

**The relative contributions of different sensory afferent and corticocortical projections on
the motor cortex during skilled motor behaviour**

by

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A thesis

presented to the University of Waterloo

in fulfilment of the

thesis requirement for the degree of

Master of Science

in

Kinesiology

Waterloo, Ontario, Canada, 2024

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

The motor system is required to perform an endless number of movements. To do this, general motor plans are created for similar groups of movements that can be adjusted for specific iterations of each movement. To ensure that the motor plan is accurate to the specific iteration of the movement, sensory information from a variety of modalities is integrated into the plan via corticocortical connections to the motor cortex. Shorter sensorimotor loops will also project to various cortical areas involved in generating the motor plan to modulate this process with updated sensory afference. However, it is still unclear exactly how these circuits interact with each other during the planning and execution of skilled motor behaviour. The current study used two transcranial magnetic stimulation paradigms to investigate these interactions. Short-interval intracortical inhibition (SICI) probes the longer corticocortical loops, while short-latency afferent inhibition (SAI) probes the shorter sensory afferent circuits. Performing both techniques during a waveform tracking task involving a planning phase and movement execution phase, the current study could investigate interactions between corticocortical and sensory afferent projections during skilled motor behaviour.

Twenty-three healthy individuals completed two sessions where SICI and SAI were quantified in the first dorsal interosseous muscle during a waveform tracking task. SICI was assessed using an unbalanced transcranial magnetic stimulus that induced a posterior-anterior current in the underlying tissue with a positive phase lasting 70 μ s (PA_{70}). SAI was assessed using a stimulus that induced a posterior-anterior current in the underlying tissue with a positive phase lasting 120 μ s (PA_{120}) or a stimulus that induced an anterior-posterior current in the underlying tissue with a positive phase lasting 30 μ s (AP_{30}). TMS stimuli were delivered at seven different time points during the task: one baseline time point where the waveform was hidden

from participants, two planning time points (-0.5s and -0.25s from movement onset), a time point at the onset of the movement, and three time points during the movement (1s, 2s, 3s after movement onset). Results showed that the effect of the conditioning stimulus was stronger for SICI than SAI across each of the time points during the task. We also found that the magnitude of difference in the weighting of SICI and SAI changed across the time point.

These findings suggest that a variety of sensorimotor loops converge on the corticospinal neuron in the primary motor cortex to shape motor output. The corticocortical connections probed by SICI play a dominant role consistent with setting the initial motor plan. In contrast, the sensory afferent projections probed by SAI play a modulatory role updating the initial plan to reflect current sensory states and providing feedback. The interactions between corticocortical and sensory afferent circuits are important for healthy motor control and explain how the motor system is able to perform a seemingly endless number of movements.

Acknowledgements

I would like to start by thanking my supervisor, Dr. Sean Meehan for his continued support towards my education, and for fostering my interest and passion in my work. I especially appreciate the many hours he put into meeting, discussing, and helping me develop this thesis, without which I could not have accomplished this milestone.

Thank you to Dr. Richard Staines and Dr. Ewa Niechwiej-Szwedo for serving on my committee. Their feedback was invaluable for developing my thesis, and the unique perspectives they gave me during this process were greatly appreciated.

Thank you to all of the current and past members of the SCiLL and SINAPs labs for their help and support with collections, practice presentations, and discussions. I would like to give a special thanks to Kara Hayes and Madison Khan for being incredible role models and dear friends.

Finally, I would like to thank my family and friends, especially my parents, Rick and Andrea, and siblings, Jill and Daniel for their unwavering support throughout this process. I could not have completed this thesis without them.

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List of Abbreviations

AP: Anterior-posterior
cTMS: Controllable pulse parameter TMS
D-wave: Direct wave
EEG: Electroencephalography
FDI: First dorsal interosseous
GABA: Gamma-aminobutyric acid
ISI: Interstimulus interval
I-wave: Indirect wave
M1: Motor cortex
MEP: Motor-evoked potential
MVC: Maximal voluntary contraction
PA: Posterior-anterior
PFC: Prefrontal cortex
PMC: Premotor cortex
PMd: dorsal premotor cortex
PMP: Premotor potential
PPC: Posterior parietal cortex
S1: Primary somatosensory cortex
S2: Secondary somatosensory cortex
SAI: Short-latency afferent inhibition
SICI: Short-interval intracortical inhibition
SSRT: Stop signal reaction time
SST: Stop signal task
TMS: Transcranial magnetic stimulation

1.0 Introduction

Skilled motor behaviour involves the coordination of many different cortical functions and the integration of various bits of information from the body and environment. The motor system stores a general plan for similar types of movements, called a generalized motor program (Schmidt, 1975, 2003). The initial plan is created based on movement goals. Information about the environment and current body state can then be used to shape the generic motor plan for different iterations of the movement (Schmidt, 1975, 2003). To integrate information about the movement requirements into the motor plan, sensory information from the periphery converges on to the motor cortex (M1) via sensory afference. This afference is used to shape the motor commands sent to effectors. The influence of sensory afference on motor output is determined by how sensory information is prioritized by the motor system (Sober & Sabes, 2003). The cortical regions involved in motor planning, such as the premotor cortex and supplementary motor area play a role in the reweighting of sensory information depending on the task being performed (Jack et al., 2021). Although research has shown sensorimotor and cortical pathways are both involved in the planning and execution of movement, it is still unclear exactly how they interact with each other to perform these functions.

Motor performance can be broken down into two phases: planning and execution. Distinct neural circuits may have dynamic influences over these phases at various stages. The planning phase involves generating the initial motor plan and incorporating information about the current body state, then modifying the initial motor command for the specific iteration of the movement and facilitating movement (Schmidt, 1975, 2003). Electroencephalography (EEG) recorded during visually guided and self generated movements show early and late components of negative activity that correspond to these processes (Smith & Staines, 2012). The early

component, beginning approximately two seconds prior to movement onset, reflects the integration of body state information into the general motor plan to generate the specific motor commands used during movement (Miall & Wolpert, 1996). The late component begins approximately 500ms before movement onset and reflects activity in M1 associated with the conscious will to move (Shibasaki & Hallett, 2006). Following this, a positive deflection called the re-afferent potential, uses sensory feedback to the somatosensory cortex (S1) to modify the initial motor command and facilitate the execution of movement (Ibanez et al., 2012). During this period of activity, there is an abrupt positive deflection just prior to movement onset called the premotor potential (PMP) that may be involved in the initiation of the movement (Bortoletto et al., 2006).

During execution of the movement, the motor system must monitor performance and overcome noise from the environment. To do this, the sensory consequences of the motor plan are predicted based on current sensory afference (Miall & Wolpert, 1996). The actual sensory feedback received during the movement is compared to this sensory prediction to determine if any errors are occurring. Sensory afference that does not match the sensory prediction is sent back to the motor system, allowing for rapid adjustment of the motor command (Sokolov et al., 2017). Errors detected during the movement can also be used to train the motor system to better predict sensory consequences of movement in the future (Wolpert et al., 1998). Planning and execution of movement involves the coordination of many different neural pathways. The specific circuits involved in the different phases of motor control and the way they interact with each other is still unclear, but they can be investigated using transcranial magnetic stimulation (TMS).

Distinct cortical and sensorimotor circuits are involved in different aspects of motor control and converge onto M1 to shape motor output (Bizzi & Ajemian, 2020). These loops help determine which actions to take, and how to move to perform these actions. The prefrontal cortex (PFC) selects relevant and suppresses irrelevant stimuli from the different sensory systems in the body (Barbas & Zikopoulos, 2010). These selections can then be used to guide behaviour and allow the PFC to choose the appropriate motor actions for a specific situation (Ridderinkhof et al., 2004). Sensory information is also used by the posterior parietal cortex (PPC) to determine spatial information, and the control of movements required to interact with the environment (Buneo & Andersen, 2006). Both of these regions will then send projections to the premotor cortex (PMC) to generate the motor plan, creating long sensorimotor loops that shape behaviour (Bizzi & Ajemian, 2020). These longer corticocortical loops do not act in isolation though. Shorter sensorimotor loops use cortical projections to monitor and modulate the behaviour of muscles (Weiler et al., 2015). These shorter sensorimotor circuits are modulated during goal-directed tasks to coordinate activity across multiple effectors and support goal-directed actions (Weiler et al., 2015). The coordination of long and short sensorimotor circuits is crucial for planning and coordinating motor behaviour.

The contributions of different sensorimotor circuits can be investigated using TMS. Two phenomena that probe these circuits are short interval intracortical inhibition (SICI) and short-latency afferent inhibition (SAI), which are both paired-pulse paradigms using TMS. SICI involves preceding a reference TMS pulse with a subthreshold conditioning TMS pulse, which can probe inhibitory cortical circuits involved in generating motor output (Kujirai et al., 1993). SAI instead precedes the reference TMS pulse with peripheral electrical stimulation, which allows for the investigation of sensory afference during motor control (Tokimura et al., 2000).

Although both circuits are distinct, with SICI acting at the level of the cortex alone and SAI using sensory afference from the periphery, both circuits have inhibitory action on motor evoked potentials (MEPs) elicited by the reference TMS pulse. There is also evidence to suggest that the two circuits interact with each other at rest (Alle et al., 2009; Udupa et al., 2014). However, there is still much to be learned about the interactions between corticocortical projections and sensory afference and the implications that these interactions have on skilled motor behaviour.

The recent introduction of controllable pulse parameter transcranial magnetic stimulation (cTMS) stimulators has opened the door to further tease apart the functional significance of cortical and sensorimotor circuits. Research showing an interaction between SICI and SAI has exclusively used conventional TMS stimulators where intensity is the sole variable and all other stimulus parameters are fixed (Alle et al., 2009; Udupa et al., 2014). However, the effect that a TMS stimulus has on the motor cortex and the resulting motor output is dependent on the intensity of the pulse as well as other parameters such as the direction of the induced current (Hallett, 2007; Ni et al., 2011), and the shape or width of the TMS pulse (D'Ostilio et al., 2016; Hannah & Rothwell, 2017). The conventional TMS stimulators used in previous research have a fixed pulse width of $\sim 82 \mu\text{s}$, and these studies have exclusively used a posterior-anterior (PA) induced current (Alle et al., 2009; Udupa et al., 2014). Manipulating the induced current direction and the pulse width of the TMS can preferentially target cells in different cortical layers (Casula et al., 2018), and target functionally distinct neural circuits that respond uniquely to different tasks (Voller et al., 2006; Asmussen et al., 2014; D'Ostilio et al., 2016; Hannah & Rothwell, 2017; Mirdamadi et al., 2017). Therefore, manipulating the current configuration (e.g. different combinations of stimulus parameters) using cTMS can provide critical information about how different sensorimotor and cortical circuits interact to shape motor output and

behaviour. Investigating the interactions between SICI and SAI with different TMS parameters is critical for understanding how interactions between these circuits relate to skilled motor behaviour.

This study took advantage of cTMS to investigate the role of unique cortical and afferent projections to the motor cortex during different phases of skilled movement. Specifically, SICI and SAI in the first dorsal interosseous (FDI) muscle motor representation were used to determine the relative contributions of cortical and afferent projections across movement planning and execution. By varying the current parameters of the TMS pulses implemented, it was possible to investigate the role of functionally unique circuits and their interactions to the different phases of planning and performing a movement. Learning about these interactions is important for understanding healthy motor behaviour, which can be used as a basis for future research in clinical populations.

1.1 Sensorimotor Loops

Motor control requires the coordination of many different cortical regions and effectors to plan and generate movements. Different aspects of motor control are determined by a variety of sensorimotor loops that converge on M1 to shape motor output (Bizzi & Ajemian, 2020). These circuits help determine which actions to take, as well as how to perform these actions. The sensory systems throughout the body provide information about the environment and the current body state to help prepare the motor plan. The PFC is an important brain region for these processes. The PFC selects relevant stimuli while suppressing irrelevant stimuli from the different sensory modalities to shape motor behaviour (Barbas & Zikopoulos, 2010). In motor planning, the PFC is largely responsible for the decision to act, as well as choosing the appropriate actions for a specific situation (Ridderinkhof et al., 2004). The PFC encodes

associations between task rules and stimulus responses, which can be drawn upon to determine the correct actions based on goals of the task (Ridderinkhof et al., 2004). Another necessary piece for planning movements is determining how to control the body. The PPC contains a dynamic representation of the body and maps representations of body position and target position (Buneo & Andersen, 2006). This body representation is necessary for planning important kinematics for movement (Delhay et al., 2018). Both the PFC and PPC are part of pathways converging on the PMC where the information they encode can be pieced together to form a motor plan (Bizzi & Ajemian, 2020). These cortical circuits cannot act in isolation though, as sensory information about the body and environment is required to create a situation-specific motor plan.

Multiple afferent loops will converge in the cortex to provide different pieces of sensory information about the body. Long-latency stretch reflexes are one way to investigate the pathways of proprioceptive information about the body. Muscles respond to a stretch with multiple bursts of activity. The early, short-latency response occurs at the level of the spinal cord, however there is a later component that is at least partially mediated by the cortex (Shemmell et al., 2010). These afferent pathways play an important role during the preparatory phase of movement. Prior to voluntary movement, when maintaining a contraction in the target muscle, the long latency response to stretch will increase as movement approaches (Hallett et al., 1981). On the other hand, no long-latency response occurs before movement onset when the muscle is at rest (Hallett et al., 1981). These sensorimotor loops are also sensitive to task demands and movement decision-making processes (Weiler et al., 2015). This allows for the modulation of these circuits to coordinate activity across multiple effectors, which can support goal-directed behaviour (Weiler et al., 2015). Interactions between the longer sensorimotor loops

that generate the motor plan, and the shorter sensorimotor loops that modulate the motor system to support these processes are necessary for effective motor control. Further investigations into the interactions of corticocortical and sensorimotor circuits will provide more insight into their functional roles.

1.2 Generalized Motor Programs

The motor system has endless possibilities of actions that it can perform, and there are an infinite number of iterations of these actions (Schmidt, 1975, 2003). For example, when performing a tennis forehand, the general movement pattern will stay the same across different iterations. The movement when hitting a ball coming in higher or faster will share a resemblance to a forehand used to hit a ball coming in lower or slower. However, each iteration of the tennis forehand will be variable in the specific motor output (e.g. specific height or speed) used to perform the action (Faisal et al., 2009). These variations are necessary to complete the movement when there are different situational requirements. To account for all of the different variations needed to perform skills in different environments, the motor system uses a set of pre-generated plans called generalized motor programs (Schmidt, 2003). If every single variation of a movement pattern required a separate motor program, the central nervous system would not be capable of storing every iteration, creating a storage problem. Instead, the motor system stores a general plan for similar movements (Schmidt, 1975, 2003). The motor plan is recalled from memory and can then be adapted for each specific iteration of a skill. Generalized motor plans are made up of invariant features, surface features, and motor schemas (Schmidt, 1975, 2003).

As the name implies, invariant features are the same across all iterations of the same class of movements (Schmidt, 2003). In the example of the tennis forehand, the invariant features would include the kinematics like relative joint angles and the muscles involved to create the

swinging motion with the racquet. The sequence of movements required to perform the skill would also be part of the invariant features. Different cortical regions that project to M1 are critical during this stage for creating the initial plan. During visually guided movements, EEG activity shows that the early component of motor planning is generated primarily in the lateral premotor cortex (Smith & Staines, 2012). The kinematics required for the skill would be generated in the premotor cortex. Self-generated movements show early component activity primarily in the supplementary motor area (Smith & Staines, 2012). This area is involved in the planning and control of sequential motor actions (Ohbayashi, 2021). The sequence of movements would be generated in the supplementary motor area. Once all of the invariant features of the motor plan have been determined, the surface features can then be integrated into the motor plan.

Surface features are the parameters of the motor plan that will vary depending on the environment and body state (Schmidt, 2003). In the tennis example, the surface features would include the speed and height of the swing required to hit the ball. The surface features are generated by exteroceptive and proprioceptive afferent signals to the central nervous system. The PPC is primarily involved in determining the surface features of the movement. The PPC's functional architecture is suited for its role in extracting surface features, as several functional subdivisions around the intraparietal sulcus are critical in converting visual reference frames into the body and effector-centered reference frames needed for motor control (Cohen & Andersen, 2002). Therefore, it is not surprising that the PPC dominates over the preparatory delay period when planning movements (Lindner et al., 2010). The PPC projects the transformed representations to other cortical areas, such as PMC (Gharbawie et al., 2011) where the sensory states are used to inform the initial plan. Adjustments are made to the initial general motor plan in this area to include the different surface features for different iterations of the skill. After the

surface features have been determined, they can be tied together with the invariant features by motor schemas.

Motor schemas are a set of rules used to relate the invariant and surface features of the motor plan (Schmidt, 2003). In the tennis forehand example, sensory cues like ball speed dictate the specific changes that need to be made to the motor plan to hit the ball. In essence, if the ball is travelling at a certain speed, the speed at which the motor plan is executed needs to be increased by a proportional amount to hit the ball. The neural basis of schemas is not clear. Schemas likely arise through the experiential reinforcement and revision of parietal to premotor connectivity (Kitago and Krakauer, 2013). Regardless of the exact neural locus of schema, it is clear that sensory afference plays a key role at many stages in the skilled motor control process.

1.3 Sensory Afference

The sensory system monitors and relays information about the body and environment to the cortex through both longer sensorimotor loops and shorter modulatory loops. This information is critical for determining the surface features needed for the generalized motor command. The visual system provides important context about the environment the action will be performed in. Visual information is processed by the visual system to extract information from the environment and objects in it, such as orientation, direction of motion, depth, form, colour and shape (Livingstone & Hubel, 1988). Visual signals are processed via two parallel streams, the ventral and dorsal pathways. The ventral stream, or “what” pathway is responsible for object recognition (Cloutman, 2013). The dorsal stream, or “where” pathway is responsible for spatial information and control of movements for interacting with objects in the visual field (Cloutman, 2013). The dorsal pathway projects to the posterior parietal lobe to provide visual information to the reference frame mapped in the PPC (Cloutman, 2013). Both streams interact with each other

to provide information to the motor system about the environment, which can be integrated with other sensory information to form the motor plan.

Information about body state is also necessary for generating motor commands. The current state of the body dictates the surface features needed to complete the movement. The proprioceptive system provides this information. Specialized cells relay signals about muscle length, muscle force, and skin stretch to S1. S1 projects to the secondary somatosensory cortex (S2) which will send information across two streams, the ventral and dorsal streams. The ventral stream projects to the PPC and insula and uses haptic and tactile information for object recognition (Sedda & Scarpina, 2012). The dorsal stream projects to the PPC and contains a dynamic representation of the body that can be used to plan exploratory hand movements (Sedda & Scarpina, 2012, Delhay et al., 2018). Brodmann area 7, which is located in the PPC, receives both visual and somatosensory input (Andersen et al., 1997). The integration of these sensory modalities allows the PPC to form a multimodal representation of space, which is critical for visually guided movements (Andersen et al., 1997) This sensory system provides the surface features of the general motor plan, such as initial state of the body, to ensure the appropriateness of the generated motor command.

1.4 Feedforward and Feedback Control

The motor system predicts the consequences of the generated motor command based on current sensory input using a form of internal modelling called the forward model. This model emulates normal behaviour, using current sensory afference and the motor command as inputs to generate the expected sensory afference at the end of the movement (Miall & Wolpert, 1996). The cerebellum plays an important role in the creation of the sensory prediction. The cerebellum receives a copy of the motor command, and in conjunction with afferent input, creates the

expected sensory consequences of the movement (Sokolov et al., 2017). Once the motor commands are executed, noise in the environment can create movement errors. To overcome this, the sensory predictions of the movement and the actual sensory consequences are compared (Faisal et al., 2008). Any signals that match can be suppressed (Sokolov et al., 2017). Sensory signals that don't match are sent back to the motor system allowing for rapid adjustment of the motor command (Sokolov et al., 2017). These errors are also used to train the internal model, allowing for better predictions in the future (Wolpert et al., 1998). The importance of the cerebellum in this process is highlighted by clinical research, where cerebellar dysfunction has been shown to cause the loss of sensorimotor coordination (Sokolov et al., 2017). As the motor system improves motor commands, muscles are grouped together into muscle synergies to allow for more coordinated movement. The recruitment of muscle synergies is dictated by functionally distinct sensorimotor and cortical circuits (Bizzi & Ajeman, 2020). Fronto-parietal loops, which involve connections between the dorsal premotor cortex (PMd) and parietal cortex integrate sensorimotor information such as gaze direction and limb proprioception and is also a circuit involved in the selection of alternative actions (Bizzi & Ajemian, 2020). Cortico-striatal loops group sub movements together into functional movement chunks (Bizzi & Ajemian, 2020). The cortico-cerebellar loops are important for the temporal patterning of muscle recruitment (Bizzi & Ajemian, 2020). All of these loops converge to shape motor output. The PMd and M1 are points of convergence for different cortical and sensorimotor circuits, and the inputs they receive allow them to modify motor control (Bizzi & Ajemian, 2020). TMS can be used to probe the neural circuits that recruit these groups of muscles.

1.5 Transcranial Magnetic Stimulation

TMS is a non-invasive method of brain stimulation that can be used to probe cortical excitability. An electrical current is passed through a magnetic coil to induce a brief, high-current pulse. An electric field is induced in the cortex perpendicularly to the magnetic field, which depolarizes neurons in the cortex and can generate an action potential (Hallett, 2007). When corticospinal neurons are excited, descending volleys of activity are generated. These volleys are called direct (D) and indirect (I) waves. Directly stimulating corticospinal neurons produces D waves, however TMS does not directly stimulate these neurons. Instead TMS excites corticospinal neurons through a series of interneurons, which produces I waves (Hallett, 2007). I waves occur in intervals of ~1.5 ms following D waves (Ziemann, 2020). This latency corresponds to the latency of activity at a single synapse and the increase of latencies with successive I waves reflects an increasing number of synapses (Ziemann, 2020). Targeting different populations of neurons by varying the types of TMS pulses used can produce different I waves (Day et al., 1989). By targeting I waves rather than D waves, TMS can be used to probe the convergence of many different transsynaptic inputs. Modifying the TMS parameters used can target specific groups of interneurons converging on the corticospinal neuron.

Manipulating the current parameters of TMS allows for the recruitment of different groups of interneurons. The two main current directions used in TMS studies are PA and AP. PA current produces larger MEPs, with AP current requiring higher stimulus intensities to produce the same amplitude MEPs (Hallett, 2007; Hannah & Rothwell, 2017). PA induced current also produces MEPs with earlier latencies than AP (Ni et al., 2011; Hannah & Rothwell, 2017). Inducing a PA current with TMS will recruit early I1-waves, while AP will preferentially recruit later I3-waves, leading to the discrepancy in MEP latency (Day et al., 1989; Di Lazzaro et al., 2012). The

differential activation of the corticospinal tracts by PA and AP currents could be related to cells in the pre- and post-central gyrus that are sensitive to orientation (Di Lazzaro et al., 2012). PA current seems to be biased toward neurons in the anterior bank of the central sulcus, while AP is likely biased towards rostral M1 or pre-motor neurons (Aberra et al., 2020). Recent advances in technology have allowed for further investigation of neural circuits probed by TMS via pulse duration.

Manipulating the duration, or pulse width of TMS stimuli can better isolate specific cortical or sensorimotor circuits. Conventional stimulators typically employ a pulse width of $\sim 70\text{-}82\ \mu\text{s}$. With controllable pulse parameter TMS, it is possible to vary pulse duration. Current durations of $120\ \mu\text{s}$ and $30\ \mu\text{s}$ have been shown to recruit distinct neural circuits (D'Ostilio et al., 2016; Hannah & Rothwell, 2017). Traditional TMS may recruit a mixture of these circuits. Pulse widths of longer latency are associated with a higher local mean field power, which suggests that they recruit more GABA_A-ergic interneurons (Casula et al., 2018). The $\sim 70\text{-}82\ \mu\text{s}$ durations of conventional stimulators may recruit other populations of neurons whose strength-duration behaviour does not scale with the excitatory neurons they are targeting (Casula et al., 2018). Manipulating pulse width can alter the proportion of early and late synaptic inputs targeted by the TMS, shown by differences in onset latencies of MEPs evoked by PA and AP current directions (Casula et al., 2018). This makes pulse width a useful tool to target a variety of neural circuits. Although these differing neural circuits have been investigated, their functional significance is still a developing area of research.

The different properties of the circuits recruited by different pulse configurations suggests that they may have unique functional purposes. PA $120\ \mu\text{s}$ (PA₁₂₀) and PA $30\ \mu\text{s}$ (PA₃₀) demonstrated similar recruitment patterns, producing MEPs of nearly identical latency and

amplitude (Hannah & Rothwell, 2017) In contrast, AP 120 μ s (AP₁₂₀) and AP 30 μ s (AP₃₀) showed decreased MEP amplitude and AP₃₀ had the longest MEP latencies of all four current configurations (D'Ostilio et al., 2016; Hannah & Rothwell, 2017). Furthermore, Hannah & Rothwell (2017) found with cerebellar transcranial direct stimulation that SAI was reduced for AP₃₀ only. These findings suggest that the cerebellum plays a role in the neural circuits probed by AP₃₀ stimuli. Considering the role that the cerebellum plays in motor control through forward modelling and feedback control, it may be possible to gain more insight into these processes using AP₃₀ TMS pulses. Further insight into the function of other circuits probed by PA current directions may also be possible by relating them to the different phases of motor control. With TMS, there are two techniques that were useful for investigating the contribution of these circuits: SICI and SAI.

1.6 Short-Interval Intracortical Inhibition (SICI)

SICI is a common TMS technique involving the conditioning of a reference TMS pulse. By preceding the reference pulse with a subthreshold TMS pulse, changes in MEP amplitude can be measured and compared to the unconditioned MEPs. When the conditioning stimulus is delivered 2ms prior to the reference pulse, the resulting MEP is inhibited (Kujirai et al., 1993). Pharmacological studies highlight that the SICI pathways are mediated by GABA. Zolpidem, diazepam and lorazepam are all GABA_A modulators that have an affinity for different GABA_A receptor subunits. Zolpidem has a high affinity for α -1 subunits, whereas diazepam and lorazepam do not, suggesting that they instead act through α -2 or 3 subunits (Di Lazzaro et al., 2007). SICI is enhanced by diazepam and lorazepam, but not affected by zolpidem, suggesting it is mediated through α -2 or 3 subunits, not α -1 (Di Lazzaro et al., 2007). This inhibition via GABA acts through corticocortical projections. By measuring corticospinal volleys, it has been

shown that the conditioning stimulus inhibits the descending activity evoked by the test stimulus without producing descending activity of its own (Di Lazzaro et al., 1998). This would suggest that the inhibition is occurring at the level of the cortex, making SICI an ideal measure to probe corticocortical connections involved in generating the initial motor plan, such as those from the PMC and SMA.

Previous research using SICI as a measure of cortical excitability provides some insight into its role in motor control and movement planning. During single pulse TMS studies, cortical excitability for the agonist muscle is increased just before movement onset (Chen & Hallett, 2014). SICI also decreases just prior to movement onset but following a different time course than excitatory circuits (Floeter & Rothwell, 1999). Inhibitory SICI circuits have not yet been examined across other phases of movement. SICI likely captures the end result of sensory information during initial motor planning, through cortical connections between areas such as PPC and PMC (Bizzi & Ajemian, 2020). However, it is unclear if the influence of these circuits changes during the course of movement planning and execution as a function of other pieces of information like sensory afference and re-afference. Other TMS techniques may provide insight into the role of sensory afference in these interactions.

1.7 Short-Latency Afferent Inhibition (SAI)

SAI is another technique involving the conditioning of a reference TMS pulse. Unlike SICI, it instead uses peripheral stimulation as a conditioning stimulus. By preceding the TMS pulse by electrical stimulation to a peripheral nerve corresponding to the target muscle, the resulting MEP will be inhibited (Tokimura et al., 2000). The descending volley from the TMS is timed to converge with the afferent volley elicited by the peripheral stimulus. For distal hand muscles, an interstimulus interval (ISI) of ~20 ms shows peak inhibition of the MEP (Tokimura

et al., 2000). Pharmacological studies also provide support for the functional differences between SICI and SAI. Both pathways are mediated by GABA, however they respond differently to various GABA_A modulators (Di Lazzaro et al., 2005, 2007). SAI is reduced by zolpidem and lorazepam, but not affected by diazepam, suggesting it is likely mediated through α -1 subunits (Di Lazzaro et al., 2007). In addition to these differences, SAI is also mediated by acetylcholine shown through its reduction by scopolamine, a muscarinic antagonist (Di Lazzaro et al., 2000). Acetylcholine is important for the modulation of circuits involved with attention, cue detection, and memory (Picciotto et al., 2012). The mediation of SAI via acetylcholine may be a way for SAI to modulate sensory projections to M1 based on attention.

The influence of attention on SAI is also specific to the sensorimotor circuits being probed by different current configurations. Visual tasks that require greater attentional load reduce AP SAI but not PA SAI, which is likely driven by reduced processing of sensory afference (Mirdamadi et al., 2017). PA SAI on the other hand is highly involved in surround inhibition. PA SAI is reduced during the preparatory phase of movement, inhibiting the muscles not involved in the movement (Voller et al., 2006; Assmussen et al., 2014). The dorsal stream activity during this phase could suggest that PA SAI is critical for monitoring the generation of the motor plan and ensuring it is accurate based on initial body state. AP₃₀ circuits are more sensitive to muscle contraction, showing increased SAI compared to other current configurations (Hannah & Rothwell, 2017). This could suggest that AP₃₀ circuits may be critical for integrating sensory afference during changes in muscle activity, as seen during movement. Investigating SAI responses during different phases of movement could shed more light on the differences between PA and AP SAI and their contributions to motor planning and execution. Since SAI uses a

peripheral conditioning stimulus, it is also the ideal technique to probe the role of sensory afference in generating motor output.

By using both SICI and SAI to investigate the role of sensorimotor and cortical projections to M1 during the planning and execution of movement, we aimed to shed light on the processes required for producing skilled motor behaviour. This study also added to our understanding of the variety of neural networks recruited by TMS, as this was the first study to assess SICI using cTMS to manipulate pulse width. The results of this study will add to the literature investigating the role of these circuits in healthy behaviour.

1.8 Eliciting SICI with cTMS

Previous research has investigated interactions between SICI and SAI, but the conclusions to be drawn from these studies are limited. Alle et al. (2009) and Udupa et al. (2014) both used a triple pulse paradigm to explore the interactions between SICI and SAI pathways. Both studies found that SICI correlated with SICI in the presence of SAI, but SAI did not correlate with SAI in the presence of SICI, suggesting that SICI dominates over this interaction (Alle et al., 2009; Udupa et al., 2014). This provides evidence for the modulatory role of short sensorimotor loops that can be probed with SAI (Weiler et al., 2015). Although these findings provide some insight, there is still critical information missing. Both studies were performed with only PA current directions using fixed pulse widths of $\sim 82 \mu\text{s}$ (Alle et al., 2009; Udupa et al., 2014). The fixed parameters using in these studies, paired with the fact that neither group investigated these interactions during a behavioural task, means that the functional role of the interactions has not been determined.

Controllable pulse parameter TMS allows for the manipulation of TMS parameters to target unique neural populations (D'Ostilio et al., 2016). This is important for teasing apart the functional properties of afferent and cortical projections to M1. It was critical when addressing the aims of this study that we were able to probe these unique circuits, rather than the mixture of circuits targeted by conventional TMS stimulus parameters. However, differences in the way conventional and cTMS stimulators manage energy to produce a TMS pulse affected how we were able to elicit SICI. SICI requires two TMS pulses to be delivered in rapid succession (Kujirai et al., 1993). With cTMS, paired pulses must be balanced using the stimulator's onboard software. In order to effectively manage this energy transfer in the 2ms ISI used during SICI, the cTMS stimulator requires a fixed intensity between the two stimuli. A way to overcome this issue is by manipulating the width of the TMS pulse.

Shirota et al. (2016) showed that it was possible to manipulate the strength of the TMS pulse via pulse width as well. By reducing the duration of the TMS pulse, the strength of the induced current was also reduced. This allowed for the indirect manipulation of intensity to produce a subthreshold conditioning stimulus. Using this protocol, it is possible to produce SICI-like inhibition, shown through recruitment curves with a similar pattern of inhibition to traditional SICI (Shirota et al., 2016). However, it is still unclear whether this inhibition acts through the same mechanisms as traditional SICI, or through different, but similar pathways. No pharmacological studies have been performed using this SICI-like inhibition, so it is still unclear whether they target the same inhibitory neurotransmitters. However, the findings of Shirota et al. (2016) along with results of the current study provide support for this protocol as a way to investigate corticocortical circuits.

2.0 Aims & Hypotheses

This study aimed to investigate the role of cortical and afferent projections to the motor cortex during different phases of skilled movement. Specifically, we looked at the relative contributions of corticocortical and sensory afferent circuits during early and late motor planning, as well as movement execution.

Aim 1: Investigate corticocortical integration using SICI during motor planning and execution while participants perform a waveform tracking task.

Hypothesis 1: PA SICI's influence will be stronger over the late planning phase of the movement and decrease during movement execution.

Aim 2: Investigate sensorimotor integration using SAI during motor planning and execution while participants perform a waveform tracking task.

Hypothesis 2A: PA SAI will be stronger over the early planning phase of the movement and decrease during movement execution.

Hypothesis 2B: AP SAI will be stronger during movement execution and will increase during this phase.

3.0 Methods

3.1 Participants

Twenty-eight healthy young adults (7 male and 21 female, mean age 22.9 years $\pm$ 2.9) were recruited. Of these participants, two were withdrawn from the study following the SAI session, so they did not complete the SICI session. One of these participants was unable to complete the SICI session as conditioning stimulus thresholds could not be established for PA 70 μ s (PA₇₀). One participant withdrew following the SAI session due to time commitment concerns. Five participants were withdrawn from the study during the first session. For four of those participants, a muscle response that was robust enough to perform the study protocol could not be elicited before reaching the maximum stimulator output, while the other was screened out due to a contraindication to TMS. The final analysis included 23 participants (6 male and 17 female, mean age 23.4 years $\pm$ 2.7). Ethics approval was obtained from the University of Waterloo's Office of Research Ethics and all participants gave informed consent.

3.2 Design and Procedure

Participants completed two separate sessions separated by at least 24 hours (Figure 1). SICI was assessed during one session and SAI was assessed during the other session while participants performed a visuomotor task. Both sessions were similar, except for the conditioning stimulus and current configurations used to assess SICI and SAI.

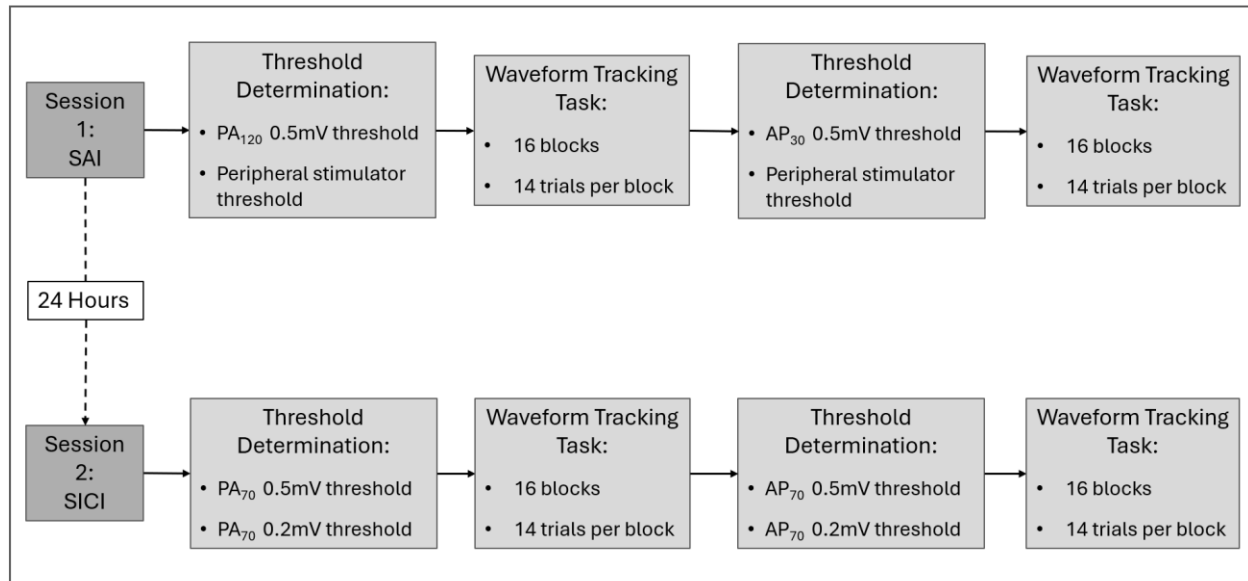


Figure 1 – Example of the experimental protocol. The order of session types (SAI and SICI) and current configurations (PA or AP) were counterbalanced across participants. Sessions were separated by at least 24 hours. Thresholds were determined for the first current configuration in each session, then participants received TMS while performing the waveform tracking task. Then thresholds were determined for the second current configuration in each session and the waveform tracking task was performed again.

In the SICI session, the reference TMS stimuli were conditioned with a subthreshold TMS pulse. TMS stimuli were delivered using one current configuration (PA₇₀) (Kujirai et al., 1993). Initially, AP 70 μ s (AP₇₀) current was also investigated during the SICI session, however limitations of the method we used to elicit SICI meant that AP₇₀ SICI could not be elicited in many participants. The conditioning stimulus pulse widths required for these participants exceeded the limits of current duration that could be employed by the stimulator during a paired pulse paradigm while ensuring the two pulses were balanced. The AP₇₀ data was removed from the analysis for the current study, however this current configuration is discussed further in the limitations section. In the SAI session, the reference TMS stimulus was conditioned by peripheral electrical stimulation of the median nerve (MNS). TMS stimuli were delivered using two current configurations (PA₁₂₀ and AP₃₀) (Hannah & Rothwell, 2017).

Both sessions consisted of two sets of trials, one set per current configuration. Each set was split into sixteen blocks of fourteen trials, alternating between blocks of unconditioned or blocks of conditioned trials (Table 1). Unconditioned trials consisted of single pulses of TMS alone, whereas conditioned trials consisted of TMS pulses preceded a subthreshold TMS pulse in the SICI session and by MNS in the SAI session. TMS stimuli were delivered at one of seven different time points during each trial.

Table 1 – Trial types and number of trials per block. Each block involved a single combination of current direction and test stimulus duration

Session 1: SAI				Session 2: SICI	
PA		AP		PA	
120 μ s		30 μ s		70 μ s	
Number of Trials	Time point (s) Relative to Movement Onset	Number of Trials	Time point (s) Relative to Movement Onset	Number of Trials	Time point (s) Relative to Movement Onset
2	-2.50 (Baseline)	2	-2.50 (Baseline)	2	-2.50 (Baseline)
2	-0.50	2	-0.50	2	-0.50
2	-0.25	2	-0.25	2	-0.25
2	0.00	2	0.00	2	0.00
2	1.00	2	1.00	2	1.00
2	2.00	2	2.00	2	2.00
2	3.00	2	3.00	2	3.00

3.3 Task

SAI And SICI were assessed while participants performed a visuomotor task to examine the relative contributions of different afferent and corticocortical loops during movement planning and execution (Figure 2). Participants were seated in front of a computer screen with a 5 cm x 4 cm thin film force-sensing resistor (RP-S40-ST, Kuuleyn, Shenzhen Yilaijia Technology Co., Ltd., China) on the desk in front of them (Figure 3). Placing their right index finger against the force sensor, participants controlled the vertical position of a red cursor on the computer screen to track a target. The target was represented by a white waveform on the screen, and participants tracked it with the red cursor by applying a graded force to the force sensor. Pushing harder moved the cursor up, and pushing less moved the cursor down. The force sensor was calibrated so that the midrange of force during the task was approximately 10% maximal voluntary contraction (MVC) of the FDI muscle. The amplitude range required to track the waveforms during the task was 0-20% MVC.

Each trial started with a straight line appearing for 4 seconds. Tracking this line required the midrange of force and was used as a baseline measure. After 4 seconds, the waveform appeared on the screen and participants had 2 seconds to prepare to track the waveform. Following the planning phase, participants tracked the waveform with the cursor. During the task, TMS stimuli occurred at one of seven time points relative to movement onset; one during baseline (-2.5s), early planning (-0.5s), late planning (-0.25s), movement onset (0s) and at three different time points during the waveform (1s, 2s, 3s). TMS stimuli were delivered at time points during the task when participants were required to use approximately 10% MVC in their FDI.

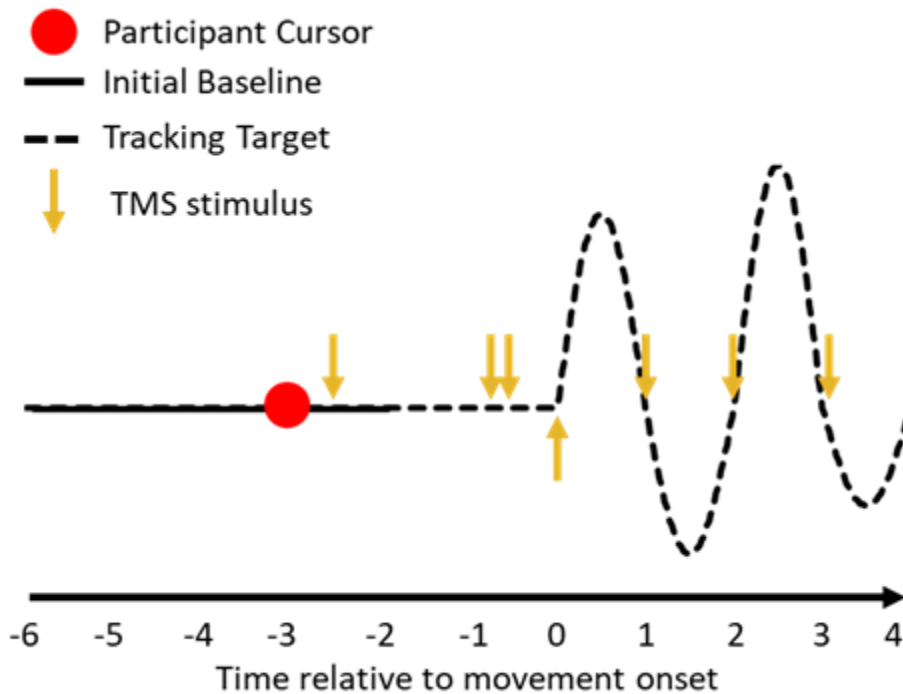


Figure 2 - Example of one trial of the visuomotor task. The **red circle** indicates the cursor that the participant controlled during the task. The **solid line** indicates the initial baseline, which appeared on the screen at the beginning of the trial. The **dotted line** indicates the target waveform, which appeared on the screen after 4s. **Yellow arrows** indicate the time points when the unconditioned or conditioned TMS stimulus might be delivered on a given trial. Only one TMS stimulus was delivered per trial. The time points chosen for delivering a TMS stimulus corresponded to positions in the waveform requiring a consistent amount of muscle contraction - approximately 10% MVC.

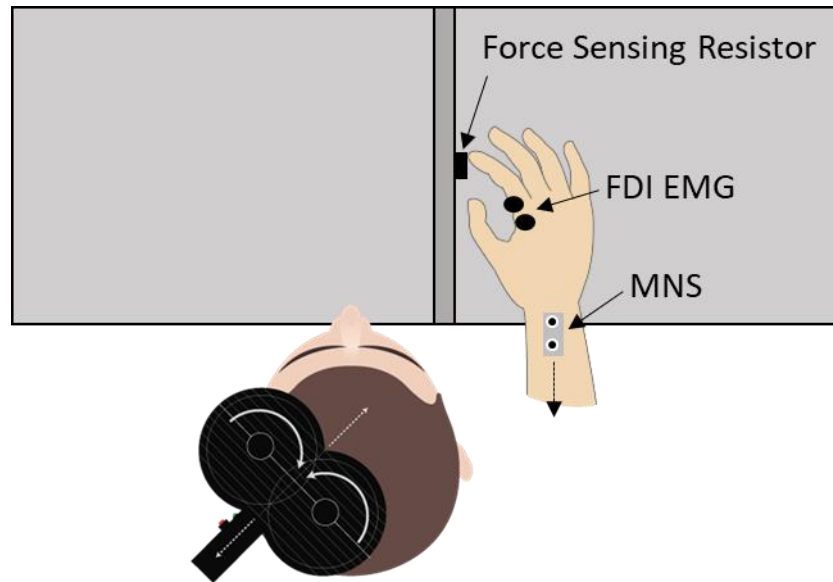


Figure 3 – Experimental Set Up. *The participants were seated at a desk in front of a computer screen. A force sensing resistor was on the desk. During the waveform tracking task, participants applied force to the force sensing resistor with the side of their index finger by flexing their FDI muscle. MEPs were measured from the FDI muscle.*

3.4 Controllable Pulse Parameter Transcranial Magnetic Stimulation (cTMS)

MEPs elicited by cTMS were recorded using LabChart 8 software paired with a Quad BioAmp and PowerLab 4/35 acquisition system (AD Instruments, Colorado Springs, Colorado, USA). Surface EMG electrodes (Ag-AgCl) were placed over the FDI using a tendon-belly montage. Surface EMG recording was triggered using a 5V TTL pulse with an epoch of -0.3 to 0.5s. During acquisition, the data was amplified (x1000), digitized (x40000 Hz) and filtered (bandpass filtered 5-1000 Hz, notch filter -60 Hz). Surface electromyography was downsampled to 5000 Hz for offline analysis. MEPs were defined as the peak-to-peak amplitude of the maximal electromyography response between 20 to 50 ms post TMS stimulation.

TMS stimuli were delivered using an Elevate cTMS stimulator (Rogue Research, Montreal, Quebec, Canada). Current direction was controlled using three different 70mm figure-8 coils. The SICI session used a medium inductance (15 μ H) coil. The SAI session used the same medium inductance coil for PA₁₂₀ and a low inductance coil (8 μ H) for AP₃₀. The geometry of the coils was the same, however the wiring of the low inductance coil was reversed to induce the AP current. The TMS coil was positioned tangentially to the scalp with the handle oriented 45 degrees posterior to the midline over the scalp position eliciting the most consistent response to PA₁₂₀ stimulation. The duration of the stimulus was controlled using the stimulator's onboard control software. The M-ratio of the pulse was set to 0.2 to emulate a monophasic pulse. The coil's position and trajectory was recorded using the BrainSight™ stereostatic system (cTMS; Rogue Research, Montreal, Quebec, Canada) and this position was used for all combinations of current direction and stimulus duration (Sakai et al., 1997). The TMS intensity was set to the stimulator output that elicited an MEP of ~0.5mV in the absence of the conditioning stimulus (subthreshold TMS pulse or peripheral electrical stimulation). This intensity was defined

independently for each current direction and stimulus duration combination using the ML-PEST method (Awiszus, 2003; Silbert, Patterson, Pevcic, Windnagel & Thickbroom, 2013). Threshold intensities were determined while the participant maintained a 10% MVC isometric contraction of their FDI muscle. AP₃₀ thresholds could not be established for some participants (26%). In all cases, these participants completed the experimental procedures for PA₁₂₀ and PA₇₀ current.

3.5 Quantification of Short-Interval Intracortical Inhibition (SICI)

SICI was elicited by pairing a subthreshold conditioning stimulus with a reference TMS stimulus (Kujirai et al., 1993). The conditioning stimulus intensity was determined by using the intensity required to elicit ~0.5mV MEPs while maintaining a 10% MVC. The pulse width of the conditioning stimulus was then reduced until active motor threshold (0.2mV) was reached, again while maintaining a 10% MVC. The pulse width was then reduced a further 6 μ s to produce maximal inhibition of the MEP, as shown through recruitment curves (Shirota et al., 2016). During unconditioned trials, no conditioning stimulus occurred and on conditioned trials, the conditioning stimulus preceded the reference pulse by 2ms.

MEPs recorded during conditioned trials were compared with MEPs elicited during unconditioned trials, and the amount of SICI was reported as a percentage of the unconditioned MEP.

3.6 Quantification of Short-Latency Afferent Inhibition (SAI)

SAI was elicited by pairing a peripheral electrical stimulus with a reference TMS pulse (Tokimura et al., 2000). Electrical stimulation was delivered using a DS7A constant current high voltage stimulator (Digitimer, North America LLC, Fort Lauderdale, FL, USA) via a surface electrode over the right median nerve at the wrist. The peripheral electrical stimulus intensity

was set to an intensity that elicits an M-wave of 0.2mV peak-to-peak (Hannah & Rothwell, 2017). The same peripheral electrical stimulus intensity was used for both PA₁₂₀ and AP₃₀ current configurations. The stimulus was applied in a constant current square wave pulse with a duration of 0.2ms, cathode proximal (Mirdamadi et al., 2017; Suzuki & Meehan, 2018, 2020). During unconditioned trials there was no peripheral stimulus delivered, and on conditioned trials, the peripheral stimulation preceded the TMS pulse by 21ms.

MEPs recorded during the conditioned trials were compared with MEPs elicited during the unconditioned trials. The amount of SAI was reported as a percentage of the unconditioned MEP.

$$SICI \text{ or } SAI = \frac{\text{Conditioned MEP Amplitude}}{\text{Unconditioned MEP Amplitude}} \times 100\%$$

3.7 Data Analyses

Statistical analyses were conducted using the R software (version 4.2.2) with the “tidyverse” (Wickham et al., 2019), “rstatix” (Kassambara, 2019), “ggpubr” (Kassambara, 2020), “ARTool” (Wobbrock et al., 2011) and “art.con” (Kay et al., 2021) packages. The assumption of normality was assessed using the Shapiro-Wilks test. If the data was determined to be normal, then we proceeded to run the parametric ANOVAs. If the data was found to be non-normal, then the data was log transformed. Following log transformation of the data, the assumption of normality was reassessed. If the data was found to be normal, then parametric ANOVAs were run on the log transformed data. If the log transformed data was still non-normal, then non-parametric ANOVAs were used. The Aligned Rank Transform (ARTool) (Wobbrock et al., 2011) procedure was used to conduct non-parametric factorial ANOVAs where at least one level of a factor violated normality. Data analysis was performed in three stages.

Stage 1 was determining the responsiveness of the motor cortex to SICI or SAI. First, pairwise t-tests with Bonferroni corrections for multiple comparisons were performed between conditioned and unconditioned MEP amplitudes for each Current Configuration to determine if the conditioning stimulus significantly reduced MEP amplitude during the baseline timepoint.

A two-way repeated measures ANOVA was then conducted to determine the effect of the conditioning stimulus depending on Current Configuration (PA_{120} , PA_{70} and AP_{30}) and Timepoint (Baseline, -0.5s, -0.25s, 0s, 1s, 2s, 3s). The magnitude of inhibition (SICI or SAI) was the dependent variable. Greenhouse-Geisser epsilon corrections were applied to account for multiple comparisons. Interactions between Current Configuration and Timepoint were decomposed using three separate one-way ANOVAs, one for each Current Configuration. The independent variable was Timepoint and the dependent variable was the magnitude of Inhibition. Pairwise t-tests with Bonferroni corrections for multiple comparisons were then used to determine which time points differed for every current configuration.

Stage 2 was determining the relative contributions of converging afferent and corticocortical loops during the visuomotor task. Unconditioned and conditioned MEPs at each time point were expressed as a function of baseline values, and pairs of current configurations were plotted as dimensions on a 2D plane (for example x coordinate = PA_{120} , y coordinate = PA_{70}) to compare their relative changes during different time points in the task across different current configurations. Unconditioned and conditioned MEPs were plotted separately to determine if there were changes in weighting due to sensory afference or cortical projections to M1. Cosine angles, which signify the relative weighting of each current configuration in the pair, were calculated for unconditioned and conditioned MEPs at each time point where TMS stimuli occurred (Figure 4). These angles were interpreted against a simulated trajectory that would

occur if the contributions of the two current configurations changed equally throughout the duration of the task. A two-way repeated measures ANOVA was conducted for each pair of current configurations (PA_{120} vs AP_{30} , PA_{120} vs PA_{70} , AP_{30} vs PA_{70}) to determine the effect of MEP type (Unconditioned, Conditioned) and Time point (-0.5s, -0.25s, 0s, 1s, 2s, 3s) on the relative weighting of each circuit. Greenhouse-Geisser epsilon corrections were applied to account for multiple comparisons.

Stage 3 was determining the magnitude of difference between the unconditioned and conditioned trials at each time point of the task. Euclidean distances between the unconditioned and conditioned stimuli, which signify the difference in magnitude of conditioned and unconditioned angles, were calculated. A one-way repeated measures ANOVA was conducted for each pair of current configurations (PA_{120} vs AP_{30} , PA_{120} vs PA_{70} , AP_{30} vs PA_{70}) to determine the effect of Timepoint (-0.5s, -0.25s, 0s, 1s, 2s, 3s) on the difference in magnitude between the MEP Types. Pairwise t-tests with Bonferroni corrections for multiple comparisons were conducted for each pair of current configurations to determine any differences in the Euclidean distances between each time point.

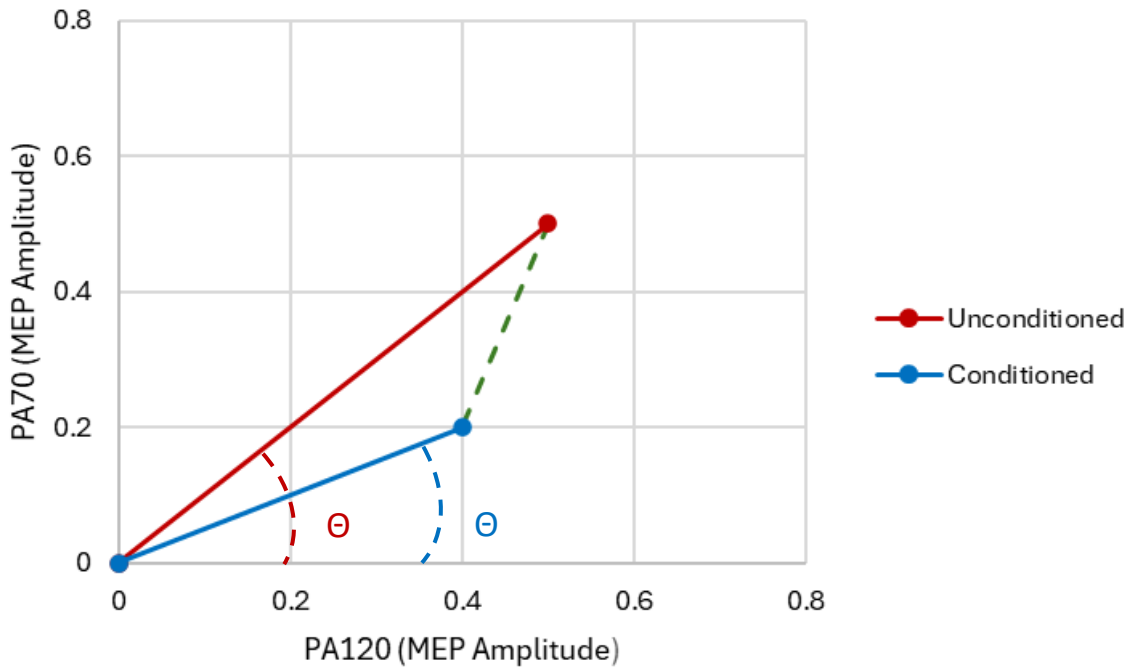


Figure 4 - Example of the cosine angles and Euclidean distances for pairs of unconditioned and conditioned MEPs at one time point of the task. Cosine angles and Euclidean distances were determined for three different pairs of current configurations (PA_{120} vs PA_{70} , PA_{120} vs AP_{30} , AP_{30} vs PA_{70}) The **red** point indicates an example of the **unconditioned** MEP amplitudes for a single time point. The **blue** point indicates an example of the **conditioned** MEP amplitudes for the same time point. The x and y components for each point indicate MEP amplitudes for PA_{120} and PA_{70} respectively. The **red** Θ indicates the cosine angle for the **unconditioned** MEPs. The **blue** Θ indicates the cosine angle for the **conditioned** values. The **green** dotted line indicates the Euclidean distance between the **unconditioned** and **conditioned** values for the time point.

4.0 Results

4.1 Participant Characteristics

Table 2 shows the means and standard deviations for general participant characteristics for each current configuration.

4.2 Inhibition

4.2.1 Baseline Inhibition

For the baseline time point, pairwise t-tests revealed significantly smaller conditioned MEP amplitudes compared to unconditioned PA₇₀, PA₁₂₀, and AP₃₀ current configurations [p.adj = 0.004, p.adj = 6.20×10^{-6} and p.adj = 4.54×10^{-4} respectively] (Figure 5). Therefore, the conditioning stimulus effectively reduced the MEP amplitude for all 3 current configurations. This also confirms that we were able to elicit SICI-like inhibition by reducing the pulse width of the conditioning stimulus instead of intensity, which supports the efficacy of this technique for investigating cortico-cortical inhibition.

4.2.2 Inhibition by Time point

The Current Configuration x Timepoint repeated measures ANOVA on Inhibition (percentage of unconditioned MEP amplitude) revealed a significant main effect of Timepoint [$F_{6,72} = 11.897$, $\epsilon = 0.530$, $p < 0.001$, $\eta_p^2 = 0.498$]. The main effect of Current Configuration [$F_{2,24} = 2.689$, $p = 0.088$, $\eta_p^2 = 0.183$] and the Current Configuration by Timepoint [$F_{12,144} = 1.650$, $p = 0.084$, $\eta_p^2 = 0.121$] interaction demonstrated moderate trends towards significance but did not reach the threshold for significance despite large effect sizes. Pairwise t-tests for the main effect of Timepoint revealed significant disinhibition from time point -0.5s to -0.25s [p.adj = 2.27×10^{-6}].

Table 2 - Summary of participant characteristics for PA₁₂₀, PA₇₀ and AP₃₀ Current Configurations. Where applicable, means and standard deviations are provided.

	PA₁₂₀^a	PA₇₀^b	AP₃₀^c
n	23	21	18
Age (years)	23.4 ± 2.7	23.5 ± 2.8	23.1 ± 2.6
Sex	6M, 17F	5M, 16F	4M, 14F
MEP Latencies (ms)	22.18 ± 1.71	22.04 ± 1.96	24.06 ± 1.55
TMS Test Stimulus Threshold (% Stimulator output)	29.3 ± 5.3	37.2 ± 8.1	66.6 ± 14.2
TMS Conditioning Stimulus Threshold (Pulse Duration [μs])*		37.4 ± 7.5	

^a Maximum stimulator output for PA₁₂₀ is 50%.

^b Maximum stimulator output for PA₇₀ is 66%.

^c Maximum stimulator output for AP₃₀ is 72%.

*Values are shown as active motor threshold - 6μs

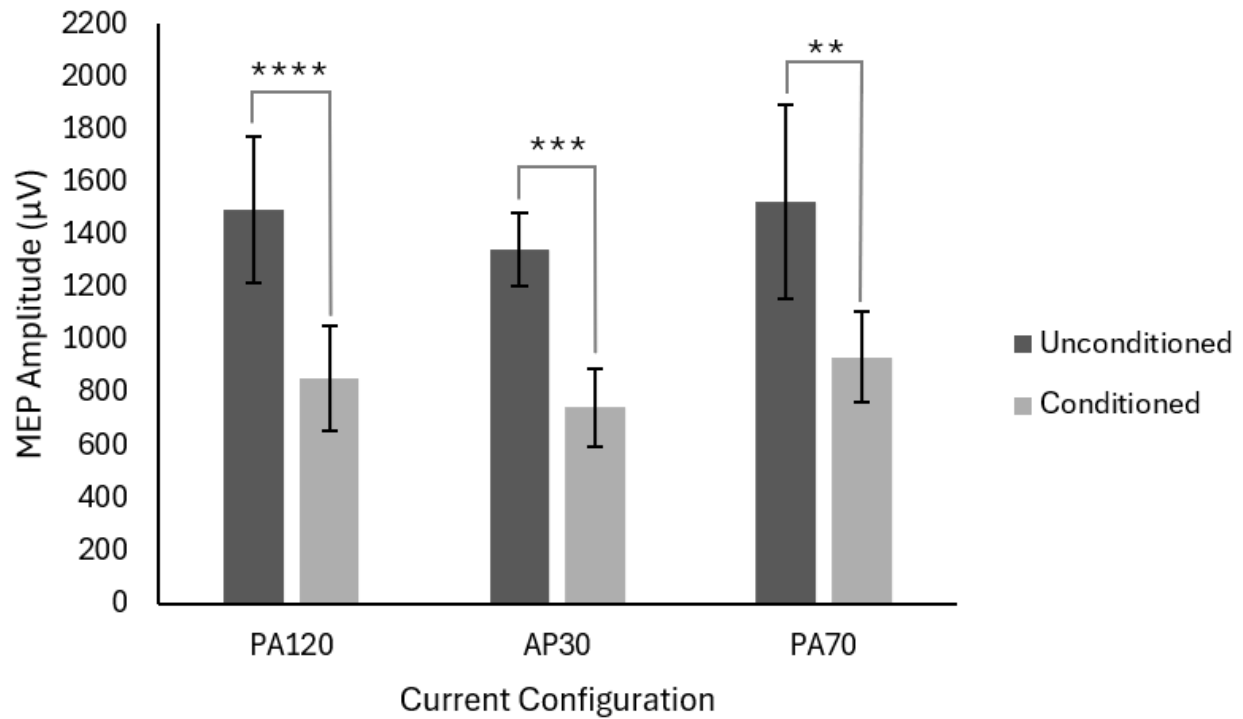


Figure 5 - Mean Baseline conditioned and unconditioned MEP amplitudes. Baseline MEP amplitudes are separated by current configuration (PA_{120} , AP_{30} and PA_{70}) and MEP type (unconditioned and conditioned). Error bars represent $\pm$ SEM. ** denotes $p < 0.01$, *** denotes $p < 0.001$, **** denotes $p < 0.0001$.

Inhibition increased from -0.25s to movement onset [$p_{\text{adj}} = 1.01 \times 10^{-6}$], then decreasing again from movement onset to 1s [$p_{\text{adj}} = 7.33 \times 10^{-4}$].

Although the main effect of time point was significant, this may be misleading. The large effect sizes seen in for the Current Configuration by Timepoint suggest that we were underpowered to detect the interaction between current configuration and time point. To investigate this interaction further, separate one-way repeated measures ANOVAs were run for each current configuration to determine the effect of Timepoint on Inhibition (percentage of MEP amplitude). For PA₁₂₀, the non-parametric ANOVA revealed a significant effect of Timepoint [$F_{6,120} = 10.697$, $p < 0.001$, $\eta_p^2 = 0.348$]. Contrasts revealed a significant decrease of inhibition from -0.5s to -0.25s [$p = 0.001$] and an increase in inhibition from -0.25s to movement onset [$p = 0.004$]. Inhibition also decreased in PA₁₂₀ progressively across the movement, shown though significantly less inhibition at 2s and 3s compared to movement onset [$p = 0.001$ and $p = 0.004$ respectively] (Figure 6A).

For PA₇₀, the ANOVA revealed a significant effect of Timepoint [$F_{6,108} = 6.767$, $\varepsilon = 0.68$, $p < 0.001$, $\eta_p^2 = 0.273$]. Pairwise t-tests revealed a significant increase of inhibition from -0.25s to movement onset [$p = 0.011$] and a significant decrease of inhibition from movement onset to 1s [$p = 0.004$] (Figure 6B). For AP₃₀, the ANOVA revealed a significant effect of Timepoint [$F_{6,84} = 4.239$, $\varepsilon = 0.747$, $p = 0.003$, $\eta_p^2 = 0.232$]. Pairwise t-tests revealed a significant decrease in inhibition from -0.5s to -0.25s [$p = 0.025$]. Although it did not reach significance, inhibition also increased from -0.25s to movement onset [$p = 0.057$] (Figure 6C). Taken together, these results show that -0.25s is a period of disinhibition in all three current configurations before increasing again at movement onset. PA current configurations show less inhibition as the

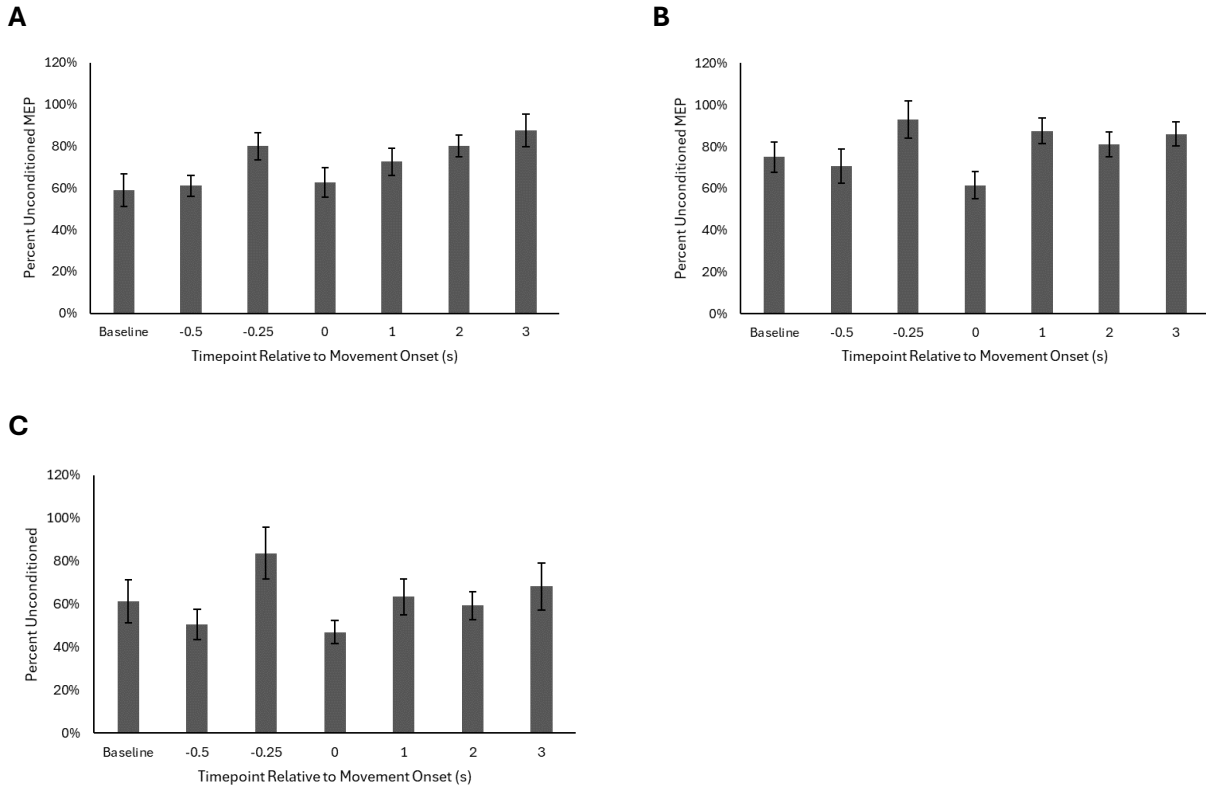


Figure 6 - Mean SICI/SAI values by time point. (A) PA_{120} SAI (B) PA_{70} SICI, (C) AP_{30} SAI. Error bars represent $\pm$ SEM. Significant differences between time points for each current configuration are discussed further in the results **Section 4.2.2**.

movement progresses from onset, however this does not occur in AP₃₀ circuits. Instead AP₃₀ shows minimal changes in inhibition across the entire task, only decreasing at -0.25s.

4.3 Angles

4.3.1 PA₁₂₀ SAI vs PA₇₀ SICI

The MEP Type x Timepoint repeated measures ANOVA on cosine angles revealed a significant main effect of MEP Type [$F_{1,18} = 7.167$, $p = 0.015$ $\eta_p^2 = 0.285$]. The main effect of Timepoint [$F_{5,90} = 0.424$, $\epsilon = 0.444$, $p = 0.678$ $\eta_p^2 = 0.023$] and the interaction of MEP Type by Timepoint [$F_{5,90} = 2.228$, $\epsilon = 0.838$, $p = 0.071$ $\eta_p^2 = 0.110$] were not significant.

This significant main effect of MEP Type was driven by a more acute angle for conditioned [$39.1 \pm 13.0^\circ$] compared to unconditioned [$45.5 \pm 11.9^\circ$] MEPs regardless of time point (Figure 7A). The more acute angle for the conditioned MEPs indicates that conditioning stimulus had a disproportionately stronger effect on PA₇₀ SICI compared to PA₁₂₀ SAI.

4.3.2 PA₁₂₀ SAI vs AP₃₀ SAI

The non-parametric MEP Type x Timepoint repeated measures ANOVA revealed a significant main effect of MEP Type. The main effect of Timepoint [$F_{5,154} = 1.852$, $p = 0.106$ $\eta_p^2 = 0.0567$] and the interaction of MEP Type by Timepoint [$F_{5,154} = 0.8918$, $p = 0.488$ $\eta_p^2 = 0.0281$] were not significant.

The significant main effect of MEP Type was driven by a more acute angle for conditioned [$36.9 \pm 14.5^\circ$] than unconditioned [$41.2 \pm 13.0^\circ$] MEP regardless of time point (Figure 7B). The more acute angle for conditioned MEPs indicates that the conditioning stimulus had a disproportionately stronger effect on AP₃₀ SAI compared to PA₁₂₀ SAI.

4.3.3 AP₃₀ SAI vs PA₇₀ SICI

The non-parametric MEP Type x Timepoint repeated measures ANOVA on cosine angles revealed a significant main effect of MEP Type [$F_{1,132} = 8.460$, $p = 0.0043$ $\eta_p^2 = 0.060$]. The main effect of Timepoint [$F_{5,132} = 0.5731$, $p = 0.721$ $\eta_p^2 = 0.021$] and the interaction of MEP Type by Timepoint [$F_{5,132} = 1.014$, $p = 0.412$ $\eta_p^2 = 0.037$] were not significant.

The significant main effect of MEP Type was driven by a more acute angle for conditioned [$46.8 \pm 14.8^\circ$] than unconditioned [$50.0 \pm 12.0^\circ$] MEPs (Figure 7C). The more acute angle for conditioned MEPs indicates that the conditioning stimulus had a disproportionately stronger effect on PA₇₀ SICI compared to AP₃₀ SAI.

4.4 Euclidean Distances

4.4.1 PA₁₂₀ SAI vs PA₇₀ SICI

The one-way repeated measures ANOVA on Euclidean Distances revealed a significant effect of Timepoint [$F_{5,90} = 10.423$, $\epsilon = 0.812$, $p < 0.001$ $\eta_p^2 = 0.367$]. Pairwise t-tests revealed that the Euclidean distance at time point -0.5s was significantly smaller than all other time points [$p = 0.0001$, $p = 0.0102$, $p = 0.0018$, $p = 0.0017$, and $p = 0.0012$] (Figure 8A). The magnitude of difference in the weighting of PA₁₂₀ and PA₇₀ circuits between conditioned and unconditioned was the smallest at -0.5s prior to movement onset. Following this time point, differences in the relative weighting between conditioned and unconditioned was much larger.

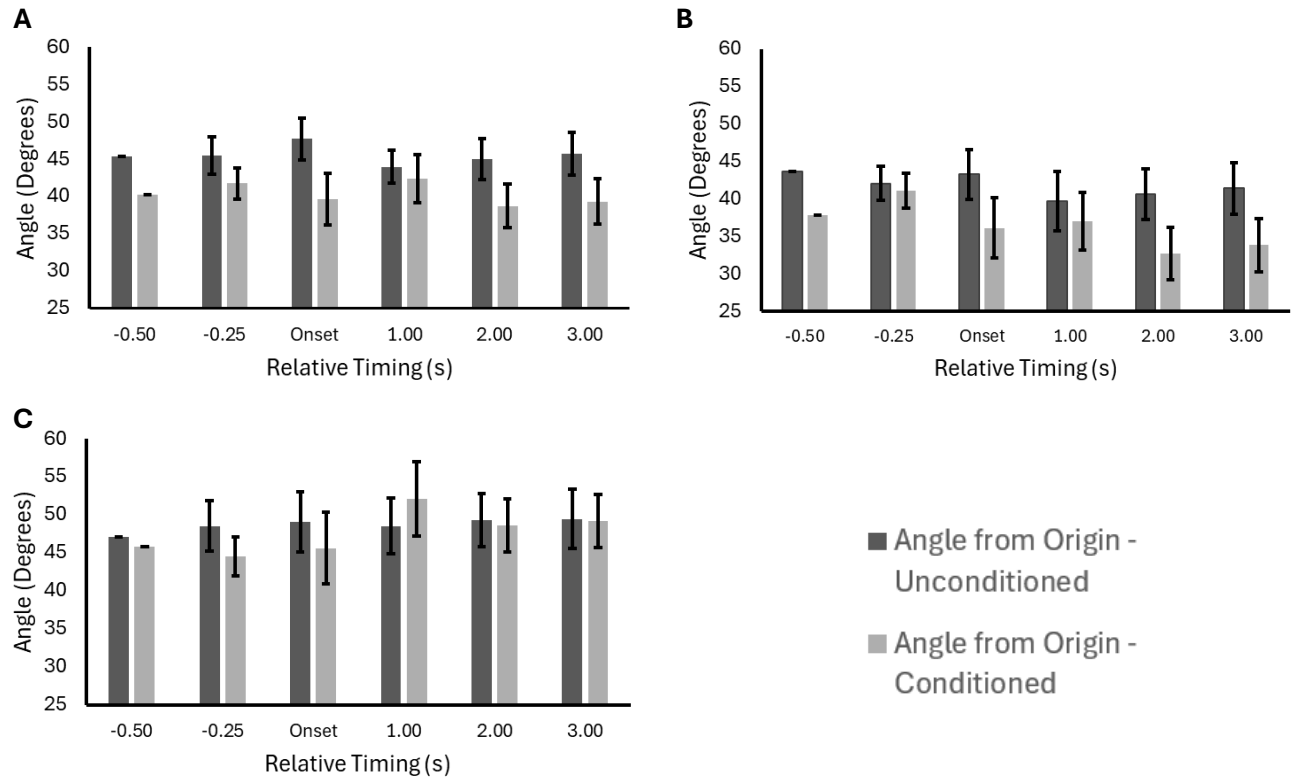


Figure 7 - Mean conditioned and unconditioned angles by time point. (A) PA_{120} SAI vs PA_{70} SICI, (B) PA_{120} SAI vs AP_{30} SAI, (C) AP_{30} SAI vs PA_{70} SICI. Angles were calculated for each time point relative to baseline. Error bars represent $\pm$ SEM. Significant differences between time points are discussed further for each pair of current configurations in the results **Section 4.3**

4.4.2 PA₁₂₀ SAI vs AP₃₀ SAI

The non-parametric one-way repeated measures ANOVA on Euclidean Distances revealed a significant effect of Timepoint [$F_{5,70} = 9.743$, $p < 0.001$ $\eta_p^2 = 0.410$]. Pairwise t-tests revealed that the Euclidean distance at -0.5s was significantly smaller than all other time points [$p < 0.0001$, $p = 0.0006$, $p = 0.0005$, $p < 0.0001$ and $p = 0.0002$] (Figure 8A). This is consistent with the results seen with PA₁₂₀ and PA₇₀, with much smaller differences seen between the weighting of conditioned and unconditioned stimuli at -0.5s compared to the other time points.

4.4.3 AP₃₀ SAI vs PA₇₀ SICI

The non-parametric one-way repeated measures ANOVA on Euclidean distances did not reveal a significant effect of Timepoint [$F_{5,60} = 2.119$, $p = 0.075$ $\eta_p^2 = 0.150$]. However, a moderate trend towards significance was observed given the large effect size observed, so contrasts were run to determine what was driving this interaction. There were no significant differences between the Euclidean distances at any of the time points in the task, however, the difference between -0.5s and -0.25s [$p = 0.0843$] as well as -0.5s and movement onset [$p = 0.0639$] were approached significance, which is consistent with the other pairs of current configurations (Figure 8C). For AP₃₀ SAI and PA₇₀ SICI, changes in differences of weighting between conditioned and unconditioned MEPs were smaller than the differences seen in other current pairs. The weighting of AP₃₀ SAI and PA₇₀ SICI are more consistent between conditioned and unconditioned MEPs compared to other pairs.

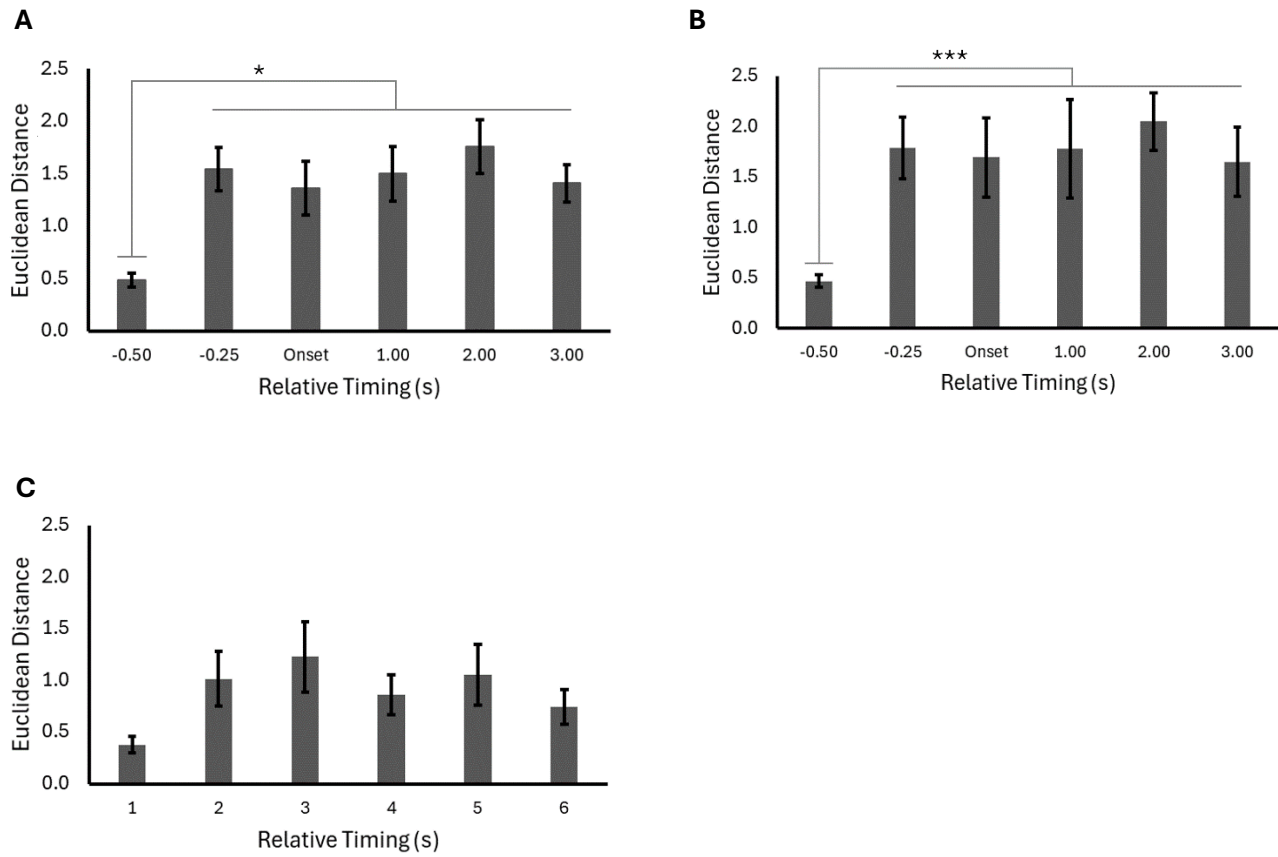


Figure 8 - Mean Euclidean distances by time point. (A) PA_{120} SAI vs PA_{70} SICI, (B) PA_{120} SAI vs AP_{30} SAI, (C) AP_{30} SAI vs PA_{70} SICI. Euclidean distances were calculated between conditioned and unconditioned stimuli for each pair of current configurations. Significant differences between time points are discussed further for each pair of current configurations in the results **Section 4.4**. * denotes $p < 0.05$, *** denotes $p < 0.001$.

5.0 Discussion

This study used SICI and SAI to investigate the interactions between corticocortical connections and sensory afference projections to motor cortex during the planning and execution of movement. The main finding was that the relative weighting of these convergent circuits vary across different phases of motor planning and execution. Cosine angles showed an increased strength of corticocortical connections probed by SICI compared to the afferent projections probed by SAI. This suggests that SICI dominates over these interactions, while SAI played a modulatory role in this relationship. This is consistent with previous work, where it was found that PA SICI dominates over PA SAI when they were co-applied. As well, the Euclidean distances were the smallest at the -0.5s time point compared to the rest of the time points in the task. Larger Euclidean distances reflect increased modulation of the motor plan, therefore time points following -0.5s are critical points where this modulation occurs. The current study expands on these findings by providing a functional context to these relationships.

5.1 Inhibition

Changes in the amount of inhibition in the three different current configurations across the task suggest they are targeting different circuits that play unique roles in motor control. Previous work using PA₁₂₀ SAI has shown that it is involved in movement-related gating, increasing in the surrounding muscles that aren't critical to the movement while inhibition is reduced in the target muscle during the preparatory phase of movement (Voller et al., 2006; Asmussen et al., 2014). Our results are consistent with these findings. PA₁₂₀ SAI showed a reduction during the second planning phase time point (-0.25s from movement onset). -0.25s is the planning time point leading up to movement onset in our task that would correspond to the

preparatory phase discussed in previous research, therefore disinhibition during this period is linked to preparation for movement.

SICI has also been shown to be reduced leading up to movement onset (Floeter & Rothwell, 1999). It is thought that this reduction in inhibition could serve to “release” cortical representations for movement and focus the following excitatory drive towards producing movement (Floeter & Rothwell, 1999). Interestingly, our results showed a significant increase of SICI at movement onset before reducing again during the movement. Although this is contradictory to previous work, the current study had participants maintaining a tonic contraction throughout the entire task, where SICI studies are typically performed at rest. Voluntary contraction reduces SICI, which would explain why the reduction in SICI just prior to movement onset is not as clear (Ridding et al., 1995).

Another important aspect of motor control that is consistent with our findings for SICI during movement onset is behavioural inhibition. During regular movement, the motor system is often required to abort actions that have been initiated. Stop Signal Tasks (SSTs) are regularly used in research to estimate a participant’s Stop Signal Reaction Time (SSRT), or the amount of time it takes to stop an initiated response (Chowdhury et al., 2019). Individuals with slow SSRTs show a complete loss of SICI when required to stop an initiated response, whereas faster SSRTs were associated with a recovery of inhibition on stop trials (Chowdhury et al., 2019). In order to abort the initial motor command and start the correct response for the SST, the motor system will inhibit the target muscle (Rawji et al., 2023). This inhibition used when anticipating a stop or change of movement is called proactive inhibition (Rawji et al., 2023). This would support the increase in inhibition seen at movement onset in PA₇₀. Participants were required to effectively “stop” the motor command they used to maintain the contraction during baseline and planning in

order to initiate the movement. Increased inhibition during movement onset reflects the ability of the motor system to transition between movements.

To our knowledge, no past work has investigated changes in AP₃₀ SAI during movement planning and execution. Increases in AP₃₀ SAI have been observed during contraction (Hannah & Rothwell, 2017). As well, cerebellar stimulation reduced AP₃₀ SAI (Hannah & Rothwell, 2017). The cerebellum is an important structure for the coordination of movement. It allows for the expected sensory consequences of a movement to be compared with actual sensory feedback (Manto & Bastian, 2007). Sensory signals that do not match the prediction can be used to rapidly adjust the motor command and correct errors (Sokolov et al., 2017). Contrary to our hypothesis, we did not see decreased AP₃₀ SAI in all of the pre-movement time points. The only time point where AP₃₀ SAI decreased was -0.25s. All other time points showed similar amounts of inhibition. This is likely related to the fact that participants were maintaining a tonic contraction throughout the entire task. Previous work showed that contraction reduced PA₁₂₀ SAI, but not AP₃₀ (Hannah & Rothwell, 2017). This explains why similar amounts of SAI were seen during the planning phase as in the movement phase. We observed a decrease in AP₃₀ SAI during the -0.25s time point which is not explained by the typical AP₃₀ SAI responses to contraction seen in the other time points during the task (Hannah & Rothwell, 2017). However, -0.25s was a point where disinhibition was seen in the other two circuits as well (PA₁₂₀ and PA₇₀). In both PA₁₂₀ and PA₇₀, this disinhibition has been related to “releasing” cortical motor representations (Floeter & Rothwell, 1999) and preparing the target muscle to initiate movement (Voller et al., 2006; Asmussen et al., 2014). Therefore, the disinhibition occurring in AP₃₀ circuits during this time point may be related to the preparation to move as well.

5.2 Cosine Angles

Investigating inhibition for each current configuration individually provided information on the sensorimotor and cortical circuits probed by PA₁₂₀, PA₇₀ and AP₃₀ in isolation, but the aim of this study was to determine how these circuits interacted to shape movement planning and execution. Comparing unconditioned and conditioned stimulus cosine angles provides insight into the role of afference and cortical-cortical projections to M1 probed by each circuit in relation to each other. Similar to the findings of Rawji et al. (2023), we found no change in the unconditioned angles across the different time points of the task for all three current pairs (PA₁₂₀ SAI vs PA₇₀ SICI, PA₁₂₀ SAI vs AP₃₀ SAI, and AP₃₀ SAI vs PA₇₀ SICI). The conditioned angles provide evidence for the differential roles of the circuits we investigated to motor planning and execution, which suggests that any angle effects in the conditioned stimuli are a result of alterations in the influence of sensory afferent or cortical-cortical projections to M1.

Previous studies have demonstrated interactions between SICI and SAI by co-applying both inputs by interleaving the cortical conditioning stimulus, peripheral conditioning stimulus and the test stimulus in a triple stimulus paradigm without a concurrent behaviour (Alle et al., 2009; Udupa et al., 2014). Although the present study did not co-apply SICI and SAI, investigating the relative weighting of these circuits in relation to each other during motor planning and execution of a visually guided movement supported the results found in triple pulse studies. The triple stimulus paradigm using conventional PA stimuli of the same pulse width demonstrated that SICI was stronger in the presence of SAI compared to SAI in the presence of SICI, suggesting that SAI may play more of a modulatory role in this relationship (Alle et al., 2009; Udupa et al., 2014). The main effect of MEP type for the PA₁₂₀ vs PA₇₀ cosine angles in the current study support the observation that SICI is a more dominant inhibitory influence

during behaviour compared to PA₁₂₀ SAI. The mean conditioned angles were decreased compared to unconditioned, indicating a stronger effect of the conditioning stimulus on PA₇₀ SICI circuits.

Alle et al. (2009) proposed a connectivity model to explain the dominance of SICI over PA SAI. In their model, the authors proposed that SICI and PA SAI are mediated by different populations of interneurons converging onto the corticospinal neuron. The interneurons mediating SICI likely synapse closer to the axon initial segment than SAI, which sets them up to have strong control over the generation of the action potential at the axon hillock (Alle et al., 2009). This dominance is also explained by the long sensorimotor loops involved in motor planning. Through a variety of corticocortical connections, selection of the appropriate action (Ridderinkhof et al., 2004) and the kinematics required to perform that action (Delhayé et al., 2018) are integrated during motor planning to set the stage for movement. SICI can probe these corticocortical connections. On the other hand, shorter sensorimotor loops use proprioceptive information to modulate these circuits and modify motor output to support goal-directed movement (Weiler et al., 2015). SAI probes these modulatory loops. The PA circuits probed by SAI and SICI play different roles in motor planning but work in conjunction to shape motor output.

Previous research has not investigated the role of AP₃₀ SAI to motor control in depth, however the stronger relative weighting of this circuit in relation to the PA circuits further supports a role of AP₃₀ SAI in movement execution. The mean conditioned angles were decreased for PA₁₂₀ SAI vs AP₃₀ SAI. These findings indicate a higher weighting of AP₃₀ SAI circuits during this task than PA₁₂₀ SAI. As discussed previously, during contraction AP₃₀ SAI is increased (Hannah & Rothwell, 2017). In the current study, participants maintained a slight

contraction throughout the task. The inputs that are recruited by PA₁₂₀ are more sensitive to voluntary contraction, shown by the attenuation of their SAI response during contraction (Hannah & Rothwell, 2017). This attenuation did not occur in AP₃₀ circuits, which would suggest these current configurations target unique circuits (Hannah & Rothwell, 2017). The increased weighting of AP₃₀ SAI in our study is consistent with these findings, showing that the tonic contraction maintained during the task increased the effect of the conditioning stimulus on AP₃₀ circuits to a greater degree than PA₁₂₀ circuits.

The cosine angles between AP₃₀ SAI and PA₇₀ SICI also support the idea that SAI plays a modulatory role in its relationship with SICI. Compared to unconditioned MEPs, the cosine angles between AP₃₀ SAI and PA₇₀ SICI were decreased for conditioned MEPs. This would indicate that conditioned MEPs are more weighted towards PA₇₀ SICI than unconditioned MEPs. As discussed previously in relation to PA₁₂₀ SICI circuits, longer sensorimotor loops are probed by SICI and set the stage for regular motor behaviour (Ridderinkhof et al., 2004; Delhayé et al., 2018). Shorter sensorimotor loops can modulate the longer loops to integrate proprioceptive information and support these motor processes (Weiler et al., 2015). The increased weighting of AP₃₀ SAI circuits compared to PA₁₂₀ SAI also suggest that these smaller modulatory loops provide unique information to longer sensorimotor loops depending on the state of the body and the external environment.

5.3 Euclidean Distances

Measuring the Euclidean distances between unconditioned and conditioned MEPs provided another dimension to interpret the effects of sensory afference or corticocortical projections to M1. Where cosine angles capture the balance between different circuits, Euclidean distances describe the absolute magnitude of difference between the weighting of conditioned

and unconditioned stimuli (Rawji et al., 2023). The Euclidean distances were smaller at -0.5s prior to movement onset than at any other time point during the task for all three pairs of current configurations. Euclidean distances reflect differing trajectories of unconditioned and conditioned stimuli. When comparing the trajectories of PA₁₂₀ vs AP₃₀ circuits during SST tasks and go-only tasks, Euclidean distances have been used to examine the role of context-dependent modulation of movement (Rawji et al., 2023). By investigating responses to the SST task, Rawji et al. (2023) found that changes in Euclidean distance reflected proactive inhibition. Our results can be partially explained by proactive inhibition, seen through the increase of SICI at movement onset (Chowdhury et al., 2019). However, larger Euclidean distances are seen across both planning and movement execution. Therefore, changes in trajectory seen our task are reflecting other forms of context-dependent modulation.

Context-dependent modulation of movement can come about by direct changes to the motor command by M1, or by modulation of the motor command by various inputs (Rawji et al., 2023). The increase in Euclidean distances later during the planning phase of the task, and throughout the movement, likely show different sensorimotor loops modulating motor output. Sensorimotor loops that converge onto motor areas provide information necessary to planning and performing movement. The selection of actions (Ridderinkhof et al., 2004), and the kinematics to produce those actions (Delhay et al., 2018) along with sensory information about the body (Weiler et al., 2015) all converge via sensorimotor loops to shape motor output (Bizzi & Ajemian, 2020). The pattern of activity generated by the motor cortex depends on these various modulatory inputs (Rawji et al., 2023).

Euclidean distances reflect these processes, and changes across the task reflect times where modulation of motor output is critical. The initial planning stage showed the smallest

Euclidean distances, so this is potentially a point during the task where less modulation of the motor command is occurring. Approaching movement onset, the Euclidean distances increase, reflecting the integration of information into the motor plan. During the movement, Euclidean distances are still relatively large, reflecting the sensory afference used for feedback control (Sokolov et al., 2017; Andersen et al., 1997). Therefore, Euclidean distances are another piece of evidence to support the importance of sensory afferent and corticocortical inputs to motor control.

6.0 Limitations and Future Directions

The current study has several limitations that should be considered for future research. First, having participants maintain a tonic contraction during the task may have influenced the results for some of the current configurations used. Voluntary contraction can have different effects on the circuits we probed during this study. Literature has shown that SICI is reduced in the presence of muscle contraction (Ridding et al., 1995; Reynolds & Ashby, 1999). Although this is a factor to consider, there are many benefits to using a tonic contraction while examining the roles of sensorimotor and cortical circuits in motor behaviour. AP₃₀ is more difficult to recruit at rest compared to other current configurations, and maintaining a slight contraction can help lower the intensity required to recruit AP₃₀ (Hallett, 2007; Hannah & Rothwell, 2017). As well, the effect of contraction on AP₃₀ SAI is minimal, while it attenuates SAI measured with other circuits like PA₁₂₀ suggesting they recruit different sets of inputs (Hannah & Rothwell, 2017). Investigating SAI using contraction can identify more unique properties of the circuits targeted with TMS. A limitation of using a tonic contraction is the ability to relate results to previous work. Typically, studies using conventional TMS stimulators with PA current direction are performed at rest. However, the higher thresholds required to elicit MEPs using AP₃₀ (Hallett, 2007; Hannah & Rothwell, 2017) and advantages of AP₃₀ currents could be lost when evaluating SAI at rest (Hannah & Rothwell, 2017) further highlight the importance of investigating these circuits with contraction, as it can provide more insight into their functional roles.

We chose to have participants maintain a 10% MVC for all time points during this task to ensure that we were able to accurately compare MEPs between time points while controlling as much as possible for changes in cortical excitability. Although using the tonic contraction may have influenced the effects of different circuits, we can still be confident that changes in the

different circuits throughout the task were not entirely caused by the tonic contraction. The conditioned MEP amplitudes at baseline were significantly smaller than unconditioned for all three current configurations that were used. This would suggest that even while maintaining a static contraction, the inhibitory circuits can still be used to effectively investigate motor behaviour.

Another limitation of this study was the limits of the cTMS stimulator. Technology is still developing for cTMS, which means there are some limitations of the stimulator itself that had to be addressed with the study protocol. SICI is typically studied by preceding a TMS pulse with a subthreshold conditioning pulse (Kujirai et al., 1993). However, cTMS does not allow for intensity to be independently manipulated for paired TMS pulses. Past work suggests the physiological effect of TMS is not about the peak induced current (e.g. pulse intensity), rather the effect is determined by the total charge (e.g. intensity over a given duration) (Shirota et al., 2016). Therefore, a shorter duration conditioning stimulus can be considered subthreshold despite having the same peak intensity as the longer duration test stimulus. The significant reduction in MEP amplitude of the conditioned stimulus compared to the unconditioned stimulus at baseline is consistent with the inhibitory effect of a conditioning stimulus with a 2 ms inter-pulse interval indicating that we elicited a SICI-like inhibition similar to traditional approaches using conventional TMS stimulus like the MagStim BiStim². However, this evidence is indirect. There is currently no direct comparison of conventional intensity-based SICI and the cTMS derived pulse duration-based SICI to confirm that both targets the same form of SICI. SAI literature has shown that manipulating current parameters such as pulse width can target distinct populations of neurons (D'Ostilio et al., 2016; Hannah & Rothwell, 2017). It is unclear whether this is the case for the corticocortical projections we targeted in this study as well. This may

make it more difficult to draw conclusions based on previous SICI research. However, as we are eliciting inhibition using this protocol, it is still a useful tool to investigate corticocortical connections. This protocol can provide some unique insight into the role of cortical circuits in motor control. Future research should focus on correlating conventional SICI and pulse duration-based SICI as well as use pharmacological interventions to confirm the involvement of the same GABA receptor subtypes.

Another limitation related to the protocol used during the SICI session were the limits on the pulse widths that could be used for the conditioning stimulus. The conditioning stimulus intensity was determined by keeping the intensity fixed and reducing the pulse width until active motor threshold (0.2mV while maintaining a 10% MVC) was reached, then reducing it by another 6 μ s (Shirota et al., 2016). The ISI we used for the SICI session was 2 ms, based on previous literature showing peak inhibition at this ISI (Kujirai et al. 1993). To ensure that energy could be effectively and safely managed by the stimulator when producing TMS pulses in such short succession, the range of pulse widths that could be used for the conditioning stimulus were limited. There was a range of ~ 23 μ s that could be used for the conditioning stimulus, while still allowing for a balanced pulse. This was rarely an issue for PA₇₀, only one participant was withdrawn from the study because a conditioning stimulus could not be determined for PA₇₀. The AP₇₀ current configuration posed more problems in this regard. AP₇₀ was not included in the current study because it was much more difficult to establish a conditioning stimulus threshold. Particularly for participants that AP₃₀ could be established in, the conditioning stimulus threshold for most participants was too long to balance the pulses. Participants with lower intensity test stimulus thresholds for AP₇₀ often required longer pulse widths for active motor threshold. Therefore, it was very difficult to produce AP₇₀ SICI and it was excluded from the current study.

As cTMS technology continues to develop, AP₇₀ should be investigated to determine its role in motor control.

Finally, given our sample size, we were likely underpowered to detect some interactions in our results. Difficulties establishing AP₃₀ thresholds can influence the differences seen in comparisons involving this circuit. It is possible that this may have influenced the results from the current study as well. For inhibition, we did not find a significant interaction between current configuration and time point, however the moderate to large effect size ($\eta_p^2 = 0.121$) suggests that we may be underpowered to detect the interaction. We were unable to detect interactions between MEP type and time point for the cosine angles of all three combinations of current configurations. Although the effect sizes were not as large as our effect size for inhibition, we cannot be certain that differences across the angles would not be present with a larger sample. Although we were underpowered to detect some of these interactions, we were still able to make strong conclusions about our data, the significant results of this study supported previous research into the importance of distinct sensorimotor and cortical circuits to motor control.

7.0 Conclusion

The current study provided a functional context to the unique sensorimotor and corticocortical circuits probed by TMS. Our results show that a variety of sensorimotor loops converge to shape motor output. Corticocortical connections probed by SICI are part of longer sensorimotor loops that set the initial motor plan. These loops play a dominant role in influencing the output of corticospinal neurons. Afferent projections probed by SAI are a part of shorter sensorimotor loops that modulate the longer loops to support motor control. These loops work in combination to shape the initial motor plan, and then update it with important contextual information prior to and during movement.

These findings provide support for the results of a wide range of studies using SAI and SICI. Changes in SAI and SICI responses previously seen at rest or with a static contraction only, such as disinhibition prior to movement, sensitivity to muscle contraction and interactions between different circuits were also noted in the current study. Investigating these phenomena using a motor task provides a functional basis for these responses and circuits. Further investigation into the cortical and sensory circuits that influence motor control will be important for understanding healthy motor behaviour.

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