SENSORIMOTOR INTEGRATION FOLLOWING TRAINING ON A TACTILE DISCRIMINATION MAZE TASK

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Lay Abstract

Sensorimotor integration refers to the combination of incoming sensory information with outgoing motor commands in the nervous system to control movement. Short-Latency Afferent Inhibition, Long-Latency Afferent Inhibition and Afferent Facilitation are three measures that probe sensorimotor integration in humans using Transcranial Magnetic Stimulation. Although these measures have been well studied in both healthy and clinical populations in a variety of contexts, the influence of sensorimotor training on these measures remains unclear. This thesis aimed to determine if SAI, LAI and AF change following training on a novel tactile discrimination maze task. Further, the relationship between changes in sensorimotor integration and improvements in maze performance was explored. SAI, LAI and AF were not shown to be influenced by training, and there was no association between the changes in these measures and improvements in maze performance.

Abstract

Sensorimotor integration refers to the process of combining incoming sensory information with outgoing motor commands to control movement. Short-Latency Afferent Inhibition (SAI), Long-Latency Afferent Inhibition (LAI) and Afferent Facilitation (AF) are three neurophysiological measures collected using Transcranial Magnetic Stimulation (TMS) to assess sensorimotor integration in humans. No studies to date have investigated the influence of tactile discrimination training on these measures. This study aimed to determine whether SAI, LAI, and AF are modulated following training on a custom-designed sensorimotor task which required participants to use their sense of touch to successfully navigate 3D printed maze with interchangeable paths. The maze training was separated into "high difficulty" and "low difficult" conditions which reflected the tactile challenge embedded within the maze. On an additional visit, no maze training was performed to serve as a control condition. Despite evidence of performance improvements during training, there were no significant changes in SAI, LAI or AF following training in either condition. Further, there was no correlation between the % change in SAI/LAI and improvements in total dwell time on the maze. As the functional significance of these measures is still unclear, these findings suggest that changes in SAI, LAI or AF may not be a valid metric to measure meaningful or functional changes related to skills or performance improvements induced by training.

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List of Abbreviations and Symbols

ACh–Acetylcholine

AD– Alzheimer's disease

ADM– Abductor Minimi Digiti

AF–Afferent Facilitation

AP– Anteroposterior direction

APB– Adductor Pollicis Brevis

A/D– Analog-to-digital

CS– Conditioning stimulus

GABA– Gamma Aminobutyric Acid

GPIO– General purpose input/output

EEG– Electroencephalography

EMG– Electromyography

FDI– First Dorsal Interosseus Muscle

ICF– Intracortical Facilitation

LAI– Long-Latency Afferent Inhibition

LICI– Long-Interval Intracortical Inhibition

M1– Primary Motor Cortex

MEP – Motor Evoked Potential

MAA– Multimodal Association Area

MSO– Maximum Stimulator Output

NIBS – Non-Invasive Brain Stimulation

NMES– Neuromuscular electrical stimulation

PA– Posteroanterior direction

PD– Parkinson's Disease

PNS – Peripheral Nerve Stimulation

RMT– Resting Motor Threshold

S1– Primary sensory cortex

SAI– Short-Latency Afferent Inhibition

SEM– Standard Error of Measurement

SICI– Short-Interval Intracortical Inhibition

SCI– Spinal Cord Injury

SDC– Smallest Detectable Change

TMS – Transcranial Magnetic Stimulation

TS– Test stimulus

UAA– Unimodal Association Area

Declaration of Academic Achievement

I, Jake Pickersgill, declare this thesis to be my own work. I am the sole author of this document. No part of this work has been published or submitted for publication or for a higher degree at another institution. To the best of my knowledge, the content of this document does not infringe on any copyrights. My supervisor, Dr. Aimee Nelson, and the members of my supervisory committee, Dr. Sukhvinder Obhi and Dr. Jim Lyons have provided guidance and support at all stages of this project. All experiments and TMS analyses were conducted by Jake Pickersgill. Dr. Aimee Nelson, Dr. Claudia Turco and PhD(c) Stevie Foglia aided conception and design of the study and my fellow lab mates and collaborators, Stephen Toepp, Stevie Foglia, Karishma Ramdeo, Ravjot Rehsi, Maria Salman, Harmanvir Dhaliwal, Stephanie Evans and Nawal Massood aided the collection of data.

1. GOALS OF THE THESIS

Transcranial magnetic stimulation (TMS) is a form of non-invasive brain stimulation used in both clinical and research settings which allows researchers to probe and measure several different neurophysiological processes. Specifically, TMS is used in motor control research to assess the excitability of the corticospinal tract by eliciting a motor evoked potential (MEP) in the target muscle in response to a brief magnetic stimulus above the cortex.

Sensorimotor integration is the process by which the nervous system takes the input from our different senses and simultaneously uses those signals to guide our voluntary movements. Processes of sensorimotor integration in the brain undergo dynamic changes and can be influenced by several factors such as movement or sensory and motor training. One way to assess sensorimotor integration in the nervous system i*n vivo* is to measure the influence of a peripheral nerve stimulus on the motor response from a muscle using TMS. These measures are referred to as Short-Latency Afferent Inhibition (SAI), Long-Latency Afferent Inhibition (SAI), and Afferent Facilitation (AF).

The primary goal of this thesis is to use these TMS measures as a reflection of sensorimotor integration and investigate if they are changed after completing a short bout of training on a tactile discrimination maze task. Further, the secondary goal of the thesis is to evaluate the relationship between changes in sensorimotor integration and

improvements in performance on the sensorimotor tactile discrimination maze. This thesis will begin by providing an in-depth review of the literature related to sensorimotor integration, the TMS measures being used and some key factors that influence these measures. This thesis will then describe the rationale, design and findings from the research study which aims to address some of the current gaps in the TMS sensorimotor integration literature.

2. LITERATURE REVIEW

2.1 Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) is a noninvasive brain stimulation (NIBS) technique which induces a brief, high current pulse in a magnetic coil of wire that produces a magnetic field perpendicular to the plane of the coil (Hallet, 2007). A diagram depicting a TMS coil held over the scalp can be seen in **Figure 1**. This rapid current causes changes in the surrounding magnetic field which induces an eddy current that can penetrate the skull and activate superficial pyramidal neurons in the cortex over the area the pulse is administered (Terao & Ugawa, 2002). This excitation of the pyramidal fibres gives rise to indirect or "I-waves", which are thought to originate at the cortical level through synaptic input from specific excitatory neuronal circuitries onto corticomotoneuronal cells by Gamma Aminobutyric Acid (GABA) releasing interneurons (Ziemann, 2020).

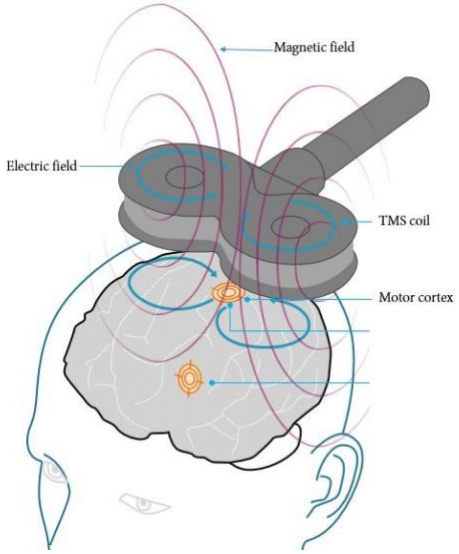

Figure 1: TMS Diagram- Figure-of-eight TMS coil inducing an electromagnetic field over the motor cortex. Adapted from (Fitzgerald, 2018).

The effect of TMS on the brain is dependent on the location of the coil on the skull, as well as the direction the coil is oriented in while held over this location on the skull. For example, TMS applied to the frontal areas of the cortex can influence cognitive functioning and executive processing (Jeurissen et al., 2014), whereas TMS above the motor cortex can influence muscle activity and motor control (Hallet, 2007). In this study, TMS will be applied over the left motor cortex to induce a descending volley towards the target muscle in the right hand. The subsequent response in the muscle can be measured using surface electromyography (EMG) and is referred to as a motor evoked potential (MEP). Regarding the direction of the TMS coil, the posteroanterior (PA) direction produces I1 waves preferentially in the hand, allowing for direct synapse onto upper motor neurons (Day et al., 1989; Sakai et al., 1997). As well, monophasic pulses are more effective if passed in the PA direction rather than the anteroposterior (AP) direction (Terao & Ugawa, 2002). Since the direction of the coil influences which underlying neural circuits are recruited (Ni et al., 2011), TMS in this study will be delivered over the motor cortex in the PA direction only.

TMS can be used to evaluate corticospinal excitability as well as several other metrics of cortical function, such as intracortical and interhemispheric inhibition or facilitation (Turco & Nelson, 2021). Further, TMS can be delivered in single-pulse, paired-pulse, or rapid-delivery paradigms which allows it to be used for a wide variety of both research and clinical applications. The next three sections of this

literature review will be dedicated to explaining three TMS measures known as SAI, LAI and AF, which are indirect measures of sensorimotor integration acquired by pairing TMS with peripheral nerve stimuli at specific time intervals.

2.1.1 Short-Latency Afferent Inhibition

SAI involves the reduction of MEP amplitude when a TMS stimulus over the motor cortex is preceded by a peripheral nerve stimulus by approximately 20ms (Ni et al., 2011; Tokimura et al., 2000). SAI is considered an indirect assessment of sensorimotor integration because it measures the reduction of the motor output caused by the activation of peripheral sensory fibres. SAI has become a focus for neurophysiology research due to evidence that this measure is reduced with aging (Brown et al., 2018), as well as in several clinical populations with impaired sensorimotor function such as Stroke (Di Lazzaro et al., 2012), Spinal Cord Injury (SCI) (Bailey et al., 2015), Alzheimer's Disease (AD) (Nardone et al., 2008) and Parkinson's Disease (PD) (Pelsoin et al., 2016). Importantly, some emerging evidence suggests that SAI may be used to monitor functional recovery post-injury in conditions like Stroke and SCI, giving it potential clinical utility (Turco et al., 2018b).

The magnitude of SAI can be experimentally modulated through multiple different factors. For example, SAI is dependent on the intensity of the TMS stimuli delivered over the Primary Motor Cortex (M1), such that increasing TMS intensity leads to a reduction in SAI (Ni et al., 2011). This relationship is suspected to be mediated by the increased

corticospinal excitability due to higher TMS intensities resulting in the nerve stimulation being less capable of having an inhibitory influence on this larger efferent output (Turco, 2018b). SAI is also influenced by the intensity of the PNS stimuli delivered, where increasing median nerve stimulation increases SAI when elicited in the PA direction (Ni et al., 2011). Since TMS stimuli delivered in the AP compared to the PA direction activates unique underlying neural populations, SAI measurements are also influenced by TMS coil direction. Specifically, SAI depth is greater when TMS is delivered in the PA direction over M1 (Ni et al., 2011). Increases in the sensory afferent volley increase the depth of SAI until a plateau is reached when all afferent fibres have been recruited (Bailey et al., 2016). Further, a positive relationship between the N20-P25 amplitude of the SEP and the depth of SAI has been demonstrated when stimulating the median and digital nerves (Bailey et al., 2016).

The reduction in MEP amplitude caused by SAI is considered to have a cortical basis, since spinal excitability is unaffected by this measure (Tokimura et al., 2000). SAI in the PA direction likely involves either a direct thalamocortical pathway to M1, or a relay via Primary Somatosensory Cortex (S1) to M1 (Turco et al., 2018b). Support of the former comes from evidence that SAI is abolished in a patient with a thalamic stroke (Oliviero et al., 2005). However, conflicting findings have been recently reported in a case study which reported SAI to be intact while the N20 component of the SEP was absent in a patient with an isolated posterolateral thalamic infarction (Alaydin et al., 2021). This

discrepancy in the literature highlights the need for future work to clarify the pathways and mechanisms underlying SAI.

Previous research suggests that SAI involves a cholinergic pathway that is modulated by $GABA_A$ activity (Turco et al., 2018a). These findings are further supported by evidence that the strength of SAI is related to the attenuation of the N100 component of the SEP (Bikmullina et al., 2009). Further, a study by Ferreri et al. (2012) that combined electroencephalography (EEG) and TMS found that SAI not only inhibits MEP amplitude, but also attenuates the amplitude of the P60 and N100 cortical responses, along with beta-rhythm decrements in phase locking. These results suggest that the suppressive effect of SAI on the excitability of the primary motor cortex is a result of the cortico–cortical activation of GABAergic-mediated inhibition onto the corticospinal neurons modulated by cholinergic activation (Ferreri et al., 2012).

Although the current understanding of the pharmacological basis of SAI is not yet complete, the cholinergic origin is also suspected because of previous findings that injection of scopolamine (muscarinic antagonist) reduces SAI (Di Lazzaro et al., 2000). Nicotine is a neuromodulator of GABA release, and evidence from animal model research in rats suggest that cortically released GABA has a tonic regulatory influence on the release of ACh in cortical and subcortical regions (Giorgetti et al. 2000). Chronic nicotine smokers have been shown to have significantly heightened

levels of SAI compared to healthy controls (Lang et al., 2008) which provides additional support for a cholinergic pathway for SAI mediated by GABA activity. SAI is believed to be mediated by pathways involving GABA receptors since the administration of benzodiazepines ($GABA_A$ receptor agonists) reduces SAI by binding to one of four subunits of the $GABA_A$ receptor (Di Lazzaro et al. 2005a; Di Lazzaro et al. 2005b; Di Lazzaro 2007). Importantly, the pharmacokinetics vary between each specific benzodiazepine such that each drug has its own unique affinity profile for a particular GABA receptor subtype. Therefore, one study explored the effects of three different benzodiazepines: diazepam, lorazepam, and zolpidem on SAI to understand which $GABA_A$ receptor subtype is most directly involved in the generation of SAI. Results indicated that lorazepam and zolpidem lead to reductions in SAI with no change caused by diazepam (Di Lazzaro et al., 2007). Based on the differences in the pharmacokinetic profiles between these drugs and their influence on SAI, the interpretation of these results was that SAI is most likely controlled by the α1 receptor subtype (Di Lazzaro et al., 2007).

SAI is influenced by ACh activity, a neurotransmitter well-known for its role in the regulation of attention (Klinkenberg et al., 2011). Consequently, evidence suggests that SAI can be modulated by the attentional state of an individual. For example, one study explored the effects of spatial attention on SAI and found that SAI was significantly increased when the participants attention was directed towards the hand on the side of the body stimulated by TMS in comparison to when attention was directed to the

hand on the opposite side of the body (Kotb et al., 2005). Another study found that SAI was reduced while performing index finger movements during both an internal and external focus of attention when compared to rest (Suzuki & Meehan, 2020). Interestingly, the internal focus of attention resulted in a less pronounced reduction in SAI, likely because the increased somatosensory afference that occurs under an internal attentional focus would maintain a greater magnitude of sensory gating on motor output (Suzuki & Meehan, 2020). Finally, Mirdimadi, Suzuki & Meehan (2017) showed that SAI elicited in the AP direction (but not in PA) was reduced when performing a high compared to low attentionally demanding visual task. These results not only highlight the role of attention in the magnitude of SAI, but also provide further support to the notion that different underlying neuronal circuits are recruited when TMS is delivered in the PA vs AP direction.

SAI is also sensitive to movement. Evidence suggests that SAI is reduced just before ballistic movements, as well as during phasic and tonic movements involving the target muscle (Asmussen et al., 2013; Voller et al., 2006). This reduction in SAI may be caused by the increased corticospinal excitability that occurs with movement or could also be the result of movement-induced gating of somatosensory signals in the cortex during movement (Turco et al., 2018b). Further, evidence from several studies have shown that adjacent muscles not involved in the task demonstrate elevated SAI prior to movement (Asmussen et al., 2014; Voller et al., 2006). These findings suggest that SAI may play a role in surround inhibition processes, yet conflicting

findings from Dubbioso et al. (2017) and Pirio Richardson et al. (2008) argue that SAI does not contribute to surround inhibition. Though these discrepancies may have been due to methodological differences across these studies, future research should attempt to design a study capable of properly establishing the relationship between SAI and surround inhibition. This is of utmost importance, since this work will help allude to the functional significance of SAI for research and clinical purposes.

The reliability of SAI has been explored briefly. In regard to relative reliability of this measure, SAI elicited in the median nerve demonstrated a poor-to-moderate relative reliability, while SAI from the digital nerve had a poor relative reliability (as determined by the intra-class correlation coefficient values) (Turco et al., 2019). For absolute reliability, SAI elicited in the median nerve demonstrated a 18% standard error of measurement, while SAI from the digital nerve showed 22% which are both considered to be a large amount of measurement error (Turco et al., 2019). From these results, authors suggested that future work should collect adequate sample sizes to use SAI as a measure of group-averaged change after some intervention, rather than to monitor change in one individual over time (Turco et al., 2019).

2.1.2 Long-Latency Afferent Inhibition

LAI refers to the reduction in MEP amplitude when a TMS stimulus is preceded with a peripheral nerve stimulus by 200-1000ms (Chen et al., 1999). Like SAI, LAI reflects a measure of the reduction in motor output as a result of peripheral sensory fibre

activation. Similarly, the depth of LAI is reduced with an increasing TMS intensity comparable to what is seen when measuring SAI (Kukaswadia et al., 2005). LAI is also influenced by the nerve stimulation intensity, however LAI increases with increasing recruitment of sensory afferent fibres until approximately 50% of the maximum sensory nerve action potential intensity (Turco et al., 2017). Therefore, LAI is thought to be less dependent on the sensory afferent volley than SAI (which is maximally elicited at 100% of the maximum sensory nerve action potential intensity).

Although LAI is currently less understood than SAI, LAI is known to have underlying neural pathways and pharmacological profile that are unique from SAI. Specifically, LAI is thought to be cortical in origin as prior studies have found that median nerve stimulation has no effect on spinal reflexes at an ISI corresponding to LAI (Chen et al., 1999). It may also involve subcortical structures and pathways which are involved in sensory processing, such as the basal ganglia-thalamocortical loop and cerebellum (Sailer et al., 2003). LAI occurs with longer intervals between TMS pulse and nerve stimulus, which may be indicative of the activation of additional cortical somatosensory areas in response to afferent sensory input (Turco et al., 2018b).

The pharmacological basis of LAI has not been explored as thoroughly as SAI yet. Nonetheless, LAI is thought to be modulated by $GABA_A$ but not $GABA_B$ activity, since

intake of Lorazepam ($GABA_A$ agonist) resulted in significant reductions in LAI while the $GABA_B$ agonist baclofen had no effect (Turco et al., 2018a). Like SAI, LAI is also reduced with healthy aging (Brown et al., 2018; Degardin et al., 2011) as well as in clinical populations such as PD (Sailer et al., 2003), focal hand dystonia (Pirio Richardson et al., 2009) and complex regional pain syndrome (Morgante et al., 2017). The differences between neurological and movement disorders affected by SAI compared to LAI may provide further evidence to support the hypothesis that they each have distinct pathways and underlying mechanisms. Still, the relationship between LAI and other neurological and movement disorders remains largely unknown to date and requires future investigation.

LAI from the median nerve has been shown to have a poor-to-moderate intersession reliability, while digital nerve LAI demonstrated moderate reliability (the highest relative reliability of all SAI/LAI measures taken) (Turco et al., 2019). However, LAI from both nerves exhibited larger measurement error values then SAI, meaning that studies using LAI as an outcome measure will likely require relatively large sample sizes to reduce this error to a tolerable level (Turco et al., 2019).

2.1.3 Afferent Facilitation

Although the inhibitory influence of sensory afferent input on motor output is often considered in TMS research, the potential facilitatory influence of this sensory input is often overlooked. AF is another indirect measure of sensorimotor integration that

can be defined as the increase in MEP amplitude when a TMS stimulus is preceded with a peripheral nerve stimulus by approximately 50-80ms (Devanne et al., 2009). AF has been explored far less often than the SAI and LAI circuits in previous research, and therefore is not currently as well understood. The precise ISI that induces the greatest facilitation of motor output has not been agreed upon, partially because it appears to vary across individuals (Ansari & Tremblay, 2019). However, the totality of the evidence appears to converge on a range of about 50-60ms for the optimal ISI to elicit AF (Ansari & Tremblay, 2019; Degardin et al., 2011; Kojima et al., 2014).

The neurophysiological mechanisms underpinning AF are only partially understood. However, one hypothesis is that AF is mediated by large afferent fibres that originate from muscle spindles, because AF was found to be present in the first dorsal interosseus (FDI), adductor pollicis brevis (APB) and extensor carpi radialis muscles when TMS was paired with median nerve stimulation, but not index finger stimulation (which have no muscle spindles) (Devanne et al., 2009). AF is believed to involve supraspinal mechanisms due to a lack of increased corticospinal excitability at this ISI (Kojima et al., 2014). AF is also thought to involve modulation of intracortical excitability since the same ISI interacts with other intracortical measures, including an increased intracortical facilitation (ICF) and a decreased short-interval intracortical inhibition (SICI) (Ridding and Rothwell., 1999; Devanne et al., 2009).

The pharmacology of AF has yet to be studied. An in-depth analysis into the mechanisms and implications of AF are warranted to uncover potential uses for the measure, since SAI and LAI have demonstrated potential for neurological research and clinical applications. AF has been shown to be reduced in patients with focal hand dystonia (Kessler et al., 2005) and restless leg syndrome (RLS) (Bocquillon et al., 2017) which are both conditions that are characterized by sensorimotor dysfunction. Though unlike SAI and LAI, there have been mixed findings on the effect of healthy aging on AF. While one study reported no significant difference between young and elderly individuals (Brown et al., 2018), another found an MEP amplitude reduction at the 55ms ISI (Degradin et al., 2011). These conflicting results may be related to differences in the ISI used to elicit AF between studies (55ms vs. N20+12ms) or due to differences in the average age of the participants in the elderly groups. Gaining an improved understanding of the mechanisms of all three of these TMS measures can be translated into enhancing current neurorehabilitation strategies to facilitate motor recovery when sensorimotor integration is impaired.

Like SAI and LAI, AF has demonstrated a low-to-moderate relative reliability using the intra-class correlation coefficient (Brown et al., 2017). Specifically, AF raw MEP amplitudes at the 32ms and 34ms ISI displayed moderate reliability but displayed low reliability when they were calculated as a ratio of the unconditioned stimulus instead (Brown et al., 2017). However, AF reliability has only been explored in this one study and should be examined further in different muscles and at several

different ISIs to gain a more complete understanding of the absolute and relative reliability of this measure.

2.2 Tactile Discrimination Training

Tactile perception refers to the ability to perceive and recognize objects or sensations through the sense of touch and is a fundamental process that must be performed successfully in order to navigate and interact with the environment. Tactile perception is very important for our ability to recognize different surfaces and textures, as well as tell them apart from one another. More specifically, tactile discrimination can be defined as a form of tactile perception in which an individual must differentiate between conflicting stimuli only through sense of touch.

There are several different types of tactile discrimination that can be assessed depending on the apparatus used. For example, temporal discrimination is the ability to distinguish between pairs or groups of stimuli with different interstimulus interval lengths (Hodzic et al., 2004). Temporal discrimination ability can be measured using a frequency discrimination task. Spatial discrimination refers to the ability to differentiate between surfaces with grooves of varying widths and is measured using the grating orientation task (Hodzic et al., 2004). Next, two-point discrimination tasks measure an individual's ability to perceive whether an object is making contact in one or two places on the skin at different widths between points and on different locations on the body (Moseley & Wiech, 2009). Finally, roughness discrimination refers to the ability to discern between

surfaces of different roughness/smoothness. Roughness perception can be assessed by presenting individuals with surfaces of different materials (ex. wool and cotton), or by presenting multiple versions of one type of material like sandpaper with varying grit numbers corresponding to the level of smoothness (Libouton et al., 2010).

It is well known that the structure and function of the sensorimotor cortex can be influenced by experience such as training. Particularly, evidence from human and animal models have demonstrated that training on tactile discrimination tasks can induce significant changes in discrimination performance as well as brain function (Hodzic et al., 2004; Sarasso et al., 2018). With regards to improvements in tactile discrimination performance after training, one study conducted in healthy adults reported that subjects underwent a rapid rate of improvement until approximately 126 trials when individuals reached a criterion performance level of getting 12 consecutive trials correct (Harris et al., 2001). During 30 tactile discrimination trials, acetylcholine release from S1 was found to be significantly increased in rats (Butt, Testylier & Dykes, 1997). Another study conducted in humans reported MEP amplitudes equally increased in the FDI and abductor digiti minimi (ADM) muscles during 16 trials of a tactile discrimination task of the finger (Master & Tremblay, 2009). No studies to date have been conducted to explore changes in TMS measures such as SAI, LAI or AF during or after tactile discrimination training, which demands further investigation in future work.

Following two weeks of 5 days per week training, neural activity is lateralized in the cortex such that activity is reduced in the ipsilateral pre and post central gyri, with increased activity in the contralateral basal ganglia, cerebellum, postcentral gyrus and thalamus bilaterally (Sarasso et al., 2018). Further, Hodzic et al., (2004) showed that the reorganization of the contralateral primary and secondary somatosensory cortex following 3 hours of tactile fingertip stimulation were associated with improvements in grating orientation tactile discrimination performance. Due to these influences on the sensorimotor systems of brain, there have been efforts made to use tactile discrimination tasks as a form of neurorehabilitation training in conditions where sensorimotor function is impaired. For example, two weeks of daily tactile discrimination training for three six-minute blocks per day reduced self-reported pain scores in patients with chronic pain, a condition associated with reduced tactile acuity (Moseley, Zalucki & Wiech, 2008).

Another group is currently attempting to validate sensory discrimination training as a form of therapy for individuals with persistent neck pain in a randomized control trial, with the hypothesis that improving tactile acuity with practice will improve symptoms of the condition (Harvie et al., 2021). Stroke is also commonly associated with loss of somatosensory function, and one study showed that tactile discrimination training of the affected limb led to clinically significant improvements in tactile acuity, brining discrimination performance to levels comparable to that of the unaffected limb (Carey, 1993).

Although not yet fully understood, there is evidence suggesting that tactile discrimination has a different effect on the sensorimotor system compared to tactile stimulation alone (Wiest et al., 2010). For example, tactile discrimination (but not tactile stimulation alone) reduced pain severity and two-point discrimination threshold for the affected limb in individuals with chronic pain (Moseley, Zalucki & Wiech, 2008). This information has important implications for sensorimotor rehabilitation. Since providing patients with sensory stimulation alone may not be enough to produce benefits, the individual may need to actively explore surfaces and compare tactile features in order to reap the benefits in the sensory neural pathways.

3. THE EXPERIMENT

3.1 Introduction

Purposeful movement in everyday life relies on dynamic interactions between incoming sensory information from the current state of the body and the environment, and the outgoing motor commands given to execute specific patterns of movement. Sensorimotor integration refers to the capability of the central nervous system to integrate sources of sensory information about the location of the body and the external environment to coordinate voluntary motor actions (Machado et al., 2010; Edwards et al., 2019). Sensory input is integral to motor control, yet rehabilitation approaches focus on restoring motor function while sensory contributions to motor control and learning are often neglected (Edwards et al., 2019). Therefore, motor training that considers somatosensory processing offers a promising avenue for motor rehabilitation.

The primary motor cortex has a general topographical and hierarchical organization which facilitates the ability of the cortex to use incoming sensory signals to precisely fine tune motor commands to achieve a goal (Monfils et al., 2005; Bizzi et al., 2000). However, sensory and motor signals are integrated in the brain (both in series and in parallel) at several medullary, subcortical, and cortical regions (Machado et al., 2010). Sensory input travels to the primary sensory area for each specific type of stimuli (ex. S1 for touch), then to cortical unimodal association areas (UAA) to integrate separated components of the same sensory modality, and finally signals from several UAA combine onto multimodal association areas (MAA) of the cortex to combine various sources of sensory information together. Sensorimotor integration processes are further complicated because they are also influenced by cognitive factors such as attention, emotion, and memory (Machado et al., 2010).

The functional organization of the sensorimotor cortex is dynamic and changes with experience. Training on a hand tracing task and a keyboard typing task have both been found lead to increased N13, N20, P25 and N30 SEP peak along with improved performance accuracy (Andrew et al., 2014). Another study found that training on a similar tracing task with the hand lead to significant changes in the amplitude of several different SEP peaks in healthy individuals that indicated changes in cortical sensory processing, including the N13, N14, N18, N20 and N24 (O'Brien et al., 2020). The increased N20 amplitude was particularly important because increases in this metric

following motor training represents an increased activation of the somatosensory cortex following motor acquisition. (O'Brien et al., 2020).

Transcranial Magnetic Stimulation (TMS) can be used to probe sensorimotor integration in humans by delivering an electrical peripheral nerve stimulus (PNS) prior to a TMS stimulus over M1 at different inter-stimulus intervals (ISI). Short-latency afferent inhibition (SAI) is elicited at an ISI of ~20-25ms (Tokimura et al., 2000), long-latency afferent inhibition (LAI) at ~200ms (Turco et al., 2018a), and afferent facilitation (AF) at ~25-80ms (Matur & Öge, 2017). SAI and LAI protocols result in a reduction of the motor-evoked potential (MEP) amplitude recorded at the muscle compared to a normal test stimulus, whereas AF elicits MEP amplitude greater than a test stimulus (**Figure 2**). Together, changes in these circuits can be used to quantify the impact of sensory afference on muscle activity in the context of motor control.

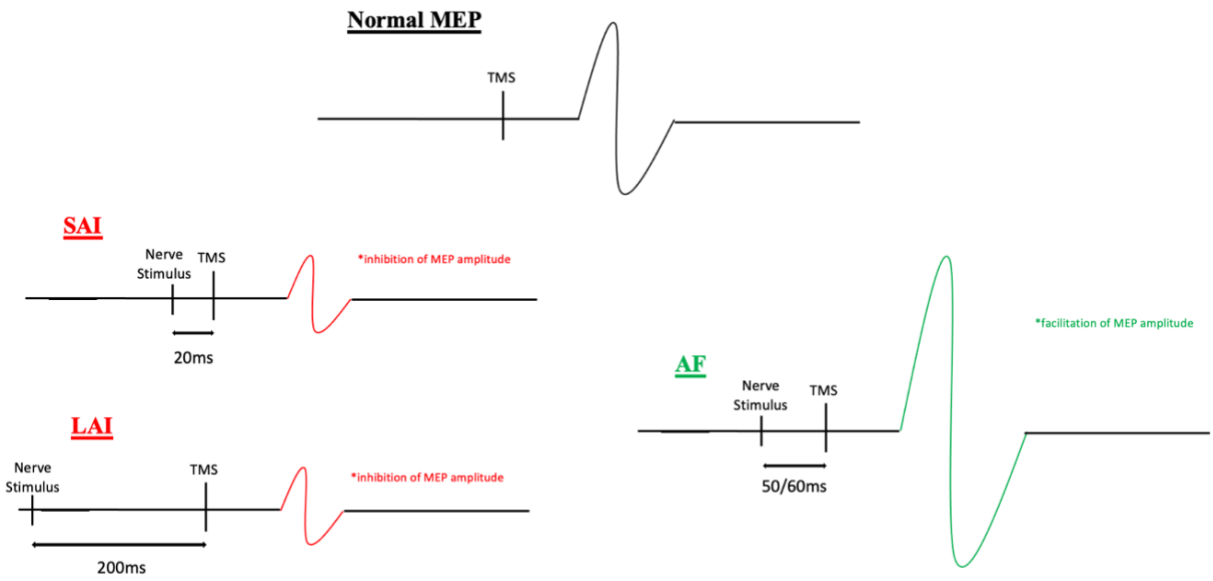

Figure 2: TMS Measures of Sensorimotor Integration- Visual representation of the MEP amplitude of SAI, LAI and AF compared to a normal MEP in response to an unconditioned test stimulus.

MEP: Motor-Evoked Potential, TMS: Transcranial Magnetic Stimulation, SAI: Short-Latency Afferent Inhibition, LAI: Long-Latency Afferent Inhibition, AF: Afferent Facilitation.

Although the neurophysiological mechanisms underlying these circuits are not yet fully understood, SAI is thought to be mediated either by a direct thalamocortical pathway to M1, or by a relay from S1 to M1 (Turco et al., 2018b). LAI most likely involves cortical (ex. Premotor Cortex, Secondary Somatosensory Area) and subcortical (Cerebellum, Basal Ganglia) sensorimotor integration regions (Sailer et al., 2003). AF is thought to be mediated by large afferent fibres that originate from muscle spindles (Devanne et al., 2009), and to involve modulation of intracortical excitability due to the interaction with other intracortical TMS measures and lack of increased corticospinal excitability at this ISI (Kojima et al., 2014).

Additionally, previous research suggests that SAI involves a cholinergic pathway that is modulated by $GABA_A$ activity, and some early evidence highlights that LAI is modulated by $GABA_A$ but not $GABA_B$ (Turco et al., 2018a). The pharmacology of AF has not yet been explored, but AF has been shown to be reduced in patients with Restless Leg Syndrome (RLS), a condition that is characterized by dysfunctional sensorimotor integration (Bocquillon et al., 2017). An in-depth analysis into the mechanisms and implications of AF are warranted to uncover potential clinical usage, since SAI and LAI are impaired in several special populations including Stroke, SCI, AD and PD among others (Turco et al., 2018b). Improved understanding of these TMS measures may potentially be translated into enhancing current knowledge about neurorehabilitation strategies to facilitate motor recovery when sensorimotor integration is impaired.

Motor training induces neural adaptations including the remodelling of the sensory and motor cortex, as well as the corticospinal tract (Rosenkranz and Rothwell, 2012). Additionally, the mechanisms of SAI, LAI and AF are known to be cortical in nature (Chen et al., 1999) which provides evidence to suggest that sensorimotor training may induce modulations in these TMS measures. Several studies have demonstrated that SAI and LAI are reduced while AF is increased by sensory influences such as vibrotactile stimulations (Brown et al., 2018; Lapole & Tindel, 2015) and neuromuscular electrical stimulation (Mang et al., 2012).

Next, there is also evidence to suggest that SAI, LAI and AF are modulated by different forms of motor training including basketball shooting (Deveci et al., 2020), ballistic pinch grips (Meunier et al. (2012) and hand tracing through a maze track (Mirdimadi & Block, 2020). However, there have been conflicting results in previous literature pertaining to the magnitude and direction of these changes which warrant further investigation. For example, SAI was shown to increase following maze tracing (Mirdimadi & Block, 2020) but not change after visuomotor tracing (Koizume et al., 2017; Paparella et al., 2020). Conversely, basketball shooting was shown to decrease LAI and increase AF after one day of training (Deveci et al., 2020). Studies have also found a positive correlation between the changes in SAI/LAI following motor training and the improvements in performance on the motor task (Meunier et al., 2012; Mirdimadi & Block, 2020; Pelosin et al., 2020). This relationship highlights the role of the somatosensory system in the acquisition of motor skills, though the exact mechanisms have yet to be discovered.

The neurophysiological underpinnings of SAI, LAI, AF and effects of sensorimotor training on these measures are still currently unclear. Further, there has not yet been an investigation into the influence of training on a tactile discrimination sensory-guided movement task on these measures. In the present study, SAI, LAI and AF were measured before and after continuous blocks of training on a novel sensorimotor finger maze task where performance relies on sensory discrimination of afferent signals originating from the same neural pathways that are used to acquire SAI, LAI and AF. Each sequential

movement within the maze relies upon a perception of roughness tactile discrimination choice, enhancing the functional relevance of the sensory input.

The primary objective of this study is to determine if TMS measures of sensorimotor integration are modulated by training on the maze task. The secondary goal of this work is to determine if these changes are related to improvements in performance on the maze. Due to the large contribution of somatosensation to maze performance, it is predicted that maze training ultimately will modulate SAI, LAI and AF similar to past works investigating the effects of sensory training on these measures (Lapole & Tindel, 2014; Mang et al., 2019). Therefore, our first hypothesis is that maze training will decrease SAI and LAI but increase AF. Secondly, it is hypothesized that the amount of change in SAI and LAI post-training will be correlated with the slope of the total dwell time on the maze during training. This hypothesis was derived from evidence from past studies showing that changes in SAI (Mirdimadi & Block, 2020; Pelosin et al., 2020) and LAI (Meunier et al., 2012) were related to improvements in task performance.

3.2 Methods

3.2.1 Participants

Thirty right-handed, healthy participants (22 females; age = 21.16 ± 2.83 years) were recruited for this study. Individuals younger than 18 were ineligible for study participation, and those above the age of 35 were excluded due to the impact of general healthy aging on TMS measures of brain activity (Brown et al., 2018). Also, in line with

common practice in TMS literature, right-handed participants were required for this study due to the influence of handedness on motor cortical representations and excitability (Nicolini et al., 2019). Participants went through an initial screening process for contraindications to TMS (Rossi et al., 2009) and handedness was determined using a modified handedness questionnaire (Oldfield, 1971). All participants provided written informed consent prior to data collection in this study. This research received approval from the Hamilton Integrated Research Ethics Board (HiREB) under application #13523. An *a priori* power analysis for a repeated measures ANOVA within-subjects factors design was performed using G*Power to determine the sample size required for this study. The power analysis was calculated based on data from Mirdimadi and Block (2020) (n=28) who compared changes in SAI before and after training on a motor training maze task. The effect size in this study was f = 0.27 and is considered small according to Cohen's (1988) guidelines. With an alpha = 0.05 and power = 0.80, the projected sample size needed with this effect size (G*Power 3.1) is n = 30.

3.2.2 Experimental Design

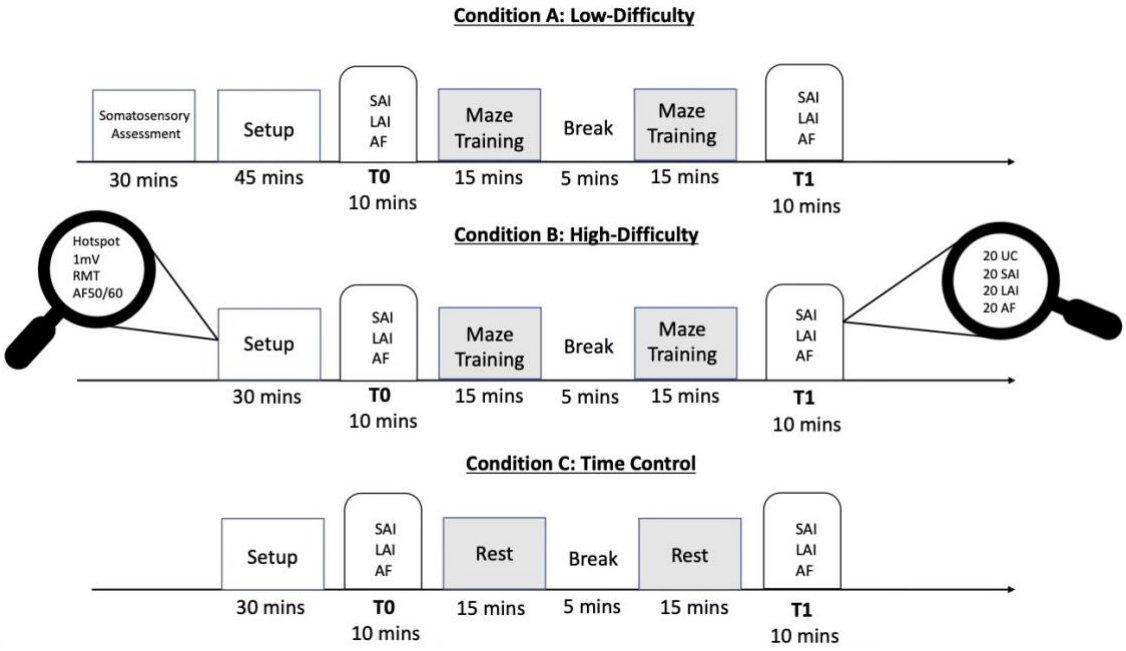

Figure 3: Experimental timeline- The study will involve three sessions, two training sessions and one time control session in counterbalanced fashion. Somatosensory Assessment- fingertip tactile acuity assessment using Brain Gauge Cortical metrics. Setup-EMG & TMS preparation, FDI hotspot, RMT, 1mv MEP, PNS intensity**.** Maze Training- repeated practice attempts on the maze.

EMG: Electromyography, TMS: Transcranial Magnetic Stimulation, FDI: First Dorsal Interosseus, RMT: Resting Motor Threshold, SAI: Short-Latency Afferent Inhibition, LAI: Long-Latency Afferent Inhibition, AF: Afferent Facilitation.

Figure 3 shows the experimental design and procedures for this study, which consisted of three conditions performed in a fully within-subjects design: low difficulty training, high difficulty training and time control. Participants performed each condition on separate days, with the order of presentation counterbalanced across participants to avoid any order effects. Sessions were separated by a 3–7-day period to allow for flexibility in scheduling and promote retention of participants. Importantly, we required all sessions across this study be in the morning hours (between 8am and 12pm) because there has

been evidence to demonstrate that afferent inhibition is influenced by circadian rhythm (Bocquillon et al., 2017; Milani et al., 2010).

During the training sessions, participants took part in two 15-minute blocks of training on the sensorimotor maze task. The difference between the sandpaper grits on the maze surface for tactile discrimination was larger in the low difficulty condition, making it easier for participants to be able to distinguish between the two options. The alternative sandpaper grits on the maze in this condition were #60 and #400. In the high difficulty condition, the difference between the alternative sandpaper grits were less obvious, making the tactile discrimination choice more challenging. The grits on the high difficulty board were #120 and #320. In all conditions, the reference sandpaper grit (which indicates the correct path to follow) was #220.

The purpose of the time control condition was to measure SAI, LAI and AF following a period of seated rest to see if there is any change in these measures without introducing any intervention. This allowed us to compare these results against changes found in the training condition within a participant to determine if any modulations that occur following training are robust. Therefore, no maze training occurred during the control visit, only TMS measures were recorded at the same time points as the other sessions. The duration of each session was approximately 2 hours in total.

3.2.3 Electromyography (EMG)

Surface electrodes (9mm Ag-Cl) were used to record activity from the FDI muscle of the right hand to collect the peak-to-peak MEP amplitude **(Figure 4).** The FDI muscle was chosen because it controls movements like abduction of the second digit which is innately involved in the sensory discrimination component of the task, and because the goal of the study was to assess somatosensory changes related to hand/digit perception. Also, measures of afferent inhibition are most well established in the muscles of the hand like the FDI (Turco et al., 2018a). Although changes in motor output from muscles controlling these shoulder and elbow movements were not assessed here, previous research suggests that the depth of SAI in FDI is comparable to muscles of the forearm and biceps brachii (Bailey et al. 2016; Helmich et al., 2005).

The active electrode was placed over the muscle belly in a tendon-belly montage, and activity was referenced to the knuckle of the first digit. In order to reduce signal noise, a dry ground was be placed on the ulnar styloid process of the wrist. EMG signals were magnified x1000 and band pass filtered between 20-2.5 kHz (Intronix Technologies Corporation Model 2024F, Bolton, Canada). An analog-digital converter was used to digitize data at 5 kHz (Power1401; Cambridge Electronics Design, Cambridge, UK), prior to being analyzed through commercial software (Signal v7.0; Cambridge Electronics Design, Cambridge, UK). The hotspot of the right FDI muscle was defined as the location on the left motor cortex that, when stimulated with TMS, consistently led to

the largest MEP in the muscle. This point was found and registered using Brainsight Neuronavigation with TMS (Rogue Research, Montreal, Canada).

Figure 4: EMG Electrode Setup- Organization of electrodes used to record muscle activity during the study. Active electrode over the muscle belly of the right first dorsal interosseus (red), reference electrode over the right knuckle (black), and ground electrode on the styloid process of the ulna (green).

3.2.4 Transcranial Magnetic Stimulation (TMS)

A figure-of-eight branding coil (50 mm diameter) connected to a MagStim 200^2 stimulator (Magstim, UK) was used to apply TMS in this study, with the coil held at a 45-degree angle in the PA direction over M1 **(Figure 5).** Monophasic single-pulse waveforms were administered over the FDI motor hotspot, defined as the location on the left motor cortex that consistently led to the largest MEP in the muscle. This point was located and registered using Brainsight Neuronavigation (Rogue Research, Montreal, Canada).

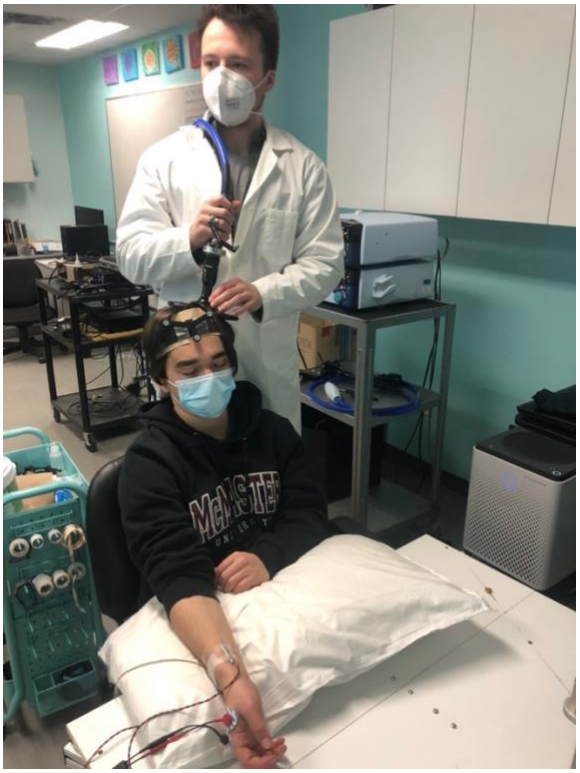

Figure 5: TMS Setup- Image of experimenter performing TMS over the left motor cortex of a participant, with the coil oriented in the PA direction.

3.2.4.1 Resting Motor Threshold (RMT)

Motor threshold was determined by delivering a single pulse paradigm to the left primary motor cortex. Resting motor threshold (RMT) was defined as the stimulus intensity (%MSO) that evokes an MEP (peak-to-peak amplitude >50 µV) 50% of the time. This value was determined using the free software *TMS_MTAT_2.0* (http://clinicalresearcher.org/software.htm). The starting stimulus intensity was set to 37 %MSO, and twenty TMS pulses were delivered over M1 with stimulus intensity being adjusted after each pulse as determined by the MTAT software based on the presence or

lack of an MEP on the previous trial (Ah Sen et al, 2017). This procedure was collected at T0 in each session and required ~5 minutes to complete.

3.2.4.2 Measures of Sensorimotor Integration

For all TMS measures of sensorimotor integration, TMS stimuli were delivered at the lowest intensity required to elicit an MEP with an amplitude of 1mV in the FDI muscle. The ISI between TMS and nerve stimulation was 22ms for SAI (Tokimura, 2000), and 200ms for LAI (Turco et al., 2018a) as used in previous work in the field. For AF, the ISI was set at either 50 or 60ms after an *a priori* determination (Ansari & Tremblay, 2019), as done previously by Ansari & Tremblay (2019). In the SAI, LAI and AF protocols, peripheral nerve stimulation consisted of 200 μs square wave pulses applied to the Median nerve with a bar electrode **(Figure 6)** at the minimum intensity required to evoke a visible twitch in the thenar muscles (Di Lazzaro et al., 2005). There were a total of 80 trials during each TMS sensorimotor integration collection: 20 unconditioned Trials (TMS only), 20 conditioned SAI trials, 20 conditioned LAI trials, and 20 conditioned AF trials. All TMS trials were presented in a randomized order to participants during each collection. For the *a priori* AF determination on the first visit, 15 unconditioned Trials (TMS only), 15 conditioned trials with an ISI of 50ms, and 15 conditioned trials with an ISI of 60ms were delivered. Whichever interval yielded higher MEP facilitation was then used for eliciting AF in that individual for the remainder of this study.

Figure 6: PNS Setup- Image of a bar electrode secured above the median nerve of the participant at the wrist to probe SAI, LAI and AF.

3.2.5 Tactile Discrimination Maze

3.2.5.1 Maze Design

An overhead image of the novel finger maze can be seen in **Figure 7.** The maze consists of a wood board with dimensions of 75cm x 45cm. The walls of the maze are composed of 3-D printed PETG plastic 2 inches tall. The paths in the maze for the finger are 24mm in width, and the sandpaper strips at the intersections are 2 inches in width and composed of one of 5 different standard grits: 400, 320, 220, 120, & 60 (*ProSand*, Norton Abrasives, USA). The range of grits used for sensory discrimination in the maze was chosen based on previous research investigating the just-noticeable differences in tactile perception of roughness using difference in sandpaper grit (Simmer-Beck et al., 2007).

To provide a tactile indication of the boundaries of the maze, the start and stop zones are composed of small felt pads with a 6cm radius.

The maze was navigated by the index finger with periodic decision points in the path composed of sandpaper for the purpose of using sensory input from the fingertip to guide movements in the absence of vision. Maze training was performed whilst blindfolded and with earplugs in. The blindfold and earplugs served to avoid the participant from seeing or hearing what changes were occurring to the maze path during training. The maze contained strips of sandpaper composed of 5 different grits ranging from coarse to smooth, and the goal is to follow the correct path by using only tactile information provided by the difference in grit between strips.

The maze was placed in front of the participant and the index finger of the right hand was placed at the start position. The participant moved their finger forward until they approached a strip of sandpaper that serves as the reference strip. The participant must evaluate the texture of the sandpaper here, then move forward where there is a small open decision area surrounded by two options for different options for paths that can be chosen ahead. Here, the participant explored the surface of different sandpaper strips at the entrance of each new paths to identify which strip has the same texture as the reference strip from the direction they came. Essentially, each intersection required participants to perform a tactile perception of roughness sensory discrimination task that will guide the movement of the index finger. The participant then proceeded down the path with the

same texture until they approached the next decision point, and they repeated this process through five intersections until they arrived at the end of the maze which was indicated by the sensation of the felt pad beneath the finger.

Figure 7: Tactile Discrimination Maze- Overhead view of the paths on the maze board. Black pathways are the maze surface explored by the finger. Start/End zones indicated by white/grey stripes.

3.2.5.2 Maze Training

During the two 15-minute maze training blocks, participants performed repeated attempts on the maze track that was presented to them in a randomized arrangement in each subsequent trial to maintain motivation and avoid early memorization of the path which would minimize the importance of the sensory discrimination component of the maze. The maze is adjustable by way of dropping in or pulling out walls that change the correct path from entrance to exit, as seen in **Figure 8** below.

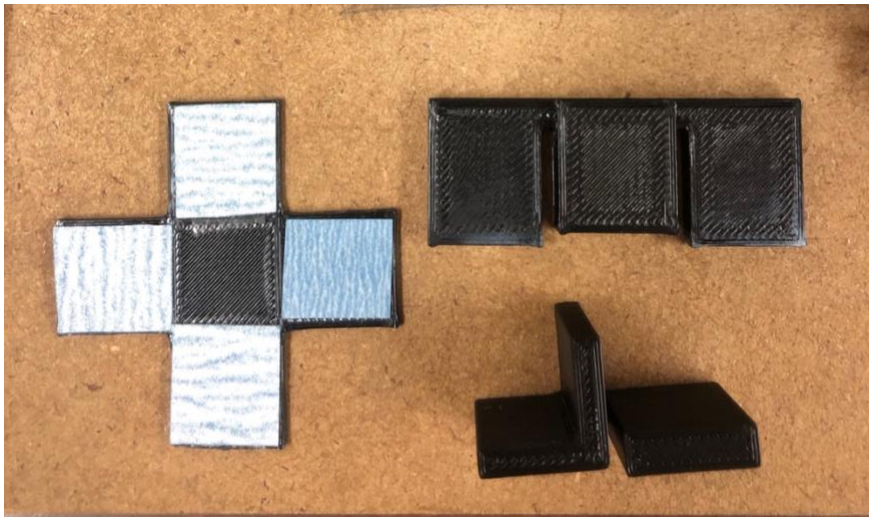

Figure 8: Maze Parts- Image of the removeable pieces of the maze. Left- intersection surface piece with sandpaper strips secured down. Right- interchangeable wall pieces.

The order of presentation of the different possible arrangements of the maze walls for each participant was chosen based on a predetermined order created by a random number generator. After confirmation that the participant understood the task, all participants were given the same set of verbal instructions: “Take your time and focus on the decisions, because you want to complete the maze as quickly as possible without sacrificing accuracy”. Then, all participants were allowed to complete one familiarization trial with the maze before real training began, to ensure they could successfully complete the maze and understood the goals of the task. During training blocks, experimenters monitored participants’ performance to ensure the task is being performed correctly. A front view of a participant performing a trial on the sensorimotor maze can be seen in **Figure 9.** Also, a link to a demonstration video of how the maze intersections are navigated can be found here.

Figure 9: Maze Training- Image of participant performing a maze training trial. Notice that participant is seated and blindfolded, forcing them to rely on tactile information from the intersections to navigate through the maze.

3.2.5.3 Maze Performance Measures

During maze training, all participants were equipped with one small rectangular neodymium magnet on the top surface and one small circular neodymium magnet on the side of the fingertip, as seen in **Figure 10**.

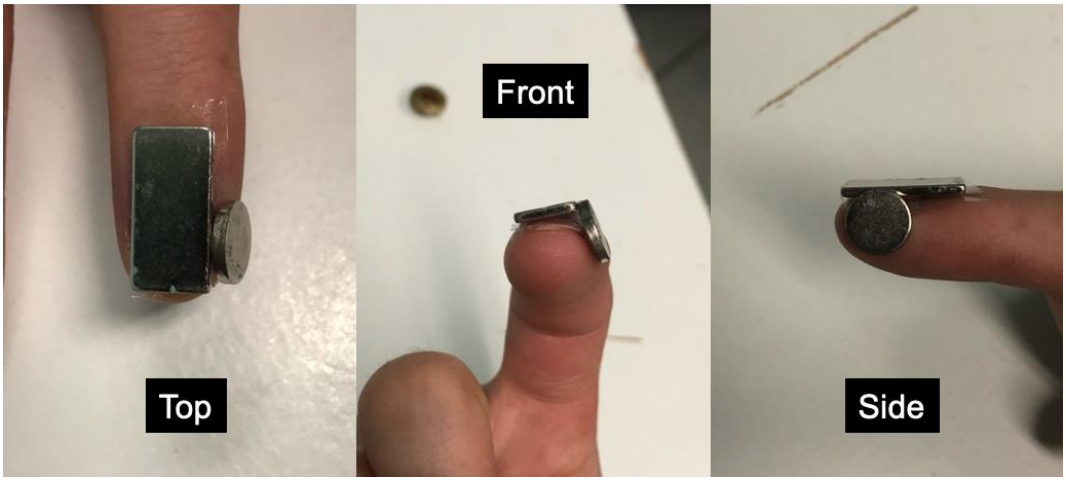

Figure 10: Finger Magnet- One small rectangular and one small circular neodymium bar magnet were taped on to the top surface of the finger in order to track finger movement through the maze during training.

These magnets were used because the start/end zones as well as the intersections of the maze were equipped with sensors (reed switches) that can detect when a magnet is in close proximity by slightly moving a small piece of metal within the sensor enough to touch an adjacent piece of metal and close a circuit. An image showing an intersection of the maze with the reed switches along the surface shown with red arrows can be found in **Figure 11.** Values from these sensors were used in order to measure movement performance during maze training by recoding when the participant starts and completes the trial, as well as the time taken within each intersection to make a tactile discrimination decision about the sandpaper texture.

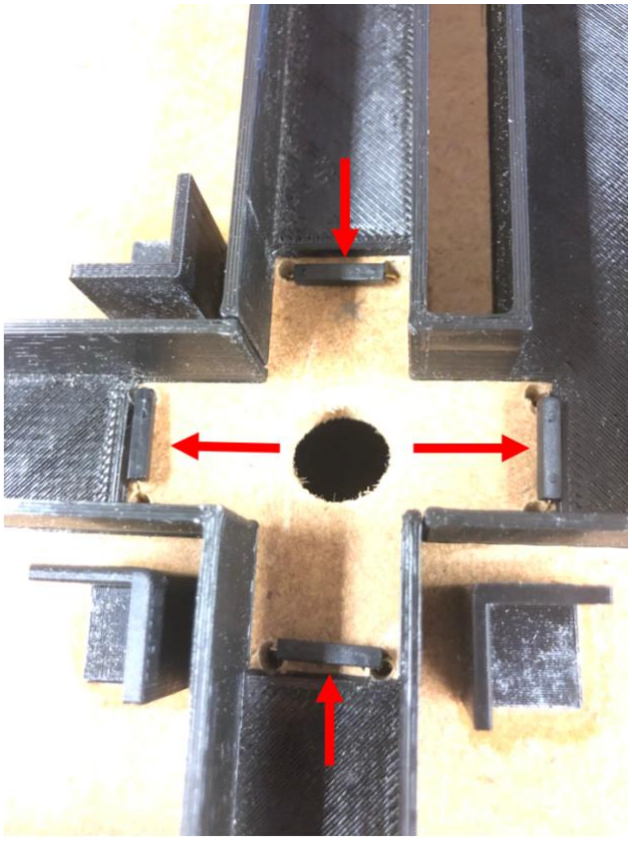

Figure 11: Maze Sensors- Red arrows pointing to the 4 reed switches that act as magnetic sensors located at the exit of each path to calculate dwell time at an intersection.

A circuit diagram depicting the maze data collection setup can be seen in **Figure 12**. Each of the sensors from the maze was connected in parallel below the board surface to their own resistor, then leads from each resistor went to one common return, which connected the maze to an analog-to-digital (A/D) converter. The A/D converter converts raw changes in voltage recorded from the sensors on the maze into a digital format which could be read by a computer in the form of numerical values. The A/D converter was directly connected to a standalone Raspberry Pi 400

(Raspberry Pi Foundation, UK) personal computer via general purpose input/output (GPIO) pin connectors to the appropriate pin numbers **(see Figure 12).**

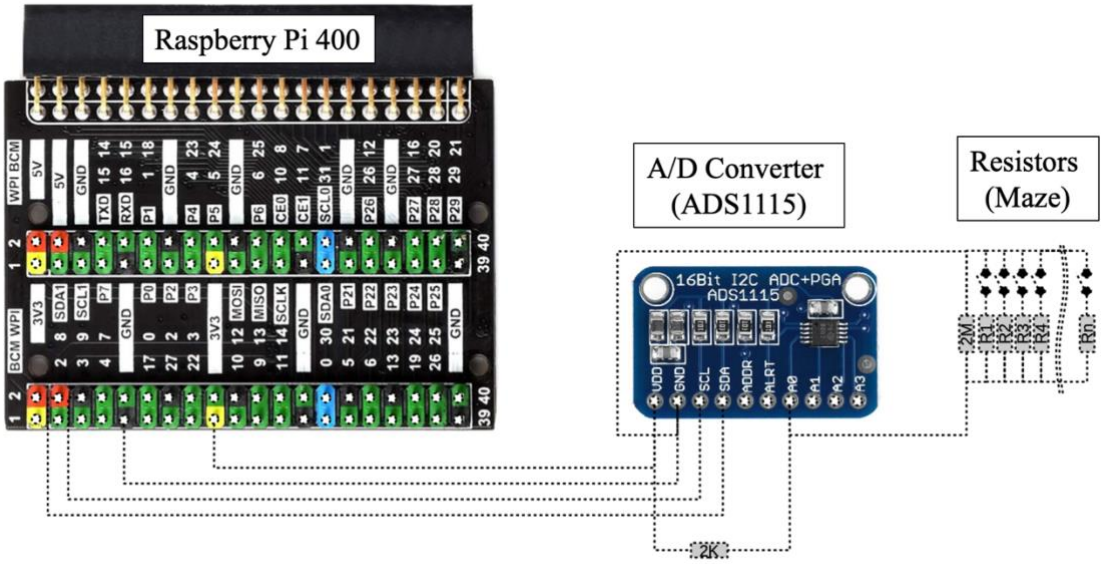

Figure 12: Maze Circuit Diagram- General overview of the electrical connections from the maze board to the personal computer for data collection. Left- GPIO extension board from the rear side of the Raspberry Pi 400 keyboard which connects to A/D converter. Middle- ADS1115 A/D converter connecting the maze to the computer. Right- Individual resistors on the maze with unique resistances from each intersection, connected to the A/D converter in parallel.

During maze trials, a custom-designed code written in Python 3 was run from the Raspberry Pi 400 which allowed for the changes in resistance values from the A/D converter to be recorded, time stamped, and labelled in a comma separated value output file depending on the location of the sensor that was triggered at that time. For example, if a participant crossed the bottom of the first intersection 1.5 seconds after the start of the trial, the following would be exported to an output file for post training analysis: "1.50s-1 Bottom." Through post-processing measurement of the duration between these time

stamped values, total time to complete the maze (start time subtracted by the end time), dwell time at each intersection (entrance time into an intersection subtracted from the exit time), and the total dwell time in the maze (sum of all 5 individual dwell times) were calculated. Whenever a participant made an error and travelled down the wrong path, the error was visually identified by experimenters during training and inputted into the data collection sheet in real time. No feedback related to the speed of performance or number of errors made was provided during training.

3.2.6 Baseline Somatosensory Assessments

Baseline somatosensory assessments of the right index fingertip were performed for the purpose of acquiring participant's baseline level of tactile acuity at the fingertip. Participants completed two tests involving sensory discrimination choices using the *Brain Gauge: Cortical Metrics* (Cortical Metrics, USA) computer mouse. An image of the *Cortical Metrics* mouse and laptop setup can be seen in **Figure 13.** Participants performed each of these assessments once with and once without the magnet from the experimental setup used during maze training (see **Figure 10**) taped on the top surface of the finger above the fingernail to see if having the magnet on the finger has an influence on tactile acuity of the fingertip. These assessments were performed in a counterbalanced fashion across participants in order to avoid any order effects.

The handheld mouse is a standard size and connects to any laptop via USB. This device is used for testing sensory abilities by delivering vibrations of differing durations and

intensities to the two small buttons on the top surface where the second- and third-digits rest on the mouse. The test software provides a familiarization trial at the start of each test to ensure that the participant is aware of the expectations prior to beginning the test. The two tests from *Brain* Gauge software used in this study were the "Sequential Amplitude Challenge", and the "SSA Challenge". The "Sequential Amplitude Challenge" required participants to determine which of two simultaneous vibrations to the fingertips was more intense, whereas the "SSA Challenge" required participants to ignore an initial vibration then discriminate between two subsequent simultaneous vibrations to the fingertips. Each of these tests consisted of a battery of five sequential protocols lasting 5 minutes each. The total time to administer these tests twice each was approximately 30 minutes total.

Figure 13: Somatosensory Assessment Equipment- *Brain Gauge: Cortical Metrics* handheld mouse and associated software on laptop screen.

3.3 Statistical Analyses

Peak-to-peak MEP amplitudes recorded from the FDI were averaged across the 20 measures collected in a trial (20 unconditioned MEPs, 20 SAI, 20 LAI, 20 AF). SAI/LAI/AF were processed in terms of ratio of afferent inhibition, calculated as the $MEP_{Conditioned}/MEP_{Unconditioned}$. To determine if significant inhibition and facilitation were present in the SAI, LAI, and AF data compared to the unconditioned MEP, two-way repeated measures ANOVAs were conducted for each condition, with STATE (TS, CS-TS) and TIME (T0, T1) as the within subjects conditions. Performance measures included the total time required to complete each maze (seconds), total dwell time (seconds), the number of errors made and the total # of maze trials completed. An error on the maze was defined as any instance where the participant follows the wrong path to a dead end and must turn back. All statistical analyses were performed using SPSS Statistical Software (Version 23, IBM SPSS, USA). Shapiro-Wilks tests were conducted on all variables to assess normality initially, and non-parametric analyses were adopted if any assumptions were violated.

3.3.1 Data/Participant Exclusion Criteria

TMS Trials with peak-to-peak EMG activity greater than 100 μV in a 100ms window prior to the TMS artifact were discarded, similar to previous work (Schambra et al., 2015; Turco et al., 2019). If >25% of trials for TMS or maze performance were excluded within a participant's dataset at any time during the study, the participant's data was excluded

entirely from data analyses and replaced by the collection of data from a new participant to ensure that an adequate sample size was collected.

3.3.2 Hypothesis Testing

Hypothesis 1) SAI and LAI will decrease, AF will increase following training

SAI, LAI and AF were each analysed independently with TIME (T0, T1) and CONDITION (high, low, and control) as the within-subject factors to determine the effect of training on these measures. The assumptions of normality and sphericity were assessed for each circuit, and Friedman Test was used as a non-parametric alternative form of analysis if assumptions of the repeated measures ANOVA were not satisfied. Bonferroni corrections for multiple comparisons were performed. Any significant main effects were subjected to post-hoc analysis using Tukey HSD (or Wilcoxon signed-rank test if non-normal).

Hypothesis 2) Changes in SAI/LAI will be related to improvements in maze performance

Bivariate correlations were calculated to determine the magnitude and direction of the relationship between changes in SAI/LAI and performance measures before and after training. Normality was assessed using the Shapiro-Wilk Test, linearity was assessed visually using a scatterplot, and homoscedasticity was assessed visually using a scatterplot of residuals versus predicted values. If any assumptions of the Pearson Product-Moment Correlation Coefficient were violated, Spearman Rank-Order

Correlation was used as a non-parametric alternative form of analysis. Significance was set at $\alpha = 0.05$ for all tests in this experiment.

3.3.3 Reliability

Absolute reliability was evaluated from the data from the control condition using the standard error of measurement (SEM) to acquire a measure of smallest detectable change (SDC) for SAI, LAI and AF. SEM is calculated as: √MSE, where MSE is the mean square error term from a repeated measures ANOVA (Weir et al., 2005). SDC_{group} and SDC_{indiv} were calculated, to determine the minimum amount of change within the group and at the individual level that is considered real with 95% confidence and not due to measurement error. The SDC_{group} from the time control condition can be used as a complement to hypothesis testing for interpreting changes in the TMS measures following training (Schambra et al., 2015).

$$SDC_{indiv} = SEM_{eas} \times 1.96 \times \sqrt{2}$$

SDC_{indiv} is calculated as:

$$SDC_{group} = \frac{SDC_{indiv}}{\sqrt{n}}$$

SDC_{group} is calculated as:

Where n=sample size

3.4 Results

TMS was well tolerated by all participants in this study, with no adverse events or negative reactions reported. Throughout the study, TMS was delivered at the lowest intensity required to elicit a ~1mV peak- peak MEP amplitude, which equated to 132± 16.72% of the RMT when averaged across all participants. In accordance with our predetermined noise and background EMG activity thresholds, <1% of the total frames were removed from analysis (131 out of 14400). Therefore, no participants had to be removed due to corrupted TMS data. However, more than 25% of maze trial dwell time data were missing from six participants, so the entirety of their data was removed from analysis in this experiment and they were replaced with other participants for a total of n=30.

3.4.1 Sensorimotor Integration

To test for the presence of SAI and LAI, a two-way repeated measures ANOVA revealed significant main effects of STATE only for each condition as shown in **Table 1** whereby CS-TS was reduced compared to TS alone. These data indicate that significant inhibition was present for SAI and LAI in all conditions. To test for the presence of AF, two-way repeated measures ANOVA showed a significant main effect of STATE in the control but not the high and low conditions. These data indicate that significant facilitation was not present in the high and low conditions.

SAI	**Effect of STATE**	**Effect of TIME**	**Interaction Effect**
High	$F_{(1,29)}$=33.23, **p= <0.001**, η_p^2=0.53	$F_{(1,29)}$=0.03, p=0.87, η_p^2=0.001	$F_{(1,29)}$=1.05, p= 0.31, η_p^2=0.04
Low	$F_{(1,29)}$=45.30, **p= <0.001**, η_p^2=0.61	$F_{(1,29)}$=0.95, p= 0.34, η_p^2=0.03	$F_{(1,29)}$=1.33, p= 0.23, η_p^2=0.04
Control	$F_{(1,29)}$=45.78, **p= <0.001**, η_p^2=0.61	$F_{(1,29)}$=0.87, p= 0.36, η_p^2=0.03	$F_{(1,29)}$=0.11, p= 0.74, η_p^2=0.004
LAI			
High	$F_{(1,29)}$=32.26, **p= <0.001**, η_p^2=0.53	$F_{(1,29)}$=0.44, p= 0.51, η_p^2=0.02	$F_{(1,29)}$=0.004, p= 0.95, η_p^2=<0.001
Low	$F_{(1,29)}$=46.91, **p= <0.001**, η_p^2=0.62	$F_{(1,29)}$=0.30, p= 0.86, η_p^2=0.001	$F_{(1,29)}$=0.88, p= 0.77, η_p^2=0.003
Control	$F_{(1,29)}$=33.82, **p= <0.001**, η_p^2=0.54	$F_{(1,29)}$=1.26, p= 0.27, η_p^2=0.04	$F_{(1,29)}$=0.31, p= 0.58, η_p^2=0.01
AF			
High	$F_{(1,29)}$=2.88, p= 0.10, η_p^2=0.09	$F_{(1,29)}$=1.61, p= 0.22, η_p^2=0.05	$F_{(1,29)}$=3.35, p= 0.08, η_p^2=0.10
Low	$F_{(1,29)}$=0.75, p= 0.39, η_p^2=0.03	$F_{(1,29)}$=0.05, p= 0.82, η_p^2=0.002	$F_{(1,29)}$=0.002, p= 0.96, η_p^2=<0.001
Control	$F_{(1,29)}$=5.36, **p= 0.03**, η_p^2=0.16	$F_{(1,29)}$=0.83, p= 0.37, η_p^2=0.03	$F_{(1,29)}$=0.27, p= 0.61, η_p^2=0.01

Table 1. Two-Way Repeated Measures ANOVA Results Between TS and CS-TS raw values for SAI, LAI and AF. Bolded p-values= significance at alpha= 0.05.

The mean ± SD of SAI at T0 and T1 across all conditions can be found in **Figure 14.** This information is also reflected in **Table 2,** which shows the mean ± SD for SAI, LAI and AF across all collections in this study. To test the effects of maze training on SAI, two-way repeated measures ANOVA revealed no significant main effects of TIME ($F_{(1,29)}$= 0.99, p= 0.33, η_p^2=0.03), CONDITION ($F_{(2,58)}$=0.24, p= 0.79, η_p^2=0.01), or their interaction ($F_{(2,58)}$=0.64, p= 0.53, η_p^2=0.02). These data indicate that there was no influence of training on measures of SAI.

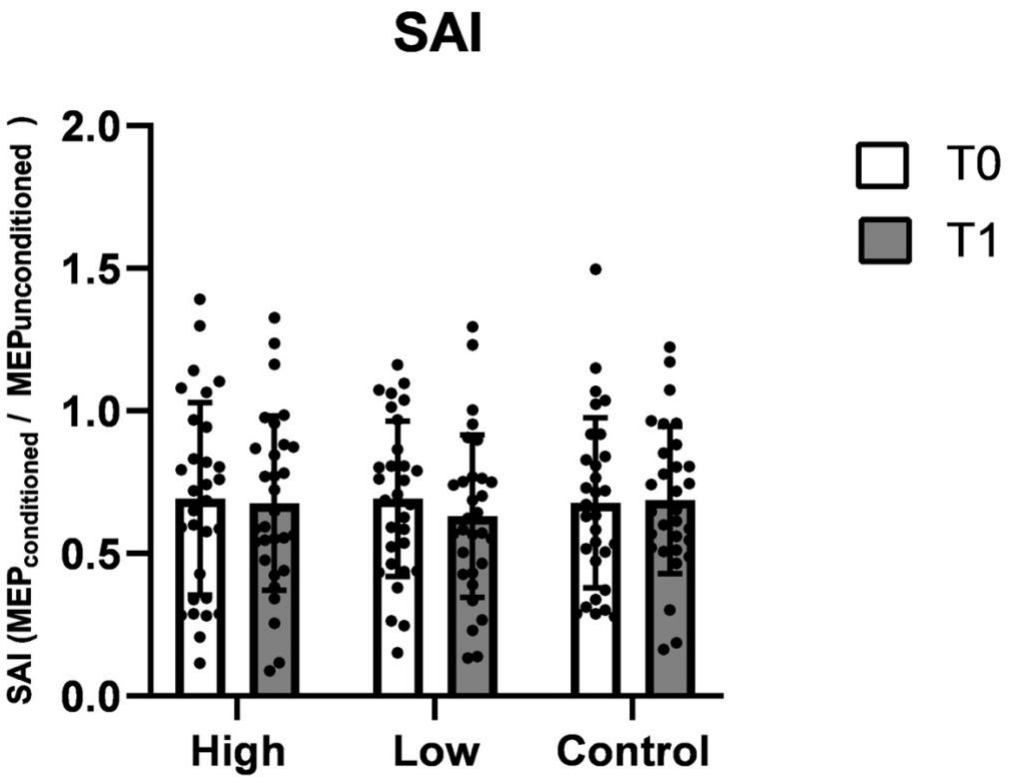

Figure 14: Group-Averaged SAI Data- Average SAI, expressed as a ratio of the average unconditioned MEP amplitude, with Standard Deviation Bars, and individual values represented as each dot. T0=White bars. T1=Grey bars. SAI did not change following high or low difficulty maze training (p=0.33).

Figure 15 plots the mean ± SD of LAI at T0 and T1 across all conditions. For LAI, a significant result from the Shapiro-Wilk test (W= 0.96, p=<0.001) indicated that LAI data departed significantly from normality, and this data could not be normalized by log or square root transformation. Therefore, the Friedman Test was performed. This analysis of LAI at T0 and T1 in all conditions revealed a Chi-square value of $\chi^2(5) = 2.44$, which was non-significant ($p = 0.79$), indicating that there is no statistically significant difference between the mean ranks of these related measurements.

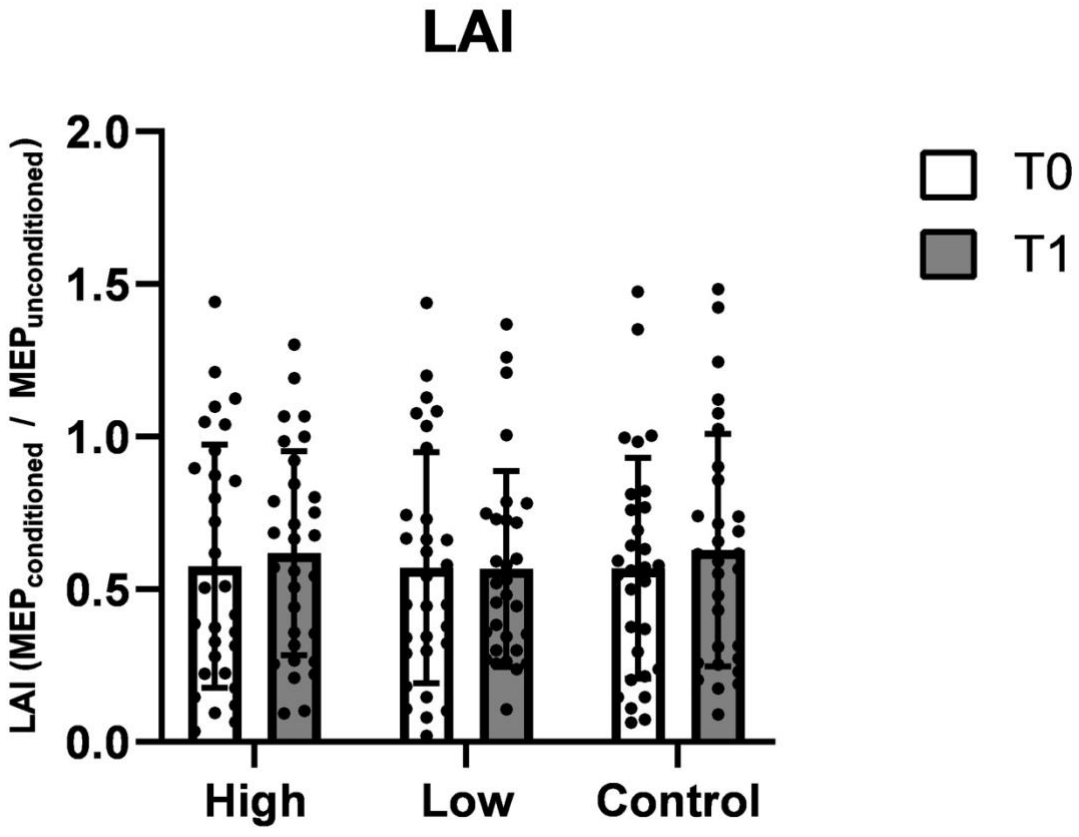

Figure 15: Group-Averaged LAI Data- Average LAI, expressed as a ratio of the average unconditioned MEP amplitude, with Standard Deviation Bars, and individual values represented as each dot. T0=White bars. T1=Grey bars. LAI did not change following high or low difficulty maze training (p=0.79).

Next, the mean ± SD of AF at T0 and T1 across all conditions can be found in **Figure 16**. Like LAI, results from the Shapiro-Wilk Test indicated that AF data also failed to meet the assumption of normality (W= 0.96, p=<0.001), and could not be normalized by log or square root transformation. Therefore, non-parametric analyses were conducted for AF. Results from the Friedman Test revealed a Chi-square value of $\chi^2(5) = 6.50$, which was also non-significant (p = 0.26) and suggests that there is no statistically significant difference between measures of AF across the study. Again, these findings suggest that maze training did not influence measures of AF at the group level.

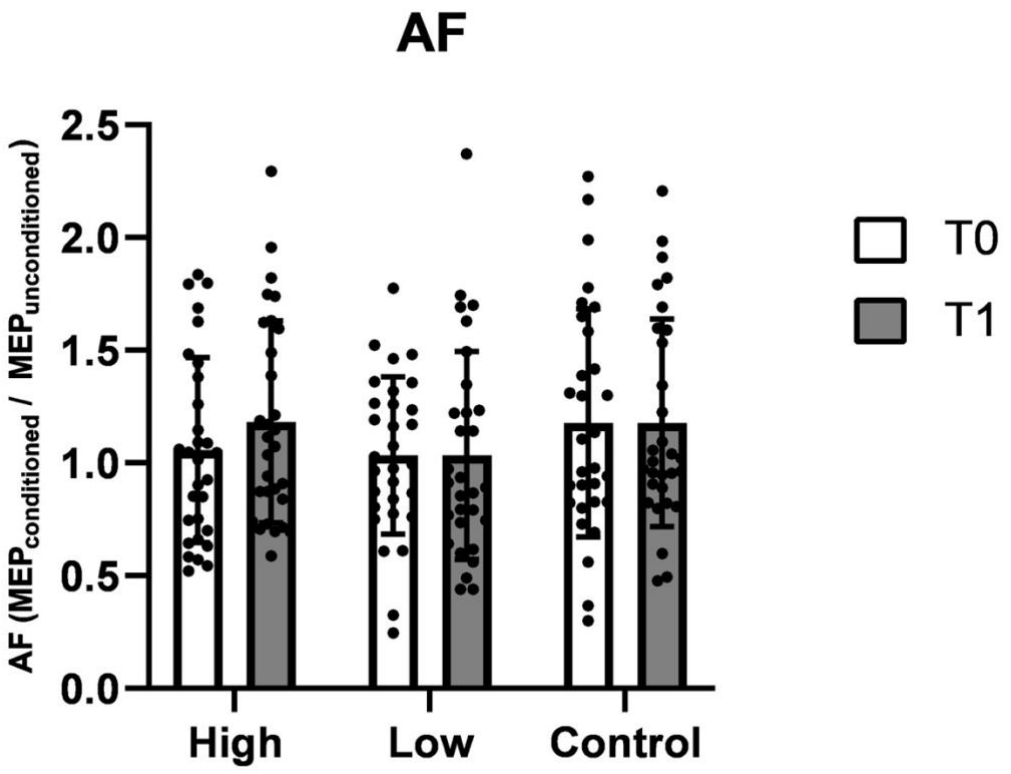

Figure 16: Group-Averaged AF Data Average AF, expressed as a ratio of the average unconditioned MEP amplitude, with Standard Deviation Bars, and individual values represented as each dot. T0=White bars. T1=Grey bars. AF also did not change following high or low difficulty maze training (p=0.26).

Condition	TMS Measure	T0 $MEP_{Conditioned}/MEP_{Unconditioned}$ (mean ± standard deviation)	T1 $MEP_{Conditioned}/MEP_{Unconditioned}$ (mean ± standard deviation)
High	SAI	0.69 ± 0.34	0.67 ± 0.31
	LAI	0.57 ± 0.39	0.62 ± 0.33
	AF	1.06 ± 0.41	1.18 ± 0.45
Low	SAI	0.69 ± 0.27	0.63 ± 0.28
	LAI	0.57 ± 0.38	0.56 ± 0.32
	AF	1.03 ± 0.35	1.03 ± 0.46
Control	SAI	0.68 ± 0.30	0.69 ± 0.26
	LAI	0.57 ± 0.36	0.63 ± 0.38
	AF	1.18 ± 0.51	1.18 ± 0.46

Table 2: Ratio of ($MEP_{Conditioned}/MEP_{Unconditioned}$) as a Mean ± Standard Deviation Before (T0) and After (T0) Training.

3.4.2 Maze Performance

Final results from maze training performance metrics across all participants in the study can be found in **Table 3.** Moreover, the group averaged total dwell time across trials in both the high and low training conditions is displayed in **Figure 17**. Participants completed an average of 20.63 mazes in the high difficulty condition, and 21.56 in the low difficulty condition. The slope of the change in the group-averaged data over the course of training was -1.17 in the high condition, and -1.14 in the low condition. Each of these negative slope values represent a decrease in total dwell time with practice.

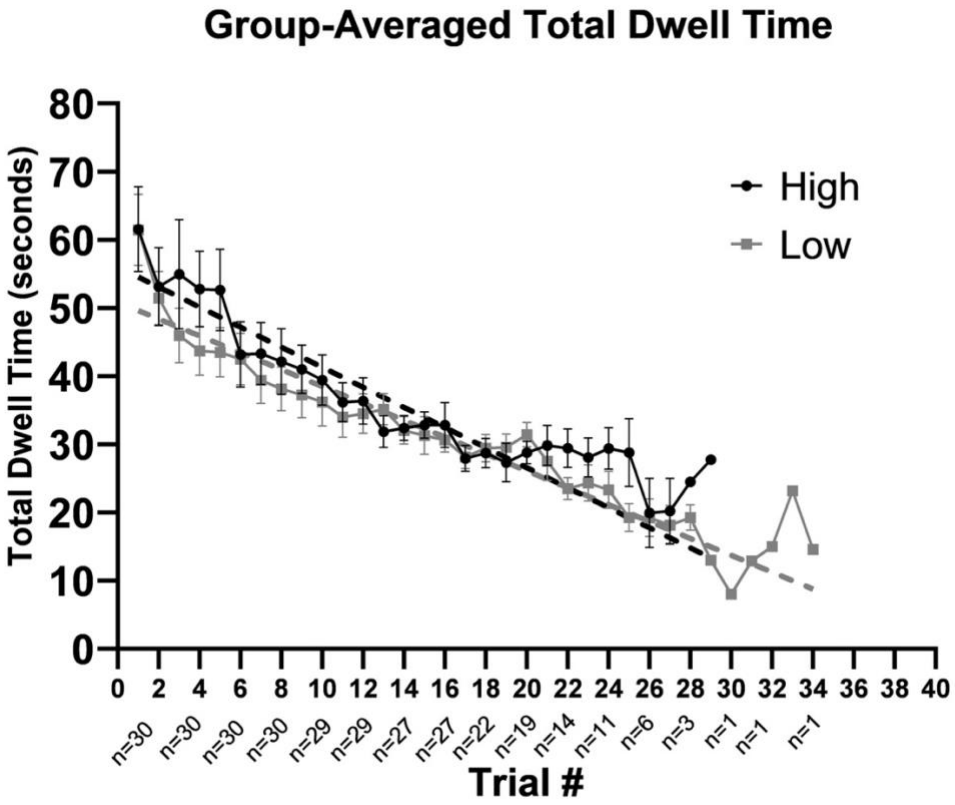

Figure 17: Group-Averaged Total Dwell Time Data- Improvements in total dwell time across maze trials in the high and low difficulty training conditions. High Difficulty=Black Line, Low Difficulty=Grey Line. Values below trial numbers indicate the number of participants contributing to the corresponding data point above, as some participants completed more trials than others. Each trial represents one successful completion of the maze.

There was a large amount of variability in the rates of skill acquisition across participants. Specifically, the slope of change of Total Dwell Time across trials ranged from cases of very large improvements (Participant A) to cases of very small changes (Participant B), as can be seen from two different participants data in **Figure 18**.

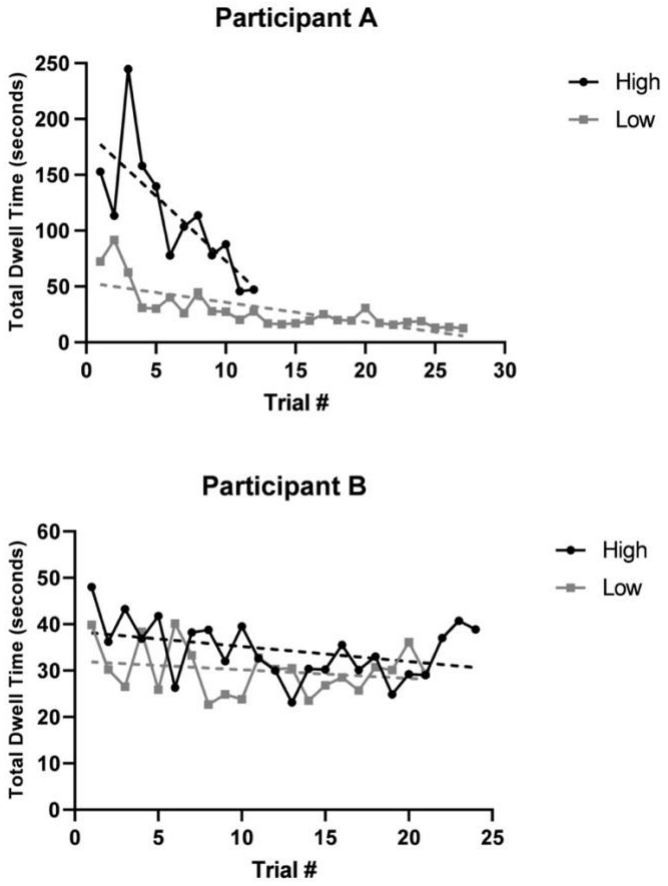

Figure 18: Differences in Performance Improvements During Maze Training- Examples of two different participants maze data in the high and low difficulty training conditions. *Participant A* had a very steep slope of improvement in the high condition, while *Participant B* had very flat slopes in both conditions, indicating less improvement across trials. Note the difference in the scale of the y-axis between graphs, also demonstrating the greater amount of improvement by *Participant A*.

A comparison of group-averaged performance in the high and low training conditions can be found in **Figure 19**. A paired samples t-test demonstrated that the total number of errors during maze training was significantly different in the high (M=25.40, SD=10.96) compared to the low (M=18.96, SD=12.27) condition, ($t(29)= 2.97$, $p = 0.006$). Further, the #of errors/#of trials completed was also shown to be significantly different in the high

(M=1.27, SD=0.51) compared to the low (M=0.95, SD=0.60) condition, (t(29)= 2.92, p = 0.007). For total dwell time, Wilcoxon Signed-Rank Test revealed no difference between the high (M=44.12, SD= 25.86) and low (M=39.29, SD= 16.78) difficulty conditions (Z = -0.71, p = 0.48). The Wilcoxon Signed-Rank Test was used as the non-parametric alternative to the paired samples t-test here because significant results from the Shapiro-Wilk Test indicated that the assumption of normality was violated in the average dwell time data in the high and low conditions (W= 0.72, p=<0.001 and W= 0.82, p=<0.001, respectively).

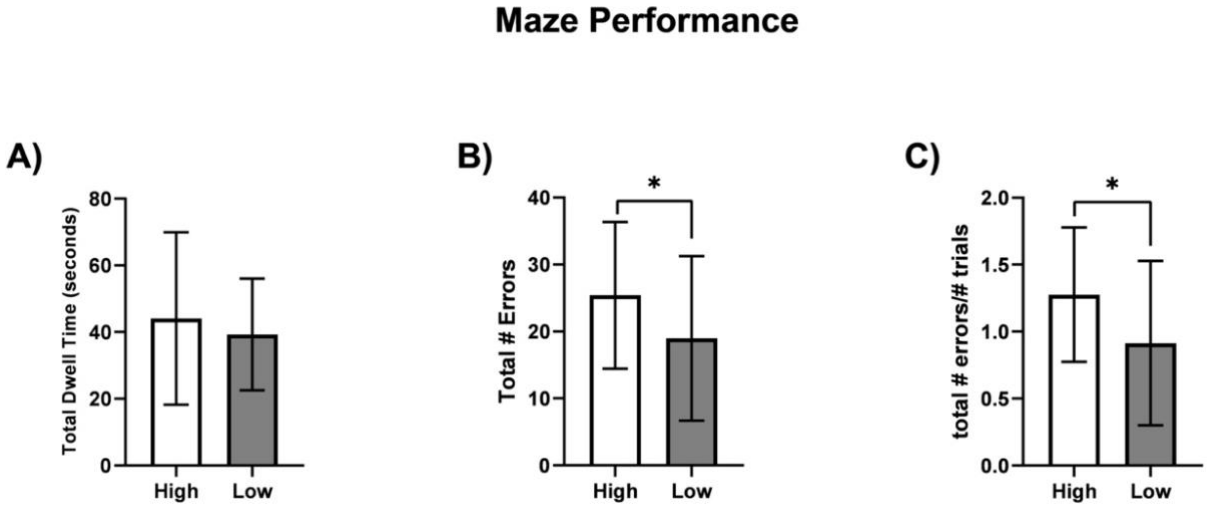

Figure 19: Group-Averaged Performance in the High and Low Difficulty Training Conditions- A) Group-averaged total dwell time in the high and low difficulty conditions shown in seconds, with Standard Deviation bars. **B)** Total # of errors made in the high and low conditions, with Standard Deviation bars. The difference between groups was significant (p=0.006) **C)** Total number of errors made/total number of maze trials completed during training, with Standard Deviation Bars. The difference between groups was significant (p=0.007).

To examine the relationship between changes in SAI/LAI following training and improvements in maze performance, correlations were performed as seen in **Figure 20**. Spearman Rank-Order Correlation was adopted as the non-parametric alternative to the Pearson Product-Moment Correlation due to non-normality. In summary, there were no statistically significant correlations observed, indicating that there was no association between changes in SAI or LAI and improvements in performance on the maze task.

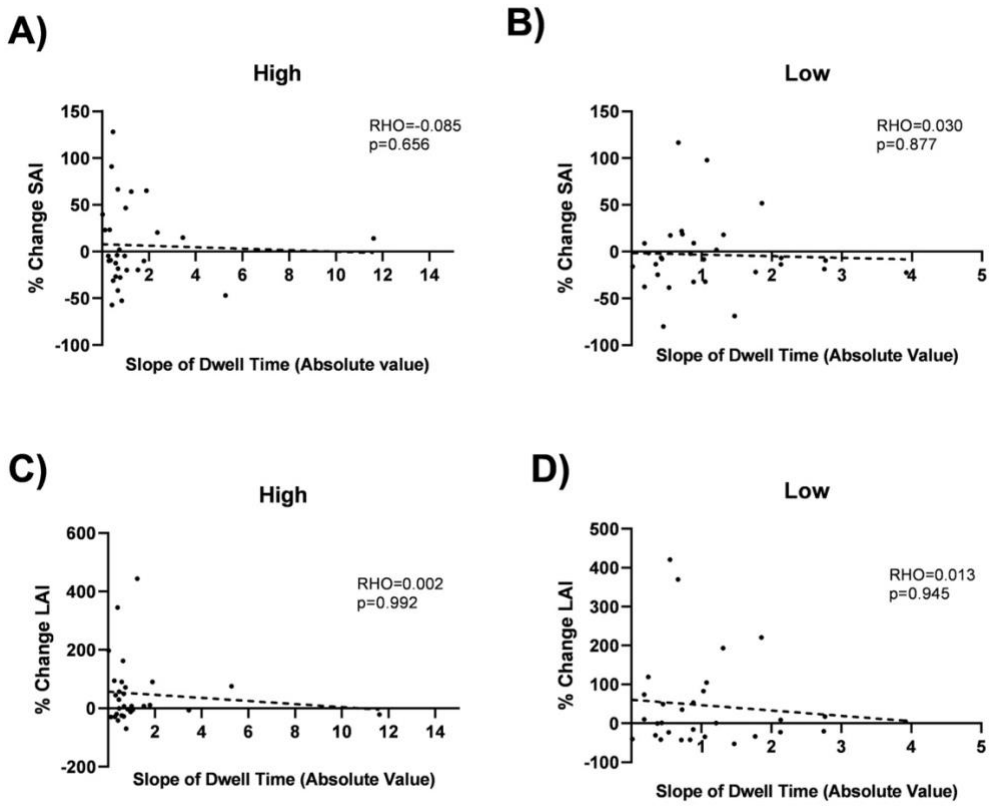

Figure 20: Correlations Between Change in SAI/LAI and Improvements in Maze Performance- A), % change SAI and slope of dwell time in the high difficulty training condition ($r_s(28) = -0.085$, $p = 0.656$). **B),** % change SAI and slope of dwell time in the low difficulty training condition ($r_s(28) = 0.030$, $p = 0.877$). **C),** % change LAI and slope of dwell time in the high difficulty training condition ($r_s(28) = 0.002$, $p = 0.992$). **D)** % change LAI and slope of dwell time in the low difficulty training condition ($r_s(28) = 0.013$, $p = 0.945$).

High Difficulty					Low Difficulty				
Participant	**# of Mazes**	**# of Errors**	**Avg. Dwell**	**Slope**	**Participant**	**# of Mazes**	**# of Errors**	**Avg. Dwell**	**Slope**
1	21	31	36.52	-1.01	1	21	14	38.84	-0.67
2	27	10	34.40	-0.32	2	25	21	30.00	-0.19
3	25	34	28.95	-1.79	3	36	42	18.89	-0.37
4	26	52	20.40	-0.46	4	17	43	38.45	-1.47
5	22	26	28.73	-0.02	5	17	20	52.61	-2.75
6	18	23	39.04	-0.96	6	24	0	27.45	-0.73
7	22	23	19.30	-0.58	7	21	20	38.99	-1.21
8	21	5	47.94	-0.67	8	17	3	61.09	-2.77
9	22	19	32.57	-0.29	9	23	16	38.83	-0.84
10	18	18	50.85	-1.24	10	24	9	32.25	-0.24
11	23	40	35.47	-0.37	11	28	34	26.06	-0.46
12	15	19	60.84	-0.74	12	11	24	77.79	-1.03
13	12	26	73.40	-3.46	13	14	25	52.13	-1.05
14	22	18	30.14	-0.77	14	23	8	26.21	-0.43
15	23	17	34.55	-0.12	15	19	14	44.80	-2.13
16	19	19	34.70	-0.68	16	25	6	30.72	-0.55
17	22	37	38.30	-0.42	17	17	9	45.04	-2.13
18	21	29	31.13	-0.84	18	26	46	24.14	0.34
19	14	23	82.75	-5.28	19	22	11	39.53	-1.31
20	24	8	29.18	-0.63	20	19	13	35.89	-1.86
21	21	41	28.20	-1.53	21	21	31	31.44	0.88
22	25	22	30.71	-0.26	22	22	6	39.99	-0.71
23	15	23	54.49	-2.36	23	17	14	48.46	-0.01
24	22	33	37.27	-0.47	24	25	30	21.35	-0.42
25	17	28	46.57	-1.90	25	28	24	27.15	-0.53
26	27	49	24.91	-0.58	26	25	4	26.98	-1.08
27	12	22	113.56	-11.6	27	27	20	28.72	-1.77
28	29	25	29.05	-0.67	28	21	24	38.96	-0.89
29	25	28	37.14	-0.40	29	19	30	36.96	0.18
30	9	14	132.47	-1.05	30	13	8	98.96	-3.92
Average	**20.63**	**25.40**	**44.12**	**-1.38**	**Average**	**21.56**	**18.97**	**39.29**	**-1.00**
SD	**4.88**	**10.96**	**25.86**	**2.21**	**SD**	**5.16**	**12.27**	**16.78**	**1.02**

Table 3: Individual and Average Maze Performance. # of mazes= total number of mazes completed during the training protocol. # of errors= total number of errors made during the training protocol. Avg. Dwell= average total dwell time across all trials in the condition. Slope= the slope of the total dwell times across all trials in the condition.

3.4.3 Smallest Detectable Change

The %SEMeas for SAI was 23.64, which reflects large amounts of measurement error. The $SDC_{individual}$ for SAI was 0.45, suggesting that a minimum change of 0.45 from T0 to T1 is necessary to be considered a real physiological change at the individual level. Further, SDC_{group} results indicated that a change of 0.08 is needed at the group level to be considered a meaningful change for our sample size of 30 participants. Based on these values, there was no real change at the group level for SAI in the high (0.02), low (0.06) or control (-0.01) conditions. However, at the individual level there was one participant who demonstrated a real increase in SAI larger than $SDC_{individual}$ following training in the high condition, and two in the low condition.

The %SEMeas for LAI was 21.77, which also reflects large amount of measurement error. The $SDC_{individual}$ results for LAI suggested that a minimum change of 0.36 from T0 to T1 is necessary to be considered a real physiological change. SDC_{group} results reveled that a change of 0.07 is needed at the group level to be considered a meaningful change in this sample. There was no real change at for LAI in the high (0.04), low (-0.003) or control (0.06) conditions. Still, at the individual level there were four participants who demonstrated a change in LAI larger than $SDC_{individual}$ following training in the high condition, and four in the low condition.

Finally, the %SEMeas for AF was 25.03, which was the largest amount of measurement error out of the three TMS measures. The $SDC_{individual}$ results for AF showed that a minimum change of 0.82 from t0 to t1 is necessary to be considered a real physiological

change. SDC_{group} calculation indicated that a change of 0.15 is needed at the group level to be considered a meaningful change. Based on SDC_{group}, there was no real change for AF at the group level in the high (0.124), low (-0.001) or control (-0.001) conditions. There were two participants who demonstrated a change in AF larger than $SDC_{individual}$ following training in the high condition, but none in the low condition.

3.4.2 Somatosensory Assessments

The mean ± SD score on the SSA and Sequential Amplitude Challenge while performing with (Magnet) and without (Control) wearing the magnet setup from the maze on the finger can be found in **Figure 21.** A paired samples t-test reported no statistically significant difference between performance in the Magnet (M = 103.733, SD = 91.472) compared to the Control (M = 119.300, SD = 91.390) condition ($t(29) = 0.982$, $p = 0.167$) on the SSA challenge. Another paired samples t-test reported no difference between performance in the Magnet (M = 43.333, SD = 22.435) compared to the Control (M = 48.800, SD = 26.468) condition ($t(29)= 0.934$, $p = 0.179$) on the Sequential Amplitude Challenge. Together, these results suggest that tactile acuity was not negatively influenced by wearing the magnet on the finger.

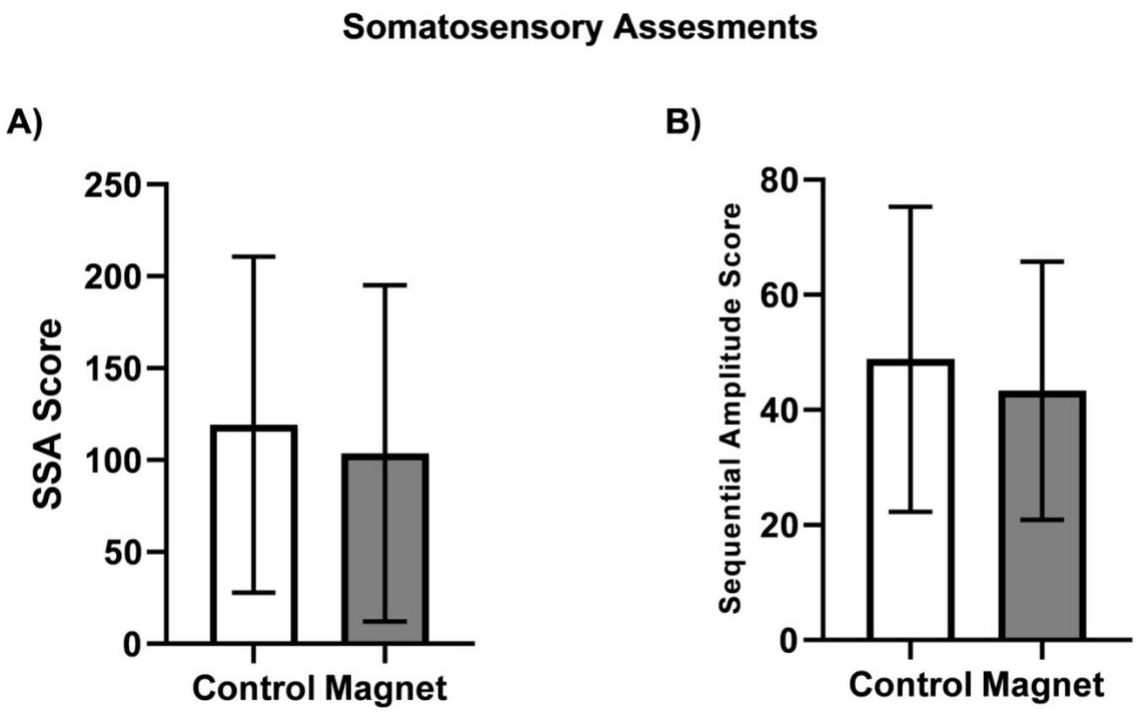

Figure 21: Group-Averaged Performance on Somatosensory Assessments- A) Mean SSA Challenge score in the control (white) and magnet (grey) condition, with Standard Deviation bars included. **B)** Mean Sequential Amplitude Challenge score in the control (white) and magnet (grey) condition, with Standard Deviation bars included.

There were no statistically significant correlations between scores on the SSA Challenge and improvements in performance in either the high or low conditions ($r_s(28) = <0.001$, $P = 0.999$ and $r_s(28) = -0.103$, $P = 0.588$, respectively). Further, there were no significant correlations between performance on the Sequential Amplitude Challenge and improvements in total dwell time in either the high or low conditions ($r_s(28) = -0.052$, $P = 0.783$ and $r_s(28) = -0.081$, $P = 0.670$, respectively). Therefore, we cannot conclude that differences baseline tactile acuity in performance were related to improvements in performance on the maze training task.

3.5 Discussion

3.5.1 Influence of Training on Sensorimotor Integration

The goal of this study was to investigate the effects of maze training on SAI, LAI and AF. To test this, SAI, LAI and AF were elicited by preceding a TMS stimulus to M1 with a PNS stimulus to the median nerve at the wrist and recording muscle activity from the right FDI muscle. These measures were collected before and after two 15-minute blocks of training on either a high difficulty maze, low difficulty maze, or time control condition on separate visits. The main finding from this experiment was that maze training did not influence SAI, LAI, or AF. The duration and design of the training protocol for this study was designed to be comparable to the protocols used in previous works that have cited changes in SAI, LAI or AF following training on other types of sensorimotor tasks (Meunier et al., 2012; Mirdamadi & Block, 2020). However, we failed to show any significant effects on these measures after a similar duration of training using a custom-designed sensory guided movement tactile discrimination maze task.

Even though the duration may have been similar, perhaps part of the discrepancy in the findings between this experiment and past studies may be due to a difference in the actual dose of training, rather than the length of time per se. More specifically, the length of time training may not be as important as what is being performed during the time allotted. For example, in our study participants completed approximately 20 trials in the 30 minutes of training, equating to 100 tactile discrimination attempts (5 intersections per trial). Yet, Mirdimadi and Block (2020) used 150 maze trials, Meunier et al. (2012) used

3 blocks of 150 movements each, and Deveci et al. (2020) used 360 basketball shots for the dose of training. Therefore, the lower dosage of training in this study may have contributed to the lack of change in SAI, LAI and AF. Also, maze training was different than the forms of motor training used in the other studies such as ballistic finger movements (Meunier et al., 2012), basketball shooting (Deveci et al., 2020), and maze tracing (Mirdimadi and Block). Future research is encouraged to consider both the dosage and type of the training protocol of the study when trying to induce neuroplasticity.

The maze training task was designed to emphasize *both* the sensory and motor systems by requiring movement of the hand to be guided by cutaneous tactile perception of the fingertip. As a result, the combination of activity in the sensory system (increased activation of S1 due to incoming sensory afference originating from the fingertip) and the motor system (increased M1 activation due to the control of hand movements through the paths) may have had opposing effects on the magnitude of SAI, LAI and AF. For example, Oda et al. (2022) reported that while tactile perception of the right fingertip suppressed corticospinal excitability, this reduction was abolished during active contraction of the FDI muscle which highlights how tactile perceptual processes are influenced by ongoing motor activity.

This phenomenon was likely to have occurred during maze training, as participants would have been performing tactile perception of the fingertip in the intersections while the FDI muscle was active to move the finger across the surface of the sandpaper. Therefore,

movement-induced gating of the reduction in corticospinal excitability during tactile perception may have contributed to the lack of change in these measures following maze training. Specifically, FDI activation eliminating the effect of the cutaneous tactile stimulation on M1 excitability would reduce the potential for tactile discrimination from the fingertip during maze training to influence the magnitude of SAI, LAI and AF, since they are measures of the influence of sensory afference on corticospinal excitability. This may be an important mechanism that contributes to surround inhibition, such that tactile perception of the fingers may suppress motor activity in the muscles controlling the neighboring fingers to increase movement efficiency (Oda et al, 2022).

Training on the maze task was a form of tactile discrimination training since participants had to investigate the perception of roughness of multiple strips of sandpaper to decide which pieces were the same texture. Human research has demonstrated that two weeks of training on shape, surface and two-point discrimination tasks led to functional reorganization of the sensorimotor cortex (Sarasso et al., 2018). Specifically, fMRI results suggested that training led to lateralization in task specific sensorimotor areas during performance of sensory and motor tasks. Another study showed that MEP amplitude is increased during shape discrimination training using the index finger (Master & Tremblay, 2009). Further, research in rats reported increased release of ACh from S1 during tactile discrimination training (Butt, Testylier & Dykes, 1997). SAI is believed to involve a cholinergic pathway, such that greater ACh release in the sensorimotor cortex would increase the depth of SAI (Di Lazzarro et al., 2000; Ferreri et

al., 2012; Turco 2018a). Yet, there was no significant effect of maze training on SAI in this study. Therefore, although ACh release was not measured in this study, the lack of change in SAI following training may suggest that increased cholinergic activity in the cortex during tactile discrimination does not persist beyond execution of the task.

The secondary goal of this study was to explore the relationship between changes in SAI/LAI and improvements in maze performance. Past research has suggested that changes in SAI or LAI during motor training highlights the importance of somatosensory processing in shaping motor output in the early stages of motor learning (Meunier et al., 2012). Yet, the % change in SAI/LAI from T0 to T1 in this study was not related to the slope of total dwell time across maze trials in either the high or low conditions. This suggests that there were not any notable relationships between the neurophysiological changes related to sensorimotor integration following training and the behavioural changes related to performance a result of practice.

Results from this experiment are supported by findings from a previous study by Turco et al. (2018c) which found no significant associations between SAI /LAI and performance on three well-established behavioural tasks used in motor control research. These tasks included the Temporal Order Judgement Task (measures temporal tactile acuity), Grating Orientation Task (measures spatial tactile acuity), and the Purdue Pegboard Task (measures fine manual dexterity). The lack of association between SAI/LAI and performance on all three tasks in this study suggested that the magnitude of SAI and LAI were not correlated with baseline sensorimotor abilities. However, SAI and LAI were

only measured at baseline in that study, so it was not possible to determine whether SAI and LAI increased or decreased following task performance. The present study was able to address this gap in the literature by providing evidence that SAI, LAI and AF are not modulated by 30 minutes of tactile discrimination training.

SAI and LAI are both measures that probe the sensorimotor system. It is well known that the neuroplastic changes occur in the sensorimotor system in response to motor learning (O'Brien et al., 2020; Pascual-Leone et al., 1995). SAI and LAI did not change in this study, but training may have induced changes in other spinal or supraspinal neural circuits that could be assessed using other TMS measures like RMT, MEP recruitment curves, cortical silent period, or paired pulse paradigms like SICI, LICI, and ICF. Future studies should continue to quantify changes in different neurophysiological measures following different types of sensorimotor training to establish a broader understanding of the impact that training can have on different regions and systems of the brain, and the functional significance of these effects.

Another possibility is that changes in sensorimotor integration (specifically LAI) may have been more apparent in the early stages of training while participants were first becoming familiar with the task and attempting to determine the optimal movement and decision-making strategies for success. This suggestion is being proposed because the neural circuitry of LAI is thought to traverse the basal ganglia (Obeso et al., 2000), which is a structure that regulates error-correction processes in the brain that are likely to occur

in the early stages of training (Seidler et al., 2013). fMRI results showed that changes in basal ganglia activation during the first 10 minutes of performance motor learning of a finger movement task was positively correlated with error rate, which indicated the involvement of the basal ganglia in early motor learning processes (Lehericy et al., 2005). Therefore, LAI may have been decreased during the first few trials of maze training while the basal ganglia was being activated while participants were adopting and implementing error-correction strategies to improve performance, similar to other studies (Meunier et al., 2012; Deveci et al., 2020).

If SAI and LAI had been measured during training while participants were still in the early stages of motor learning and learning to correct their mistakes, there may have been changes in the magnitude of these measures. But by the end of 30 minutes of training when there is some familiarity with the task and strategies are more established, these measures may have returned towards baseline levels. This was the case in the work of Deveci et al. (2020), who found that LAI and AF were changed during the early stages of learning but returned to pre-training levels after the fifth day of training once participants have become more familiar with the task and developed movement strategies. Perhaps since the maze training task was not as complex of a motor skill as basketball shooting, participants corrected their performance and reached a level of familiarity with the task earlier than with basketball shooting, which caused sensorimotor integration processes to regress towards baseline during the first training session rather than after several sessions. In summary, afferent inhibition and facilitation may have experienced moment-to-

moment alterations in magnitude during skilled motor performance in order to integrate incoming somatosensory information with the control of movement that did not persist beyond task execution.

3.5.2 Maze Performance

The negative slopes from the group-averaged performance across trials shown in **Figure 19** highlighted how participants decreased total dwell time with training in both in the high and low difficulty conditions. The slope of total dwell time in these two training conditions was very similar and not significantly different from one another. One potential reason for this similarity may be that although one condition was more difficult than the other, the degree of challenge for both tasks was in a range that allowed for noticeable improvements in performance to be made in a relatively short period of time (30 minutes). If the task was "too easy", there would have been no room for improvement because they would have been performing at near optimal levels almost immediately. Conversely, if the task was "too difficult" there would have been little (if any) indication of improvement in performance with practice because the participants would have been unable to acquire the skills needed to perform well consistently. The similarity of the slope of decreases in total dwell time in both conditions suggests that the difficulty of both the high and low training conditions was at an appropriate level to promote improvements in performance in the amount of time allotted for training in this experiment.

Group-averaged total dwell time for a maze trial was not significantly different in the high compared to the low condition, which suggested that the task difficulty of the two different conditions did not have a major effect on speed at which participants made their tactile discrimination decisions when evaluating the texture of the sandpaper in the intersections of the maze. However, there were a higher number of errors made/number of trials completed and total # of errors in the high compared to the low training condition on average. Therefore, the task difficulty of the maze conditions appears to have had a more pronounced effect on the accuracy of participant's tactile discrimination decision making in the maze.

3.5.3 Smallest Detectable Change

The control condition was included in this study to acquire measures of smallest detectable change (SDC) for SAI, LAI and AF. The SDC is a metric of absolute reliability used to determine the minimum amount of change in a particular measure that is considered real (Beckerman et al., 2001; Weir et al., 2005). In the context of this study, any amount of change less than the calculated SDC for that measure would be assumed to be caused by measurement error rather than a true physiological change. SDC_{group} results emphasized that there were no real changes in any of the TMS measures from T0 to T1 larger than SDC_{group}. In simpler terms, no real physiological change was reported for SAI, LAI or AF following maze training in the high or low difficulty training conditions. These results support the findings from the primary analyses demonstrating no change in SAI, LAI or AF in response to training. The alignment of the SDC results with those

from the primary analyses offers a complimentary source of evidence that 30 minutes of training on the maze did not have any meaningful influence on SAI, LAI or AF.

3.5.4 Somatosensory Assessments

The purpose of performing the somatosensory assessments in this study was to determine if the experimental setup on the finger from maze training (small rectangular neodymium magnet taped to the top surface of the finger above the fingernail, see **Figure 10**) had any effect on measures of tactile acuity at the fingertip, as well as quantify each participants tactile acuity abilities at baseline. First, it was demonstrated that wearing the magnet did not have any negative effect on performance on the SSA or the Sequential Amplitude Challenge, which are both somatosensory assessments of tactile acuity collected using the *Brain Gauge: Cortical Metrics* software. These findings were critical to demonstrate that wearing the magnet on the finger did not negatively influence tactile acuity at the fingertip. This is an important consideration because if tactile acuity was reduced by the setup on the finger, it would hinder performance on the maze which relies on sensory-guided movement.

The relationships between underlying sensory abilities and measures of performance improvements during maze training were also examined. Specifically, performance on the SSA and Sequential Amplitude Challenge at baseline were not associated with improvements in total dwell time in the high or low difficulty conditions. Therefore, the differences in performance improvements across participants was not related to

differences in baseline levels of tactile acuity in this sample. Still, it could be speculated that there was no relationship between these variables because the somatosensory assessments of tactile acuity used may not have been assessing the exact same sensory abilities that are relied upon for the maze task. The SSA and Sequential Amplitude Challenge require participants to differentiate between vibrotactile stimulations of different intensity, whereas the maze requires participants to differentiate between surface textures of varying roughness. Indeed, it has been shown that the neural mechanisms underlying the perception of roughness differ from those involved in spatial acuity (Libouton et al., 2010). Perhaps a stronger relationship would have been reported between baseline sensory abilities and improvements in performance if the initial somatosensory assessments were another form of perception of roughness tactile discrimination tasks instead.

3.6 Limitations

There are several limitations to this experiment which require discussion. Firstly, the sample demographics were limited to healthy young adults. Due to evidence from previous research that SAI, LAI and AF are affected by healthy aging, our results may not be generalizable to older adults (Brown et al., 2018; Degardin et al., 2011). Future work is encouraged to explore changes in SAI, LAI and AF in older and clinical populations following tactile discrimination training, to determine if these individuals show a better response to training than healthy controls like the ones in this study. If so, these changes could be studied more closely to determine if these forms of training offer

the potential to improve or regain some of the sensorimotor function that is impaired during aging or disease.

Next, SAI, LAI and AF were only elicited by stimulating the median nerve and recording from the FDI muscle in this study. However, SAI, LAI and AF could also be measured by stimulating other nearby nerves such as the digital or ulnar nerve, and by recording EMG activity from other muscles of the hand such as the APB or ADM. Therefore, this experimental design only permits a confident interpretation that maze training did not have a significant effect on SAI, LAI and AF elicited in this muscle and nerve. However, future experiments should compare changes in sensorimotor integration following training in a design that probes SAI, LAI and AF by stimulating multiple different nerves independently, and recording from multiple muscles; one that is involved in the task and another that is not and determine if there are any significant differences between them.

It is important to note that afferent inhibition measures were assessed for the hand, even though maze training also required some arm movement at the shoulder and elbow to navigate the maze. The FDI was chosen because the purpose was to assess somatosensory changes related to hand/digit perception, which was most directly involved in the task. Also, measures of afferent inhibition are most well established in the muscles of the hand like the FDI (Turco et al., 2018b). Although we did not assess changes in SAI and LAI in muscles controlling these shoulder and elbow movements, previous research suggests that

the magnitude of SAI in FDI is comparable to muscles of the forearm and biceps brachii (Bailey et al. 2016; Helmich et al., 2005).

The ISI at which SAI, LAI and AF are elicited has varied across past studies (Ansari & Tremblay, 2019; Turco et al., 2018b). In this experiment, predetermined ISI durations of 22ms for SAI, 50/60ms for AF, and 200ms for LAI were used, which were all derived from previous research. However, probing SAI at an individualized interval of the participant's N20 latency+2ms has been cited as a method to maximally induce SAI (Bailey et al., 2016; Tokimura et al., 2000). Therefore, the results from this study are limited to the specific ISIs that were investigated in the experimental design. Future work should address this limitation by recording MEPs at multiple ISIs ranging from 20ms to 1000ms before and after tactile discrimination training. This would allow for a more precise examination of how the sensorimotor integration profile across a larger range is affected by training instead only at 3 specific intervals which may not have been influenced by training as much as other intervals not tested in this study.

Sensory threshold in the APB muscle from peripheral nerve stimulation and M-waves were not recorded in this study. This is a limitation to the experiment because the magnitude of SAI, LAI and AF are dependent on the intensity of stimulation (Ni et al., 2011), so there was no control for variations in the stimulation intensity over time. In the protocol for this experiment though, the intensity of PNS delivered to elicit the visible

twitch in the APB muscle was assessed immediately before the T0 and T1 measurements of SAI, LAI and AF in order to confirm that the correct intensity was used.

Another limitation to this study was that no additional TMS measures were collected in conjunction with the measures of sensorimotor integration. Including other TMS assessments like measures of intracortical or interhemispheric inhibition and facilitation would have created a more comprehensive neurophysiological evaluation that may have identified some other interesting effects. The technical and time restraints related to the sessions in this protocol did not allow for the inclusion any additional outcome measures, however further research is encouraged to investigate if maze training has an influence on any of these other well-studied neural circuits.

The findings from this study are also limited to the specific form of training used in the experiment. The sensorimotor tactile discrimination maze was a novel task custom-designed to provide participants with a challenge that required sensory-guided movement to successfully navigate through. Although the very complicated design and operation of the maze allowed for the creation a unique and specific sensorimotor task of interest, it also limits the generalizability of the results in this experiment. Future research can help bring context to these findings by measuring changes in SAI, LAI and AF for a similar duration of training on other more established forms of tactile discrimination training (ex. temporal, spatial, or two-point discrimination) to determine if these forms of training have a greater effect on sensorimotor integration than the maze used here.

The lack of a retention or transfer test on a separate visit can be cited as another limitation to the design of this experiment. These assessments would have allowed us to measure the amount of motor learning that was present following a brief washout period. Future studies are encouraged to address this gap in knowledge by designing a similar study with the addition of a retention tests in the design to determine how well people transfer the information acquired during training from their sensory systems to their short-term memory, and from short-term to their long-term memory. Also, the inclusion of transfer tests using other tactile discrimination assessments would allow for a better understanding of to what extent training on the maze task facilitates performance on other tactile discrimination tasks.

3.7 Conclusions

This study was the first experiment dedicated to investigating the influence of tactile discrimination training with a novel maze task on three TMS measures of sensorimotor integration: SAI, LAI and AF. In contrast to the initial hypotheses of this experiment, 30 minutes of training did not modulate any of these measures. In addition, there was no association between the behavioural changes that occurred and neurophysiological changes induced by training. These results have implications for other research groups attempting to understand the factors that influence SAI, LAI and AF. Future research is encouraged to explore changes in SAI and LAI using other experimental protocols to determine if these results are limited to the muscles and specific ISIs tested in this experiment.

4. GENERAL DISCUSSION

4.1 Physiological and Behavioural Effects of Maze Training

The novel tactile discrimination maze task used for training in this study was specifically created to emphasize activation of both the sensory and motor systems. To achieve this, the task required participants to move the index finger through maze paths based on incoming somatosensory information. Specifically, participants had to use the index finger to make tactile discrimination choices based on their perception of sandpaper roughness at the intersections of the maze. Training on this maze could be considered a serial task as opposed to discrete or continuous, because it involved connecting a series of discrete movements together to perform a more complicated skilled movement pattern (Schmidt & Lee, 2019). The classification of maze training as either an open or closed skill is not as simple. Open skills refer to those that are performed in a dynamic and unpredictable environment, whereas closed skills refer to those performed in a predictable and stable environment (Galligan, 2000). Although the arrangement of the maze walls was adjusted after every trial, performing each individual trial would be classified as a closed skill because the maze is a fixed environment and movement time is dependent on the performer. Still, this task required constant adaptations by the participants in order to respond to the changes in the maze arrangement between each attempt.

The sandpaper in the intersections of the maze provided exteroceptive feedback to the fingertip of participants by activating cutaneous receptors of the finger. There are four

main types of mechanoreceptors in the skin. Ruffini endings and Merkel Cells are slowly adapting receptors that respond to texture and skin stretch, and Meissner and Pacinian Corpuscles are rapidly adapting receptors that respond to skin indentation and vibration (Johnson, 2001). Each of these receptor types may have been activated in the finger during maze training in some capacity. However, the slowly adapting mechanoreceptors are likely to have made major contributions since they convey the perception of texture and skin stretch which would occur when evaluating the surface of the sandpaper to determine roughness. In support of this, Yoshioka (2001) showed that spatial variation in the firing of Merkel Cells was the only neural coding mechanisms responsible for the perception of roughness for both coarse and fine textures.

Cutaneous receptors then transmit the sensory signals from the finger towards the spinal cord via first-order Aβ afferent fibres (McGlone & Reilly, 2010). Proprioceptive information related to the location and movements of the hand through the maze would also be transmitted to the brain via Aα sensory fibres throughout training (Kandel et al., 2012). From the dorsal root ganglion, these signals travel through the ascending pathways of the spinal cord towards S1. Specifically, proprioceptive information is transmitted towards Area 3a of S1, whereas the afferent input from cutaneous receptors is transmitted to area 1 and 3b (Kaas, 1985).

Along with S1, sensory information is also relayed to other areas such as the secondary somatosensory cortex, and association areas like the insular cortex, posterior parietal

cortex and motor cortex for more complex sensory integration (Hoffer et al., 2005; McGlone & Reilly, 2010). The cortico-cortical connections between sensory and motor regions along with projections from subcortical and association areas allow for incoming sensory information to be integrated with motor commands to augment control of movement (Donoughe, 1995; Pearce et al., 2000). Importantly, sensory information from tactile input has a prominent influence particularly on the activity of neurons controlling hand and finger movements to allow for the fine control of movement and interaction with objects (Kandel et al., 2012).

During tactile discrimination at each intersection, participants underwent a stimulus identification stage, a response selection stage, followed by a movement programming stage to determine which way to move (Schmidt & Lee, 2019). Stimulus identification was accomplished when the participant dragged the fingertip across the sandpaper to experience the sensory stimulation associated with the level of roughness. Next, response selection occurred after the participant felt all the sandpaper options available in the intersection, when they made a choice about which option felt the same as the reference grit. Finally, the movement programming stage is the last step in which the participant initiated the motor command to move the finger down the path of the sandpaper strip that they chose to follow. Dwell time reflects the speed at which participants moved though these stages and made a tactile discrimination decision in each intersection. Therefore, the more efficiently participants were able to move through these stages, the shorter their dwell time were.

There are several different forms of learning which can take place during training or practice of a motor skill. For example, error-based learning can be defined as using sensory feedback to develop a strategy for identifying and correcting errors made during task performance (Ownsworth et al., 2017). Error-based learning would have occurred when participants chose the wrong path in an intersection and had to accommodate that information into their motor schema in order to avoid making this error again. Alternatively, reinforcement (or reward-based) learning is an implicit process that involves changing behavior by increasing the likelihood of repeating movements that provide rewarding outcomes (Therrien & Wong, 2021). Therefore, reinforcement learning during maze training may have occurred after the reward of making the correct choice on tactile discrimination decisions in the intersections. In other words, participants may have improved over time by remembering the rewarding feeling of making the correct choices and repeating this many times to strengthen the neural pathways involved in making these decisions. This type of learning tends to be slower because the reward of successful performance provides less information than correcting an error (Schmidt & Lee, 2019).

Differences in performance across participants may have been related to the movement and decision-making strategies adopted by participants. There were some who kept their hand steady and the finger very vertically oriented throughout the trial, while others preferred to adjust the angle of their hand and wrist more in each intersection to get a

larger surface area of the pad of their finger onto the sandpaper strips. When some experience has been gained after several attempts on the maze, participants began to establish strategies whereby they began to adopt a more a predictable and repetitive pattern to evaluating the corners (ex. slow and methodic, or fast and rushed). While some participants touched each strip multiple times before deciding, others only checked once. Participants who checked several times displayed longer dwell times with fewer errors, as they allowed themselves the opportunity to process the relevant tactile information to inform their decision. Alternatively, those who rushed their decisions displayed shorter dwell times but more errors.

These findings relate to the concept of the speed-accuracy trade-off. Even though the same set of instructions were given to all participants prior to training ("Take your time and focus on the decision, you want to complete the maze as quickly as possible without sacrificing accuracy"), inevitably there still were some participants who prioritized the speed of their performance. This is reflected by the large number of errors made by some participants, especially in the high difficulty condition. Focusing on speed generally led to many incorrect decisions being made, resulting in longer completion times along with a higher number of errors. As a result, those who prioritized accuracy tended to perform better on the maze.

Habituation or desensitization to the tactile stimuli from the fingertip after performing many repetitive trials is another potential neurophysiological effect of

maze training that may have influenced performance. Habituation refers to a form of behavioral plasticity where there is a progressive decrease in the amplitude or frequency of a neural response to repeated stimulation not caused by receptor adaptation or motor fatigue (Schmid et al., 2015). Habituation is believed to be caused by changes in the firing patterns of neural circuits that have been activated in a repetitive manner for a prolonged duration (Groves & Thompson, 1970). Specifically, one of the primary mechanisms of habituation relates to changes in the presynaptic neuron due to repetitive activation which cause reductions in neurotransmitter release that consequently results in a decreased firing rate of the post-synaptic neuron (Groves & Thompson, 1970). Desensitization is a habituation process whereby repetitive exposure to a stimulus leads to progressively smaller responses to that stimulus (Watts, 1971). The concept of desensitization is utilized in psychology as a form of therapy known as “exposure therapy”, whereby emotional responsiveness to an undesirable stimulus is reduced over time with repeated exposure to that stimulus in a controlled and stepwise fashion (Tryon, 2005).

The dual-process theory of habituation proposed by Groves & Thompson (1970) posits that when a stimulus is first encountered, habitation and sensitization processes are activated simultaneously. While one is causing an increase in responsiveness (sensitization), the other is causing decreased responsiveness (habituation). The final outcome reflected in the actual behavior of the individual is the result of the effect of the sum of these two processes on the neural circuit. There

has been evidence to suggest that the underlying mechanisms and neurotransmitters involved in habituation and sensitization are distinct from one another (Groves & Thompson, 1970). There is also behavioral evidence to support this notion. While habituation is thought to be mainly be stimulus specific, sensitization often generalizes to other similar stimuli as well (Haddad et al., 2012).

During maze training, the repetitive interactions between the finger and the maze paths could have led to habituation of the sensory afferent signals originating from the finger. This would cause a reduction in the ability to perceive the roughness of the sandpaper being evaluated, which would result in more difficulty making the tactile discrimination choices. In turn, participants would be forced to evaluate the texture for a longer duration before being able to confidently decide which path is correct. Somatosensation from the finger can be influenced by the amount of pressure applied to the surface (Lamb, 1983). Consequently, participants may have also had to push down on the sandpaper strips with more force towards the end of training in order to maintain the ability to perceive the differences in texture between grits. This theory was not able to be tested in this experiment directly, because the maze was not equipped with any force transducers to quantify the amount of pressure applied to the sandpaper during tactile discrimination.

4.2 Maze Training and Sensorimotor Integration

Over the last few decades, neuroscience research has demonstrated that adult brains have capacity to undergo neuroplastic changes in the sensorimotor cortex in response to experience or training in a particular skill (Ostry & Gribble, 2016). This research study sought to understand neuroplastic changes that may occur in the brain following sensorimotor training by measuring changes in SAI, LAI, and AF after 30 minutes of practice on a tactile discrimination maze task. The other aim of this work was to contribute to the body of knowledge related to factors that influence sensorimotor integration in humans using TMS, and how neurophysiological changes relate to behavior.

Contrary to the initial hypotheses of the study, 30 minutes of training on the novel tactile discrimination maze task did not have any significant effect on the group averaged measures of SAI, LAI or AF in either the high or low difficulty conditions. Further, the magnitude of change in SAI and LAI following training was not strongly correlated with the amount of improvement in maze performance at the group level. There are numerous potential factors which may have influenced the outcomes of this study, and they will be discussed along with their implications in the context of sensorimotor integration and neuroplasticity in the following paragraphs. **Figure 22** provides a simplified visual representation of the neural pathways of SAI, LAI, AF and some of the main topics that will guide the remainder of this discussion.

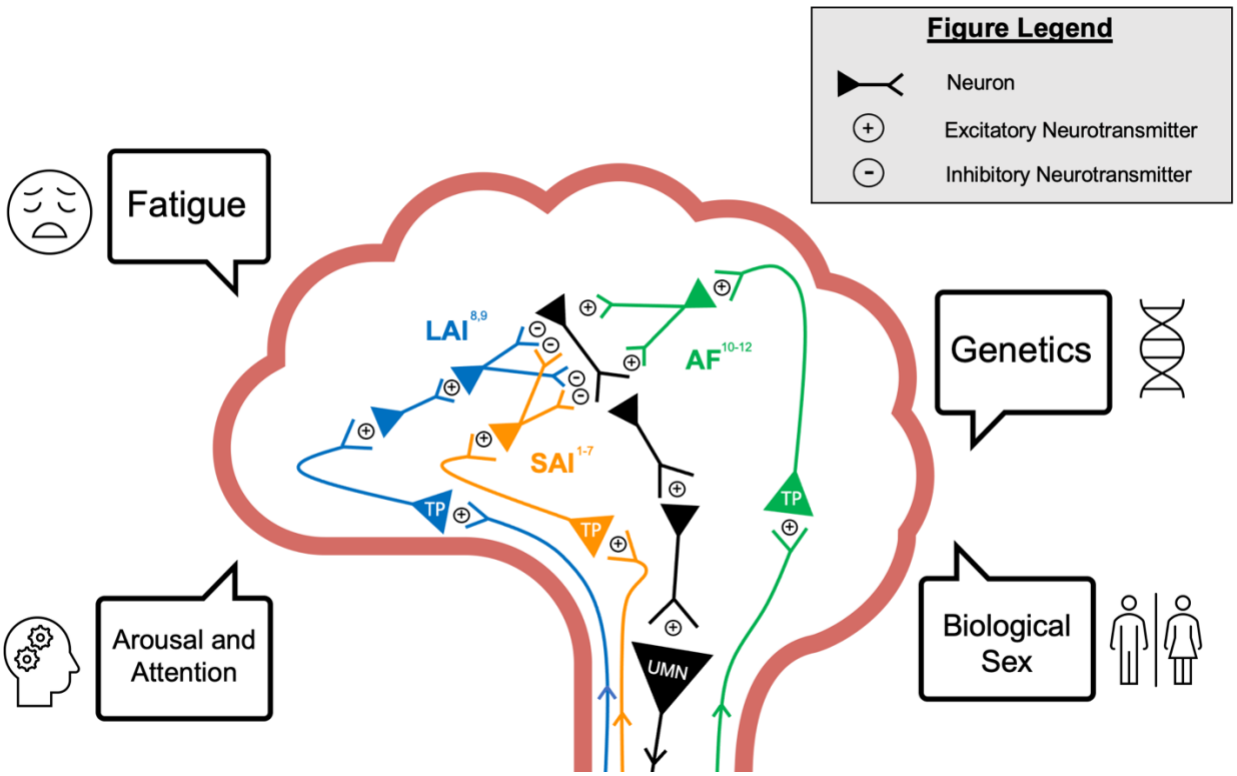

Figure 22: Potential Factors Modulating the Neurophysiological Response to Maze Training- A basic schematic for SAI, LAI and AF are provided within the brain; this depiction is simplified and not neuroanatomically accurate. The factors influencing the response to training discussed in this thesis are shown in bubbles around the brain. TMS over M1 activates the black cortical interneurons which excite the upper motor neuron (UMN), which sends descending signals to alpha motor neurons in the ventral horn of the spinal cord and eventually towards muscles to initiate an MEP. Incoming sensory afference from the periphery preceding TMS at specific intervals either activates SAI and LAI circuits (~20 and 200ms, respectively) which have an inhibitory influence on these cortical interneurons in M1 that decreases output from the downstream UMN (afferent *inhibition*), or the AF circuit (~60ms) which has an excitatory influence resulting in increased motor output (afferent *facilitation*). The *SAI* pathway (orange pathway) is thought to travel from thalamic projections (TP) either directly to inhibitory interneurons in M1(Bertolasi et al., 1998[1], Di Lazzaro et al., 2012[2]; Di Lazzaro et al., 2013[3]; Oliviero et al., 2005[4]; Tokimura et al., 2000[5]), or from S1 to M1 (Jacobs et al., 2014[6]; Tsang et al., 2014[7]). Due to the longer interval of LAI and reduction in individuals with PD, the *LAI* pathway is believed to involve higher order sensory areas or subcortical structures (Chen et al., 1999[8]; Sailer et al., 2003[9]) which is why the LAI pathway has more neurons than SAI and AF in this figure (blue pathway). The exact cortical *AF* pathway (green pathway) is not fully understood, but the intracortical origin has been suggested from several studies (Devanne et al., 2009[10]; Kojima et al., 2014[11]; Ridding and Rothwell, 1999[12]).

UMN= Upper Motor Neuron. TP= Thalamic Projection. SAI= Short-Latency Afferent Inhibition. LAI= Long-Latency Afferent Inhibition. AF= Afferent Facilitation.

4.2.1 Attention and Arousal

SAI is a cholinergic circuit shown to be influenced by the attentional state of the participant during measurement (Kotb et al., 2005; Mirdimadi, Suzuki & Meehan, 2017; Sukuski & Meehan, 2020). This is worth mentioning, because no instructions were provided to direct participant's attention during the collection of SAI, LAI and AF. Nonetheless, this remained consistent across all participants and is not an uncommon practice in the collection of TMS measures. Therefore, the lack of control over where or what the participants attended to during TMS collection was not suspected to have a major influence on these measures.

The attentional state of the individual during maze training would impact performance. Participants were instructed to try to focus on the feeling of the sandpaper when they attempted navigate the maze. Since participants were blindfolded during training and performance relied on the ability to effectively focus on sensations and perceptions from the fingertip, participants likely adopted an internal focus of attention. An internal focus of attention involves directing the attention to the bodily motions and sensations during performance. An external focus of attention refers to focusing on the movement outcomes during performance as opposed to the movement itself (Peh et al., 2011). Previous research has shown that an external locus of attention is the ideal form of attention to use during motor performance (Wulf, 2013). Still, there is other evidence suggesting that an internal focus of attention is preferable over an external focus of attention when a

beginner is first learning a task (Schmidt & Lee, 2019). Since participants only performed 30 minutes of training on this unfamiliar task, participants would be classified as beginners and therefore may have benefitted from focusing their attention on the sensations experienced during training.

Attention has also been shown to influence neuroplasticity. The M1 plasticity inducing effects of paired associative stimulation were shown to be present when participants attended to the hand being stimulated but negated when the participant was distracted by a cognitive task (Stefan et al., 2004). Also, a stimulus is more likely to result in perceptual learning and neuroplastic processes if an individual directs their attention towards that stimulus when it occurs. (Liu et al., 2005; Moseley et al., 2008). Thus, participants who were able to more effectively direct their attention towards the tactile perception at the finger during evaluation of roughness during training may have experienced greater amounts of use-dependant plasticity from their sensorimotor interactions. However, there was no subjective or objective measures of attention collected in this study, so this suggestion remains speculative.

Nonetheless, attention is a limited resource (Reimer et al., 2015). More importantly, sustained attention is decreased with prolonged periods of information processing (Schmidt & Lee, 2019). The repetitive trials of maze training in this study involved a prolonged duration of sustained attention towards somatosensory information processing. This extended duration of sensory processing may have led to decreases in sustained

attention across the 30 minutes of training that would be a limiting factor of maze performance.

Although commonly confused with attention or thought to be synonymous, arousal refers to the state of being physiologically, alert, awake and attentive. It can also be described as the level of excitement produced under stress in the context of motor control (Schmidt & Lee, 2019). Still, arousal and attention are both multi-dimensional psychological processes that closely interact with one another (Coull, 1998). Arousal levels in the brain are controlled by the reticular activating system, which is modulated by several neurotransmitters including ACh (Steriade, 1996). SAI is also dependant on cortical ACh levels (Di Lazzarro et al., 2000; Ferreri et al., 2012; Turco 2018a). This may help to explain why arousal has implications with the magnitude of SAI as well as neurophysiological changes that occur in response to motor training. Koizume et al. (2017) showed that SAI was decreased during a vigilance task which attenuated the arousal state of the participant. Further, they suggested that variations in participant arousal may be a major contributor to the inter-individual differences in changes in corticospinal excitability that occur in response to motor learning (Koizume et al., 2017). Therefore, if participants were experiencing low levels of arousal during training, this could have limited the magnitude of training induced changes in sensorimotor integration.

The arousal levels of participants during training also could have influenced maze performance results. Specifically, the maze was a repetitive task performed for an extended duration while seated and without vision. Therefore, it is possible that the arousal levels of participants may have been relatively low due to the prolonged seated position in in the absence of vision. Decreased arousal would be determinantal to performance, as the well-established "Inverted-U Hypothesis" posits that arousal levels too high or low can result in impairments in performance (Yerkes & Dodson, 1908). Instead, there is an optimal level of arousal for peak performance, and this level varies slightly between individuals and in different contexts (Raglin & Turner, 1993). Due to this inter-individual variability, some participants may have been performing at an optimal arousal level, while others. Although no physiological or self-reported measures of arousal were collected in this study, this inter-individual variability would suggest that those who performed best were operating near their optimal arousal level, whereas those who performed worse may have been experiencing suboptimal levels of arousal.

4.2.2 Fatigue

Another potential implication of training that may have influenced the outcomes of this study is fatigue. Neither baseline, nor training-induced measures of fatigue were collected in this experiment. Yet, extended durations of exercise and performing repetitive movements progressively induces fatigue (Proschinger & Freese, 2019). Maze training was a repetitive motor task performed for two 15-minute blocks with a 5 minute halfway through to offer a brief cognitive and muscular rest. However, past studies have reported evidence of rapid rates of muscle fatigue occurring as soon as

only seconds into a 20-second finger flexion/extension task performed at maximal intensity (Rodrigues et al., 2009). Although finger movements in the maze may not have been performed at maximal speed, participants were still moving with the intent to complete the task as fast as possible and for much longer than just a few seconds. EEG studies also showed that the "motor potential" component of the movement related cortical potentials over the supplementary motor and sensorimotor areas were increased as a compensatory mechanism for the muscle fatigue induced during three blocks of 40 trials on a hand grip task (Johnston et al., 2001). Therefore, it is highly likely that the duration of maze training in this study induced central or peripheral of fatigue in the participants during training.

Fatigue is a highly complicated process that can have several different definitions depending on the context. There are psychological, physiological, performance, and subjective descriptions of fatigue (Phillips, 2015). In the context of this thesis, fatigue can be defined as a reduced capacity to do work and decrements in perception, attention, decision making and skilled performance (Cercarelli & Ryan, 1996). Acute fatigue is the direct result of performing a task requiring effort for an extended duration (such as maze training), whereas chronic fatigue refers to prolonged feelings of drowsiness or tiredness related to dysfunctional neuroendocrinology (Cleare, 2003). Definitions of fatigue have also been divided into central and peripheral sites. While central fatigue refers to the reduced functioning of the brain and nervous system with fatigue, peripheral fatigue involves

the exercise or movement-induced reduction in force generating capacity at the muscle (Cè et al., 2020).

Fatigue has been measured in many ways because it is such a complex and multifaceted phenomenon. From a neurophysiological perspective, past research has used EMG (Rampichini et al., 2020), EEG (Wang et al., 2018), fMRI (De Lange et al., 2004) and TMS (Gruet et al., 2013) among other neuroimaging methods quantify neurophysiological indices of central and peripheral fatigue. Latella et al. (2020) found a reduction in MEP amplitude and ICF along with an increase in SICI from the FDI muscle in response to sustained maximal isometric finger abductions. These results suggest that fatigue-related firing of muscle afferents from the hand limited motor cortical excitability during exercise. Similarly, individuals who complained of fatigue and cognitive difficulties during the COVID-19 pandemic have been shown to have altered corticospinal excitability and neurotransmission within M1 (Ortelli et al., 2022). Specifically, those with fatigue presented with reduced MEP amplitude and increased RMT, along with longer cortical silent periods compared to healthy controls. Fatigue also impaired long-interval intracortical inhibition (LICI) and SAI, which suggested that $GABA_B$ergic and cholinergic neurotransmission may have been affected (Ortelli et al., 2022). Further, SAI has been shown to be reduced along with MEP amplitude in the FDI following repetitive finger movement (Miyaguchi et al., 2017). Therefore, fatigue induced by navigating the hand through the maze may have reduced levels of afferent inhibition in the brain immediately after training. This

influence would have had the opposite effect that the physiological influences of tactile discrimination training would have had on afferent inhibition (Master & Tremblay, 2009), which could have resulted in the overall null effect of training found in this study.

Since fatigue is directly related to decrements in performance as well, progressive fatigue during training may have affected participant's maze scores in this study as well. The influence of fatigue on tactile discrimination performance has been demonstrated in one study that reported significant increase in two-point discrimination distance in both males and females when compared to rest, which indicates a decrease in performance (Han et al., 2015). During maze training, acute central and peripheral components of fatigue could have occurred. Peripheral fatigue could have been induced due to the constant movements of the hand through the maze paths, and the repetitive physical interactions with the sandpaper strips on the maze. Alternatively, the prolonged duration of training without vision may have eventually led to reductions in attention or motivation that would contribute to increases in central fatigue (Boksem et al., 2006).

4.2.3 Biological Sex

The imbalance of the participant demographic (22 females: 8 males) in this experiment raises the question of the potential role of sex differences in the results. Biological sex refers to the set of anatomical and physiological attributes of an individual which are present at birth and classified as either male or female. Sex is distinct from gender, which

refers to socially constructed roles, behaviours, expressions and identities, and is not confined to a binary classification system. Though both constructs are important, the remainder of this section will focus on the role of biological sex on the outcomes of this study. Sex differences are an important factor to consider in human research, as there is a breadth of biological differences between sexes. Perhaps most notably, females have higher estrogen levels, a hormone known to have a significant influence on brain function (Gillies et al., 2010).

In the context of neuroscience, sex differences have been identified from structural differences at the macroscopic level down to the microscopic level. Males have larger brain volume, intracranial volume, and amounts of gray and white matter (Van der Linden et al., 2017). Alternatively, females have greater cortical thickness and functional connectivity in the sensorimotor cortex (Ritchie et al., 2018). There are also sex differences related to neurotransmission of GABA (Grachev and Apkarian, 2000), dopamine (Gillies et al., 2014) and serotonin (Weiss et al., 2005) which are known to be involved in motor cortex excitability (Di Lazzaro et al., 2005; Gerdelat-Mas et al., 2005; Hosp et al., 2009). Nonetheless, the functional significance of the sex differences within the brain is not yet fully understood and still under investigation (De Vries, 2009). Consequently, neuroscience research has tended to overlook biological sex differences when interpreting results in the past and assume generalizability across sexes (Prager, 2017).

Despite known differences in brain structure and function between sexes, most of the previous research has found no significant differences in TMS measures such as MEP amplitude (Cantone et al., 2019), RMT (Akilan et al., 2020) and ICF (Zoghi et al., 2015). Still, there have been a few cases of studies reporting sex differences in TMS measures, such as females having lower MEP amplitude (El-Sayes et al., 2019b), greater SICI (Shibuya et al., 2016) and greater interhemispheric inhibition (De Gennaro et al., 2004). Perhaps most importantly though, SAI and LAI were found to be equal in males and females, which led authors to suggest that these measures may not be sensitive enough to enough to detect the subtle sex differences in sensorimotor activity that may result from differences in brain structure or function (Turco et al., 2019).

Although measures of SAI and LAI appear to be equal between sexes at rest (Toepp et al., 2021; Turco et al., 2019), no studies to date have examined if males and females measures of SAI, LAI and AF respond differently to sensorimotor training. However, there has been past research showing that neuroplasticity induced by NIBS is greater in females than males (Kuo et al., 2006), and therefore it was suggested that exercise induced plasticity is likely to be higher as well (El-Sayes et al., 2019a). However, upon further investigation El-Sayes et al. (2019b) showed that there were no differences in exercise-induced neuroplasticity in the FDI muscle following 20 minutes of lower-limb cycling in young heathy adults. Therefore, the evidence suggesting that females have either an equal or greater propensity for use-dependant neuroplasticity would suggest that

having a greater proportion of females in this study was not likely to be the reason there was no significant changes in SAI LAI or AF following the maze training task.

There are also sex differences related to somatosensory processing and performance on sensorimotor or tactile discrimination tasks that are worth discussion.
For example, women have lower thresholds and higher sensitivity to pain and temperature compared to males (Meh & Denislic, 1994). Although sex differences related to tactile perception have been reported to be small and inconsistent, some studies have shown that males perform better on haptic perception tasks (Kaas & Mier, 2006; Zuidhoek, Kappers, & Postma, 2007). Conversely, females have been shown to be more accurate than males in texture discrimination (Gliner, 1967). Another study supporting these findings found that females had lower tactile detection thresholds than men (Boles & Givens, 2011). These findings are in line with a previous study examining the gender differences in cortical responses to performing a tactile discrimination task which reported differential activation of the dorsal premotor cortex that might suggest greater interhemispheric interactions in the brain of females (Sadato et al., 2000). Together, these findings suggest that the sensory processing abilities of females may promote better performance on the maze task which relied on sensory-guided movement.

This study did not have a balanced sample demographic due to recruitment limitations and because sex differences were not a primary interest of this study. However, when comparing the male and female performance data that was collected, two trends were

apparent. First, females had a lower average dwell time in both the high and low conditions compared to males. This is in support of the research presented in this discussion which propose females perform better on tactile discrimination tasks (Boles & Givens, 2011; Gliner, 1967), as it indicates that females processed the sensory information to inform their decision with more speed compared to males.

Second, males showed greater improvements in performance in both conditions as indicated by higher slope of dwell time values compared to females. This finding also supports the research discussed above. It suggests that while males may have had slower performance to begin with, they had more room for improvement and consequently decreased their dwell times to a greater extent as they became familiar with the task and developed strategies to inform their decision making during tactile discrimination. Females' times improved too, but it was not as large because there was less room for improvement. Both of these findings are coincidentally well reflected in **Figure 18**. Participant A is male, and Participant B is female. The male began with high dwell times but was able to improve performance substantially by the end of training. Conversely, the female did not have as much room for improvement across trials, because she had far lower dwell times to begin with.

Together, the results discussed in this section have identified several differences between males and females with regards to brain structure and function, with specific focus on the processing of somatosensory information and performance on tasks associated with this

sensory processing such as tactile discrimination training. Although these differences are not yet fully understood, the evidence presented here suggests that biological sex was not likely to be the cause for the lack of change in SAI, LAI and AF in response to training. However, sex differences related to sensory processing were a likely candidate for differences in maze performance identified in the dwell time data.

4.2.4 Genetics

Another biological factor that should be considered when evaluating the neurophysiological responses to sensorimotor training in this study is the BDNF genotype of the participants. A genetic variation of the neurotrophic factor BDNF known as Val66Met can occur where valine is replaced by methionine, and this genetic variation is present in as much as 30-50% of humans (Mang et al., 2013). BDNF has been established as a biomarker of neuroplasticity (Knaepen et al., 2010), and this genetic variation has understandably been found to influence neuroplastic processes in the brain. Specifically, some studies have shown that the BDNF Met allele causes less activity-dependant release and recruitment of BDNF neurons and altered neurotransmission (Lemos et al., 2016).

For example, motor training has been shown to increase corticospinal excitability and memory in healthy control but not individuals with the Val66Met polymorphism (Hopkins et al., 2012; Kleim et al., 2006). Val66Met carriers also show reduced M1 responsiveness to NIBS plasticity-inducing protocols such as 5-Hz rTMS (Li Voti et al.,

2011), intermittent theta burst stimulation (Lee et al., 2013), and anodal transcranial direct current stimulation (Fritsch et al., 2010). Moreover, these individuals also have been found to perform worse on cognitive assessments (Pearson-Fuhrhop & Cramer, 2010) and motor tasks (McHughen et al., 2017).

Despite these results, there has been conflicting evidence as well. Cirillo et al. (2012) showed that despite reduced use-dependant plasticity in Val66Met carriers, there was no differences in performance on a simple ballistic finger movement task, or a complex visuomotor tracing task. Likewise, another study found that BDNF genotype had no influence on the effects of acute aerobic exercise on motor skill acquisition and retention (Mang et al., 2017). Specifically in relation to sensorimotor integration, another study reported no differences in SAI following 1 or 5 days of motor training, regardless of BDNF genotype (Deveci et al., 2020). BDNF genotype did not have any influence on changes in afferent inhibition in that study, which provides some evidence to suggest that it also may not have played a major role in the lack of change in SAI, LAI or AF found in this experiment.

Collectively, the evidence presented in this discussion showed that Val66met carriers appear have a reduced propensity for both exercise and non-exercise induced neuroplasticity. Yet, there is conflicting evidence related to the effect of this genetic variation on motor learning and performance. Further, there is currently not enough evidence related to the effect of this polymorphism on sensorimotor integration to

conclude that this would have influenced the outcomes of this study. Yet, the BDNF genotype of participants was not assessed in the present experiment, so this relationship could not be assessed directly. Future studies measuring sensorimotor integration and activity-dependant plasticity are encouraged to determine the BDNF genotype of participants in order to improve the understanding of the variation in responses across participants, as well as expand the literature demonstrating the role of this genetic variation in neuroplasticity.

4.3 Functional Significance of SAI, LAI and AF

In this study, the experiment protocol was designed to expose effect of maze training on SAI, LAI and AF. Yet, training did not induce changes in any of these measures of sensorimotor integration. The absence of change may not be a shortcoming of the task, since the maze was shown to be a challenging sensorimotor tactile discrimination task with evidence of improvements in performance with training. Instead, the lack of change in SAI, LAI and AF may reflect the rather stable nature of these measures and suggest that no lasting changes in these measures should be expected following sensorimotor training. Therefore, changes in these measures following training do not appear to be a meaningful indicator of improvements in motor performance. However, the duration of training was only 30 minutes in this study, and participants only performed this task on two sessions. It remains possible that if participants performed this task for a longer period of time, or for a greater number of sessions, training would have changed the magnitude of SAI, LAI and AF. Alternatively, changes in these measures may be more

meaningful when they occur in the context of task performance, rather than at rest after training when they were assessed in this experiment.

In this study, we found that the group-averaged SAI and LAI measures demonstrated significant inhibition compared to the unconditioned MEP amplitude in each condition. These results were not surprising, since SAI and LAI are both well studied inhibitory neural circuits which have been clearly demonstrated extensively in previous research (Ni et al., 2011; Tokimura et al., 2000; Turco et al., 2018b). In contrast, AF was not present at the group level in the high and low conditions. This is not uncommon, as past studies measuring AF have reported similar findings (Kojima et al., 2014; Mang et al., 2012). Although there were some individuals who did show afferent facilitation, there was a large amount of variability across the group like in past studies (Devanne et al., 2009). Some individuals displayed a large amount of facilitation (ex. 141%), some displayed only very minor facilitation (ex. 105%), and others even showed inhibition (ex. 24%). This is not surprising, as an investigation of the reproducibility of TMS measures of afferent interactions found that healthy participants can shift from showing MEP inhibition at a certain ISI one day, to MEP facilitation another day with no noticeable change in health status or behaviour (Toepp et al., 2021).

One potential cause for this variation in AF may be related to inter-individual differences of the ISI that elicits facilitation (Ansari & Tremblay, 2019; Kojima et al., 2014). Examples of ISIs used to measure AF in past studies range from as low as 25ms (Deletis

et al., 1992; Lapole & Tindel, 2014) to 80ms (Komori et al., 1992; Devanne et al., 2009). Though it appears that AF can be elicited at different intervals, this inconsistency on what ISI to use may be a contributing factor to the relative lack of previous research dedicated to studying AF when compared to SAI and LAI. Additionally, the pharmacology of AF has not been explored in any previous studies, meaning that there is no scientific evidence of the neurotransmitters and substrates in the brain that contribute to this measure. Due to these results, it could not be concluded that this measure represents a true sensory-motor interaction that has any value in the context of understanding of sensorimotor integration and motor control.

SAI and LAI have gained attention in the neurophysiology research community in the past due to the observation that they are not present in special populations characterized by impairments in sensorimotor or cognitive functioning such as Stroke, SCI, AD and PD (Bailey et al., 2015; Di Lazzaro et al., 2012; Nardone et al., 2008; Pelsoin et al., 2016). SAI also has potential clinical utility, as it may be a useful tool to monitor functional recovery of sensorimotor function during rehabilitation after a neurological insult such as Stroke (Turco et al., 2018b). This information has led researchers to suggest that these measures may play an important role in normal human function.

Yet, it has proved difficult to establish the relationship between TMS measures such as SAI//LAI/AF and motor performance in past studies to determine their functional significance (Turco et al., 2021). The results from this study also faced the same challenge, as there was evidence of behavioural changes from maze training based on

improvements in performance, but no association with the changes in SAI or LAI. Therefore, these measures may not be tools that can be used to monitor functional changes in sensorimotor skills following training. Further investigation into the significance of these measures in the context of motor control and learning must be considered in future studies in order to effectively fill these significant gaps in the literature.

4.4 Conclusions

In conclusion, no changes in SAI, LAI or AF were found following maze training, and there was no relationship between changes in these measures and improvements in performance. Though these results did not support the initial hypotheses of the study, there were several potential influencing factors that may have affected the outcome of this study which have been discussed throughout this thesis. The findings from this study have implications for understanding SAI, LAI and AF in the context of somatosensation and motor control. However, suggestions have been provided for future studies on how to address some important gaps that still exist in the literature and disentangle the neurophysiological underpinnings of SAI, LAI, AF.

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