes at baseline (i.e., at rest, undertaken before and after the movement blocks) revealed that CSE was greater after the experiment (*M*=2.18mV, *SD*=1.89mV, 95%CI[1.38, 2.93]) than before (*M*=1.76mV, *SD*=1.63mV, 95%CI[1.10, 2.43]); however the difference did not meet the a-priori level of significance, *t*(22)=2.017, *p=.056, d=.238.* This increase was likely due to short-term movement related potentiation and was not considered to have impacted the results, as we were most interested in the temporal evolution of CSE during movement preparation and execution. MEP amplitudes throughout the experiment were significantly greater than baseline (Figure 6) which indicated a generic task related excitation of the CST, perhaps related to attention/arousal effects.

A) BLOCKED B) MIXED

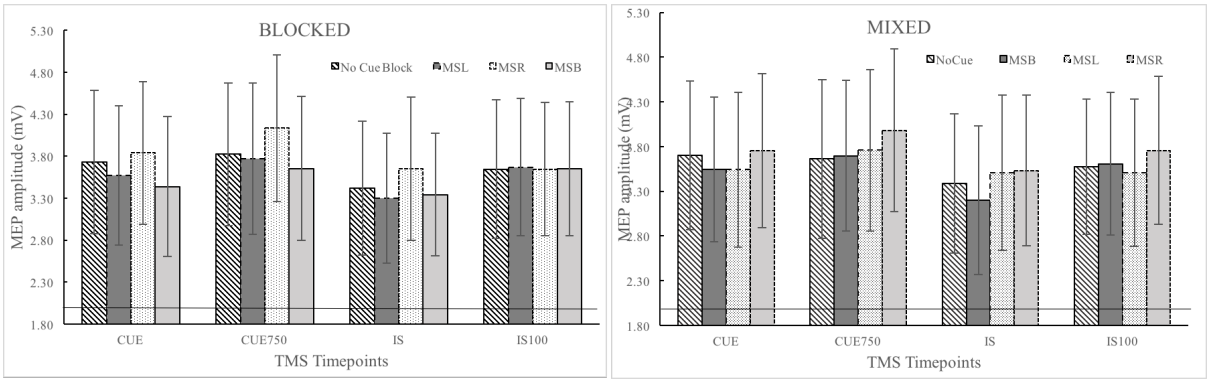

Figure 6: Comparison of MEP amplitude across all cue types and time point in the A) blocked and B) mixed conditions. Error bars represent 95% CI. The baseline (horizontal line at 1.96mV) is included to show a comparison of MEPs in the FDI when the muscle was engaged in a task compared to when it was at rest.

CSE During Global vs. Selective Stopping

The main effect of cue type was significant F(2, 44)=6.251, *p*=*.004,* η_p^2=.211 indicating that participants modulated CSE according to the cue provided: CSE was greater in the MSR condition (*M*=3.82mV, *SD*=2.03mV, 95%CI[2.94, 4.69]) than the MSL (*M*=3.57mV, *SD*=2.03mV, 95%CI[2.70, 4.45]) and MSB (*M*=3.48mV, *SD*=1.94mV, 95%CI[2.64, 4.32]) conditions (Figure 7). Post-hoc comparisons revealed that while there was no significant difference in left hand CSE between global (MSB) and selective (MSL) cued trials (*p*=.536, *d*=.05), CSE was significantly greater in MSR cued trials than both MSL (*p*=.046, *d*=.12) and MSB (*p*=.032, *d*=.17) cued trials, indicating that participants modulated excitability depending on whether the left hand was cued to potentially stop (MSB, MSL) or not (MSR). There was a significant main effect of time F(2,44)=4.314, *p*=*.019,* η_p^2=.164, however no significant main effect of block type, and no significant two or three way interactions (all *p*>*.151,*all η_p^2<.075)

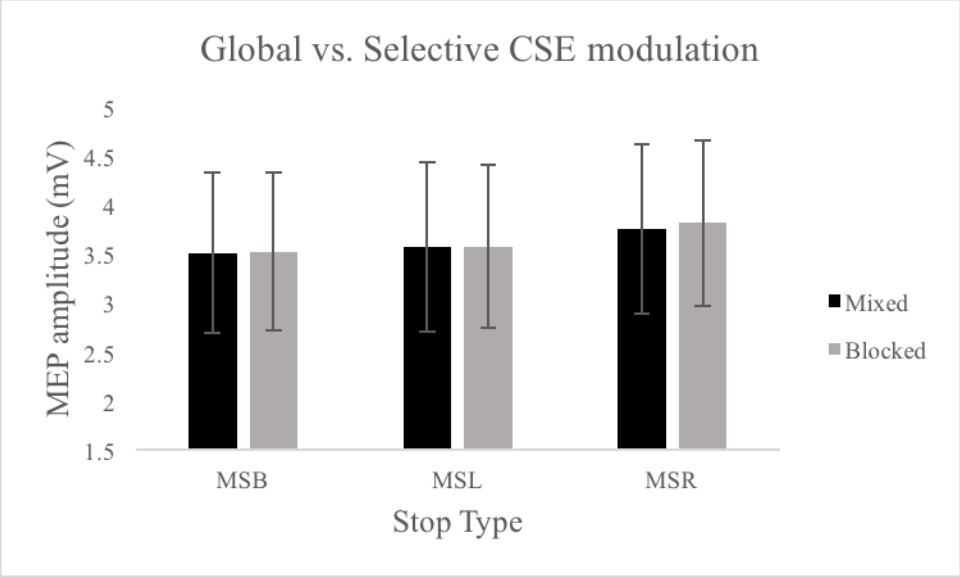

Figure 7: Comparison of MEP amplitude (mV) in selective (MSL/MSR) and global (MSB) stopping in mixed and blocked conditions. Data are averaged across TMS time-points. Error bars represent 95% CI.

Facilitation vs. Suppression of CSE During Selective Stopping

The main effect of cue type was significant F(2,44)=5.107, $p=.010$, $\eta_p^2=.190$ with CSE in the MSR condition (M=3.82mV, SD=2.03mV, 95%CI[2.94, 4.69]) greater than CSE in both the NoCue (M=3.62mV, SD=1.99mV, 95%CI[2.78,4.46]) and MSL cued trials (M=3.57mV, SD=2.03mV, 95%CI[2.70, 4.45]). Post-hoc comparisons revealed that the difference in CSE between MSL and NoCue conditions was not significant ($p=.755$ $d=03.$). The difference in CSE between MSR and NoCue also failed to meet the a-priori level of significance and was associated with a small to negligent effect size (p=.115, d=.09). However, the difference between MSL and MSR was statistically significant (p=.046 d= .12). These results suggest that participants modulated excitability, potentially to facilitate a rapid response when cues indicated that hand *would not* be required to stop. There was also a statistically significant main effect of time F(1.349, 29.686)=4.941, $p=.025$, $\eta_p^2=.183$, but no significant main effect of block type, or any significant two or three way interactions (all $p>.316$, all $\eta_p^2<.052$).

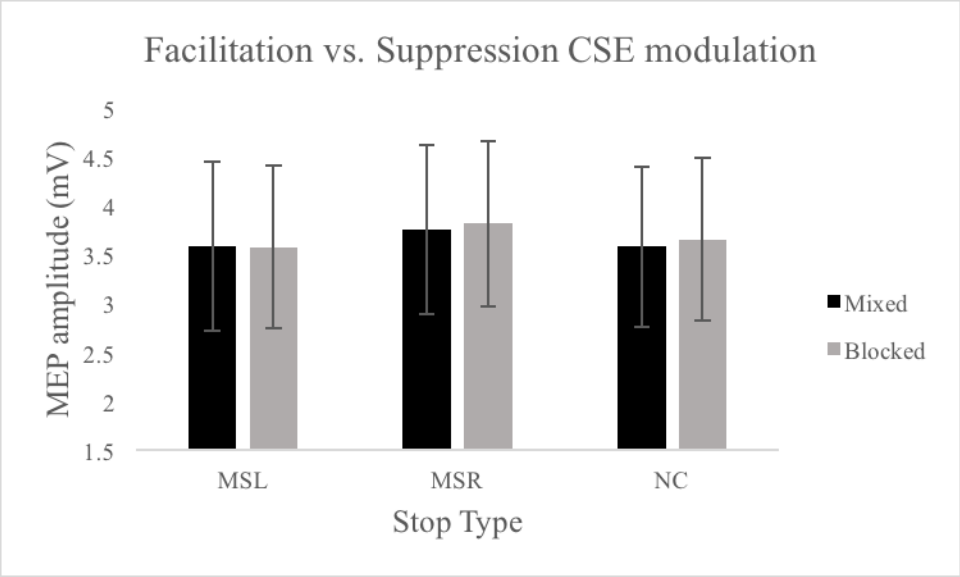

Figure 8: Comparison of left hand MEP amplitude (mV) in selective stop cued trials in which the left hand maybe be required to stop (MSL) and not required to stop (MSR), relative to NoCue. Data is shown for mixed and blocked conditions. Data are averaged across TMS time-points. Error bars represent 95% CI.

Discussion

The current study investigated the neurophysiological and behavioural correlates of inhibitory control. TMS was used to probe CSE while participants engaged in a selective vs. global SST. Specifically, we aimed to examine how participants modulated CSE when given cues about whether a limb may be subsequently required to withhold a planned action.

Behavioural Measures of Stop Signal Task Performance

Response Times During Go Trials

When a SS was not presented, BiGoRT was shorter in blocked conditions compared to mixed conditions. This difference was likely due to the reduced complexity associated with deciphering both the varying cue conditions, and subsequent competition resolution associated with selecting and executing the required response in the blocked (compared to mixed) conditions. That is, in blocked conditions the cue remained the same throughout the 100 trials and the number of possible response options ranged from two (in MSL, MSR, & MSB blocks) to four (in NoCue), whereas in mixed blocks there were always four different cues that resulted in 10 different cue-response combinations. A major part of cognitive control is the ability to choose the appropriate and goal related response out of several competing options. The more numerous or conflicting the response options, the harder it is to respond quickly and correctly (Eriksen, 1995; Eriksen & Schultz, 1979).

Stop Trial Performance (SSRT, SSC)

The significant main effect of cue in the SSRT analysis showed that when the cue was informative about which hand may have to stop, overall stopping ability was improved. Consistent with previous literature (Cai et al., 2011; Claffey et al., 2010), the significant main effect of cue in the SSC analysis showed that the cost associated with selectivity of stopping was reduced when informative cues were provided. Accordingly, researchers such as Cai et al. (2011) have argued for an independent mechanism of selective stopping, that could be observed when proactive information was provided.

The current study aimed to determine whether there were separate inhibitory mechanisms employed for global and selective stopping. However, findings indicated no significant difference in stopping performance between selective (unimanual) and global (bimanual) stops in either cued or uncued conditions, demonstrated by a non-significant main effect of cue type and a non-significant post-hoc comparison between MSB and MSL cues. Models that propose separate global and selective mechanisms predict that stopping a bimanual response will require less time, as indexed by SSRT, whereas a selective mechanism will require more time due to its increased complexity (Cai et al., 2011; Claffey et al., 2010; Majid et al., 2012). The current study supports recent evidence proposing that selective stopping is facilitated by interplay between two concurrent mechanisms, a global breaking of action and the release of inhibition on a selected response representation (Hinder et al., in press, MacDonald, McMorland, Stinear, Coxon, & Byblow, 2017). As such, selective stopping does not take substantially longer than bimanual stopping, although small difference may be observed due to the increased complexity of the response.

We observed significantly shorter SSRTs in the informatively cued versus NoCue conditions. In contrast, Claffey et al. (2010) found that that SSRT was longer in cued (compared to non-cued) conditions. These authors speculated that selective (and proactive) stopping was *slower* because its mechanism comprised a fronto-basal ganglia pathway with greater synaptic connections however, this is yet to be established empirically. The contrasting finding of the current study supports a more generic mechanism of inhibition in which selectivity can be facilitated by the provision of cues or training (Xu et al., 2015). If so, providing a cue in the current study reduced the overlap between two different response tendencies, subsequently

resulting in behaviourally improved (i.e., faster) stopping performance, and a reduced SSC. This suggestion is further supported by the non-significant difference in SSRT and SSC between bimanual (global) and unimanual (selective) stops.

Proactive CSE Modulation During Action Preparation

Global vs Selective CSE Modulation

Analysis of MEPs during movement preparation revealed no differences in proactive left hand CSE when the cue indicated that the left hand may be involved in a selective or global stop (MSL vs. MSB). This finding suggests that a single neural mechanism may be involved in both selective and global stopping, which is further supported by the non-significant difference in SSRT between selective and global stopping. This finding contrasts with prior research suggesting global and selective inhibition employ independent mechanisms, with global inhibition faster and easier to implement. As such, it would be expected that participants would use this mechanism when it suited their goals (e.g., proactive bimanual stopping; Badry et al., 2009; Majid et al., 2012). The current study could not determine if suppression in reactive bimanual stopping was more widespread than in proactive conditions, however this could be accomplished in future research by determining if suppression is apparent in leg, or other hand muscles not primarily involved in the go response (Majid et al., 2012).

Consistent with previous literature (Claffey et al., 2010; Majid et al., 2012), the current results fail to support the re-start hypothesis in proactive selective inhibition, which proposes selective stopping is achieved via output from a widespread global stopping mechanism followed by the initiation of the selected movement. It is possible this process occurred in the uncued conditions however, as

CSE was measured in the preparatory period before the participant processed the IS, it couldn't be neurophysiologically determined. Electrophysiological support for a global stopping mechanism comes from studies whereby reduced MEPs are observed in task irrelevant muscles on reactive stop trials after the IS occurs (Badry et al., 2009; Majid et al., 2012) as well as electroencephalography (EEG) evidence that successful stopping and inhibitory reactions to unexpected events show similar patterns of activation (Wessel & Aron, 2017). However, it remains unclear whether this inhibition is obligatory and whether it employs different mechanism to that allowing selective and proactive inhibition.

Our behavioural results are consistent with one aspect of the re-start hypothesis, with a significantly greater SSC in uncued conditions relative to cued conditions. Indeed, according to Xu et al. (2015), large SSCs are indicative of a global stopping mechanism followed by the initiation of a selected response. However, the magnitude of the difference in SSC between cued and uncued conditions was 25 ms which is not large enough to indicate a separate mechanism. In fact, neither 101ms (cued SSC) nor 126ms (uncued SSC) are enough for the employment of two consecutive mechanisms. It is more likely that the ATM of response inhibition proposed by Macdonald et al. (2017) occurred, whereby a global breaking of action raises the threshold for a selective response, thus explaining the additional time needed to respond to a selective stop compared to a global stop. This model proposes that an uncued SS initiates two coupled responses, one that globally affects the motor system, and another that simultaneously initiates the subsequent response. This model can explain why the current study found a small difference in stopping performance between selective and global stopping, but it failed to meet *a* priori levels of significance.

Facilitation vs Suppression of CSE in Selective Stopping

MEP analysis revealed that participants modulated excitability depending on whether the left hand was cued to potentially stop (MSL), not be required to stop (MSR), or uncued (NoCue). Here we showed that the significant difference in CSE between maybe stopping and non-stopping hands was due to an increase in excitability in the left hand following the MSR cue as opposed to a suppression of left hand excitability following the MSL cue. While the differences relative to NoCue were not significant, they were in the expected directions with a greater and more meaningful difference between MSR and NoCue than between MSL and NoCue (See Figure 8 and associated analysis). This modulation appeared to be behaviourally functional as the SSC was significantly reduced for cued trials, indicating that providing a cue facilitated the response of the non-stopping hand.

In contrast, Cai et al. (2011) used a similar paradigm to support the suppression model, whereby CSE in the hand required stop was significantly reduced compared to 'null'. In this study null referred to a condition whereby no response was required (i.e., the hands were at rest). A limitation of Cai et al. (2011)'s study was that using null as a baseline could not dissociate suppression resulting from CSE modulation in response to the cue from that occurring as part of the impulse control mechanism (Hinder et al., in press; Duque & Ivry, 2009). To determine whether active suppression or the release of inhibition in the non-stopping hand drives selective stop performance, CSE in the hand cued to maybe stop and the hand cued to not stop was compared to CSE when no cue was provided. This permitted investigation as to whether cueing resulted in additional CSE modulation to that occurring as premature response prevention during a behavioural task.

Accordingly, the results of the current study point to a facilitation model of CSE modulation whereby participants prepare for a selective response by releasing inhibition in the non-stopping hand in response to a cue. We suggest that during a proactive stop signal task, both hands are initially inhibited due to an impulse control mechanism (Hinder et al., in press, Duque & Ivry, 2009) and upon processing an informative cue, release inhibition in the hand that is required to respond (and cued that it *won't* have to subsequently stop). Alternatively, non-significant (relative to NoCue) additional suppression is placed on the hand if it is cued to maybe stop.

The main effect of time in both MEP analyses, and absence of any interactions with block or cue type, show that participants temporally modulated their excitability in a consistent pattern during preparation of movement. There were differences in CSE between cue onset, 750ms after cue onset, and IS, regardless of whether the cue was informative, indicating that CSE modulation was occurring generically during movement preparation. Furthermore, neither the analysis comparing global and selective stopping, nor the analysis investigating the facilitation vs. suppression models showed any difference in CSE modulation between mixed and blocked design which, importantly, suggests that young adults can modulate excitability proactively based on cues in a block by block and trial by trial basis. This suggests a flexible modulation of MEPs, which may assist in optimising inhibitory performance when faced with rapidly changing environmental cues.

An important future direction for this research is a comparative study with a sample of older (+65 y/o) adults. Australia has an ageing population (Australian Bureau of Statistics, 2016), thus researchers are interested in how it may be possible to prolong the independence of older adults as a way of addressing the imminent

economic burden of the cost of care for this population (Australian Government, 2013). Understanding how motor control, and in particular inhibitory control, changes as a function of ageing can allow interventions to be developed that may be able to mitigate some of the mobility issues that result in reduced independence in older adults. It would be hypothesised older adults would show significant impairment in modulating excitability on a trial by trial basis compared to young adults.

Previous literature supports this hypothesis, for example a study by Fujiyama et al. (2012) tested older and younger adult's performance on a RT task whereby a cue was followed by an IS requiring speeded thumb flexion in response on go trials, or no response on no-go trials. At different times throughout movement preparation (i.e., between the cue and IS) and during movement execution (i.e., between IS and the participant's response), TMS was administered that was either single or paired-pulse. An increase in CSE, relative to cue onset, was observed in both groups during response execution, with younger adults eliciting earlier and more prominent increases in CSE relative to older adults. Furthermore, older adults did not demonstrate the reduced short-interval intracortical inhibition throughout response preparation that was observed in younger adults. Regression analysis revealed task related increases in CSE were associated with faster RT. Thus, these authors suggested the impaired ability to modulate CSE on a trial by trial basis could explain the behavioural slowing observed in older adults on RT tasks (Williams et al., 1999). To further investigate the extent of inhibitory control impairment in older adults, a comparative study should investigate CSE changes and stopping performance in a design whereby the cue and stop type remain constant throughout each block.

Overall, the current findings show that the provision of an informative cue results in selectivity at the motor level. Importantly, this selectively in unlikely to be due to an independent mechanism of inhibition. Rather, findings support a generic mechanism of inhibition that can be elaborated on when information is provided about the upcoming response. Furthermore, cueing allowed participants to modulate CSE to facilitate a correct selective stop by releasing inhibition in the hand that was required to respond (i.e., will not have to stop). These novel findings extend previous work by Hinder et al. (in press) showing that the increased release of inhibition that enables response execution in cued trials is apparent before IS is processed.

Limitations and Implications

The calculation of SSRT (one of our dependent measures) is limited theoretically. This method assumes going and stopping are independent processes; however, this is not confirmed. Indeed, there is some evidence to suggest they interact (Verbruggen & Logan, 2009; Xu et al., 2015). More research is required to determine whether this method of calculating SSRT is the most appropriate way of measuring stopping performance. However, it is currently the only effective option and is widely used throughout the literature (Cai et al., 2011; Claffey et al., 2010; Majid et al., 2013, 2012).

Our design was limited in that SSD staircases were not set for each warning signal type independently within the mixed blocks therefore there was no discernible difference in stop performance between cued and uncued conditions. Due to this limitation, we did not include cue type as a factor within SSRT analysis of mixed blocks. A different method of calculating SSRT (i.e., an integration method) rather than a mean method may still be able to reveal differences in performance by

analysing trial by trial rather than taking an average of all trials, however this is beyond the scope of this thesis. Furthermore, SSD was reset at the beginning of each block, thus for mixed and NoCue blocks the staircases were not able to converge on exactly 50% accuracy. The initial SSD of 130ms was too low, as such participant's accuracy was greater than 50%, especially in the first half of the block while the algorithm converged towards 50% from a much higher successful stopping percentage. However, accuracy was consistent across all cue types and blocks, which allowed reliable comparisons of SSRT and SSC that were not conflicted by underlying differences in stopping ability.

As we measured MEPs in the left hand, it can only be inferred that CSE findings would be similar in the right hand. As this method is common practise and behavioural results were comparable to other studies it is not considered a concerning limitation, however further research utilising dual coil techniques (i.e., measuring CSE of both hemispheres within the same trial, Grandjean et al., 2017) would elucidate further clarity on the mechanisms of proactive modulation of CSE during SS tasks.

Research aimed at understanding the mechanism of inhibitory control has important implications for understanding of conditions such as ADHD, Schizophrenia, and Autism Spectrum Disorder (Lipszyc & Schachar, 2010). This research also provides excellent scope for expansion in the context of healthy ageing. A comparative study using a cohort of older adults is a necessary and interesting future direction for this research. Further future directions involve combining stimulation techniques like TMS with neuroimaging techniques such as fMRI to investigate the pathways of selective and global inhibition.

Conclusion

The current study investigated temporal modulation of CSE during the preparation of motor movements. Specifically, the effect of informative and uninformative cues on stopping performance and CSE was investigated. Consistent with previous literature, results supported increased selectivity in stopping based on a cue. In contrast to previous literature (Claffey et al., 2010), we found that participants were better (i.e., faster) at stopping in cued conditions compared to uncued conditions. MEP results revealed there was no difference in CSE between selective and global stopping, however there was a significant difference between the CSE of the non-stopping hand and the hand that was required to stop (in either a global or selective manner), thus supporting a facilitation model. These findings point to a generic mechanism of stopping that can be modulated by external stimuli to facilitate behavioural outcomes. We suggest that cues reduce the overlap between different response representations and therefore facilitate stopping performance and concurrently reduce the cost associated with making a selective movement. The novel findings of the study contribute to a body of literature that aims to elucidate the neural underpinnings of inhibitory control. Understanding how the motor system can modulate CSE to facilitate responses to rapidly changing environmental stimuli is important for understanding how it is impaired in various conditions and how it declines as a function of ageing.

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Appendix A: Ethics Approval Letter

From: Katherine Shaw (katherine.shaw@utas.edu.au)

Sent: Monday, 5th May 2017, 11:06am

To: Mark Hinder (mark.hinder@utas.edu.au)

CC: Jeffery Summers, Hakuei Fujiyama, Tino Stoeckel, Rohan Puri, Sara Waitzer, Sara Forni Zervoudaki, Sarah Kemp, Abbey Lack, Anna Read, Pola Reissig, Angus Reynolds

Subject: Ethics Amendment Approval: H0012358 Brain connectivity during movement planning and execution in young and older adults

Dear Dr Hinder

Ethics Ref: H0012358
Title: Brain connectivity during movement planning and execution in young and older adults

This email is to confirm that the following amendment was approved by the Chair of the Tasmania Social Sciences Human Research Ethics Committee on 28/4/2017:

- Addition of Honours students Abbey Lack and Anna Read.
- Revised Information Sheet and Information Sheet for behavioural testing.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the National Statement on Ethical Conduct in Human Research (NHMRC 2007, updated May 2015).

This email constitutes official approval. If your circumstances require a formal letter of amendment approval, please let us know.

Should you have any queries please do not hesitate to contact me.

Kind regards
Katherine

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Appendix B: TMS Pre-Screening Form

TMS PRE-SESSION SCREENING FORM

Name: ……

Age: ……..

Sex: M / F / Unspecified

Do you have any difficulties with vision? (please detail) ……..

If so, are these difficulties corrected, and how? ……

Are you currently taking any medication? (please detail) ……..

Before receiving TMS, please read the following questions carefully and provide answers. For a small number of individuals, TMS may carry an increased risk of causing a seizure. The purpose of these questions is to make sure that you are not such a person. You have the right to withdraw from the screening and subsequent session if you find the questions unacceptably intrusive. The information you provide will be treated as strictly confidential and will be held in secure conditions. If you are unsure of the answer to any of the questions, please ask the person who gave you this form or the person who will be performing the study.

Have you ever had an adverse reaction to TMS?	**Y / N**
Do you have a heart condition?	**Y / N**
Do you or does anyone in your family have epilepsy?	**Y / N**
Have you or anyone in your family ever had a seizure?	**Y / N**
Have you ever had neurosurgery or a serious head injury requiring hospitalisation?	**Y / N**
Have you ever had a stroke?	**Y / N**
Do you have any metal in your head (outside the mouth) such as shrapnel, surgical clips, or fragments from welding or metalwork?	**Y / N**
Do you have any implanted devices such as cardiac pacemakers, aneurysm clips, cochlear implants, shunt, stent?	**Y / N**
Have you ever had any other brain related condition, or illness that has caused brain injury?	**Y / N**
Are you taking or have you in the past taken any psychiatric or neuroactive medications (e.g. antidepressants)?	**Y / N**

Are you pregnant or could you possibly be pregnant?	**Y / N**
Have you ever been told that your blood pressure is specifically high or low?	**Y / N**
Do you have diabetes?	**Y / N**
Do you have arthritis?	**Y / N**
Do you or have you ever suffered from giddiness?	**Y / N**
Have you ever experienced loss of consciousness (i.e. syncope or fainting)?	**Y / N**
Have you ever had a concussion?	**Y / N**
Do you suffer from migraines, or frequent/severe headaches?	**Y / N**
Do you have haemophilia (a disorder impairing the body's ability to control blood clotting/coagulation)?	**Y / N**
Have you ever undergone electroconvulsive therapy (ECT)?	**Y / N**
Do you have any hearing problems or ringing in your ears?	**Y / N**

If you answered 'yes' to any of the above questions or have any other serious physical condition, please provide details below:

.....
.....
.....
.....
.....
.....
.....

IMMEDIATE HISTORY

To minimise the risk of TMS causing an adverse effect, it is important that you answer the following questions accurately before we begin the session.

In the last 12 hours, have you consumed more than 3 units of alcohol?
Y / N

In the last 12 hours, have you consumed any recreational drugs?
Y / N

Did you get a good night's sleep last night, and do you feel alert?
Y / N

In the last two hours, have you consumed more than 2 cups of coffee, or any other caffeinated drinks?
Y / N

Would you like to be provided with any further information regarding TMS?
Y / N

I have read and understood the questions above and have answered them correctly.

Signed…….. Date……

In the presence of …… (Name) …….(Signature)

Note: It is a formal requirement of the Human Research Ethics Committee (Tasmania) Network that the information provided on this questionnaire be

held securely to comply with confidentiality regulations and to protect your privacy. You can be assured that information will be available only to the principal researcher and not to any other party. The questionnaire will be destroyed following completion of the project.

HANDEDNESS INVENTORY

For each of the activities below, please tell us:

1. Which hand do you prefer for that activity?
2. Do you *ever* use the other hand for the activity?

	Preferred hand?		Ever use other hand?	
Writing	L	R	Y	N
Drawing	L	R	Y	N
Throwing	L	R	Y	N
Using scissors	L	R	Y	N
Using a toothbrush	L	R	Y	N
Using a knife (without fork)	L	R	Y	N
Using a spoon	L	R	Y	N
Using a broom (upper hand)	L	R	Y	N
Striking a match	L	R	Y	N
Opening a box (lid)	L	R	Y	N

Do you ever confuse left and right? ……..

How many people in your immediate family are left handed? ……

COLOUR-BLIND SCREENING

Please write your responses for the six images below (write the number that you see, or if you don't see a number, write 'no number')

Image 1:
Image 2:
Image 3:
Image 4:
Image 5:
Image 6:

THANK YOU FOR YOUR PARTICIPATION!

Appendix C: Information Sheet

INFORMATION SHEET

Brain connectivity during movement planning and execution in young and older adults

Chief Investigator: Dr Mark Hinder
Co-Investigators: Prof. Jeffery Summers, Dr Hakuei Fujiyama, Ms Sarah Kemp, Rohan Puri
Student investigators: Ms Abbey Lack

Background and Benefit

You are invited to voluntarily participate in a research project examining the role of particular brain areas during the preparation and execution of voluntary movements. The aim of this research is to improve our understanding of how healthy ageing affects how different brain areas are utilised during movement. The research will aim to improve interventions/strategies to enhance or maintain motor function in older age. This research is funded by a grant from the Australian Research Council.

The study will be conducted in the Human Motor Control Laboratory in the Psychology Research Centre at the University of Tasmania. You may be asked to participate in multiple sessions. If this is the case the investigator will inform you before you begin of the number of sessions involved. A single session will last approximately two hours and multiple sessions will be separated by at least 48 hours. Every effort will be made to schedule multiple sessions at mutually convenient times.

Study procedures

The following procedures will be used in this research: (a) recording of muscle activity (EMG), (b) transcranial magnetic stimulation (TMS), (c) voluntary movements of the hands/arms/legs.

(a) EMG: EMG is a technique to record the electrical activity of muscles both in response to TMS - see (b) - and during your movements – see (c). At the beginning of the experiment, small, self-adhesive recording electrodes will be affixed to the skin over the muscle of interest. Wires will be connected to the electrodes to allow the muscle activity to be recorded by a computer. To ensure the best possible recording, the skin will be prepared by scrubbing it with a mildly abrasive paste and then cleaning it with an alcohol wipe. If there is excessive hair on the skin (e.g., forearm muscles) a small area may be shaved using a disposable razor. This

procedure may produce some minor irritation of the skin (e.g., redness). The adhesives used on the electrodes are hypoallergenic.

(b) Transcranial Magnetic Stimulation (TMS): During the experiment activity of the brain areas involved in movement will be measured using a technique called Transcranial Magnetic Stimulation (TMS). TMS is a safe, painless and commonly used technique to study brain activity. It is used extensively by investigators in the Human Motor Control Laboratory. Electromagnetic 'pulses' will be delivered through one or two coils held against your scalp by the investigator. To ensure the coil/s is always positioned in the same place, a felt-tip pen will be used to mark the location/s on your scalp. This mark will be removed at the end of the session using an alcohol wipe. When the pulse is delivered you will hear an audible 'click' and muscles of the hand/arm will 'twitch'. You may also feel a 'tap' sensation on your scalp and muscles around the eye may twitch, causing the eye to blink. This may feel a bit strange but it is not painful.

(c) Voluntary movements: You will be asked to perform a certain type of voluntary movement tasks using your hands and arms and legs. Examples include rapid finger movements or tapping, force control tasks, pushing buttons is response to visual or auditory signals and coordination of both arms or hands (e.g. tapping both index fingers, flexing-extending your wrist). These tasks are not physically demanding, but they may be performed for up to one hour which may cause some minor muscle fatigue. To minimise this, frequent rest periods will be provided throughout the session. The experimenter will explain exactly what movements you are required to perform before you begin the session.

Inclusion and Exclusion criteria

Individuals (male and female) between the ages of 18 and 80 years of age are invited to participate in this research. Interested volunteers should have normal or corrected-to-normal vision, and have no known neuromuscular or neurological disorders, or recent injuries of the hands or arms.

TMS is a very safe technique; however there are certain conditions that will exclude some people from participating. These include:

- epilepsy, or a family history of epilepsy
- history of unexplained seizures (fits)
- serious head injury (e.g., concussion) requiring hospitalisation within the last three years
- implanted electronic devices such as pacemakers
- metal implants or metal fragments in the head (excluding dental work)
- history of migraines
- pregnancy

Please ask the experimenter if you are unsure of any of these.

Certain medications (for example some types of anti-depressant medications) can influence how the brain responds to sensory stimulation and voluntary movements.

Therefore, we ask that you inform the experimenter if you are taking any medication prior to participating in the study.

Risks and Discomforts
There are few risks associated with the procedures used in this study. The TMS pulse may cause muscles of the scalp to 'twitch' (e.g., can cause the eye to blink). This may feel 'odd', but is not painful. On rare occasions TMS can cause a 'muscle tension' type headache. If at any time you feel you have a headache, please let the experimenter know immediately. The electrodes that record muscle activity and TMS responses may cause some mild skin irritation and redness. You may experience some minor muscle fatigue as a result of performing voluntary movements. If your muscles become uncomfortable as a result of the movements, please inform the experimenter. In generally, if at any time you feel uncomfortable for any reason, please inform the experimenter and the procedures can immediately be stopped.

Payment
I understand that I will receive course credit for the total time that I am involved in the study, or will be eligible for a voucher to compensate me for time/travel costs.

Confidentiality and Anonymity
Your individual experimental data will be coded alpha-numerically and stored on a secure computer server that will be available only to the investigators via a password system. All future use of your data will be by the alpha-numeric code only to ensure anonymity. Your data will be retained securely at the University of Tasmania for at least five years. When it is no longer required by law, your data will be destroyed by the deletion of electronic files and shredding of documents.

Voluntary participation
Participation in the study is completely voluntary. If you agree to participate, you are free to withdraw from the study at any time without prejudice. If participation is for course-credit and you withdraw, you will receive credit for the time you have participated. If you withdraw from the study, any data that you have supplied can be identified through the alpha-numeric coding system and withdrawn from the study if you wish. You will be asked to sign an informed consent form to evidence your consent to participate in the study. Consent forms will be locked in a filing cabinet in the Human Motor Control Laboratory at the University of Tasmania and kept separately from your data.

Contact persons: If you wish to obtain more information, please contact one of the following researchers:
Dr. Mark Hinder (6226 2945 or Mark.Hinder@utas.edu.au)
Prof. Jeff Summers (6226 2884 or Jeff.Summers@utas.edu.au)

This study has been approved by the Tasmanian Social Sciences Human Research Ethics Committee. If you have concerns or complaints about the conduct of this study, please contact the Executive Officer of the HREC (Tasmania) Network on (03)

6226 7479 or email human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. Please quote ethics reference number H12358.

You will be provided with a copy of this information sheet and a statement of informed consent to keep. When finalised, results of the study will be posted on the University of Tasmania website, http://www.scieng.utas.edu.au/psychol/index.asp. It can be expected that results of individual studies will be available within a year of data collection.

Appendix D: Consent Form

School of Psychology

Informed Consent Form

1. I have read and understood the Information Sheet for this study.

2. I understand that this experimental session will lasting approximately 2 ½ hours and that I may have been asked to undertake multiple sessions.

3. I understand that transcranial magnetic stimulation *may* cause a little discomfort during stimulus delivery to the scalp.

4. I do not have a cardiac pacemaker, metal implants, or medical pumps in my body. I do not have any metal in my head such as shrapnel, surgical clips or fragments from welding. I do not suffer from seizures and there is no history of seizures in the members of my immediate family. I have not had neurosurgery and I have not had a head injury severe enough to require hospitalisation. I do not suffer from frequent or severe headaches. I do not have haemophilia.

5. I understand that I will receive course credit for the total time that I am involved in the study, or will be eligible for a voucher to compensate me for time/travel costs.

6. I understand that all research data will be securely stored on the University of Tasmania premises for a period of 5 years. Electronic data will be stored on a password protected computer. All data will be destroyed at the end of 5 years.

7. Any questions that I have asked have been answered to my satisfaction.

8. I agree that research data gathered for the study may be published provided that I cannot be identified as a subject.

9. I agree to participate in this investigation and understand that I may withdraw at any time without any effect. Following completion of the experiment, please contact a researcher if you wish to have your data withdrawn from the study for any reason. Data can be withdrawn at any time until submission of the manuscripts for publication (~ 6-12 months following completion of data collection).

Name of Participant:

_____

Signature of Participant: _____Date:_____

I have explained this project and the implications of participation in it to this participant, and I believe that the consent is informed and that he/she understands the implications of participation.

Name of Investigator:
_____

Signature of Investigator: _____Date:_____

Appendix E: Colour Blind Screening Stimuli

IMAGE 1: If you see a number in the image below, please write it down. If you do not see a number, write 'no number'.

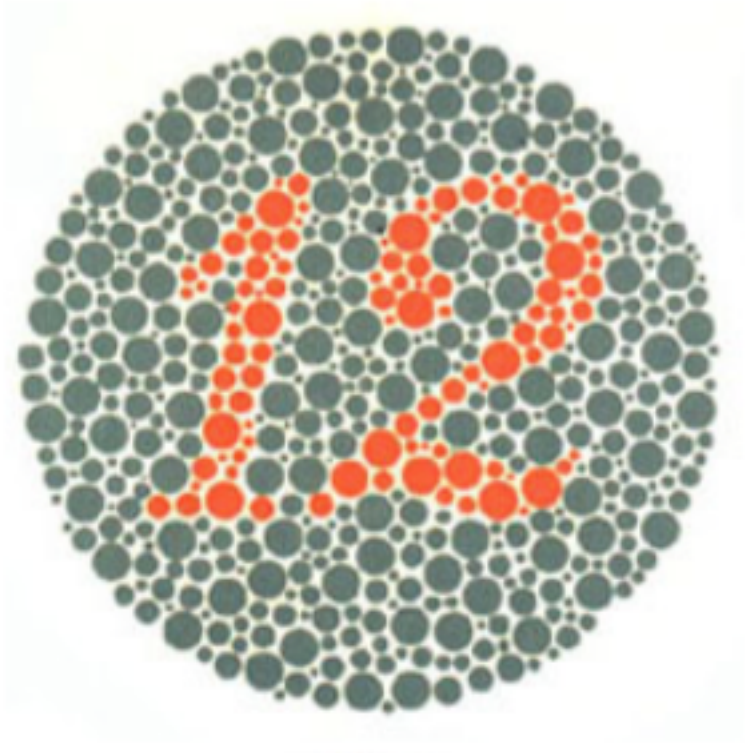

Plate 1: Demonstration plate. Everyone, even people with red-green colour deficiency, should be able to see the number 12.

IMAGE 2: If you see a number in the image below, please write it down. If you do not see a number, write ‘no number’.

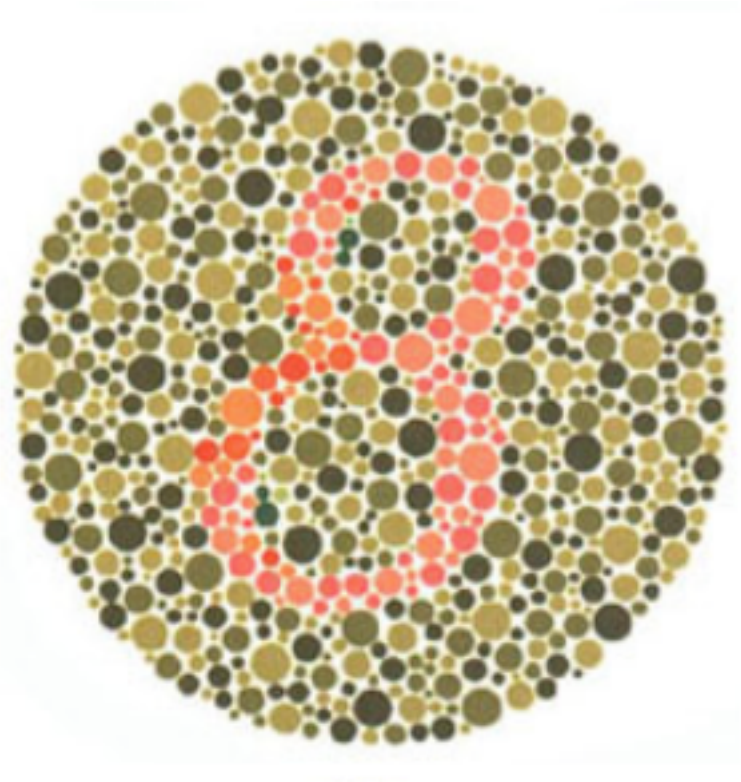

Plate 2:

Normal Vision: 8

Red-green deficiency: 3

IMAGE 3: If you see a number in the image below, please write it down. If you do not see a number, write ‘no number’.

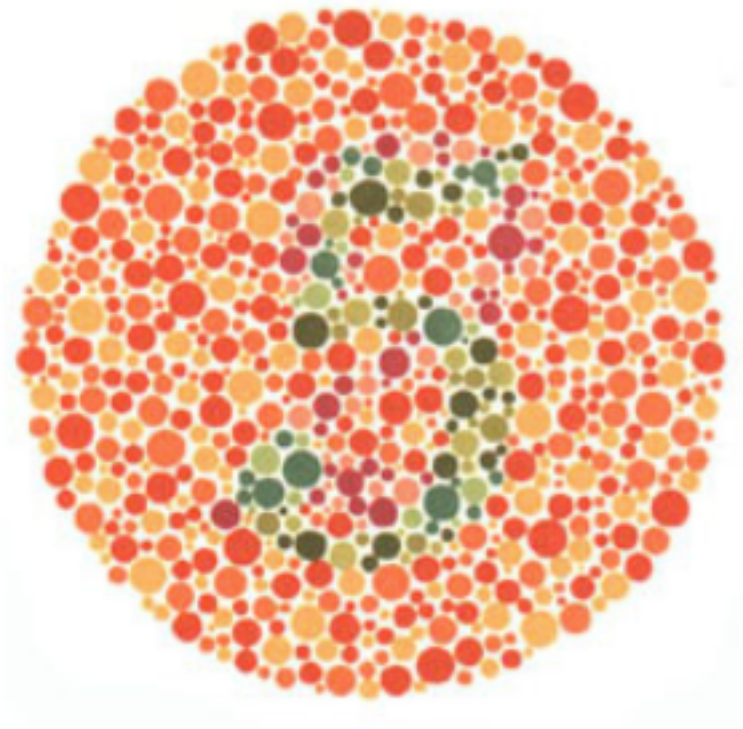

Plate 6:

Normal Vision: 5

Red green deficiency: 2

IMAGE 4: If you see a number in the image below, please write it down. If you do not see a number, write ‘no number’.

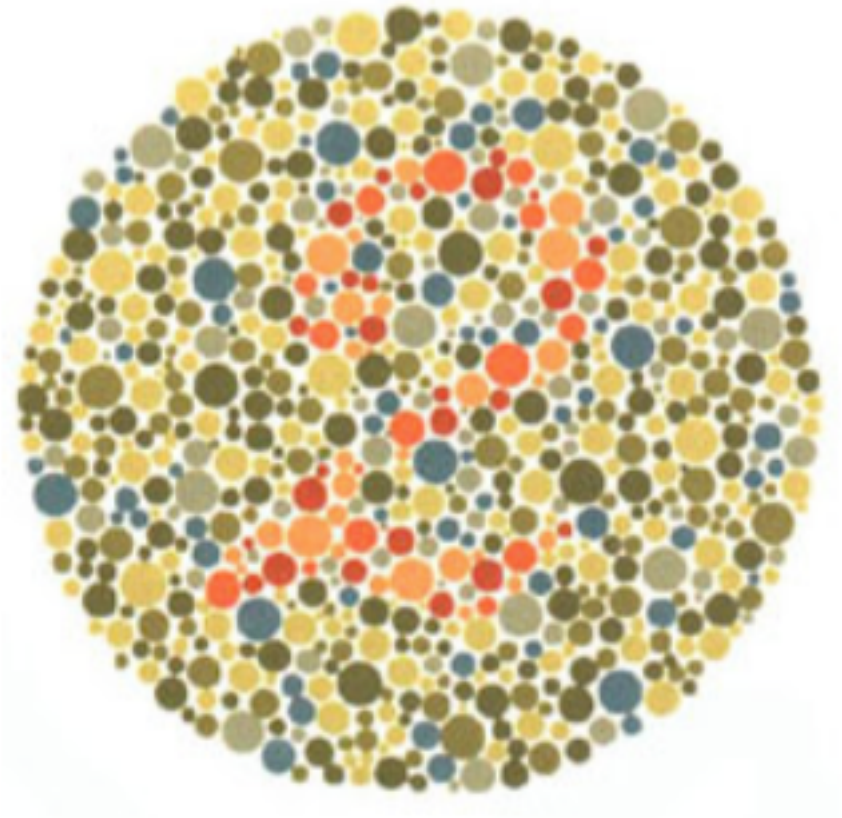

Plate 10:

Normal Vision: 2

Red green deficiency: Most people don’t see anything; or see something incorrect

IMAGE 5: If you see a number in the image below, please write it down. If you do not see a number, write ‘no number’.

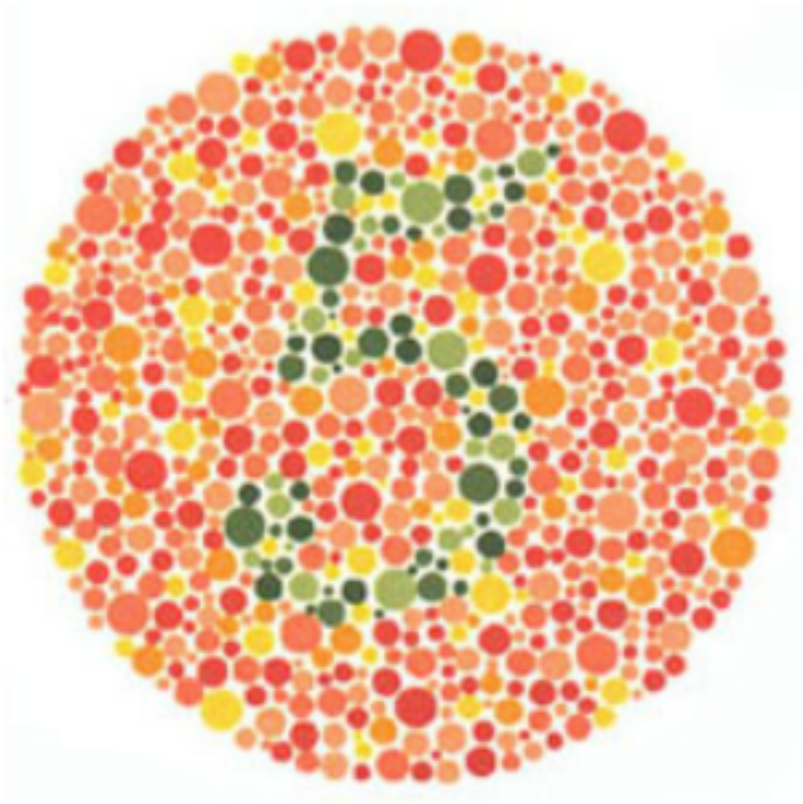

Plate 14:

Normal Vision: 5

Red green deficiency: Most people don’t see anything; or see something incorrect

IMAGE 6: If you see a number in the image below, please write it down. If you do not see a number, write ‘no number’.

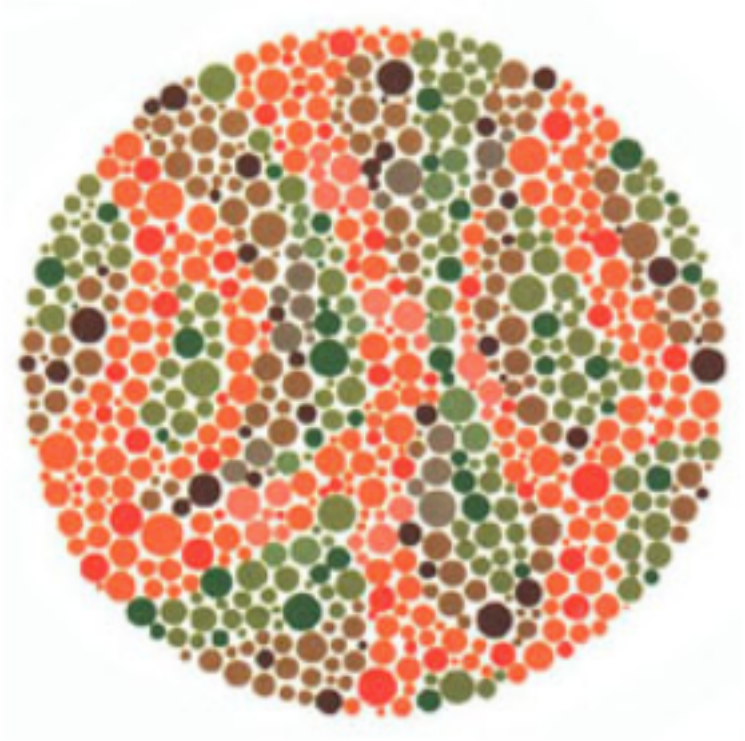

Plate 18:

Normal Vision: Nothing (no number)

Red green deficiency: 5