The Effect of Working Memory on Corticospinal Excitability

by

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AUTHOR DECLARATION

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

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ABSTRACT

Skilled behavior is dependent upon the ability to extract and integrate sensory afference into appropriate output from motor cortex. This process is dynamic with executive control, guided by declarative knowledge (i.e. facts and semantics) and able to shape subconscious processes guided by procedural knowledge. Previous work by Suzuki et al.[1] used short-latency afferent inhibition to show that verbal working memory demands (a declarative construct) change afferent projections to the cortical motor output neurons, providing a route by which executive control shapes motor cortical output. Whether other variants of working memory have the same influence on motor output and whether the same neuronal circuits are involved is unknown. Therefore, the current study sought to investigate the influence of spatial working memory on different afferent projections converging on the corticospinal neuron in the motor cortex.

Short- (SAI) and long-latency afferent inhibition (LAI) were assessed in seventeen participants during the maintenance period of a spatial or verbal working memory task conducted over the course of two sessions per participant. Either session consisted of one of the two working memory tasks. In the spatial memory task, participants were required to encode a spatial array and maintain the array in working memory to determine whether a probe matched or did not match the original display. The probe consistent of a single dot and participants indicated whether the probe was part of the initial set. The spatial array consisted of either two or six dots around a central fixation cross. In the verbal memory task, participants were required to encode an array of letters and maintain the array in working memory to determine whether a probe matched or did not match the original display. The probe consistent of a single letter and participants indicated whether the probe was part of the initial set. The verbal set consisted of either two or six letters. The effect on different afferent circuits was assessed by manipulating the direction of induced current used in the assessment of SAI and LAI. The "PA" afferent circuit was recruited using TMS induced current in the posterior-anterior direction, and the "AP" afferent circuit was recruited using TMS induced current in the anterior-posterior direction. The order of task and current direction was randomized across participants with TMS current in each direction (AP/PA) conducted within both sessions. Baseline assessments of spatial and verbal working memory capacity evaluated the influence of working memory on sensorimotor circuits.

Increasing verbal working memory load increased SAI from circuits recruited by current in the PA but not AP direction. Verbal working memory load had no impact on either PA or AP circuits mediating LAI. In contrast, spatial working memory load had no effect on either PA or AP circuits mediating SAI. Instead, increasing spatial working memory load increased LAI recruited by AP circuits.

These results suggest that spatial and verbal working memory influence the AP- and PA-mediated afferent circuits that converge on the corticospinal neuron to shape motor output. These different inputs may provide distinct pathways by which declarative knowledge can shape representations of motor skills.

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LIST OF ABBREVIATIONS

Ach – Acetylcholine

AP – Anterior-posterior

DLPFC – Dorsolateral prefrontal cortex

ERP – Event related potential

FDI – First dorsal interosseus

GABA – Gama aminobutyric acid

LAI – Long-latency afferent inhibition

MEP – Motor evoked potential

PA – Posterior-anterior

PTN – Pyramidal tract neuron

RMT – Resting motor threshold

SAI – Short-latency afferent inhibition

SEP – Sensory evoked potential

SMA – Supplementary motor cortex

SWM – Spatial working memory

TMS – Transcranial magnetic stimulation

VWM – Verbal working memory

WM – Working memory

1.0 INTRODUCTION

Skilled action involves an intricate balance between conscious and subconscious knowledge. Explicit strategies that emphasize consciously accessible, declarative knowledge about a skill (e.g., the facts or semantics of skill) can interact with the subconscious, procedural knowledge of the skill (e.g., movement kinematics and kinetics) to disrupt skill execution. Although there is strong behavioural evidence that the declarative and procedural memory systems interact, these memory systems are typically prescribed to distinct neural substrates. The specific substrates by which these two memory systems interact is unknown. One possibility is that the increased conscious effort, associated with increased reliance on declarative knowledge, changes how sensory afference is integrated into motor commands.

Somatosensory afference is integral to skill acquisition and performance, providing information on body state and shaping motor cortex excitability. One method to investigate the conscious, declarative influence on somatosensory processing is afferent inhibition. Afferent inhibition determines the influence from the afferent somatosensory volley on motor cortical excitability by preceding transcranial magnetic stimulation (TMS) of motor cortex with excitation of the corresponding peripheral nerve. Short-latency afferent inhibition (SAI)[2] occurs when the peripheral stimulus precedes the TMS stimulus by ~20 msec. SAI is an excellent candidate by which declarative knowledge may shape subconscious processes. SAI is sensitive to constructs, such as attention and working memory, that support increased conscious effort. SAI is also modulated by acetylcholine, a key neurotransmitter of the attentional system.

Manipulating the direction of current induced in neural tissue by the TMS stimulus provides a method to recruit distinct sensorimotor circuits that may mediate the afferent effect on motor cortical excitability. Using a TMS stimulus that induces posterior-anterior (PA) current in the underlying neural tissue excites the corticospinal output neurons in the motor cortex through a circuit more simplistic in structure than induced current in the anterior-posterior (AP) direction[3]. The simple PA and more complex AP circuits appear to have different functional contributions, shaping the excitability of motor cortex output. Investigating the sensitivity of simple and complex circuits to verbal and spatial working memory will provide critical insight into different afferent pathways, their functional significance and their potential role in mediating conscious, declarative influence over subconscious, procedural motor control processes. Longer-term, this knowledge is critical to maximizing motor recovery following brain injury through a better understanding of how a clinician's instructional cues affect the balance between declarative and procedural process

1.1 Interacting Memory Systems for Motor Control and Learning

To identify the substrates mediating the interaction between declarative and procedural memory systems, it is essential to understand the psychomotor evidence that supports the difference between conscious and unconscious processing for skill performance and learning. An external focus of attention, allocated towards the outcome of the body's actions, is associated with less conscious effort. By comparison, an internal focus of attention stresses the control of specific body segments involved in the action and is associated with greater conscious effort. Evidence suggests that when an external focus of attention is implemented, the likelihood of successful performance is higher[4]. This has been demonstrated in the context of skilled motor performance as it pertains to movement outcomes[4] and kinetic and kinematic efficiency[5,6]. In contrast, the relative decline in movement outcomes and efficiency under an internal focus of attention is thought to arise from the accumulation of excessive declarative rules. More declarative rules, in turn, increases the demands on working memory and attention through the need to monitor the individual actions of multiple effectors under internal focus rather than the net outcome of these effectors on the environment. The increased emphasis on the conscious control of individual effectors under an internal focus is thought to disrupt automatic, subconscious, procedural processes leading to declines in performance and poorer learning outcomes.

As noted, an external focus of attention facilitates learning across various tasks, likely as a result of its ability to provide a more subconscious and automatic strategy to avoid constraining the motor system. This idea is further supported by evidence that displays the additional performance benefits associated with an external focus directed farther from the body[7]. A comparison of performance outcomes across studies indicates that focus at an increased distance from the body (i.e., on the head of a golf club)[8] is more advantageous than the external focus at a shorter distance from the body (i.e., on the wheels of a balance platform just below the feet)[4]. A comparison of near and far external focus conditions within a single task further suggests that an increased distance at which performers focus their attention leads to improved learning outcomes. Additionally, internal and near focus conditions are proposed to constrain the motor system by exerting active control over natural movement dynamics. The learning outcomes associated with external vs. internal focus provide further support for the constrained action hypothesis[9], which acts as a model to account for the discrepancies in performance observed between attentional focus strategies. Additionally, adopting an external focus also proves to enhance the learning of motor skills[4,10]. Although there is much support for an external focus of attention that enhances learning, theories suggest novices require a more conscious strategy to develop the skills necessary to achieve automatic performance[11,12,13]. Therefore, an internal focus may benefit someone who does not yet have the knowledge required to utilize external focus, for example, learning the proper way to stand and hold a golf club before making a shot. Despite this exception for novice learners, an external focus of attention remains an essential component to be adopted by all performers at some point to facilitate improvements. Specific models, such as the constrained action hypothesis and optimal control theory, have proposed mechanisms explaining this behaviour pattern.

The constrained action hypothesis dictates that internal focus results in a form of conscious control that interferes with automatic processes and therefore constrains the system[9,14]. External focus allows for automatic control through unconscious processes and results in more unconstrained and often successful performance. However, where the constrained action hypothesis is limited in its detail about movements outside of performance outcomes, optimal control theory aims to explain how attentional focus changes the movement itself[15]. As a more mechanistic theory of attention for movement, the optimal control theory focuses on the kinematics of motor performance. According to this theory, attention dictates whether aspects of goal-relevant dimensions (factors that allow for the success of the final objective) or bodily dimensions (factors pertaining to elements of the movement like joint angles) are controlled within the action. When focusing attention externally, the motor system optimizes the task's goal vs. treating the bodily dimensions in focus as the goal, which leads to better performance[15]. Greater variability amongst bodily dimensions allows the coordination between these dimensions to compensate for noise and error[15]. On the other hand, strict movement patterns lead to reduced variability in goal-relevant dimensions and accumulated variability in redundant dimensions[15].

Although an external focus is generally associated with better performance, this does not mean that a novice learner can not benefit from an internal focus strategy. Suppose novices have not learned of the association between movement variables leading to distal outcomes. It is more difficult for them to control these aspects of movement for success and, therefore, may benefit from a more internal focus at this stage[15]. The optimal control theory identifies the more specific details of movement that distinguishes between attentional strategies and proposes a mechanism that accounts for performance outcomes based on the form of attention implemented. The constrained action hypothesis and optimal control theory provide the framework for how increasing conscious control may disrupt subconscious processes dependent on procedural knowledge. However, declarative and procedural memory systems are typically associated with distinct neural substrates, the point of interaction between which is not clear.

1.2 Neural Substrates of Declarative and Procedural Memory

Declarative memory involves the rapid learning of specific events where representations are flexible and accessible to awareness, meaning that declarative memory is conscious and easily recalled[16]. Declarative knowledge about a motor skill can be verbally expressed. Early declarative knowledge is derived from external sources such as action observation or external instruction. Declarative knowledge can also be acquired autogenously through practice[17]. Explicit information is declarative in that it refers to consciously expressed and directly measurable, factual knowledge of a task[17]. Key cortical structures of the declarative memory system include the hippocampus and parahippocampal gyrus within the medial temporal lobe (MTL)[16]. The importance of the MTL for declarative memories is evident in the case of patient H.M. who underwent bilateral MTL resection, destroying a large portion of his hippocampus and parahippocampal gyrus. The result was both antero- and retrograde amnesia: the inability to form new or access old memories[18]. Not only did this finding influence the idea of memory as a distinct cerebral function, but it also displayed the importance of this area for the function of memory retrieval. As was discovered, however, H.M.'s ability to learn skills without recollection of practice indicated a preserved form of memory that must function in the absence of MTL. This finding supports the concept of a procedural system that functions for unconscious working memory of skilled action.

The procedural system is distinct from declarative in its function and anatomical neural network. Procedural knowledge is skill-based information that cannot be consciously recalled but is acquired through practice and expressed through refinement and automaticity associated with skill performance[16,19]. Just as the explicit information is associated with the declarative system, implicit information falls within the procedural construct and is measured indirectly through responses facilitated by task knowledge[17]. Known procedural regions include the cerebellum[20], basal ganglia, motor cortex[21], and supplementary motor area (SMA)[22], which act to facilitate distinct functions. One concept within the scope of procedural processing is that of perceptual learning: a form of implicit memory that accounts for improvements in detection or discrimination of stimuli[23]. Perceptual learning also involves distributed functional changes throughout the brain but is quite evident through observation of neurons in the primary visual cortex. Another implicit concept is that of priming, which refers to the improved or changed identification of a stimulus due to previous recognition or association[19]. Despite their anatomical dissociation, declarative and procedural regions do interact, fulfilling an important requirement in the execution of skill performance and throughout the learning process.

Regions of both declarative and procedural systems act synchronously in order to processes different forms of information pertaining to task demands. fMRI distinguishes between activity profiles of selective areas when engaged in both declarative and non-declarative conditions[24]. For instance, the caudate nucleus of the basal ganglia becomes significantly active in a feedback-based (non-declarative) condition, whereas the MTL appears deactivated compared to baseline. Similarly, in a paired-associate (declarative) condition, MTL displays significant activity, whereas the caudate is inactive. An information-dependent negative relationship such as the one observed implies a competition between memory systems, where the mechanism controlling the organization of processing is responsible for reciprocal changes in different brain regions. This trend is evident with learning as observed in the non-declarative condition, where the MTL is most active in the early stages and quickly becomes inactive, giving way to caudate activity. Shifts in brain activity have also been observed during visuomotor sequence learning[25]. The DLPFC and pre-SMA are significantly more active during the early stages of learning when the task requires more attention. In the more advanced stages, the intraparietal sulcus and SMA become dominant when behaviour is associated with faster reaction times and better accuracy[25], coupled with decreased activity in the dorsal premotor cortex[22]. This shift in activity from frontal to parietal regions displays less reliance on premotor and planning areas as the task allegedly becomes more familiar. In terms of specific networks, functional interactions between the cortico-striatal (CS) and cortico-cerebellar (CC) systems have been associated with the transition from early to the automatic phase of learning[26]. As individuals move towards automatization, the CS becomes more active for sequential skills, whereas the CC is more active in motor adaptation. The consolidation of motor activity consists of larger-scale interconnectivity involving both CC and CS systems. With automaticity, a decrease in connections within the network eventually leads to a retention of functional links specifically within the CC system[26]. The synchronous activity between brain regions allows for the successful execution of both declarative and procedurally based tasks, but regardless of task, a shift from declarative to procedural regions occurs with learning. A key concept within these interactions is distinguishing between the specific groups or circuits of neurons within the sensorimotor cortex by which areas like frontal cortex shape motor cortical output to effectors.

Given that focus of attention shapes motor control strategy, one possibility is that the frontal cortex influences afferent input to the motor cortex, and therefore corticospinal output. Evidence to support prefrontal influence to the sensorimotor cortex comes from fMRI recording during a somatosensory attentional task[27]. When an attentional task involved vibrotactile stimuli to be counted, activation in the contralateral sensory cortex increased, whereas activity in the ipsilateral sensory cortex was suppressed. These results support a gating mechanism selective to task-relevant somatosensory stimulation where activity in regions processing relevant stimuli is increased, and activity in regions processing irrelevant stimuli is suppressed. The involvement of the prefrontal cortex supports the idea that this region plays a role in gating sensory information by means of regulating access of task-relevant information to the sensory cortex[27]. However, a decrease in sensory cortex activity was observed with attention directed to a vibrotactile grading task while ignoring visual stimulation[28]. This supports the idea that intermodal selective attention results in gating information to the sensory cortex. Further evidence to support intermodal influences on somatosensory processing arises from modulation to early somatosensory evoked potential (SEP) components[29]. A reduction in P27 amplitude was observed specifically during visual tracking as opposed to the increase in P50 amplitude that was observed in tactile tracking. Additionally, a decrease in parietal N140 amplitude was observed in visual tracking. In each case, the opposite modality acted as a distractor that was spatially related. These results demonstrate the relevancy of the modality as well as the spatial and temporal properties of stimuli in the regulation of somatosensory information processed in the sensory cortex[29]. Although these results shed light on the interconnectivity of regions within various attentional conditions, they are limited in their ability to identify the specific circuitry involved in the excitatory and inhibitory input to the sensorimotor cortex. However, one method to determine the possible substrates by which declarative knowledge influences procedural motor control is short-latency afferent inhibition (SAI). SAI is a form of transcranial magnetic stimulation (TMS) where the stimulus is timed to converge with the arrival of somatosensory afference generated by stimulation of the peripheral nerve. The magnitude of SAI is directly tied to the strength of the somatosensory afferent input. SAI is also sensitive to changes in acetylcholine (Ach), a key neurotransmitter that mediates attention. As a result, changes in SAI can be associated with changes to attentional function, which may provide a link between declarative processing and sensorimotor outcomes.

1.3 Short-latency Afferent Inhibition

TMS is a form of non-invasive brain stimulation able to probe the excitability of the motor system through the activation of specific neuron pools. In the cortex, an induced current can cause a change in the membrane potential of superficial dendrites from a neuron, leading to depolarization and, eventually, the firing of an action potential. The direct excitation of axons and indirect, transsynaptic excitation of the pyramidal neuron can be quantified through cervical epidural recordings[30]. These recordings demonstrate the preferential generation of Indirect waves (I-waves) at near-threshold stimulation intensities beginning 1.5 msec after the shortest possible latency that can be achieved by directly stimulating the pyramidal neuron axon itself (e.g., the Direct or D-wave). I-waves can be recruited in succession leading to multiple early (I_1, I_2) and later waves (I_3, I_4) depending on stimulation type and intensity. Different models to explain the behaviour of I-waves have been proposed, including the canonical microcircuit model used to evaluate whether descending waves can be explained by the interaction of stimuli and cortical circuits[31]. According to this model, the D-wave may originate from direct excitation of P5 axons, whereas the I_1-wave may originate from monosynaptic excitatory connections between P2, P3, and P5 cells. It also proposes that GABAergic interneurons are responsible for the control and ability to selectively recruit late I-waves in the absence of I_1. In addition to stimulation intensity, the propensity to recruit different combinations of D- and I-waves depending upon coil orientation and current direction suggests that different populations of neurons can be investigated with TMS[32].

Passing a current through the TMS coil windings from anterior to posterior induces a posterior to anterior (PA) current in the brain. Likewise, passing current through the coil from posterior to anterior induces an anterior to posterior (AP) current in the brain. The vast majority of past research has strictly employed induced current in the PA direction. The different current directions produced by TMS have differential effects on I-waves generated. Larger MEPs are evoked at lower stimulation intensities with PA current, and I-waves are recruited 1-3ms earlier than AP[33]. The lower intensity is thought to reflect the preferential recruitment of early I-waves (e.g., I_1) and, as a result, reflects a more direct path to the corticospinal neuron[3]. In contrast, AP current preferentially recruits later I-waves (I_3, I_4). The longer latency of I_3 and I_4 suggests that the AP current preferentially depolarizes an axon that is further removed from the pyramidal neuron itself[3]. An advantage to stimulating with different current directions is that it is thought to recruit distinct sensorimotor circuits. Investigating alternate ways to influence sensorimotor integration may uncover differential processes by which declarative information influences procedural motor processing.

One method utilizing TMS to probe sensorimotor integration is that of SAI. This method involves TMS positioned over the motor cortex and paired with a preceding peripheral conditioning stimulus by ~20ms[2]. The motor response from TMS is subject to inhibition that is cortical in origin due to the afferent signal timed such that it converges on the corticospinal neurons of the motor cortex at the onset of TMS[2]. LAI is another method to probe sensorimotor integration, of which the only difference is the interstimulus interval (ISI) of ~200ms prior to TMS onset[34]. Reduced excitability of the motor cortex is evidenced by the reduction of I_2 and I_3 waves when TMS is paired with the peripheral conditioning stimulus[2]. The late I-waves inhibited through SAI are more evident with PA than AP current (elicited at a lower intensity), which further supports differing neuronal populations in the I-waves generated by either current direction[3]. Importantly, the magnitude of SAI is directly tied to the intensity of this afferent stimulus[35], the mechanism of which is dependent on how information is transmitted from sensory to the motor cortex. Both median and digital nerve stimulation display SEPs that correlate with SAI amplitude, indicating that sensory cortex activity is linked to cortical motor inhibition and that a relay through the sensory cortex mediates this response[35]. This relay is driven by pyramidal GABAergic inhibitory cells within the sensory cortex that have projections to the motor cortex and selectively influence its upper layers, increasing inhibition of late I-waves[35]. Since SAI is driven by the afferent stimulus, changes to inhibition support a gating mechanism by which the magnitude of information that reaches the sensory cortex is altered. This gating effect, in turn, modifies the response from the motor cortex through the sensory GABAergic projections that mediate SAI.

Pharmacologically, SAI and LAI are mediated by elevated levels of GABA and acetylcholine (Ach), specifically involving the $GABA_A$ receptor subtype bearing the α1 subunit[36]. GABA-controlled release of Ach in the cortex and brainstem indicates key involvement of a cholinergic pathway in SAI[36]. One method of determining whether responses of inhibition involve specific forms of neurotransmission is through the introduction of drugs like Scopolamine, Lorazepam, and Baclofen. Reduction in SAI following injection of a muscarinic antagonist like Scopolamine indicates that these inhibitory processes are mediated by cholinergic transmission[37]. Similarly, a reduction in SAI observed with the introduction of Lorazepam, a positive allosteric inhibitor of the $GABA_A$ receptor, supports GABAergic neurotransmission in SAI[37]. Additionally, the lack of reduction observed with Baclofen indicates that SAI is $GABA_A$ but not $GABA_B$ receptor modulated. LAI follows the same trend in response as SAI, supporting the idea that similarly, LAI is mediated by $GABA_A$ neurotransmission. Processes such as those involved in executive control are similarly mediated by cholinergic properties and, therefore, indicate potential interaction with SAI. Methods like SAI also provide a means by which to probe abnormalities in sensorimotor pathways within clinical populations. For instance, when SAI is measured in patients with spinal cord injury, significant changes in the peripheral afferent volley are apparent where SEPs remain unchanged[38]. SEPs measured in parietal cortex would presumably reflect the any changes in afferent activity that would in turn, modulate SAI. Since no change in SEPs could explain changes in SAI, this would suggest that SAI is generated via a route independent of sensory cortex and possibly by way of thalamocortical projections to the motor cortex. SAI provides one method to examine how sensory input acts to modify the motor system; however, engagement of executive function may pose an interference to this process. Engagement of attentional resources, for instance, introduces cognitive demand with the potential to influence sensorimotor outcomes.

A specific focus of attention is shown to have implications for the performance of motor tasks[4]. Attentional resources also provide a key component within working memory to accommodate varying task demands. Both verbal and spatial working memory represent different forms of cognitive processing, suggesting that they differentially influence motor control. Evidence for the distinction between verbal and spatial processing is supported by fMRI data that reveal the left ventral prefrontal cortex contributes to verbal working memory where the right dorsolateral prefrontal cortex contributes to spatial working memory[39,40]. Verbal working memory is also thought to be preserved in older adults and relied upon for the processing of implicit sequences to compensate for other implicit cognitive deficienies[41]. The relationship between working memory and the motor system is displayed through changes to motor cortex that influence working memory outcomes and vice versa. TMS that disrupts motor cortical activity results in slowed response times for both spatial and verbal working memory tasks, indicating that motor-based strategies are potentially linked to rehearsal and important for working memory performance. Evidence that links spatial working memory to visuomotor sequence learning shows that lower spatial working memory capacity is associated with reduced performance on a visual learning task[41]. Additionally, verbal working memory is shown to reduce motor output as greater demand leads to depleted resources that, as a result, are unavailable for motor control[42]. These examples highlight the distinctions between how both verbal and spatial working memory influence the motor system. A comparison between how these constructs modulate SAI allows for the examination of how different processes within the brain can influence sensorimotor integration.

Measuring SAI as influenced by different forms of working memory, represents a method by which declarative tasks manipulate procedural processing. This allows for the investigation of how these two memory systems interact. As verbal working memory involves more explicit information and spatial may be more implicit, distinctions between their outcome on SAI will indicate how processes associated with either system influence motor control. Stimulation with both PA and AP current direction will provide insight into the functional roles of different circuits that mediate sensorimotor processing. When verbal working memory demand is high, SAI is shown to be reduced across both AP and PA current directions[1]. Despite MEPs evoked at a longer latency with AP current, the similar reduction of SAI across both directions suggests that these sensorimotor circuits both similarly influence the motor cortex with the engagement of verbal working memory. When SAI is measured in conjunction with an attentional task, only AP-mediated SAI is reduced as opposed to PA, which did not change[43]. Therefore, this work supports the functional role of the PA circuit as related to processes outside of attention while remaining associated with working memory.

1.4 Conceptual Model of Working Memory and SAI

Attention is thought to aid in the extraction of relevant information for use by working memory. As a perceptual process, attention acts as a filtering or temporary storage mechanism to help identify relevant from irrelevant stimuli[44,45]. Working memory is thought of as a cognitive control function that guides attention by actively maintaining stimulus-processing priorities. Increasing working memory load is thought to lead to a breakdown in the attentional filtration system responsible for enhancing relevant and suppressing irrelevant representations of stimuli[46]. This process is known as attentional gating which scales the activity of sensory brain areas where increases in gating are reflected by reduced activity within a particular brain region. As mentioned, SAI is dependent on the magnitude of the sensory afference. As a result, the manipulation of afferent information through attentional gating in a working memory task would influence the directional change in SAI.

A study by Suzuki et al.[1] that examined the effect of verbal working memory on SAI found that across both AP and PA current directions, SAI was significantly reduced with an increase in working memory demand[1]. The investigators also measured SEPs from EEG recordings in the parietal and frontal cortex. They found that the parietal N20-P30 SEP component was reduced and that the frontal N30-P25 component increased. This led to the development of a conceptual model to explain the change in SAI and the associated change in SEPs resulting from increasing working memory demand (Figure 1). It was theorized that input from the parietal N20 generator facilitated the reduction in PA-mediated SAI. Reduced activity in Parietal N20 was thought to occur as a result of attentional gating due to increased working memory demand[1]. Although the frontal N30 was thought by investigators to influence the AP

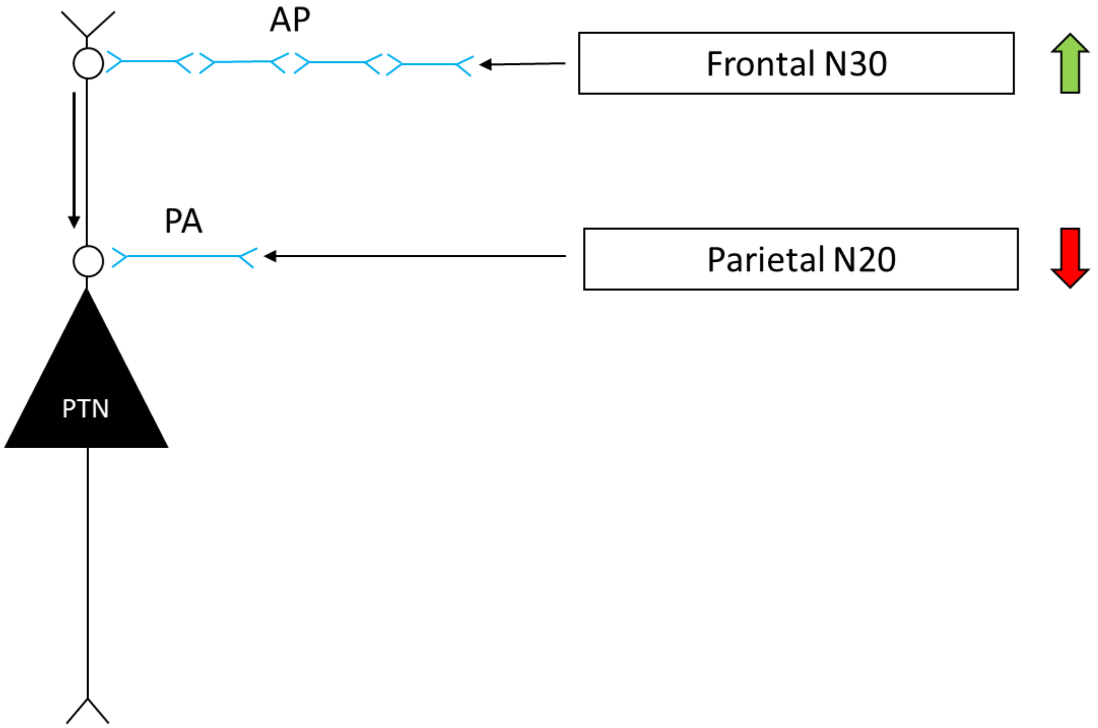


Figure 1 – A Conceptual model based on the interpretation of findings from Suzuki et al.[1] *. The model depicts the interaction between SEP generators from frontal and parietal cortices, their input to AP and PA-mediated circuits and the eventual input on to a pyramidal tract neuron (PTN) at different sites. The AP circuit synapses farther from the cell body of the PTN whereas the PA circuit synapses closer to the cell body. Activity observed from the frontal N30 is increasing with greater working memory demand and parietal N20 is decreasing.*

circuit, the N30 increased in activity opposite to the N20. Since AP-mediated SAI decreased similar to that of PA, the investigators theorized that the parietal N20 generator influenced the AP-mediated circuit in addition to the PA. The additional input from the parietal N20 would account for the similar decrease in SAI across both current directions with increasing working memory. Since the PA circuit is thought to input to the PTN closer to the cell body, the motor outcome from AP circuit recruitment was suggested as influenced by PA input downstream, leading to a net reduction in SAI.

2.0 AIMS AND HYPOTHESES

Three major aims and associated hypotheses were developed based on the expected SAI/LAI response within each task, across current direction, and in relationship to baseline tasks:

Aim #1: Identify the change in SAI and LAI response within both spatial and verbal working memory task conditions.
Hypothesis #1: It was hypothesized that a reduction of both SAI and LAI would be apparent in the six compared to the two-item condition within both the spatial and verbal working memory task.

Aim #2: Identify the difference in SAI and LAI between AP and PA current directions within both spatial and verbal tasks.
Hypothesis #2: It was hypothesized that SAI and LAI would be reduced across both current directions for both the spatial and verbal working memory task conditions. It was also hypothesized that there would be a greater reduction in SAI and LAI within the AP current direction compared to PA within the spatial task but a similar reduction for both directions in the verbal task.

Aim #3: Identify the relationship between baseline measures of working memory, experimental task accuracy, and change in SAI and LAI.
Hypothesis #3: It was hypothesized that the individuals who displayed greater working memory capacity would perform with better accuracy on both the verbal and spatial WM tasks compared to those displaying a lower capacity. It was also hypothesized that individuals with greater working memory capacity and task accuracy would display increased SAI and LAI within two- and six-item memory sets.

3.0 METHODS

3.1 Participants

Seventeen adults (16 right-handed, 1left-handed, 5 male, 12 female, 23 ± 3 years) with no history of neurological disease or contraindications to TMS provided informed consent and participated in the experiment. The study protocol was approved by the University of Waterloo Ethics Committee.

3.2 Experimental Design and Procedure

The experiment consisted of two sessions (both outlined in figure 2). At the start of the first session, baseline spatial and verbal working memory ability was assessed using the Corsi block tapping test[47], digit forwards[48], digit backwards[48], Thurston's card rotation test[49], and reading span test[50]. Participants then completed 180 trials of a modified spatial or verbal Sternberg working memory task[51], while monophasic TMS stimuli were applied over the left motor cortical hotspot for the first dorsal interosseous muscle. The same 180 working memory task trials were then repeated with monophasic TMS stimuli employing the opposite current direction. Within each set of 180 trials, TMS stimuli were either delivered alone or preceded by an electrical conditioning stimulus over the contralateral median nerve. The second session was similar to the first session except 1) the baseline assessments were not repeated, and 2) the Sternberg working memory task variant was changed. The order of task variant was randomized across sessions while the order of monophasic TMS current direction was randomized within the session.

3.3 Baseline Assessments of Verbal and Spatial Working Memory

3.3.1 Corsi Block Task

The Corsi block test[47] was used to assess short-term (forward) and serial (backward) visuospatial memory. For the forward test, nine squares were displayed on a 24" touch screen monitor (Dell P2418HT). On a given trial, a specified number of square targets sequentially turned green. The square target remained green for 1s before changing back, at which point the next square in the pattern changed. After the target sequence was complete, participants re-produced the pattern of green squares by tapping on the corresponding target on the screen. The task always began with a two square series. If the participant-generated the correct target sequence, the number of squares in the subsequent target sequence increased by one. If the

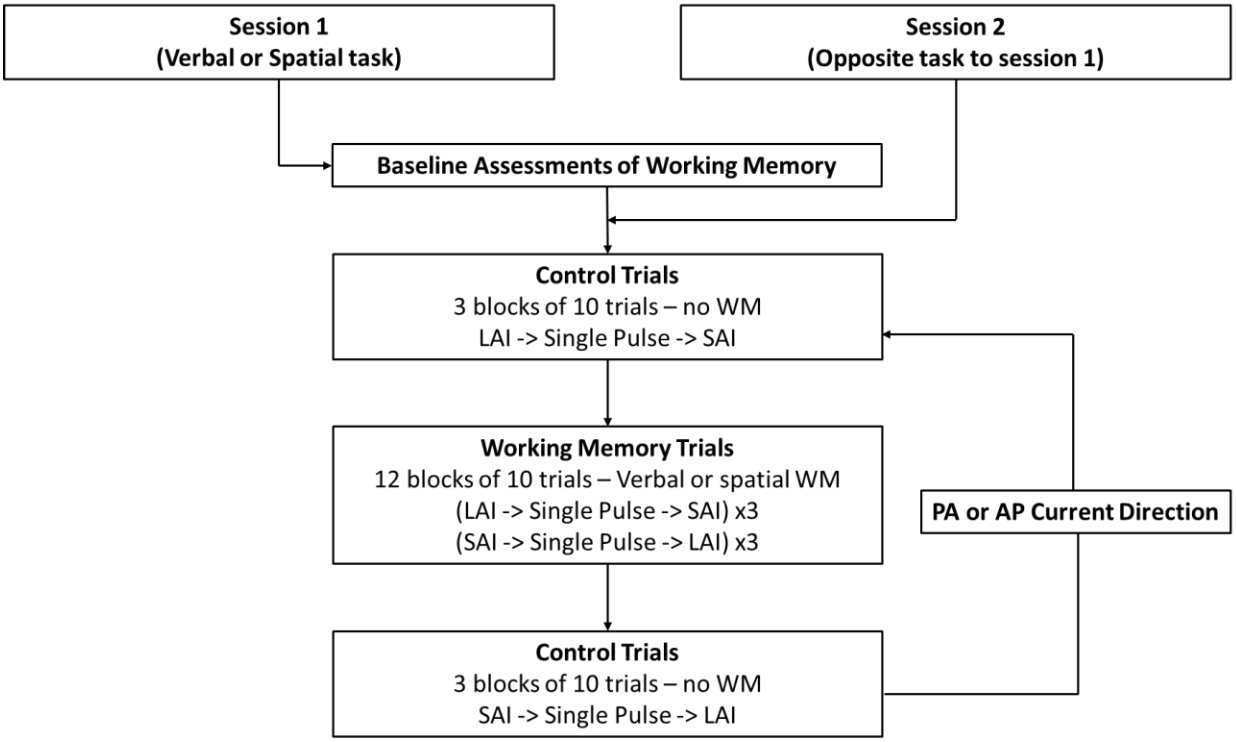


Figure 2 – Experimental Protocol for a given session where the TMS protocol is repeated for PA and AP current direction. The entire protocol is repeated across two sessions involving either the verbal or spatial working memory task.

participant touched the targets in an incorrect sequence, a new target sequence of equal length was presented. If the participant made a second error in reproducing the sequence, the task was terminated. The participant score was represented by the length of the last successful sequence completed. The backward test was similar to the forward test except that the participant was instructed to tap on the targets in the reverse order in which they were presented sequentially.

3.3.2 Card Rotation Test

The card rotation task was used to assess mental rotation abilities[49]. The test was completed with a pen and paper containing 11 rows of symbols. Each row consisted of a 2D image on the left, followed by eight images on the right. Participants were asked to mark which of the eight images on the right were the same shape. The participant score was represented by the difference between correct and incorrect responses.

3.3.3 Digit Span

The Forward and Reverse Digit Span from WAIS-R tasks[48] was used to index short-term verbal working memory and verbal working memory, respectively. The Forward Digit Span task required the participant to recall a list of three digits presented aurally at one digit per second. If successful, the length of the list was increased by one digit, and the process repeated until the participant could recall the digit list correctly on two consecutive trials. The participant's score was represented as the length of the last successful list recalled.

The Reverse Digit Span Task was similar to the Forward task except that the list was recalled in reverse order.

3.3.4 Reading Span

The reading span task was used to identify the baseline capacity of verbal WM[50]. Participants read a set of two sentences aloud at their own pace. After all sentences were read, the participant recalled the last word in each sentence of the set. If participants recalled both words correctly, the set size increased to three sentences. If participants made an error, two new sentences were presented. The set size was increased to a maximum of six sentences. Participant score was the last level at which they correctly recalled all three words.

3.4 Experimental Task

3.4.1 Verbal Task

The verbal component of the experimental task was designed as a variant of the Sternberg short-term memory task[51] and presented on a computer screen (Labview 2019, National Instruments, Austin, Texas, USA). Participants were seated in front of the screen with their left index and middle finger on adjacent response keys. A trial started with the presentation of a fixation cross. Following 500 msec, a set of two or six letters appeared arrayed around the fixation cross (Figure 3). Possible elements in the set included all letters between A and L. Each letter appeared at a distinct location around the cross (12 possible locations total). The set of letters remained visible for 1500 msec during which time participants were instructed to encode the set regardless of their locations. Following the encoding period, the letter set disappeared. After a 3000 msec maintenance period, the cross was replaced by a single probe letter. Participants were required to respond as to whether the probe letter was part of the original set of letters presented during the encoding phase. If the participant failed to respond within 1500 msec, an incorrect response would be recorded and the next trial would begin. The probability that the probe was drawn from the original set of letters was 50% regardless of set size. Control trials were also included and maintained similar timing with the two- and six set size trials, however, all twelve possible letters were presented, one at each possible location, and presented as either red or green (Figure 4). The probe consisted of a single white letter for the control and participants were simply instructed to press a designated response key based upon set color when the probe appeared.

3.4.2 Spatial Task

The spatial working memory task[51] proceeded similar to the verbal working memory task except that: 1) the spatial array of letters was replaced by a spatial array of dots, 2) the probe letter was replaced by a single dot presented at the center of the screen and 3) the participants were instructed to identify as to whether or not the probe dot was part of the original array presented during the encoding phase (Figure 5). Similarly, a control condition was implemented within the spatial task where dots were presented as either red or green in each possible location around the fixation cross (Figure 6). As with the verbal condition, individuals were to respond as to whether the previous set was red or green. Low load trials for the spatial task consisted of two dots[51] and high low trials consisted of six dots[51].

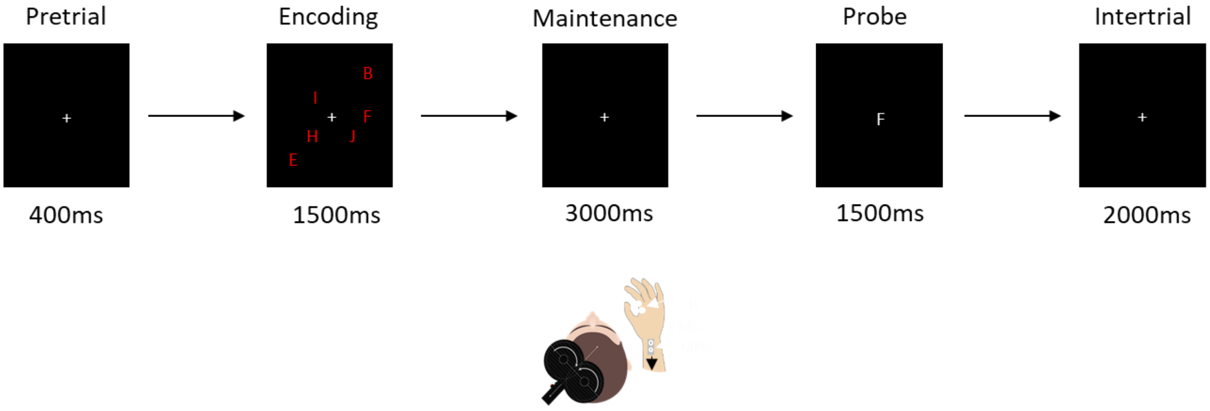


Figure 3 – Outline of the verbal WM task with TMS during the 3000ms maintenance period

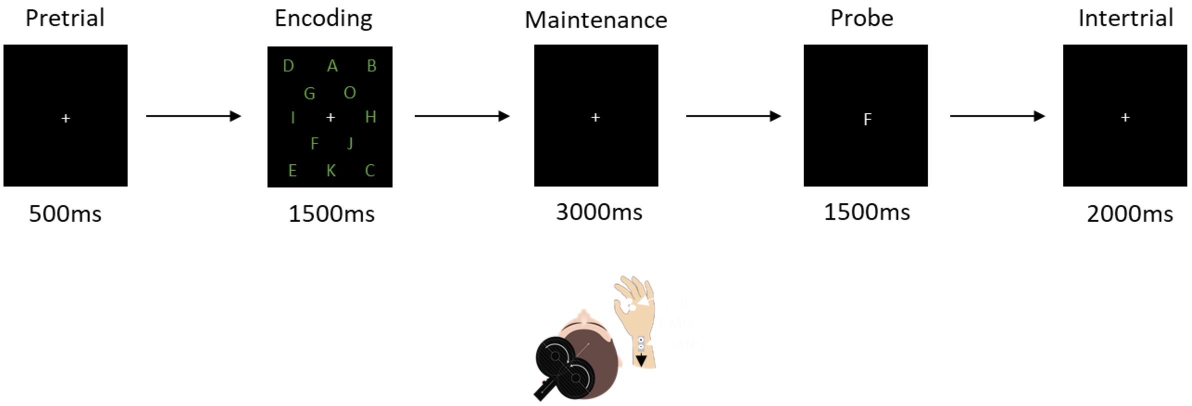


Figure 4 – Outline of the control task for the verbal working memory task condition with TMS during the 3000ms maintenance phase.

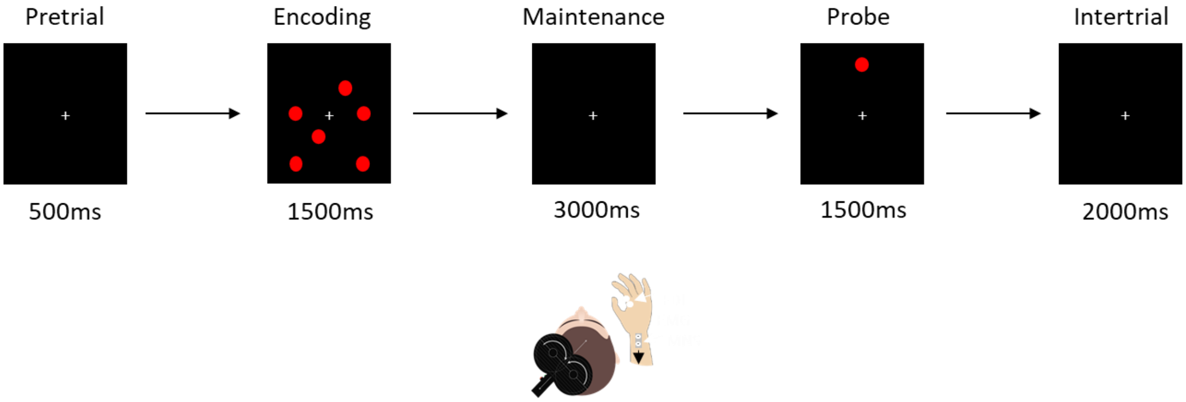


Figure 5 – Outline of the spatial WM task with TMS during the 3000ms maintenance phase.

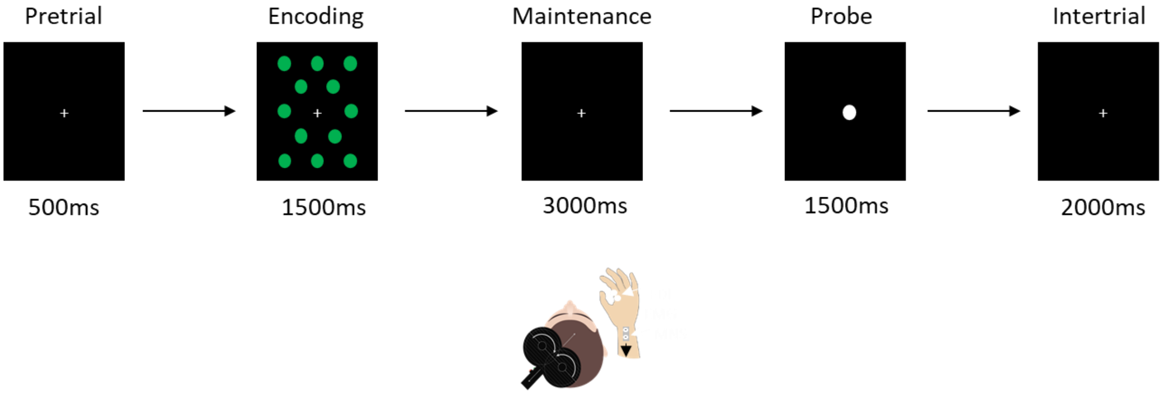


Figure 6 – Outline of the control task for the spatial working memory task condition.

3.5 Transcranial Magnetic Stimulation (TMS)

Motor evoked potentials (MEP) were elicited by TMS during the 3000 ms delay (i.e. memory maintenance) of the experimental memory task performed in each session. MEPs were recorded using Labview 2019 software (LabVIEW 2019, National Instruments, Austin TX) in conjunction with a 2024F 4-channel amplifier (Intronix Technologies Corp., Bolton, ON) and a USB-6341 X Series DAQ (National Instruments, Austin TX). Surface electromyography electrodes (Ag-AgCl) were placed over the first dorsal interosseous muscle using a tendon-belly montage. Surface electromyography recording was triggered using a 5V TTL pulse with an epoch of -0.3 to 0.5s. During acquisition, data was amplified (x1000), digitized (x4000 Hz) and filtered (band pass filtered 1-1000 Hz, notch filter – 60 Hz). The MEP was defined as the peak-to-peak amplitude of the maximal electromyography response between 20 to 50 ms post-TMS stimulation. Trials were excluded from subsequent analysis if the root mean square error of the electromyographic signal from the first dorsal interosseous muscle exceeds 15 µV during the pre-TMS stimulus interval (-50 to 0 ms).

TMS was delivered using a Magstim 200^2 stimulator (Magstim Company Ltd, Wales, UK) and 50mm figure-8 coil (D60 Alpha B.I.). The coil was placed tangential to the scalp at 45 degrees to the midline over the left motor cortex. Two different current directions were used. To induce the typical posterior-anterior (PA) current in the underlying tissue, the coil was oriented such that current flow in the coil moved from anterior to posterior. To induce anterior-posterior (AP) current in the underlying tissue, the coil was rotated 180 degrees to reverse the current flow.

The left FDI motor cortical hotspot was defined as the scalp position that elicits the largest and most consistent response following PA stimulation. The location and trajectory of the coil on the scalp at the hotspot was recorded using the BrainSight™ stereotactic system (Rogue Research, Montreal, Québec, Canada). The same hotspot was used for AP stimulation[52]. RMT was defined using the maximum likelihood parameter estimation by sequential tracking (ML-PEST) adaptive threshold-hunting method[53,54]. This method uses a binary, yes, or no response to model an S-shaped function of the probabilistic nature of evoking a motor potential at a given stimulus intensity. The binary criterion was an MEP 50uV peak-to-peak. TMS intensity for SAI was set to the stimulator output that elicited a peak-to-peak MEP of 1mV. TMS test stimulus intensity was derived using the ML-PEST method[53], except the binary criterion was set to 1mV[54].

3.6 Short and Long-latency Afferent Inhibition (SAI/LAI)

SAI consists of a peripheral electrical stimulus paired with TMS. Electrical stimulation was delivered using an SD9 constant current high voltage stimulator (Grass Astro-Med, West Warwick, RI). Stimulation was applied over the median nerve at the right wrist (constant current square wave pulse, 0.2 ms duration, cathode proximal). Electrical stimulation intensity was set to an intensity in order to produce a slight thumb twitch[55] or and MEP of ~20mv peak-to-peak. For SAI, electrical stimulation preceded TMS by 21 ms[2,3] where for LAI, electrical stimulation preceded TMS by 200ms[56]. Both SAI and LAI were derived by expressing the conditioned MEP amplitude as a percentage of the unconditioned MEP amplitude within each task variant and trial type.

$$\%\ \text{SAI or LAI} = \frac{\text{Conditioned } MEP}{Unconditioned\ MEP}\ x\ 100$$

3.7 Data Analysis

Statistical analyses were performed using the R environment for statistical computing (version 3.6.1)[57]. The following packages were used: “rstatix”[58] and “tidyverse”[59]. Separate two-way set-size (2-item, 6-item) x Current Direction (PA, AP) repeated measures ANOVAs were conducted to assess the effects of reaction time and accuracy within each task (Verbal, Spatial). Significant interactions were decomposed using pairwise comparisons or by simple main effects. Similarly, separate two-way Set Size x Current Direction repeated measures ANOVAs for each task were conducted for both SAI and LAI within each task. Significant interactions were again decomposed using pairwise comparisons or by simple main effects.

Pearson-product moment and Spearman rank correlations were used to determine the relationship between change in accuracy of the experimental task performance from 2-items to 6-items and the change in SAI from 2-items to 6-items within a specific task. As performance on the 2-item condition may be subject to a ceiling effect, correlations were also used to determine the relationship between baseline assessments of verbal and spatial memory ability and the change in SAI from two- to six-items.

4.0 RESULTS

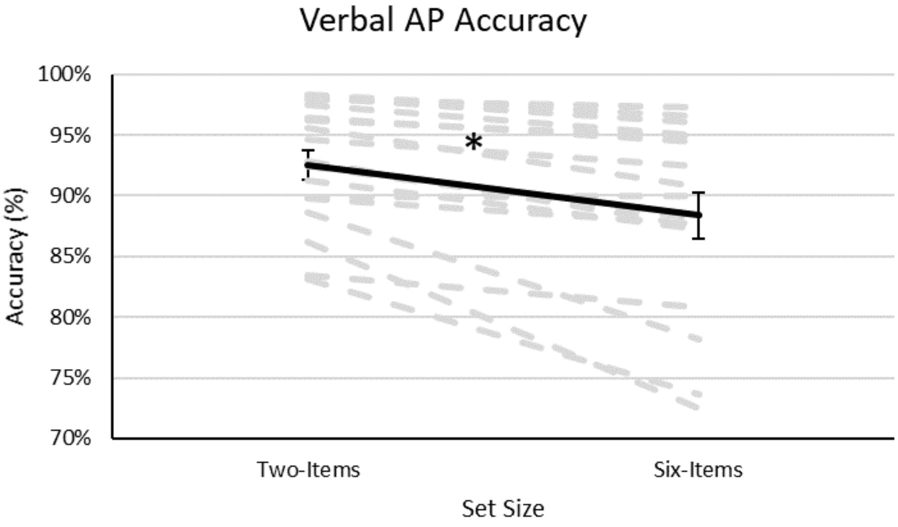
4.1 Behaviour

The two-way repeated measures ANOVA on verbal task accuracy revealed a significant main effect of Set Size [$F_{1,16} = 28.059$, $p = 0.0000723$, $\eta^2 = 0.1$]. Neither the main effect of Current Direction [$F_{1,16} = 0.055$, $p = 0.82$, $\eta^2 = 0.0007$] or the Current Direction by Set Size interaction [$F_{1,16} = 0.07$, $p = 0.8$, $\eta^2 = 0.00008$] were significant. The main effect of Set Size was driven by a significant decrease in accuracy as set size increased from two- to six-items [two-items: 92±1%, mean±standard error, six-items: 88±1%] (Figure 7a & b).

Similarly, results of the ANOVA for the spatial task revealed a significant main effect of Set Size [$F_{1,16} = 54.93$, $p > 0.00000147$, $\eta^2 = 0.32$], indicating that accuracy in the six-item condition [87±1%] was significantly lower compared to the two-item [95±1%] (Figure 8a & 8b). Again, neither the main effect of Current Direction [$F_{1,16} = 0.03$, $p = 0.88$ $\eta^2 = 0.0002$] or the Current Direction by Set Size interaction [$F_{1,16} = 0.03$, $p = 0.86$, $\eta^2 = 0.0002$] were significant.

The two-way repeated measures ANOVA for reaction time (RT) on the verbal task revealed a significant main effect of Set Size [$F_{1,16} = 75.13$, $p < 0.000000193$, $\eta^2 = 0.064$]. The main effect was driven by significantly slower RTs in the six-item [948±23.2ms] compared to two-item [882±21.2ms] trials (Figure 9a & 9b). Neither the main effect of Current Direction [$F_{1,16} = 2.53$, $p = 0.13$, $\eta^2 = 0.015$] or the Current Direction by Set Size interaction [$F_{1,16} = 0.15$, $p = 0.70$, $\eta^2 = 0.0000607$] were significant for the verbal task. The corresponding ANOVA for the spatial task revealed a significant main effect of Set Size [$F_{1,16} = 99.98$, $p = 0.0000000275$, $\eta^2 = 0.177$]. RT in the six-item condition [908±22.8ms] was significantly greater than the two-item [796±19.2] (Figure 10a 10b). Neither the main effect of Current Direction [$F_{1,16} = 0.04$, $p = 0.85$, $\eta^2 = 0.000175$] or the Current Direction by Set Size interaction [$F_{1,16} = 0.15$, $p = 0.70$, $\eta^2 = 0.000518$] were significant in the spatial task.

A



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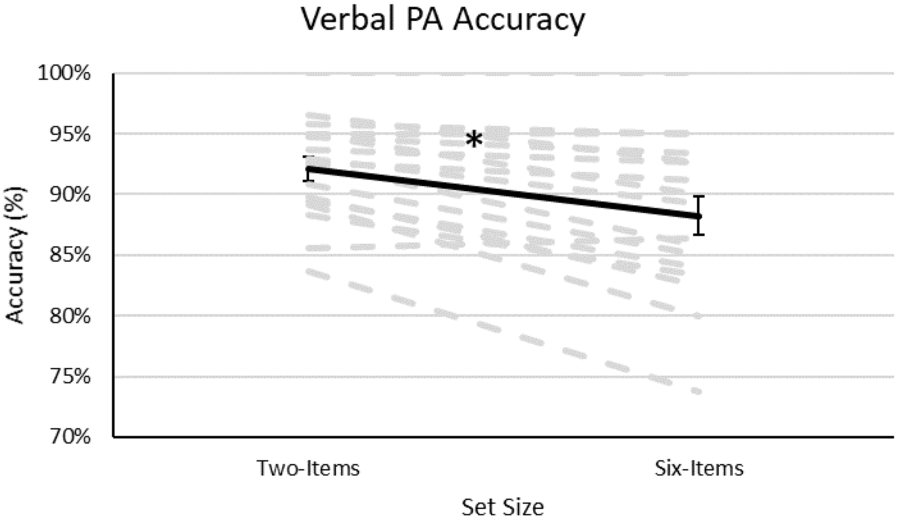
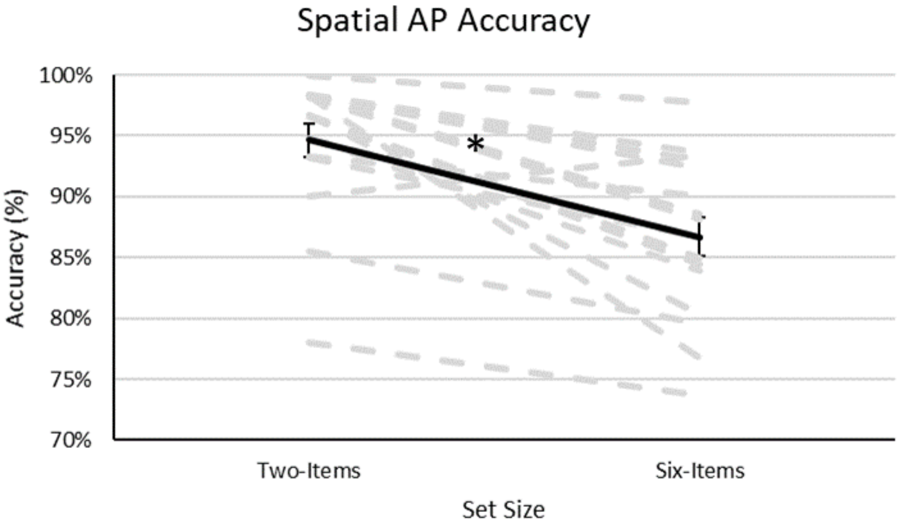


Figure 7 – Accuracy for the verbal task across set size for AP (A) and PA (B) current directions

A



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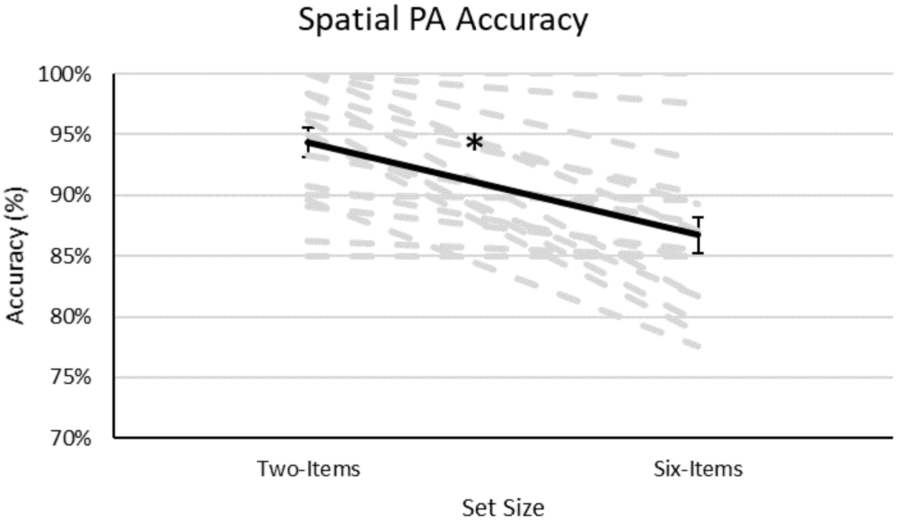
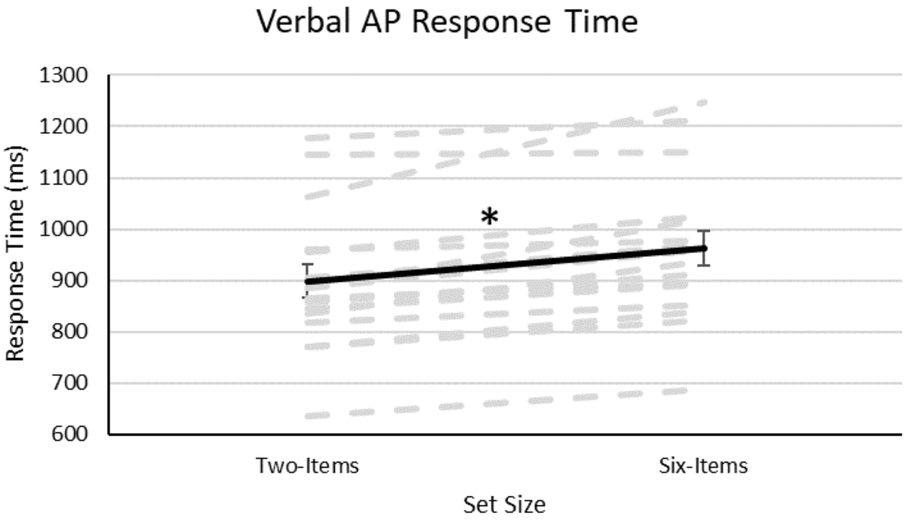


Figure 8 – Accuracy in the spatial task across set size for AP (A) and PA (B) current directions

A



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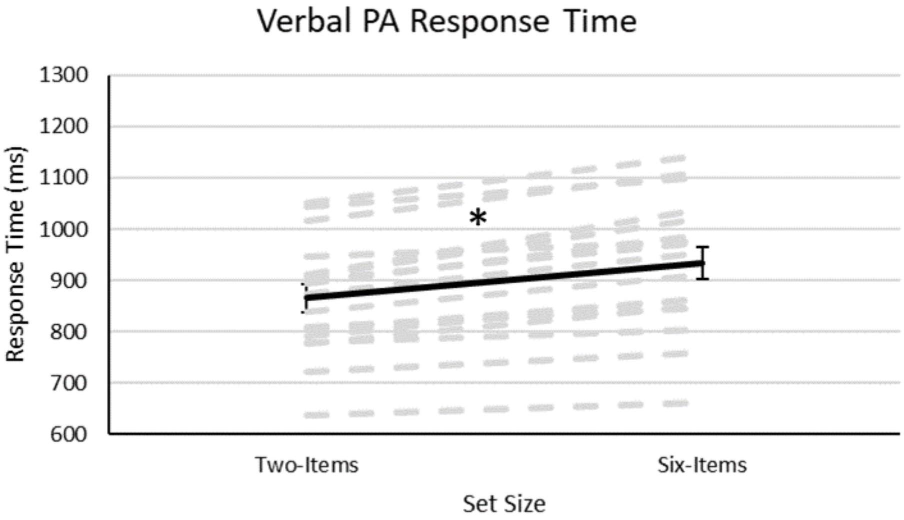
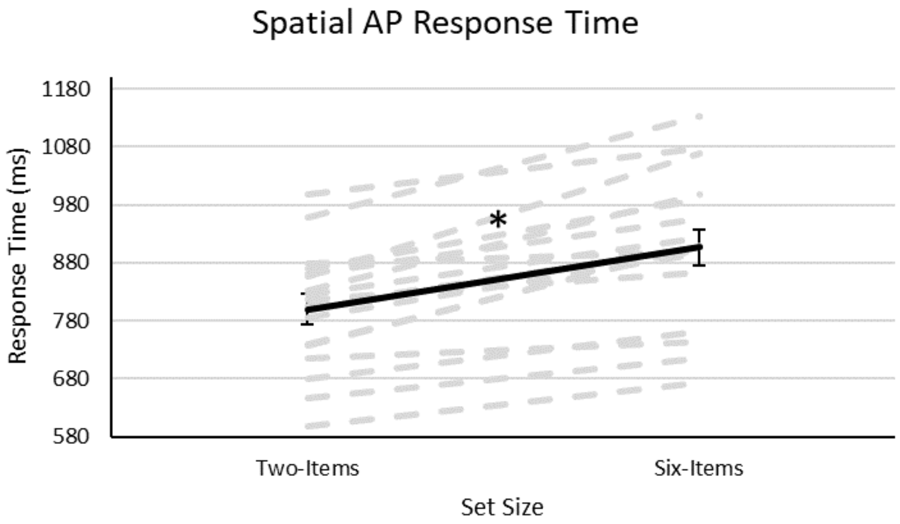


Figure 9 – Response time in the verbal task across set size for the AP (A) and PA (B) current directions.

A



B

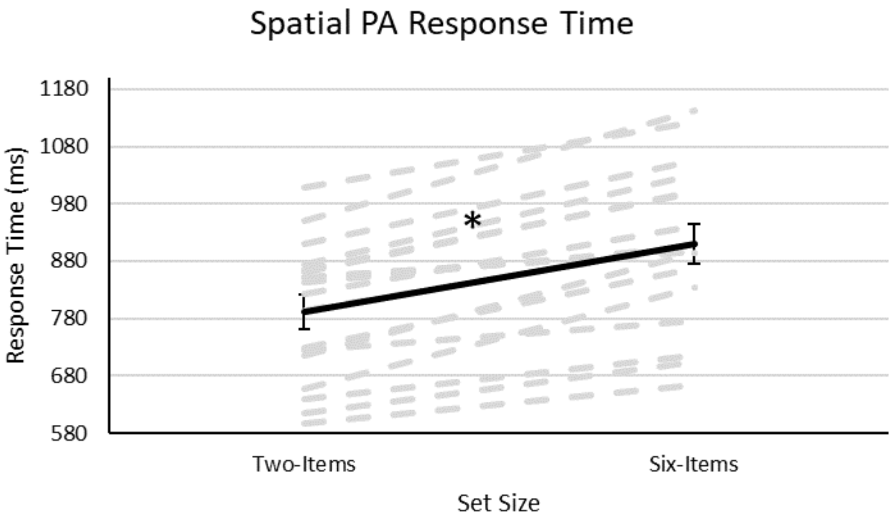


Figure 10 – Response time in the spatial task across set size for AP (A) and PA (B) current directions.

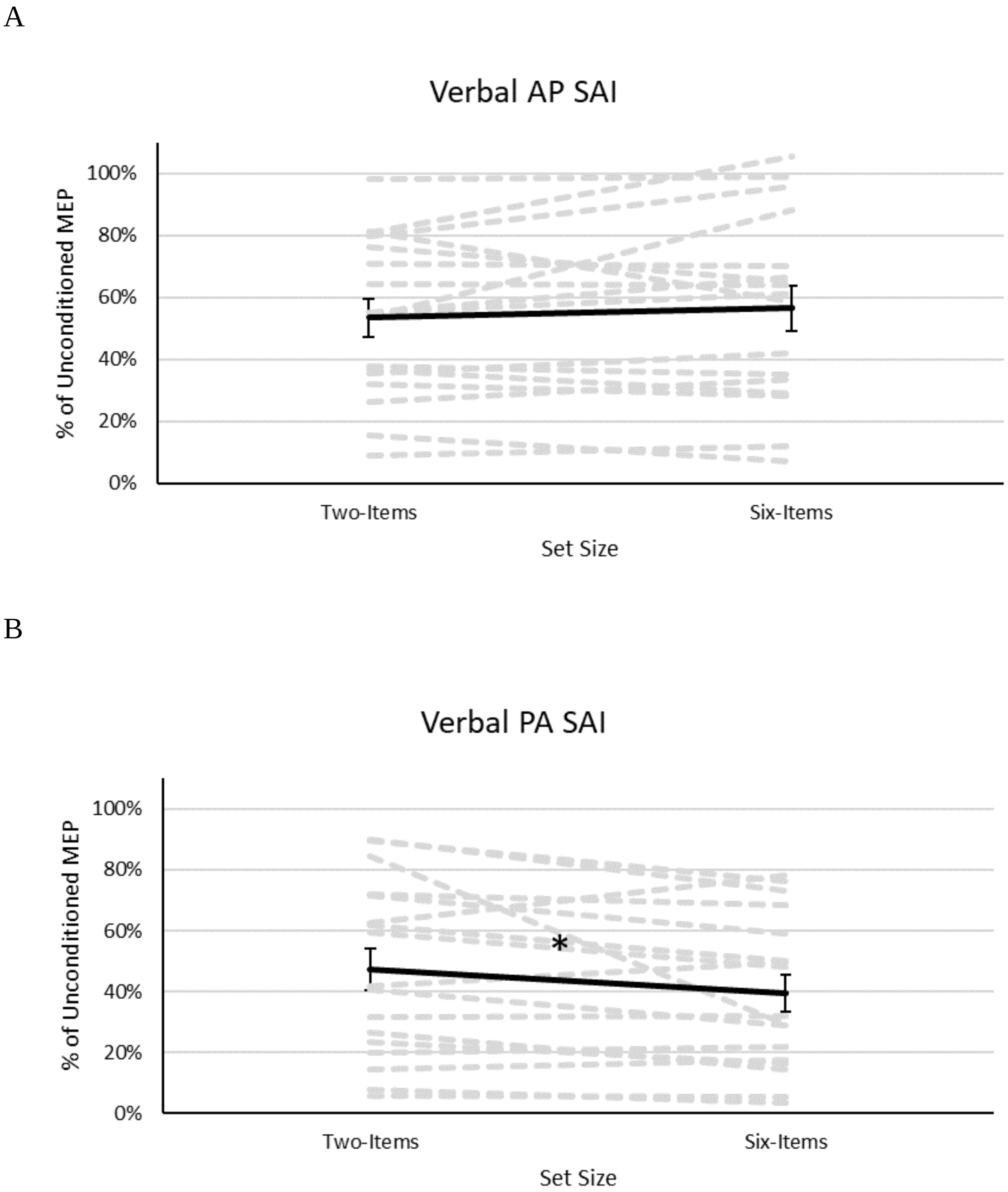


Figure 11 – Change in SAI across set size within the verbal task for AP (A) and PA (B) current directions.

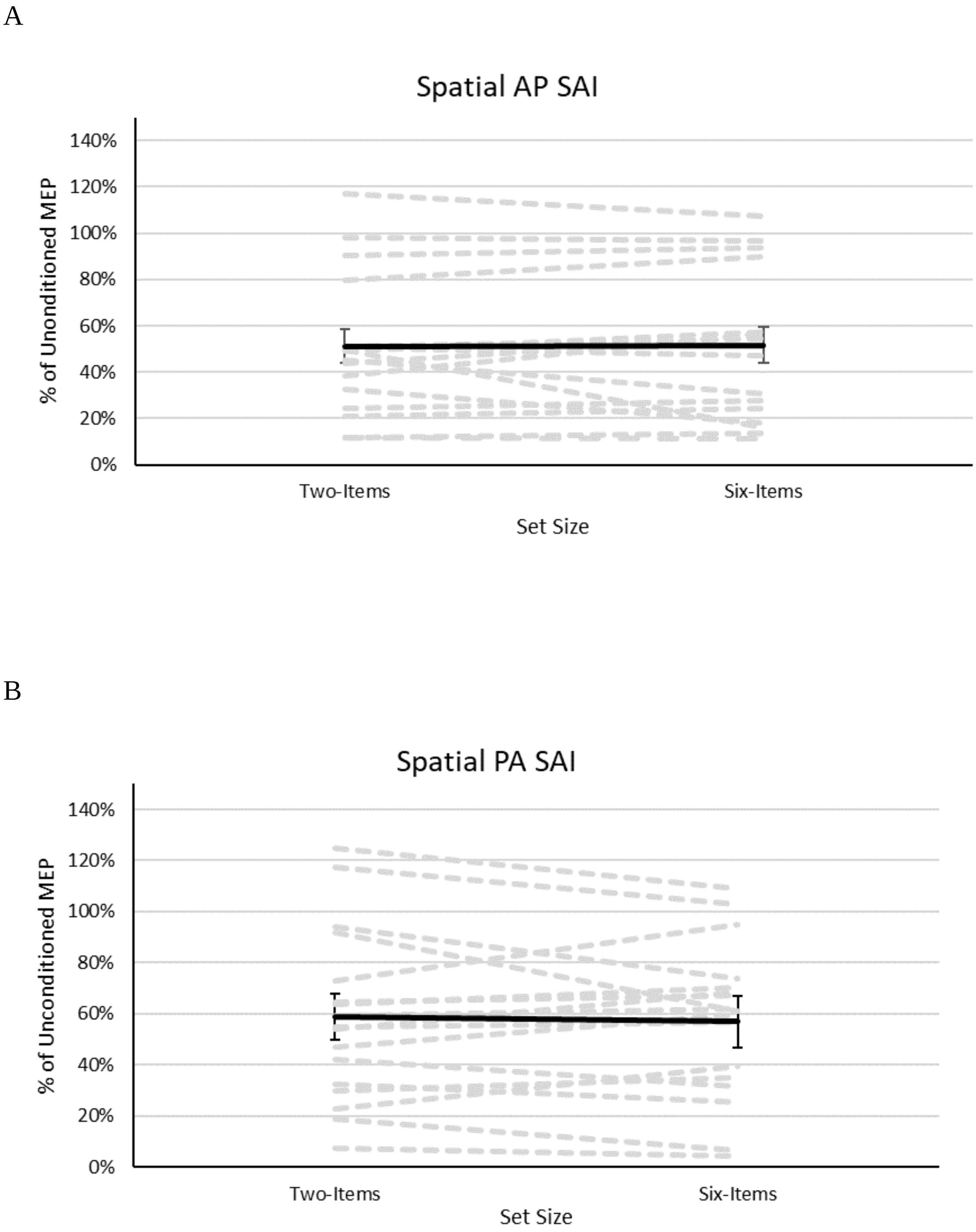


Figure 12 – Change in SAI across set size within the spatial task for AP (A) and PA (B) current directions

4.2 Short-Latency Afferent Inhibition (SAI)

The two-way repeated measures ANOVA on SAI during the verbal task revealed a significant main effect of Current Direction [$F_{1,16} = 5.22$, $p = 0.04$, $\eta^2 = 0.044$] and Current Direction by Set Size interaction [$F_{1,16} = 4.90$, $p = 0.04$, $\eta^2 = 0.010$]. The main effect of Set Size was not significant [$F_{1,16} = 0.08$, $p = 0.78$, $\eta^2 = 0.002$]. Decomposition of the Current Direction by Set Size interaction revealed a significant increase in PA SAI as set size increased from two- to six-items [$F_{1,16} = 4.55$, $p = 0.049$, $\eta^2 = 0.021$; Two-Items = 47±6%; Six-Items = 40±6%] (Figure 11b) although there was no difference in AP SAI across two- and six-items [$F_{1,16} = 0.87$, $p = 0.37$, $\eta^2 = 0.03$; Two-Items = 53±6%; Six-Items = 56±7%] (Figure 11a).

The two-way repeated measures ANOVA on SAI during the spatial task failed to reveal any significant effects [$\text{Main Effect}_{\text{Current Direction}}$: $F_{1,16} = 1.58$, $p = 0.23$, $\eta^2 = 0.011$; $\text{Main Effect}_{\text{Set Size}}$: $F_{1,16} = 0.78$, $p = 0.78$, $\eta^2 = 0.000124$; $\text{Interaction}_{\text{Current Direction x Set Size}}$: $F_{1,16} = 0.20$, $p = 0.67$, $\eta^2 = 0.000262$] (Figures 12a & 12b).

4.3 Long-Latency Afferent Inhibition (LAI)

The two-way repeated measures ANOVA on LAI during the verbal task failed to reveal any significant effects [$\text{Main Effect}_{\text{Current Direction}}$: $F_{1,16} = 2.29$, $p = 0.15$, $\eta^2 = 0.02$; $\text{Main Effect}_{\text{Set Size}}$: $F_{1,16} = 0.96$, $p = 0.34$, $\eta^2 = 0.004$, $\text{Interaction}_{\text{Current Direction x Set Size}}$: $F_{1,16} = 0.85$, $p = 0.43$, $\eta^2 = 0.002$] (Figure 13a & 13b).

The two-way repeated measures ANOVA on LAI during the spatial task revealed a strong trend for a Current Direction by Set Size interaction [$F_{1,16} = 4.35$, $p = 0.053$, $\eta^2 = 0.007$]. The strong trend was driven by a significant increase in AP LAI as set size increased from two- to six-items [$F_{1,16} = 9.28$, $p = 0.008$, $\eta^2 = 0.025$; Two-Items = 65±10%; Six-Items = 53±8%] (Figure 14a). In contrast, there was a slight, but not significant decrease in PA LAI as set size increased [$F_{1,16} = 0.084$, $p = 0.776$, $\eta^2 = 0.000231$; Two-Items = 65±9%; Six-Items = 67±10%] (Figure 14b). Neither the main effect of Set Size [$F_{1,16} = 4.28$, $p = 0.055$, $\eta^2 = 0.005$] or Current Direction [$F_{1,16} = 2.13$, $p = 0.16$, $\eta^2 = 0.009$] were significant.

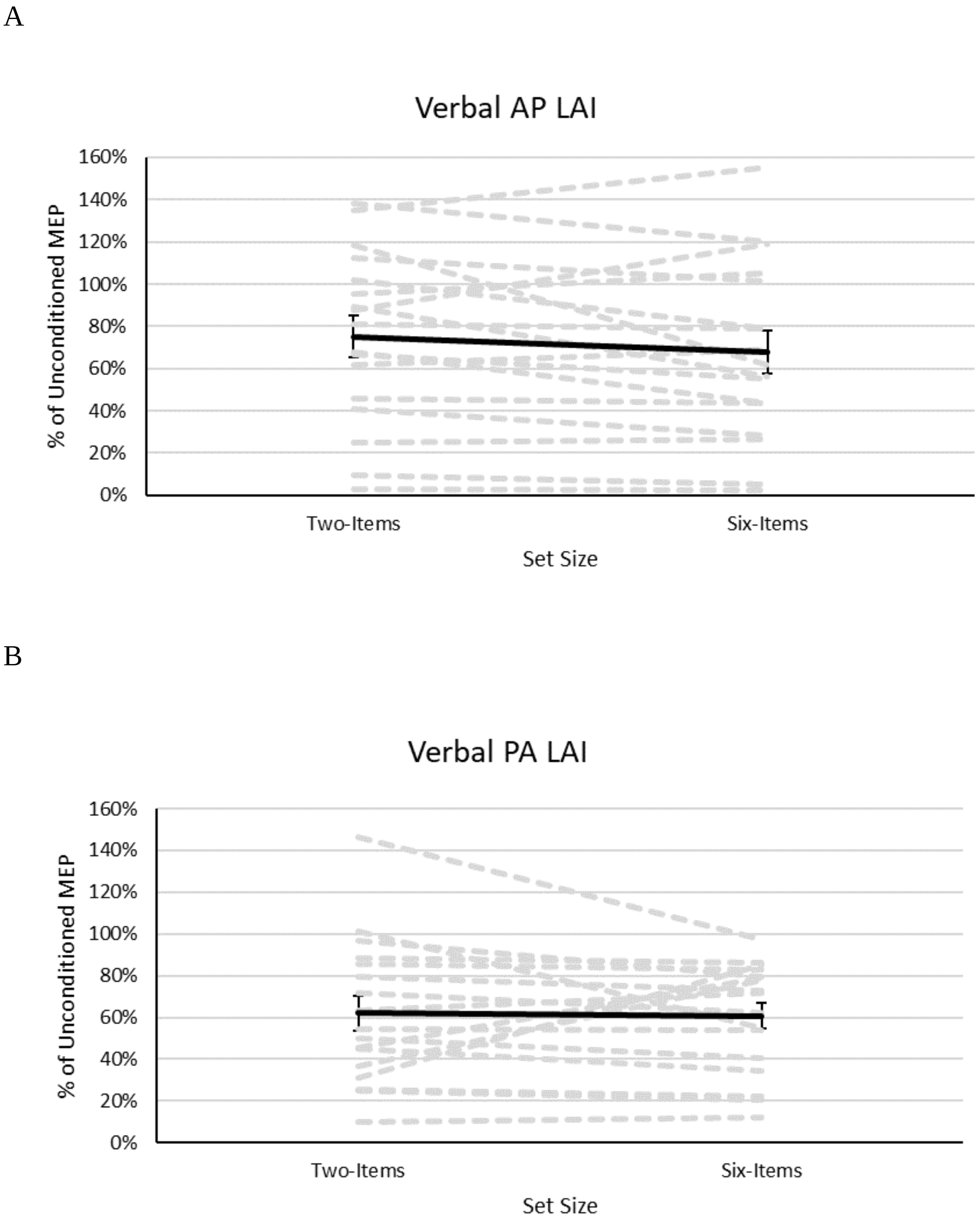
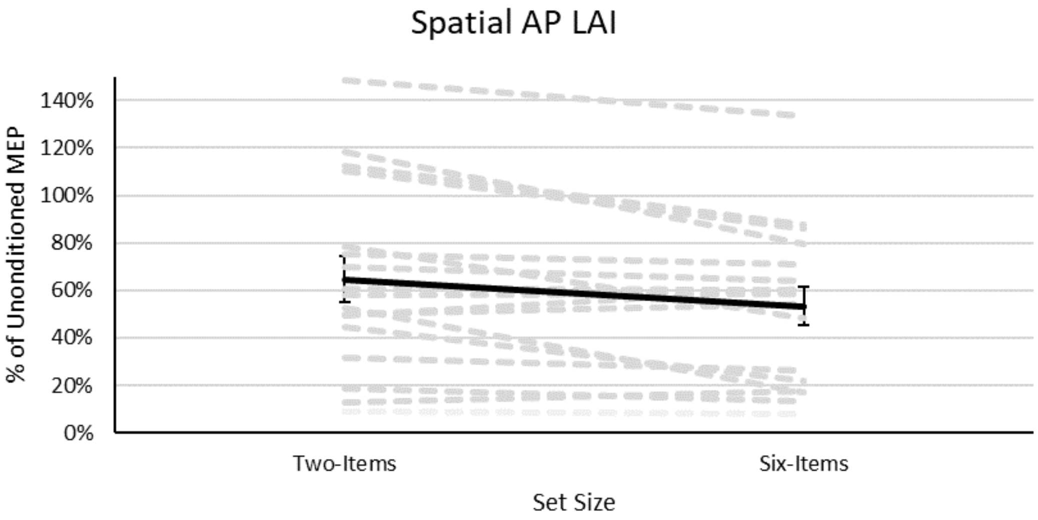


Figure 13 – Change in LAI across set size within the verbal task for AP (A) and PA (B) current directions

A



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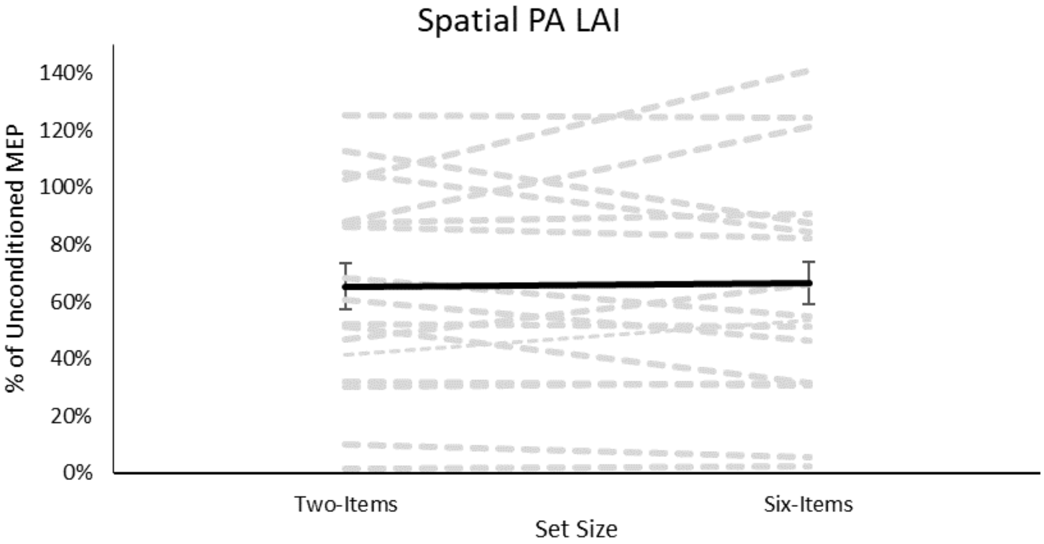

Figure 14 – Change in LAI across set size within the spatial task for AP (A) and PA (B) current directions

4.4 Relationship Between Change in Task Performance and Change in Sensorimotor Excitability

4.4.1 Short-latency Afferent Inhibition (SAI)

None of the correlations between change in spatial task accuracy from two- to six-items and change in SAI from two- to six-items for the PA or AP current directions reached significance (Appendix A & Figure 16, Appendix B).

None of the correlations between change in verbal task accuracy from two- to six-items and change in SAI from two- to six-items for the PA or AP current directions reached significance (Appendix A & Figure 18, Appendix C).

4.4.2 Long-latency Afferent Inhibition (LAI)

None of the correlations between change in spatial task accuracy from two- to six-items and change in LAI from two- to six-items for the PA or AP current directions reached significance (Appendix A & Figure 17, Appendix B).

None of the correlations between change in verbal task accuracy from two- to six-items and change in LAI from two- to six-items for the PA or AP current directions reached significance (Appendix A & Figure 19, Appendix C).

4.5 Relationship Between Baseline Working Memory Capacity and Change in Task Performance

4.5.1 Spatial Task

None of the correlations between any of the baseline measures of working memory capacity and the change spatial task accuracy were significant for either the AP or PA current directions (Appendix D & Figures 20, 21 & 22, Appendix E).

4.5.2 Verbal Task

None of the correlations between any of the baseline measures of working memory capacity and verbal task accuracy were significant for either the AP or PA current directions (Appendix D & Figures 23 & 24, Appendix F).

4.6 Relationship Between Baseline Working Memory Capacity and Change in Sensorimotor Excitability

4.6.1 Short-latency Afferent Inhibition (SAI)

None of the correlations between any of the baseline measures of working memory capacity and the change in SAI from two- to six-items during the spatial task were significant for either the AP or PA current directions (Appendix G & Figures 25, 26 & 27, Appendix H).

None of the correlations between any of the baseline measures of working memory capacity and the change in SAI from two- to six-items during the verbal task were significant for either the AP or PA current directions (Appendix G & Figures 31 & 32, Appendix I).

4.6.2 Long-latency Afferent Inhibition (LAI)

None of the correlations between any of the baseline measures of working memory capacity and the change in LAI from two- to six-items during the spatial task were significant for either the AP or PA current directions (Appendix G & Figures 28, 29 & 30, Appendix H).

The Spearman’s rank correlation between reading span score and verbal task LAI was significant for the PA current direction [$r(13) = 0.54$, $p = 0.04$]. The corresponding correlation was not significant for the AP current direction [$r(13) = 0.31$, $p = 0.26$]. None of the correlations between change in LAI and digits forwards/backwards were significant (Appendix G & Figures 33 & 34, Appendix I).

5.0 DISCUSSION

This study used afferent inhibition to determine the influence of spatial and verbal working memory on different afferent intracortical circuits that converge and shape corticospinal output. The main finding was that verbal but not spatial working memory load influenced SAI, whereas spatial but not verbal working memory appeared to influence LAI. Further, the effect of verbal working memory on SAI was specific to PA-sensitive circuits, whereas the effect of spatial working memory on LAI was driven by AP-sensitive circuits.

The increase in PA-mediated SAI with increasing set size was not in accordance with the current hypotheses or previous work using a similar verbal working memory task[1]. Past work has suggested that increasing perceptual workload results in the increase of afferent gating, while cognitive demand (e.g. working memory) reduces gating and leads to the increased potential for distraction[46]. Suzuki et al.[1] proposed that the reduction in PA SAI within their findings was driven by gating unrelated somatosensory afference as working memory load increased[29,60]. However, this interpretation maintains the preservation of attentional mechanisms as verbal working memory load increases. One explanation for the present increase in PA SAI is that the current working memory task loaded processing for cognitive control whereas the working memory task employed by Suzuki et al.[1] loaded processing for perception.

A key methodological difference between the current verbal working memory task and that employed in past work was the total number of possible elements within the memory set/probe. The past work utilized number-based stimuli ranging from 1-9, presented in a single line. For the six-item condition, there was a 66% chance of the probe being in the memory set. Therefore, participants may have adopted a strategy minimizing cognitive load by favoring a "yes" response. Such an approach may have reduced, rather than increased, working memory load as set size increased to six-items while still leading to increased errors when their affordance was incorrect. Reduced cognitive workload would presumably allow for stronger gating of distractor stimuli, leading to a decrease in the magnitude of SAI. A similar reduction in SAI could also be achieved if the numbers were stored as a single representation rather than unique units. The current study reduced the probability of such alternative strategies first, through drawing the memory set and probe from a pool of twelve letters. The larger pool reduces the likelihood of the probe being part of the memory set and additionally, the benefit of any affordance. Second, the letters were presented in a spatial array around the screen to minimize associations. These changes enhanced the likelihood that a set size of six would represent an increase in memory load.

In past work, the parietal N20 ERP component was identified as a likely input to the PA-mediated circuit due to the correlation between parietal N20 SEP amplitude and PA SAI amplitude. Similarly, support for the frontal N30 as a potential input to the AP-mediated circuit was noted through this generator's localization to SMA and the precentral gyrus[61], which aligns with the possible origins of later I-waves recruited by AP current[62]. An explanation to account for the differences in AP- and PA-mediated SAI is that each circuit is being differentially influenced by generators like the parietal N20 and frontal N30.

Past work has proposed that input to both AP and PA-mediated circuits by way of the N20 accounted for a similar decrease in SAI across current directions. This concept provides evidence to account for the lack of significant change in AP-mediated SAI within the current findings. If the N20 is influencing the AP circuit to some extent, this would presumably limit the decrease in AP SAI from N30 input. Since SAI is observed to be dependent on the magnitude of the afferent stimulus[35], an increase in SAI indicates an increase in afferent input to the cortex. This response represents a breakdown of attention if the gating mechanism responsible for filtering out irrelevant stimuli is no longer active under high working memory conditions, leading to increases in afferent input.

Neither AP nor PA mediated SAI was influenced by spatial working memory demand. The working hypothesis was simply that both the verbal and spatial forms of working memory would produce the same sensorimotor changes. This hypothesis was supported by results from Thomason et al.[63] who demonstrated similar performance between participants engaged in both a spatial and verbal iteration of the Sternburg working memory task. However, the dissociation of PA SAI across verbal and spatial tasks supports models of working memory that suggest a distinction between the two. The influence of spatial working memory on SAI may be different from that of verbal based on the nature of how spatial stimuli are encoded. For example, the array of dots in the spatial task may require a global strategy, such as a single mental snapshot of the screen, to hold these items in working memory. However, in the current verbal task, each letter may be encoded individually rather than as a whole, therefore enhancing the demand required in the verbal condition.

The differences in processing verbal vs. spatial information may change the nature of how either cognitive task influences sensorimotor outcomes. Additionally, evidence supports a difference in lateralization of activity across hemispheres when engaged in both spatial and verbal working memory[63]. In the same study by Thomason et al.[63], activity dominant to the right hemisphere was observed with spatial working memory where verbal working memory was left dominant. The current experiment employed a somatosensory stimulus, the source of which was localized to the right hand. Therefore, the afference to the left motor cortex may be more susceptible to change observed with verbal working memory if the processing is dominant in the left hemisphere.

Although this theory explains why no observable change in SAI is present within the spatial task, it cannot resolve why there appears to be a strong trend for a differential effect of spatial task set size driven by an increase in AP LAI. Earlier stages of sensorimotor processing such as afferent gating and the selection of relevant stimuli may be influenced more by verbal working memory, whereas spatial working memory could influence later stages of integration. The earlier influence of verbal working memory compared to spatial may be due to the explicit nature of verbal processing. The implicit nature of spatial working memory, on the other hand, supports the influence of sensory afference in a more abstract manner. Processing this form of spatial information may occur at a longer latency compared to verbal and, therefore, would be observable with LAI. Another explanation again involves the lateralization of activity between working memory tasks. If verbal working memory elicits activity in the same hemisphere that receives somatosensory afference[63], this supports the influence of the earlier SAI generator driving the results within this condition. The later LAI generator may be driven more bilaterally and therefore is likely to display evoked changes in this task. Additionally, the results that display changes in AP-mediated LAI with spatial working memory are supported by the notion that the AP-circuit is generated in an area like SMA, which implies less lateralization[64].

One limitation of the current study is that we did not achieve the sample size required to detect a moderate effect size. Therefore, the current study may have been underpowered to detect statistical significance in the interaction term, capturing the differential effect of spatial set size across the different current directions. The targeted sample size of 22 participants was based upon the sensitivity to detect a moderate effect in SAI across the current direction and set size. These effect sizes are consistent with those observed in past work investigating SAI using similar paradigms[1,43]. Relatively little work has investigated LAI, making it difficult to estimate potential effect sizes. The presence of a strong trend may simply reflect a relatively weaker effect of the interaction between spatial set size and current direction on LAI relative to SAI. The strong trend towards statistical significance with a sample size of 17 participants suggests that a moderate to large effect is likely representative of the true outcome. However, it must be acknowledged that the 5.3% chance that the strong trend may arise due to sampling error is still above the accepted 5% convention.

Aside from measures of sensorimotor integration, intracortical mechanisms could be more involved in processing spatial information, suggesting observable changes in short and long-latency intracortical inhibition (SICI and LICI) rather than SAI and LAI. Previous work has highlighted the interaction between intracortical inhibition and cognition, which may have implications for both verbal and spatial working memory demand[65,66]. SICI is shown to be influenced by spatial attention directed to somatosensory stimuli applied selectively to different hands[65]. Although changes in attentional demand did not influence SICI, the direction of attention did significantly alter SICI in the absence of changes in single pulse MEP amplitude. Similarly, when LICI was applied over the DLPFC during the performance of a working memory task, greater levels of LICI were observed and correlated with enhanced working memory ability[66]. This evidence supports the idea that intracortical circuits represent additional pathways by which verbal and spatial working memory influence motor cortex.

Long-latency afferent inhibition represents a temporally distinct influence of sensorimotor integration. In contrast to SAI results, within the verbal task, the change in LAI was not significant for either AP or PA current directions with increasing working memory demand. Although LAI is thought to be $GABA_A$ meditated similar to SAI[37], the difference in latency of the evoked response is likely responsible for the difference in its interaction with verbal working memory. LAI is evoked at a latency of 200ms after the conditioning stimulus; therefore, the pathway by which motor cortex is inhibited is likely different from that of SAI evoked at a latency of 20ms after the conditioning stimulus. The opportunity for widespread activation in different areas during the longer interval between median nerve stimulation and the TMS pulse in LAI suggests that a more complex pathway may be involved. Areas such as bilateral primary and secondary sensory cortex, in addition to the contralateral posterior parietal cortex, are active at latencies after 40ms allowing for their involvement in LAI over SAI[67,68].

Additional regions active within LAI compared to SAI support a differential sensitivity to verbal vs. spatial working memory since the more functionally distinct areas that support a circuit, the more variance integrated within the response. Various regions active with LAI may respond to spatial and verbal working memory differently and, therefore, may influence the net result of inhibition on motor cortex leading to a response distinct to SAI. Further support for the involvement of differential pools of neurons between SAI and LAI is the interaction between these sensorimotor circuits and intracortical circuits such as SICI and LICI. SAI has been shown to interact with both SICI[69] and LICI[70], whereas LAI has been shown to interact with LICI but not SICI[71]. The differential interactions between SAI/LAI and intracortical inhibitory circuits suggests that SAI and LAI are mediated by different neural mechanisms. Another difference between SAI and LAI is how either responds to Parkinson's Disease (PD). SAI in PD is shown to be normal but is reduced in the on-medication state, whereas LAI in PD is reduced regardless of medication[72]. Additionally, one area thought to be involved in LAI is the basal ganglia-thalamocortical loop, which is shown to be impaired in PD and may account for the reduction in LAI[72,73]. If SAI and LAI consist of differential pools of neurons and reflect circuits that are functionally independent, then it stands to reason that LAI does not respond to verbal working memory in the same manner that SAI does. If LAI is not sensitive to verbal working memory, this response may reflect the processing of functions that occur at a longer latency from the afferent stimulus such as processing spatial over verbal stimuli.

Although neither change across current direction was significant for the spatial task, there was a strong trend of increasing AP-mediated LAI with increasing working memory demand. As previously mentioned, LAI occurs at a longer latency than that of SAI, allowing the potential for the involvement of other brain regions contributing the influence on motor cortex. Regions like secondary sensory areas, as well as those within frontal cortex, may be specifically involved in LAI[67,68]. One example of an ERP related to spatial attention of somatosensory stimuli is the N140[74,75]. The generator of the N140 remains uncertain, although regions such as the anterior cingulate gyrus[76] as well as secondary sensory cortex and SMA[64] have been implicated as potential regions of interest. This evidence supports the idea of multiple generators of sensorimotor pathways captured within the latency of the LAI response. Therefore, one of these generators may be sensitive to spatial working memory and reflect responses from the AP-mediated circuit driving the change in LAI.

Previous studies have observed a significant enhancement of the N140 component associated with attended vs. unattended somatosensory stimuli presented between participant's hands, suggesting that this measure is sensitive to selective spatial attention[77,78]. In stroke patients, cutaneous stimuli were presented on their paralyzed upper arm, where they were to selectively respond to target stimuli while ignoring distractors[79]. After training discrimination of the cutaneous stimuli, the patients displayed significant increases in N140 amplitude compared to untrained controls. This difference in SEP response suggests that the N140 is not only involved in functioning for spatial attention but is also susceptible to manipulations from attentional training. In addition to the N140, observed changes in the P100 with shifts in somatosensory-based spatial attention support further evidence of early somatosensory processing changes in these conditions. In older adults, greater suppression of P100 amplitude is apparent in irrelevant distractor conditions of a spatial-tactile attention task[80]. This suggests that older adults do not gate distractor stimuli to the same extent as younger controls and that the P100 plays a role in this relationship. Interestingly, younger adults display increased N140 amplitudes in response to distractor stimuli[80]. This response has been observed specifically in low attentional load conditions and is nullified with increasing demand[81]. The abnormal response from older adults suggests a discrepancy in perceived cognitive demand between age groups and supports the role of the N140 in more abstract somatosensory processing. Based on previous evidence, both the N140 and P100 appear to play a significant role in spatial attention of somatosensory stimuli. These findings suggest that an ERP component such as the N140 or P100 may account for the present results pertaining to changes in LAI associated with spatial working memory.

The increase in PA-mediated SAI observed in the verbal task was thought to be driven by input from the parietal N20 generator shown to be more active as a result of increased working memory demand. To account for the increase in AP-mediated LAI within the spatial task, input from a generator like the N140 may represent a similar explanation. Of course, later ERP components have also been observed to interact with somatosensory processing such as the N170 and P250[82]. For instance, the N170 and P250 components are shown to reflect modulation of the sensory cortex resulting from observation of touch[82]. The presentation of both human and object touch were shown to differentially modulate ERP components where human touch resulted in shorter latencies and larger amplitudes in parietal-temporal N170 and N250. The authors suggested that the simultaneous ERP effects at 170 and 250ms post-stimulus reflect the integration of social touch or observation processing in central and temporal-parietal regions. The P170 has also been shown as altered in PD patients, which is thought to result from either enhanced activity from bilateral primary or secondary sensory areas[83]. Abnormal activity displayed by the P170 in PD accompanied by typical early (e.g., N90) SEP responses implicates the involvement of late SEPs in sensory processing. The later ERP components responding to sensory stimuli suggest that processing spatial information requires integrative mechanisms that occur at longer latencies in comparison to verbal. This supports the functional role of circuits mediating LAI in processing spatial working memory captured by the longer latency. If the input from a generator such as the N140 increases in activity with greater spatial working memory demand, this would explain the increase in LAI response as a result of a breakdown in attentional function. The increase in AP LAI from the current results implies that the AP-mediated circuit is sensitive to spatial working memory whereas the PA-mediated circuit for LAI may not be involved in processing for working memory at this latency. As mentioned, spatial working memory may be processed at a latency later than that of verbal. This would support the significant increase in AP-mediated LAI despite the lack of change observed in the verbal condition.

Exploratory correlations between experimental task accuracy and SAI/LAI were assessed for both verbal and spatial tasks. Since none of the correlations reached significance, this suggests that accuracy on the verbal and spatial working memory performance does not systematically predict the influence on sensorimotor integration. This is supported by the results of correlations between baseline measures of working memory capacity and accuracy, along with correlations between baseline measures and SAI/LAI. Out of all comparisons, one correlation was found to be significant, suggesting that the majority of the data supports no relationship between spatial and verbal working memory capacity and changes in accuracy or SAI/LAI response. The statistical power of these exploratory correlations is low as the current study was powered to detect significant differences across tasks and current direction rather than systematic relationships between neurophysiology and behavioural measures. Further, the two-item condition was associated with ceiling performance as the majority of subjects achieved perfect accuracy. Together, these results suggest that working memory abilities are not indicative of changes to sensorimotor processing. An absent relationship between working memory abilities and change in SAI/LAI suggests that capacity does not influence the mechanism by which SAI/LAI is modulated. However, the increase in SAI and LAI observed with greater working memory demand indicates that the effect of the load was still present regardless of performance.

The significant correlation between PA LAI in the verbal task and the Reading Span task reveals that better performance on the Reading Span task is associated with greater LAI as working memory load increases. This result may suggest that participants in both the high and low scoring groups displayed LAI in different directions. This would, in turn, mask the effect at the group level where overall, there was no significant change in PA-mediated LAI within the verbal task. One explanation as to why this significant trend may not be meaningful within the interpretation of results is that the vast majority of participants finished the Reading Span task on the second level (score of 2). Only four participants scored higher than two on the task, and although they displayed increases in LAI, only one participant who scored 3 displayed a greater change in LAI compared to others with a lower score, which appears to be driving the effect (Figure 23b, Appendix F). Alternatively, this relationship may represent a mechanism specific to how the processing for verbal working memory influences changes in PA LAI, however, this requires further investigation.

The current results expand upon the model of PA and AP pathways mediating SAI reported by Suzuki et al.[1] An updated model is required to reflect the findings of the current study regarding the influence of PA and AP-mediated circuits on the corticospinal neuron and to incorporate findings from LAI. In order to incorporate the significant increase in SAI response to increasing verbal working memory load, the new version of the model depicts the frontal N30 and parietal N20 generators with activity in opposite directions where the N20 is increasing in activity and the N30 is decreasing (Figure 13). Similar to the previous model, both generators act in opposite directions due to increasing verbal working memory demand where the N20 acts specifically on the PA circuit and the N30 acts on the AP circuit. Also similar is that the generator with input to the PA circuit is driving the overall SAI response regardless of the direction of the generator with input to the AP circuit. Specifically, that the N20 generator influences the AP circuit directly in addition to PA, or that the PA circuit, through its synapse on the PTN closer to the cell body, influences the overall SAI response regardless of the circuit recruited. LAI, conversely, was shown as sensitive to spatial working memory as opposed to verbal and through the AP-mediated circuit as opposed to PA. In this case, increases in the N140 generator is proposed to influence the AP circuit, which may involve areas like SMA and secondary sensory cortex at longer latencies. Since PA-mediated LAI is observed to have no effect on the corticospinal neuron, it is proposed that the PA circuit is not sensitive to verbal or spatial working memory at this latency.

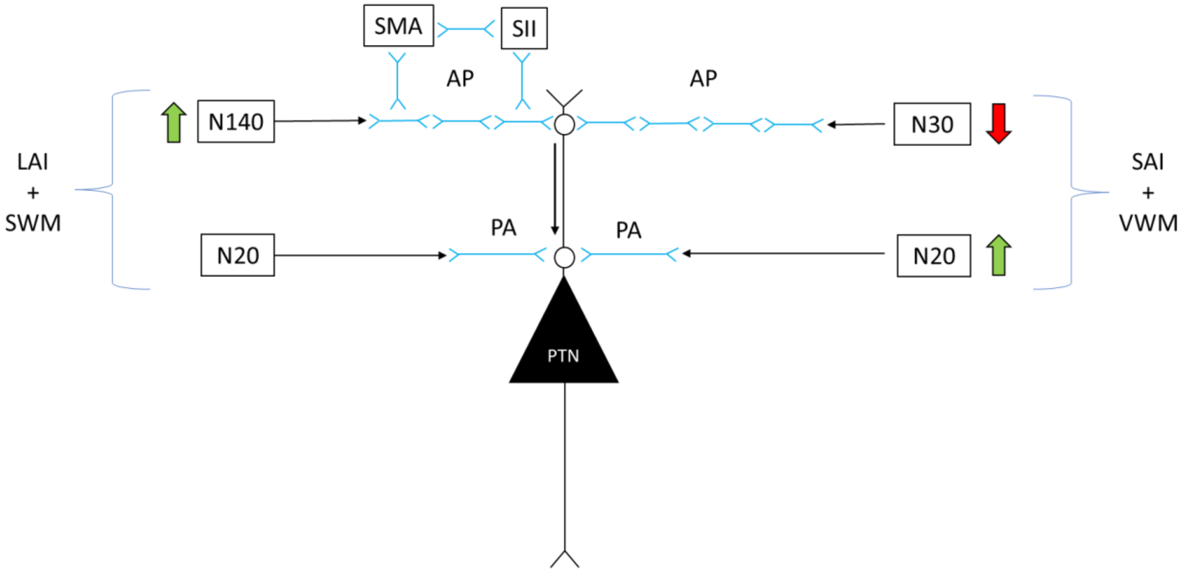

Figure 15 – Updated model depicting the influence of AP and PA-mediated circuits on the corticospinal neuron recruited by both SAI and LAI. Green and red arrows represent the response in activity from generators as a result of increasing working memory demand. The significant effect of SAI in response to verbal working memory (VWM) and strong trend of LAI in response to spatial working memory are represented in the figure.

6.0 LIMITATIONS

The current study has several limitations that should be acknowledged. The first limitation is that the MagStim 200[2] stimulator has a pulse duration of ~80μs. This pulse duration recruits a mix of unique AP-sensitive inputs to the cortical spinal neuron[84] that may have different functional properties[85]. Therefore, it is possible that our assessment of AP SAI and AP LAI may reflect a homogenous mix of influences over corticospinal excitability. Increased variability in responses depending upon the exact composition of circuits recruited by the AP current is a possibility. Future work should employ controllable TMS stimulation to better isolate the different AP (and potentially PA) sensitive circuits by using different pulse durations[84].

A second limitation is that the current study only quantified SAI and LAI at fixed latencies of 22 ms and 200 ms, respectively. SAI is known to occur at peripheral electrical, central TMS inter-stimulus interval ranging from ~18-24ms[2]. The 22 ms inter-stimulus interval was chosen as it is, on average, the point at which SAI is the strongest. Since SAI is dependent on the magnitude of the sensory afference[35], some of the variation in SAI within a set-size and the change in SAI across set size may reflect variability in the conduction time from the wrist to thalamus/primary somatosensory cortex. Future work should use N20 SEP latency to account for variation in conduction time. A second limitation of the fixed 22 ms interstimulus interval is that the effect of working memory across the different circuits tested may be dynamic across the interstimulus window. LAI is relatively less studied compared to SAI, however, similar limitations with using a fixed 200 ms interstimulus interval are also possible.

A third limitation of the current study was the fixed timing within the maintenance period of the experimental task at which SAI and LAI were assessed. The timing of the SAI assessment during the memory maintenance window was based upon past work by Suzuki et al.[1]. As the TMS pulse occurred randomly between 1.5 and 2.25 seconds within this period, this does not allow for sensitivity to any change in SAI or LAI in response to set size that may have occurred during early periods of memory maintenance. It is possible that PA and AP circuits mediating SAI and LAI may be differentially engaged by verbal and spatial working memory at different points of the maintenance period. Therefore, future work should assess PA and AP SAI/LAI at different points following the removal of the memory set from view.

A final limitation is there is a large disparity in the strength of the magnetic field needed to elicit MEPs induced by AP relative to PA current. While we were able to elicit robust MEPs in all participants, we were unable to achieve an MEP of 1 mV for AP current in 9 individuals as the TMS stimulator did not have enough capacity. As a result, the 1mV test stimulus intensity was set to 95% of stimulator output for these individuals. The thresholding procedure was used to ensure an unconditioned MEP of 1 mV in all participants. As the unconditioned MEP is used as a reference for the effect of the peripheral conditioning stimulus upon the same TMS stimulus, a slightly smaller unconditioned MEP for AP current may have increased variability in the effect of increasing set size upon AP SAI/LAI.

7.0 FUTURE DIRECTIONS

In addition to future directions to address specific limitations outlined above, there are several avenues to pursue for enhancing our understanding of the underlying mechanisms involved in cognitive influence to sensorimotor outcomes.

One such direction is to assess the relationship between SEPs and sensorimotor integration in response to increasing working memory load. Identifying SEP components, elicited by the same peripheral electrical stimulation used to elicit SAI/LAI, that are sensitive to the same working memory manipulations would identify potential sources of afference feeding into the PA and AP sensitive circuits. The discussion of the current study identifies potential generators for changes to SAI based on work done by Suzuki et al.[1] where SAI and SEP changes in response to verbal working memory load were conducted but in separate cohorts. Understanding the origins of somatosensory afference feeding into the PA and AP pathways mediating SAI is critical to refining functional models of sensorimotor control. In addition, SEP recording could verify proposed generators accounting for the LAI response to working memory as well. The N140 and N170 were two proposed examples of SEPs that might influence the LAI response based upon their relative timing to the ISI used for LAI. Establishing a relationship between change in LAI and amplitude from these SEPs would provide more substantial evidence for their involvement in sensorimotor function.

Another future direction for this research is examining intracortical circuits through methods such as SICI and LICI. As previously mentioned, SICI and LICI have been shown to interact with cognitive function, suggesting that these circuits may be involved in working memory's influence on the motor system. Additionally, PA SAI is known to interact with both SICI and LICI. Whether the sensitivity of SICI and LICI to cognitive function reflect a unique functional process or is a result of their interaction with SAI is critical to understanding the organization of inputs to the corticospinal neuron. One possibility that should be addressed in future work is that SICI/LICI represent the procedural memory of skilled movement and SAI/LAI provides a means by which to modify procedural memory motor representations.

One final future direction involves the influence of cross-modal attention or working memory on sensorimotor outcomes. Although the current task already involves engagement across visual and somatosensory modalities, a task that builds in multimodal elements may influence SAI/LAI in a different manner. Cross-modal processing during an attentional task has shown to influence different ERP components depending on the modality of both the target and distractor stimulus[28,29]. The influence of multimodal engagement on sensorimotor integration allows for further examination of the mechanisms that mediate interaction across memory systems. Another idea to modulate the experimental task could be for the purpose of relating motor performance to changes in sensorimotor outcomes. One method to examine this relationship would be to incorporate a movement task within the experiment in order to identify how SAI/LAI may change with performance. This could have more direct clinical implications, as relating motor skill proficiency with changes in SAI/LAI would provide an indicator of how other factors influencing sensorimotor outcomes might similarly influence movement.

8.0 CONCLUSION

The current study demonstrates the influence of cognitive load on sensorimotor integration. In the verbal working memory task, the sensorimotor circuit sensitive to the PA current direction elicited a significant increase in SAI. In the spatial working memory task, the sensorimotor circuit sensitive to the AP current direction elicited an increase in SAI. Our first and second hypotheses that SAI and LAI would decrease from 2- to 6-items and would be apparent across AP and PA induced current, were not confirmed. Overall, working memory appears to increase SAI through the PA circuit when the task is verbal, suggesting that processing verbal working memory releases gating of sensory afference under higher loads. This is similarly the case for spatial working memory, which appears to increase LAI through the AP circuit. The third aim of the current study was to identify the relationship between baseline capacity of working memory, experimental task accuracy and change in SAI/LAI. Since all but one of these correlations were not significant, the hypothesis that greater working memory capacity is associated with greater accuracy and increased SAI/LAI was not confirmed. Based on these results, it appears as though changes in SAI and LAI occur in certain cases with greater working memory load, regardless of baseline capacity or accuracy on the task.

A more direct PA circuit appears to influence SAI within the verbal task due to the explicit nature of verbal working memory, suggesting a role for processing declarative information through this circuit. A more complex AP circuit appears to influence LAI within the spatial task due to the implicit nature of spatial working memory, suggesting a role for processing procedural information through this circuit. SAI and LAI differ according to the latency by which the motor response is evoked as verbal information appears to be processed at an earlier latency and spatial at a longer latency. The sensitivity of specific circuits mediating SAI and LAI to the demands of spatial and verbal working memory provides further evidence that the circuits reflect distinct pathways by which executive control and declarative knowledge can influence subconscious processes mediated by procedural motor memory.

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APPENDICES

Appendix A – Relationship Between Accuracy and Sensorimotor Integration

Table 1 - Correlations between Spatial task accuracy and SAI/LAI

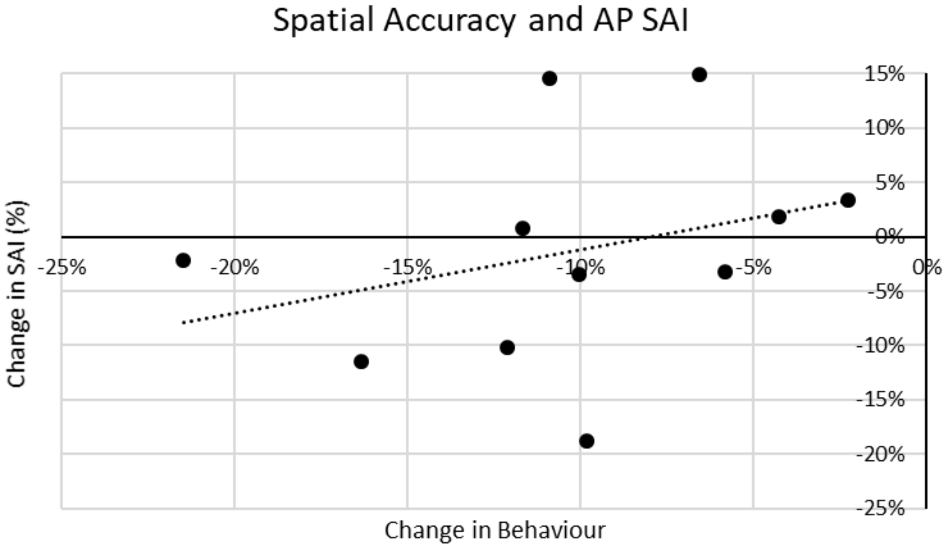
TMS Method	**Current Direction**	**Correlation Coefficient**	***p*-value**
SAI	AP	$\rho = -0.07$	0.76
	PA	$r = -0.33$	0.19
LAI	AP	$r = -0.10$	0.69
	PA	$\rho = -0.04$	0.87

Table 2 - Correlations between Verbal task accuracy and SAI/LAI

TMS Method	**Current Direction**	**Correlation Coefficient**	***p*-value**
SAI	AP	$r = -0.11$	0.68
	PA	$r = -0.21$	0.41
LAI	AP	$\rho = 0.13$	0.61
	PA	$r = 0.05$	0.99

Appendix B – Correlation Figures of Spatial Accuracy and SAI/LAI

A



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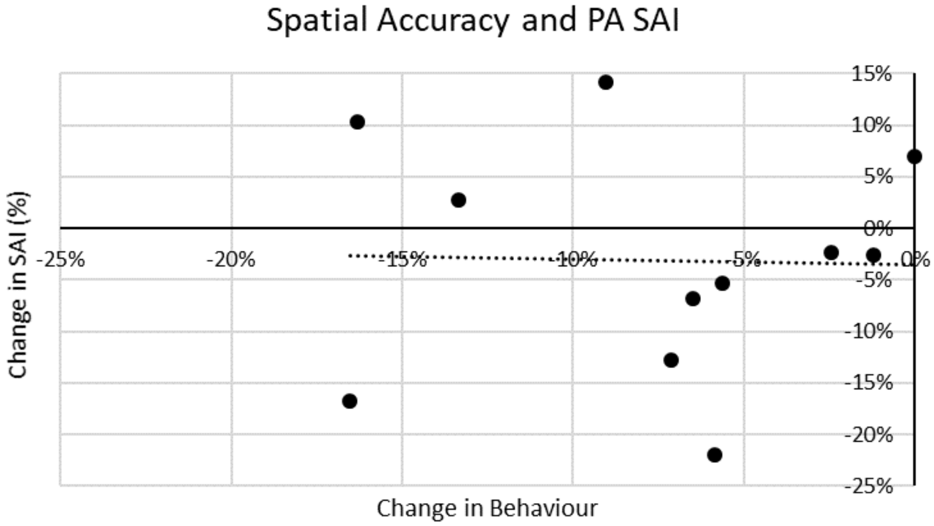
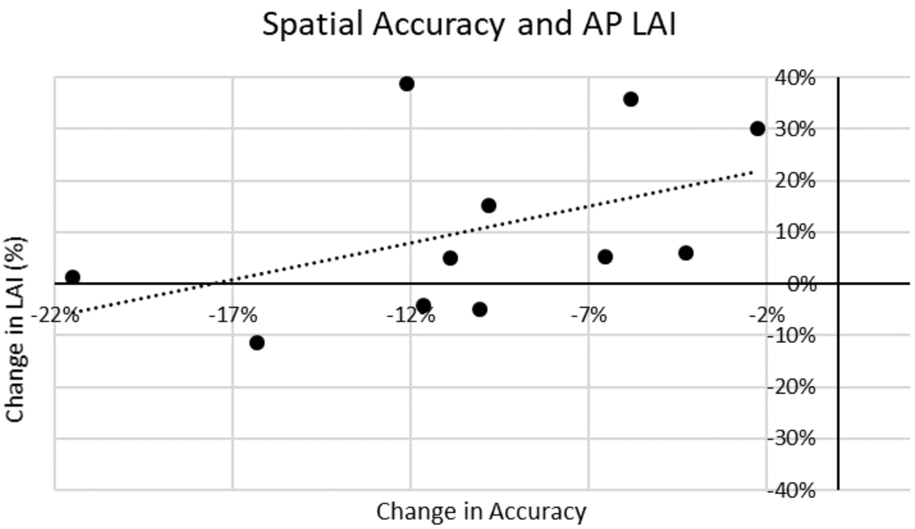


Figure 16 - Relationship between accuracy and both AP (A) and PA (B) SAI within the spatial task

A



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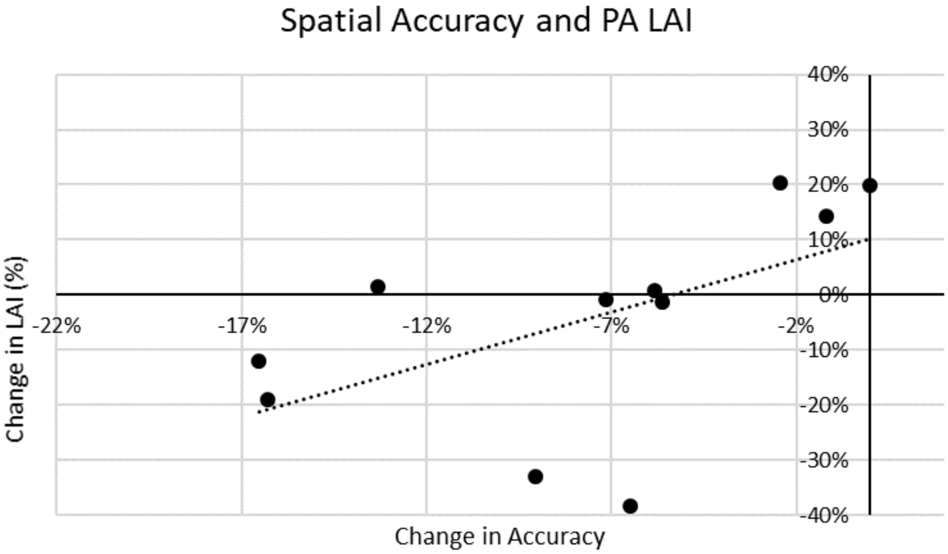
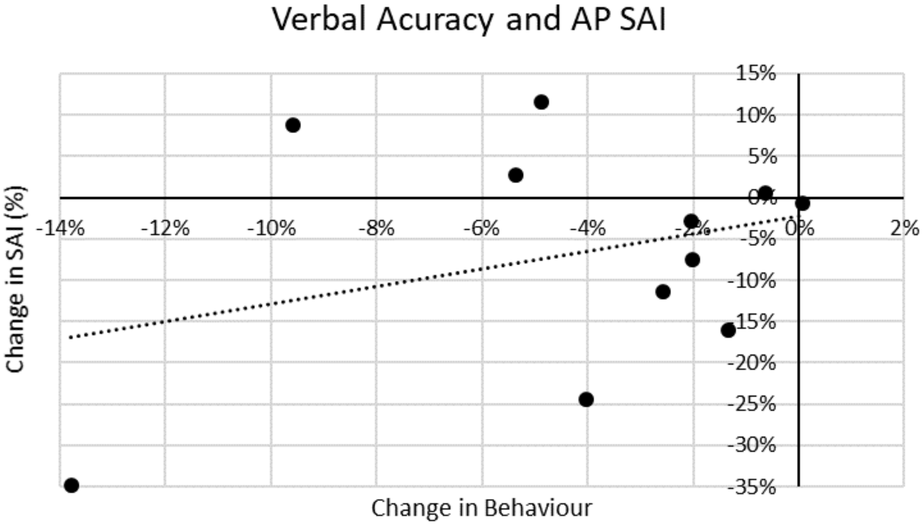


Figure 17 - Relationship between accuracy and both AP (A) and PA (B) LAI within the spatial task

Appendix C – Correlation Figures of Verbal Accuracy and SAI/LAI

A



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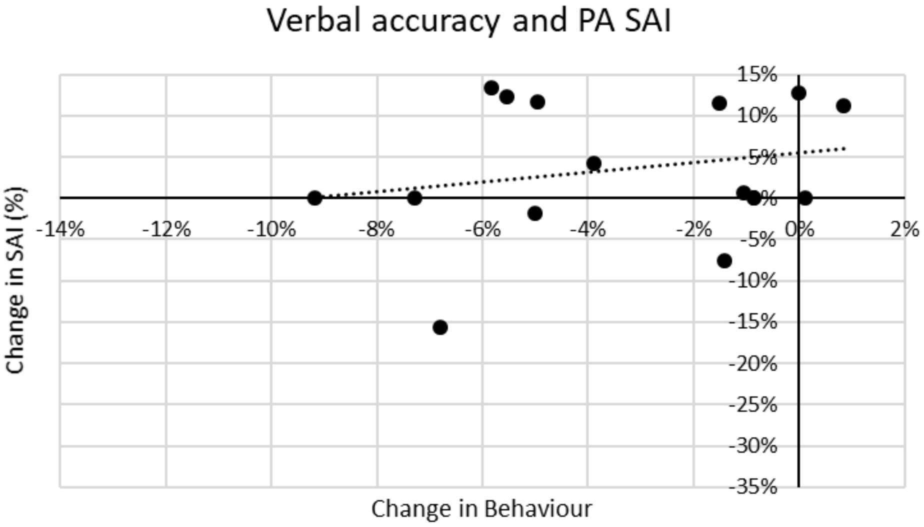
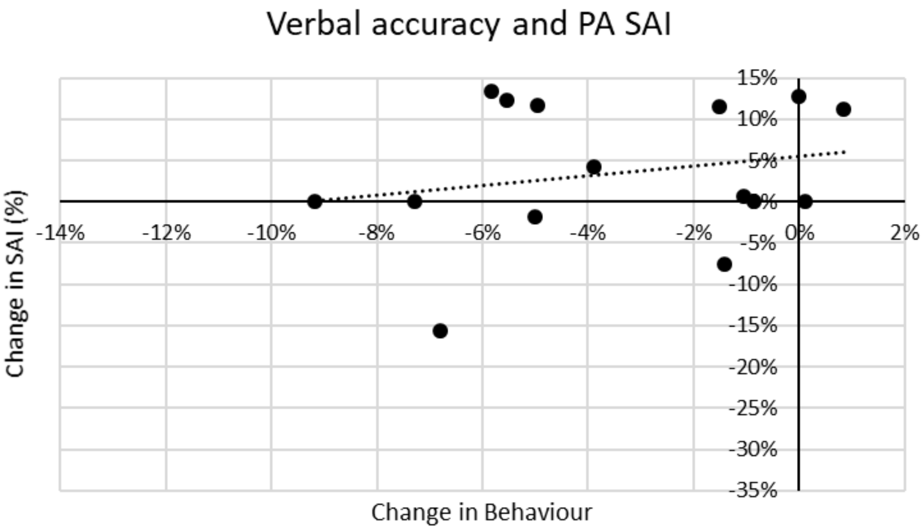


Figure 18 - Relationship between accuracy and both AP (A) and PA (B) SAI within the verbal task

A



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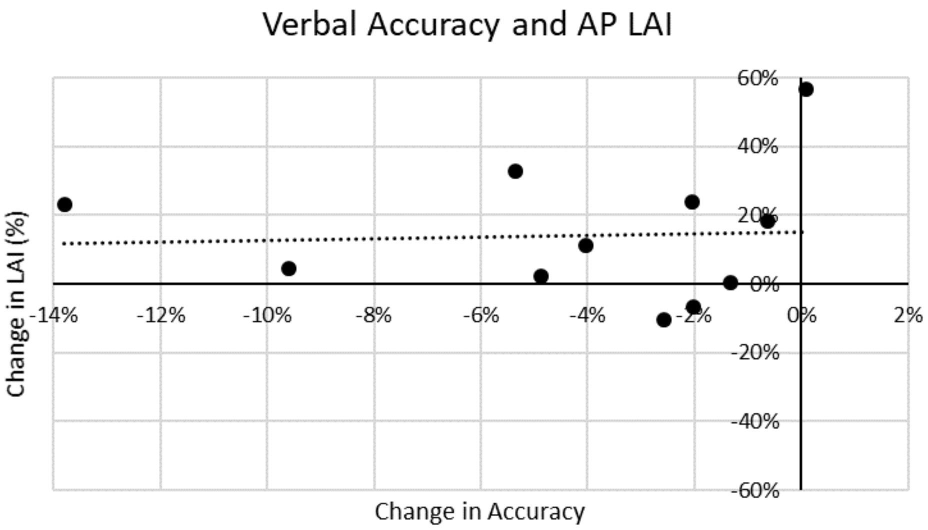


Figure 19 - Relationship between accuracy and both AP (A) and PA (B) LAI within the verbal task

Appendix D – Relationship Between Baseline Working Memory Capacity and Accuracy

Table 3 – Correlations between baseline tasks and accuracy within the spatial task

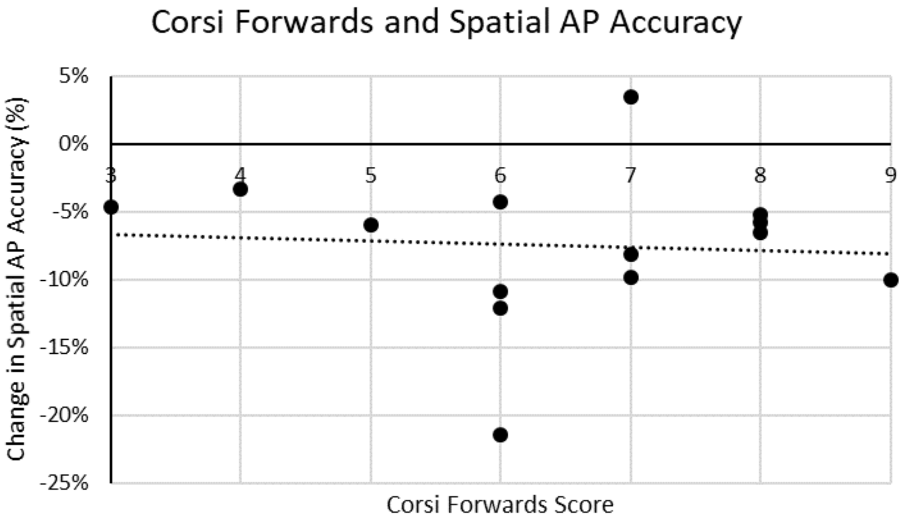
Task	**Baseline Task**	**Current Direction**	**Correlation Coefficient**	***p*-value**
Spatial	Corsi Forwards	AP	r = -0.07	0.81
	Corsi Forwards	PA	r = 0.20	0.49
	Corsi Backwards	AP	r = -0.24	0.38
	Corsi Backwards	PA	r = -0.01	0.98
	Card Rotation	AP	r = 0.19	0.47
	Card Rotation	PA	r = -0.14	0.58

Table 4 – Correlations between baseline tasks and accuracy within the verbal task

Task	**Baseline Task**	**Current Direction**	**Correlation Coefficient**	***p*-value**
Verbal	Digit-Span	AP	r = 0.21	0.44
	Digit-Span	PA	ρ = 0.11	0.70
	Reading Span	AP	ρ = 0.34	0.22
	Reading Span	PA	ρ = 0.50	0.06

Appendix E – Correlation Figures of Baseline Working Memory Capacity and Spatial Accuracy

A



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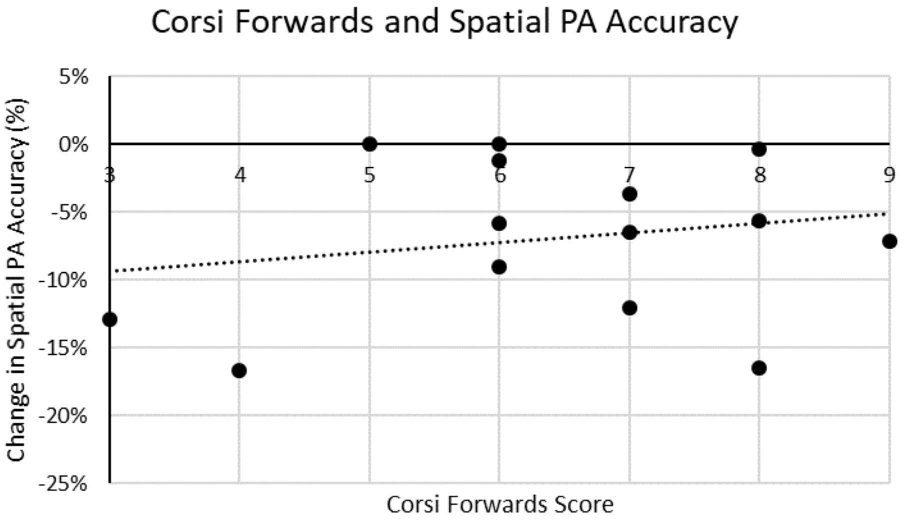
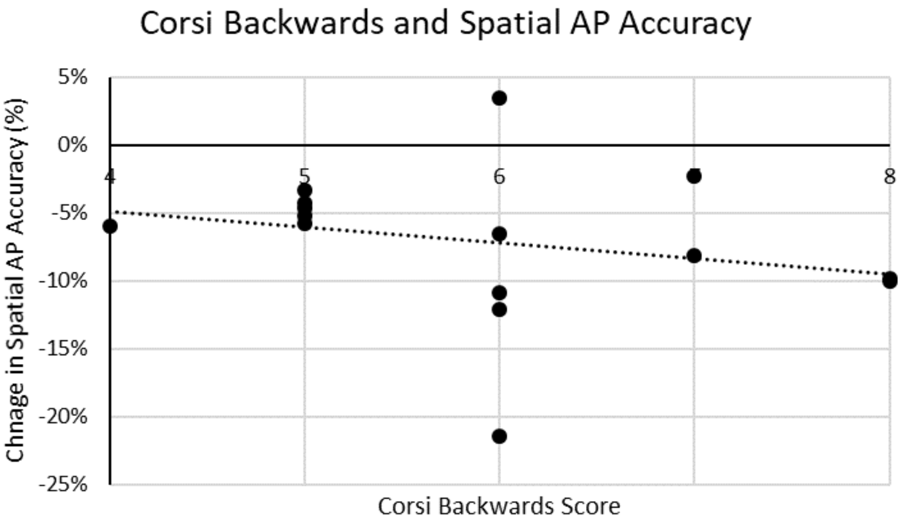


Figure 20 – Relationship between Corsi Forward Score and both AP (A) and PA (B) accuracy within the Spatial task

A



B

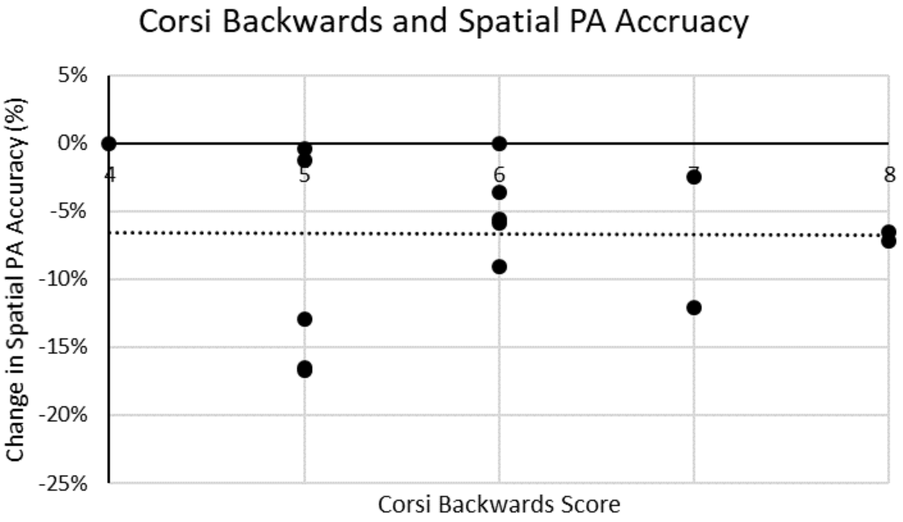
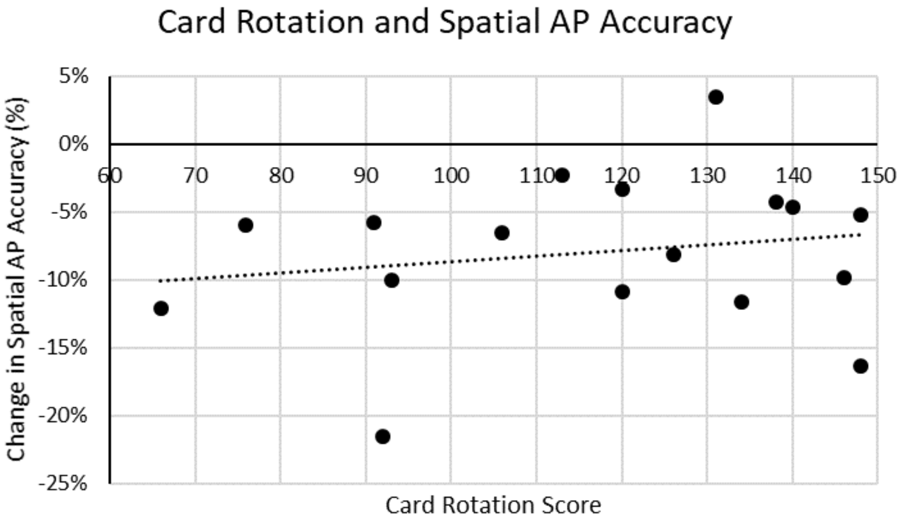


Figure 21 - Relationship between Corsi Backwards Score and both AP (A) and PA (B) accuracy within the Spatial task

A



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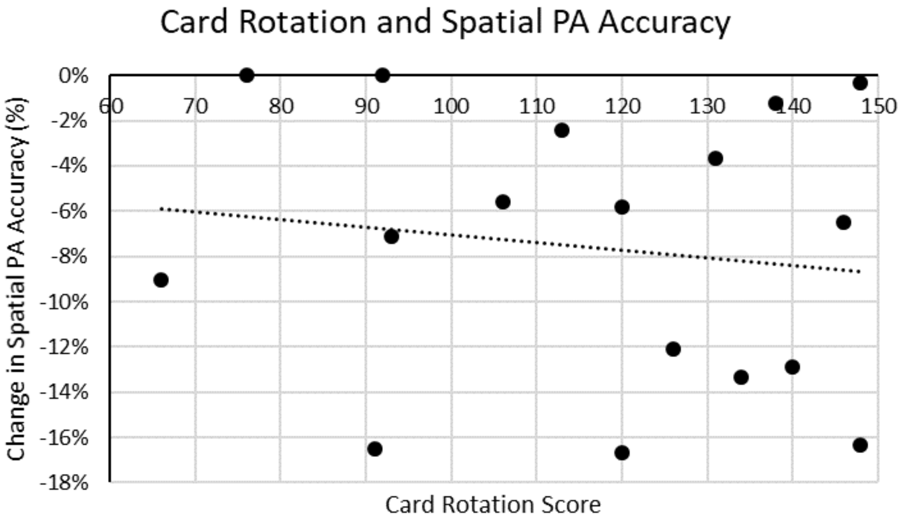
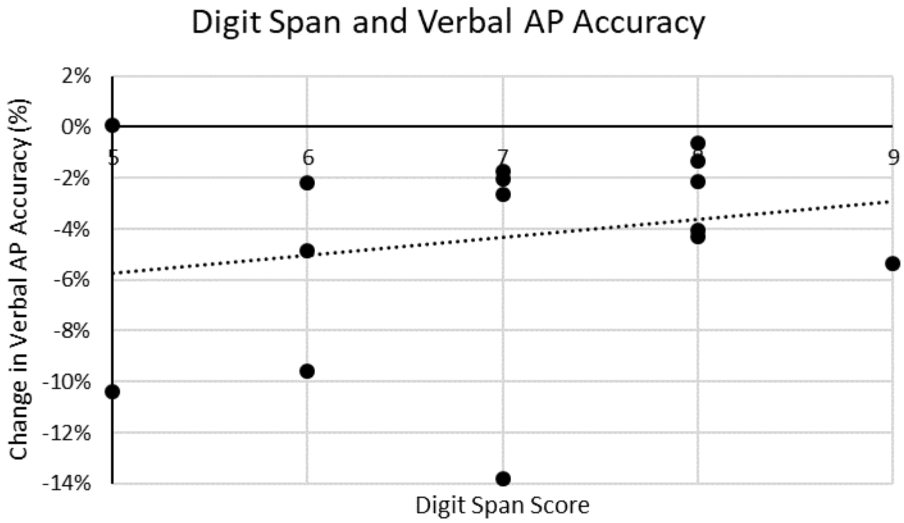


Figure 22 - Relationship between Card Rotation Score and both AP (A) and PA (B) accuracy within the Spatial task

Appendix F – Correlation Figures of Baseline Working Memory Capacity and Verbal Accuracy

A



B

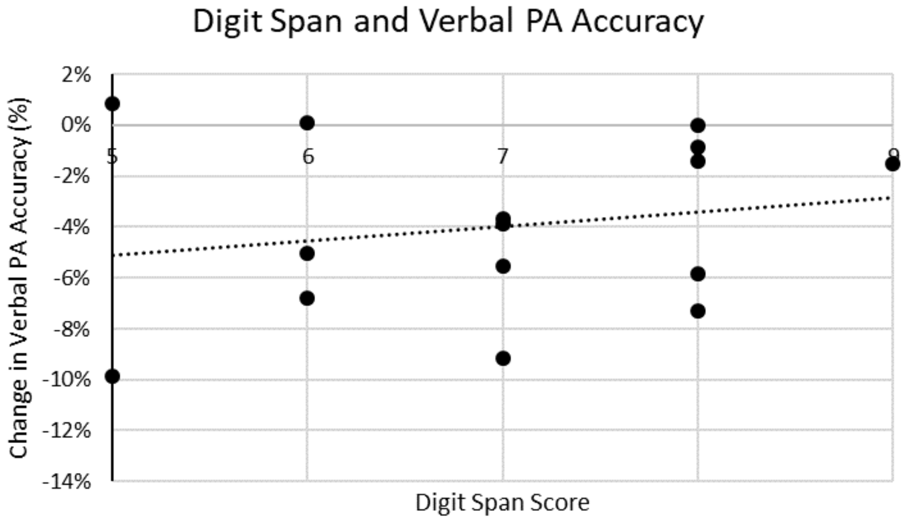
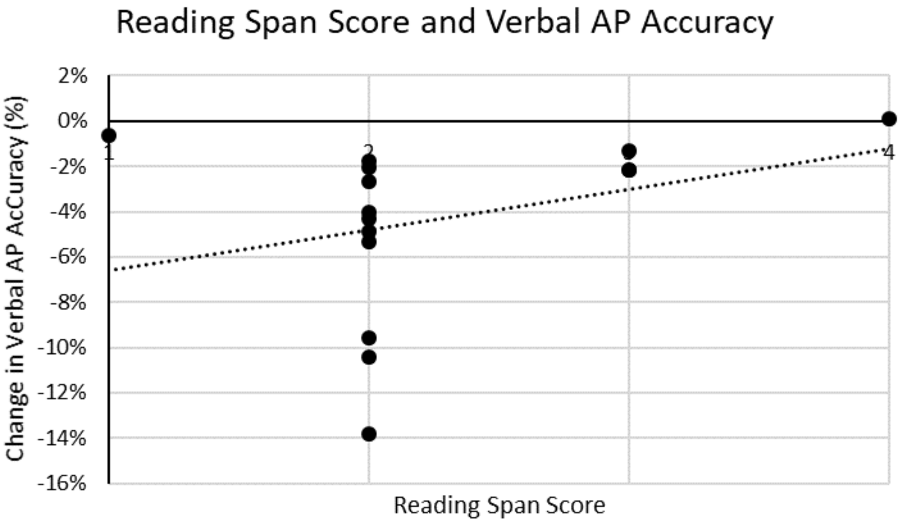


Figure 23 - Relationship between Digit Span Score and both AP (A) and PA (B) accuracy within the Verbal task

A



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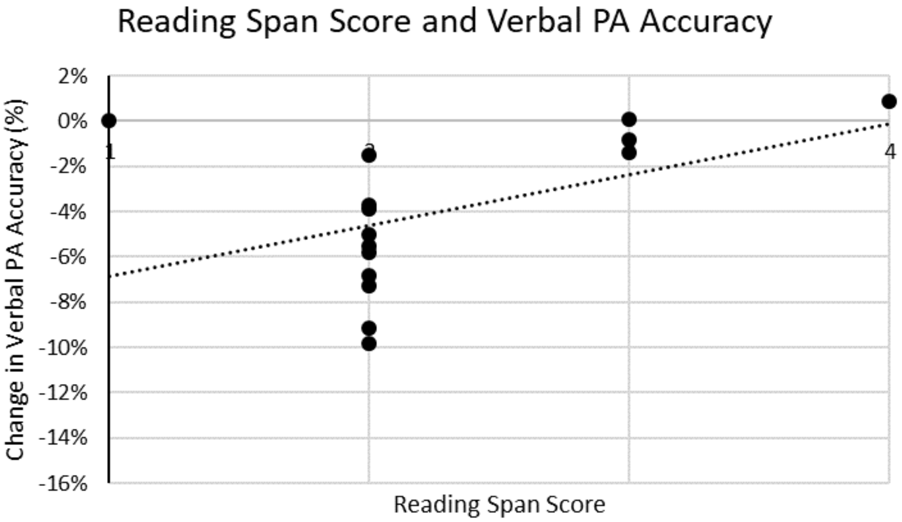


Figure 24 - Relationship between Reading Span Score and both AP (A) and PA (B) accuracy within the Verbal task

Appendix G – Relationship Between Baseline Working Memory Capacity and Sensorimotor Integration

Table 5 – Correlations between baseline tasks and SAI within the spatial task

Task	**TMS Method**	**Baseline Task**	**Current Direction**	**Correlation Coefficient**	***p*-value**
Spatial	SAI	Corsi Forwards	AP	r = 0.31	0.28
		Corsi Forwards	PA	r = 0.01	0.99
		Corsi Backwards	AP	r = 0.03	0.91
		Corsi Backwards	PA	r = 0.21	0.46
		Card Rotation	AP	r = 0.24	0.36
		Card Rotation	PA	r = 0.40	0.11

Table 6 – Correlations between baseline tasks and SAI within the verbal task

Task	**TMS Method**	**Baseline Task**	**Current Direction**	**Correlation Coefficient**	***p*-value**
Verbal	SAI	Digit-Span	AP	r = -0.09	0.76
		Digit-Span	PA	ρ = -0.35	0.21
		Reading Span	AP	ρ = 0.05	0.86
		Reading Span	PA	ρ = 0.30	0.28

Table 7 – Correlations between baseline tasks and LAI within the spatial task

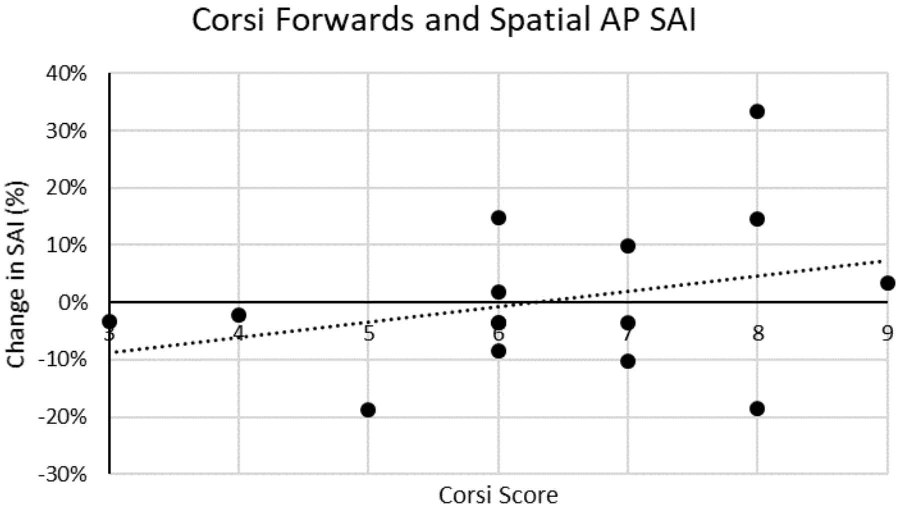
Task	**TMS Method**	**Baseline Task**	**Current Direction**	**Correlation Coefficient**	***p*-value**
Spatial	LAI	Corsi Forwards	AP	r = -0.06	0.84
		Corsi Forwards	PA	r = 0.23	0.42
		Corsi Backwards	AP	r = 0.12	0.68
		Corsi Backwards	PA	r = 0.34	0.21
		Card Rotation	AP	r = -0.18	0.48
		Card Rotation	PA	r = -0.13	0.63

Table 8 – Correlations between baseline tasks and LAI within the verbal task

Task	**TMS Method**	**Baseline Task**	**Current Direction**	**Correlation Coefficient**	***p*-value**
Verbal	LAI	Digit-Span	AP	r = -0.01	0.97
		Digit-Span	PA	ρ = 0.23	0.41
		Reading Span	AP	ρ = 0.31	0.26
		Reading Span	PA	ρ = 0.54	**0.04***

Appendix H – Correlation Figures of Baseline Working Memory Capacity and Spatial SAI

A



B

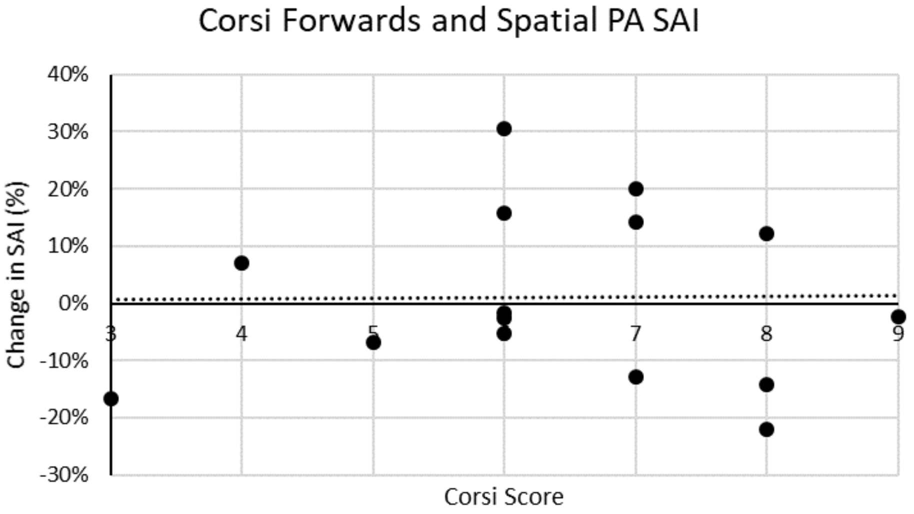


Figure 25 – Relationship between Corsi Block Forwards score and the change in both AP (A) and PA (B) SAI within the spatial task

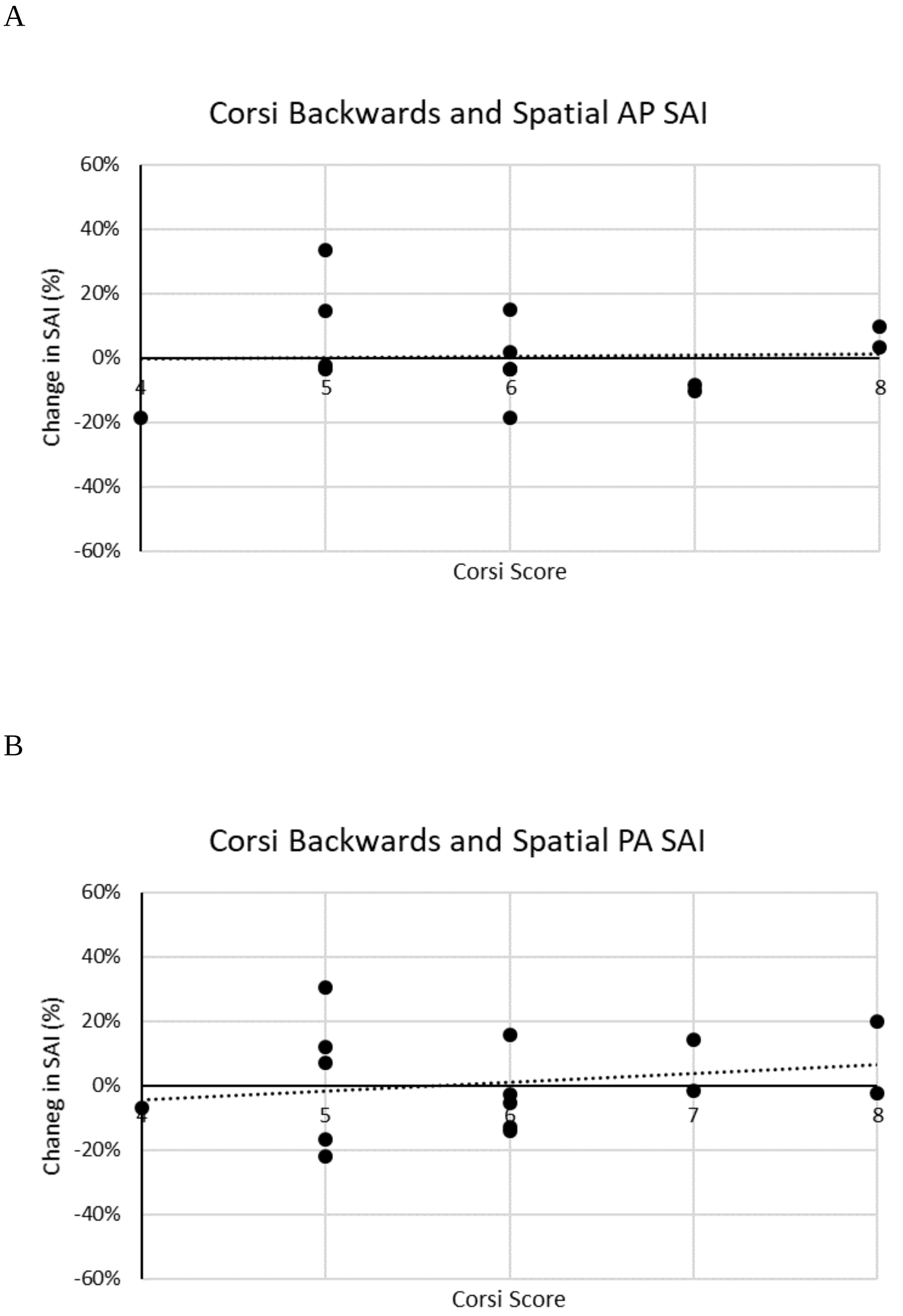


Figure 26 – Relationship between Corsi Block Backwards score and the change in both AP (A) and PA (B) SAI within the spatial task

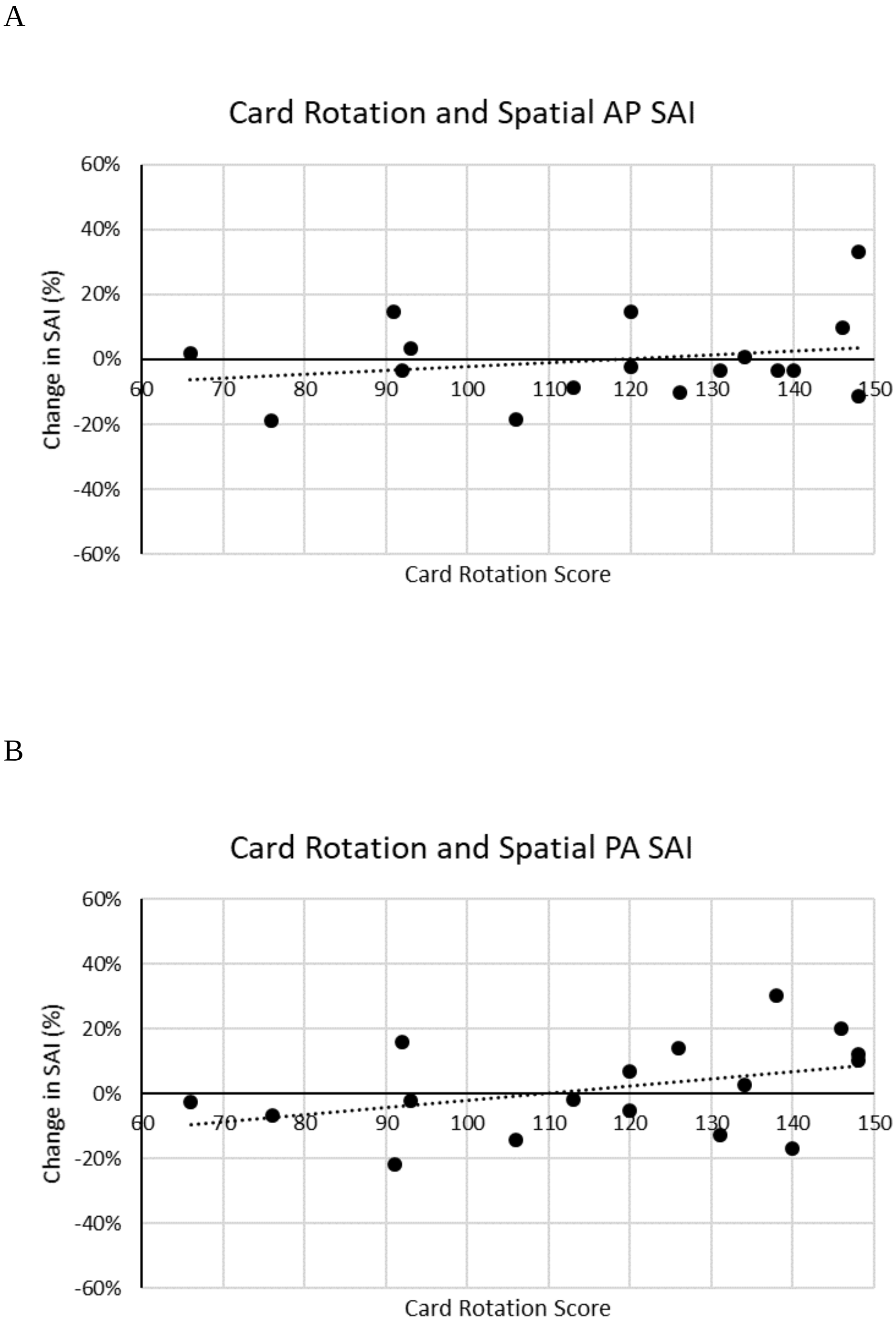


Figure 27 – Relationship between card rotation score and the change in both AP (A) and PA (B) SAI within the spatial task

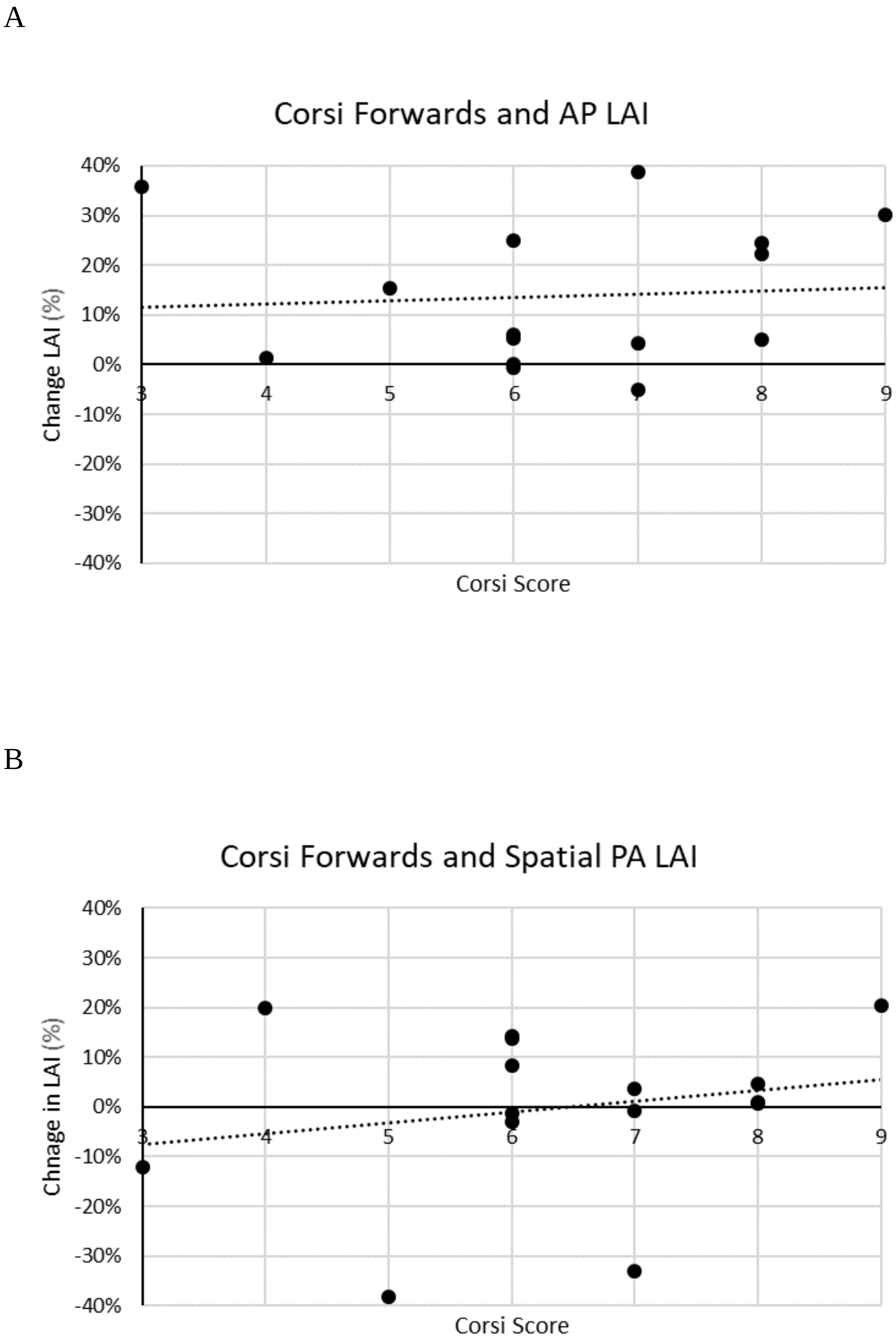


Figure 28 – Relationship between Corsi Block Forwards score and the change in both AP (A) and PA (B) LAI within the spatial task

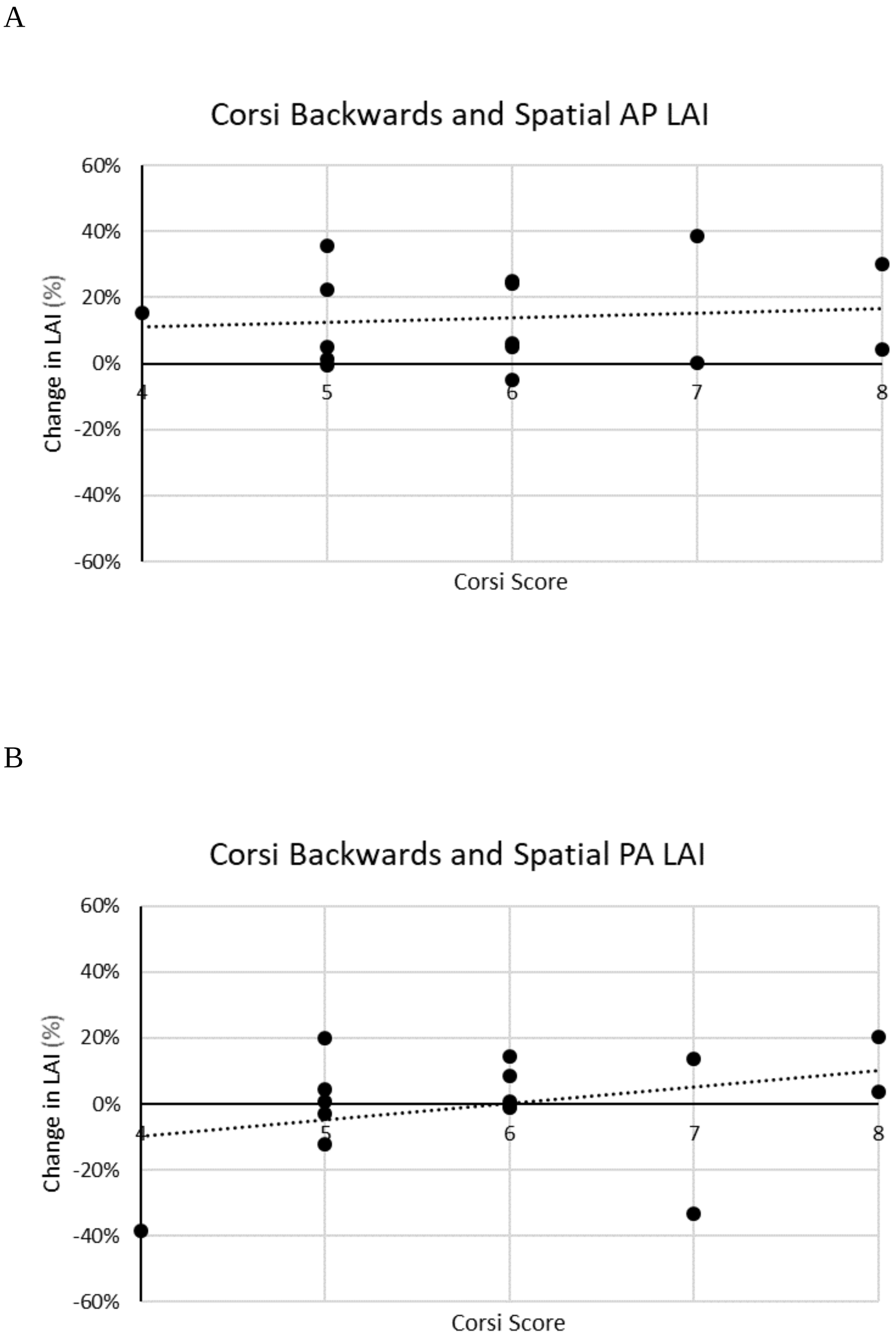


Figure 29 – Relationship between Corsi Block Backwards score and the change in both AP (A) and PA (B) LAI within the spatial task

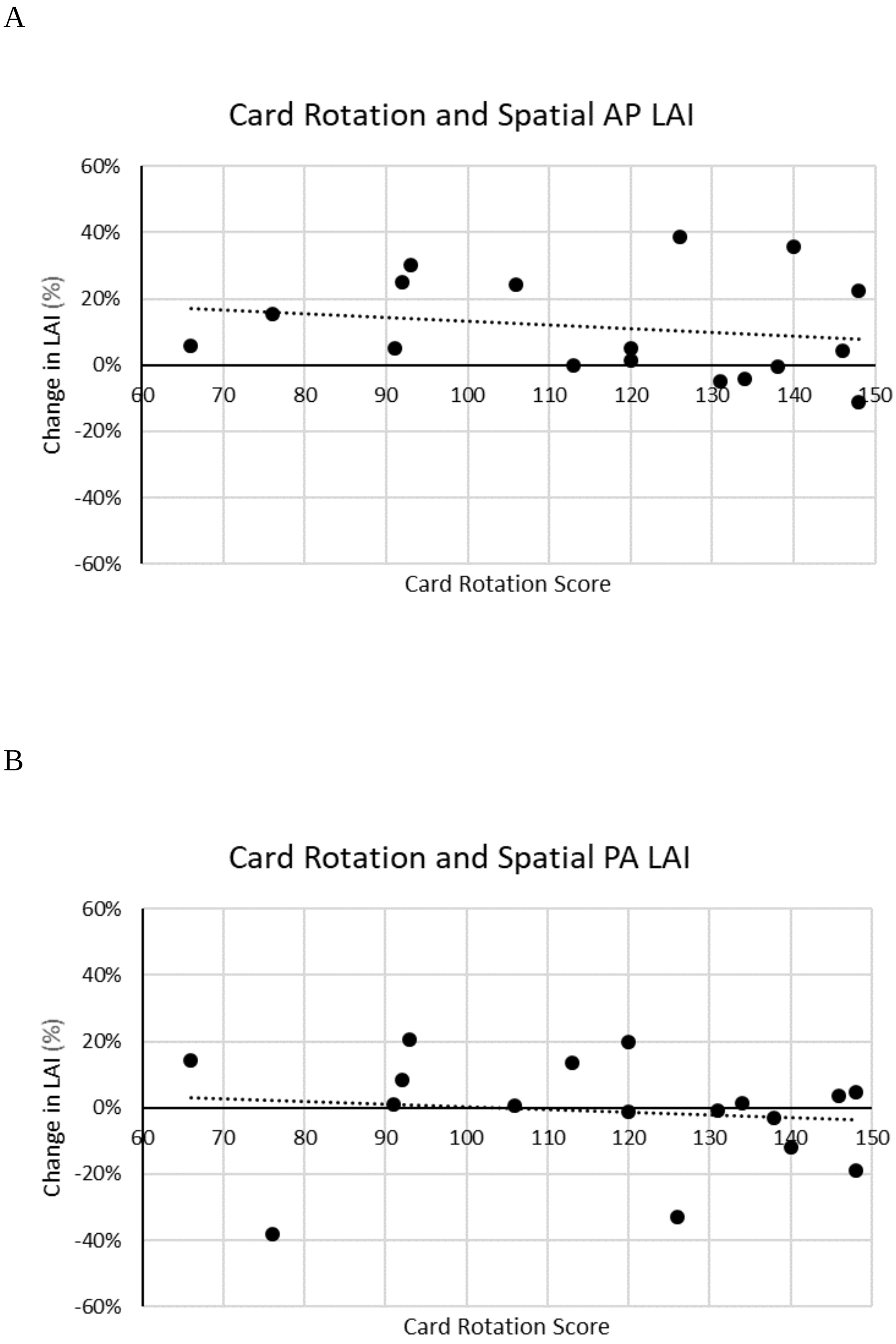
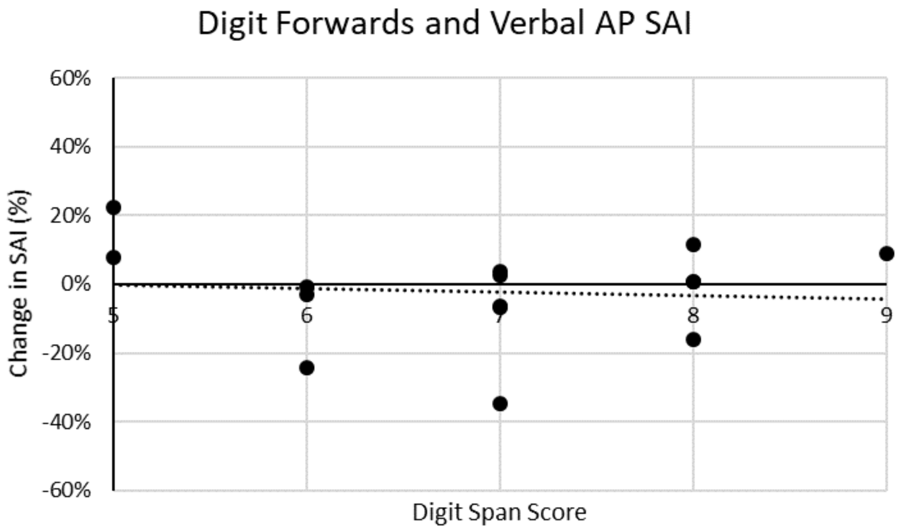


Figure 30 – Relationship between Card Rotation score and the change in both AP (A) and PA (B) LAI within the spatial task

Appendix I – Correlation Figures of Baseline Working Memory Capacity and Verbal SAI/LAI

A



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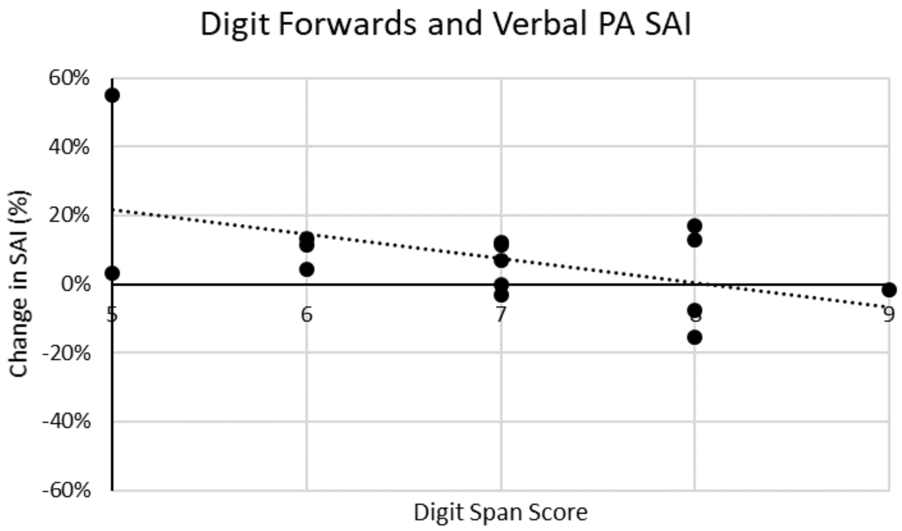


Figure 31 – Relationship between Digit Span Forwards score and the change in both AP (A) and PA (B) SAI within the verbal task

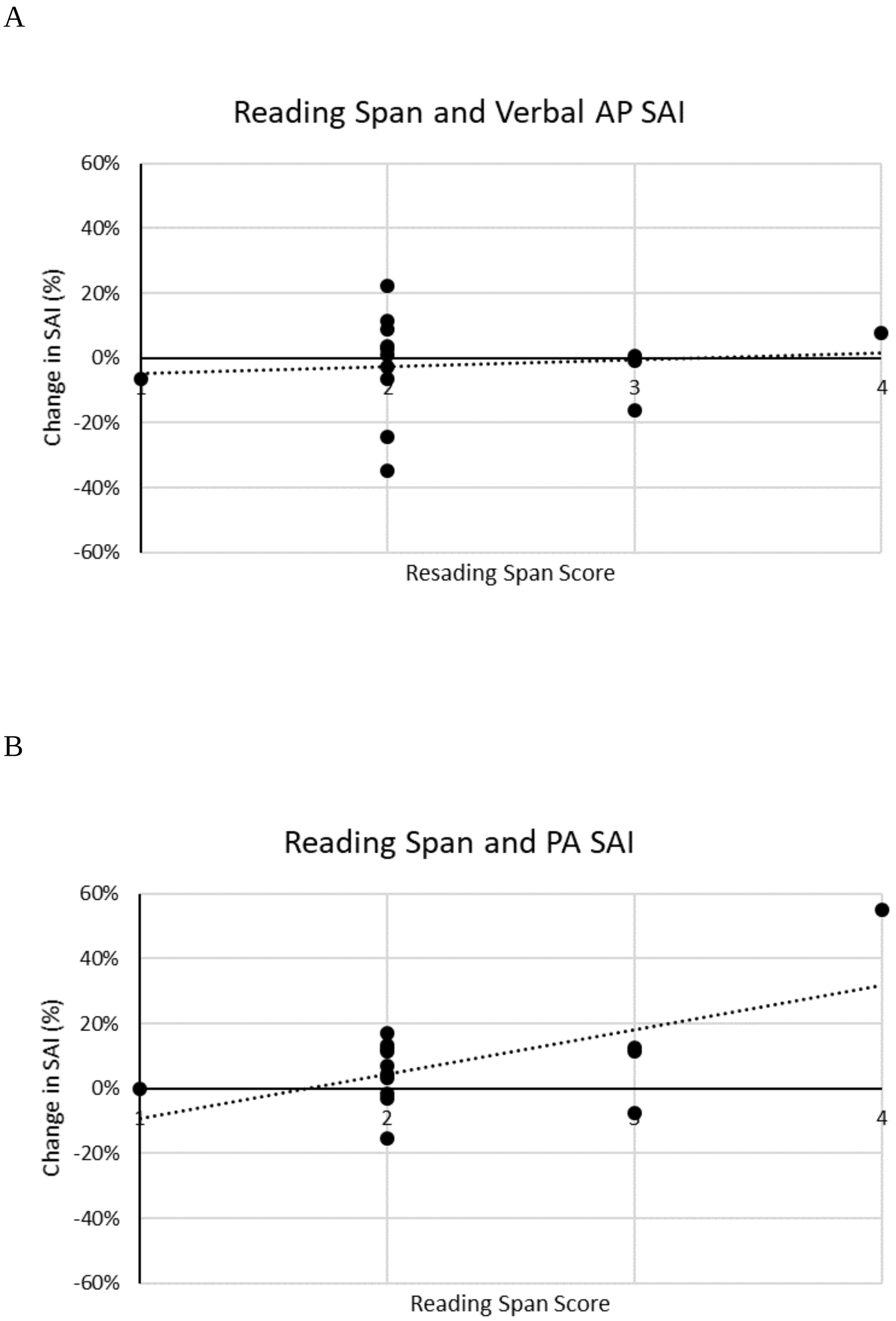


Figure 32 - Relationship between Reading Span score and the change in both AP (A) and PA (B) SAI within the verbal task

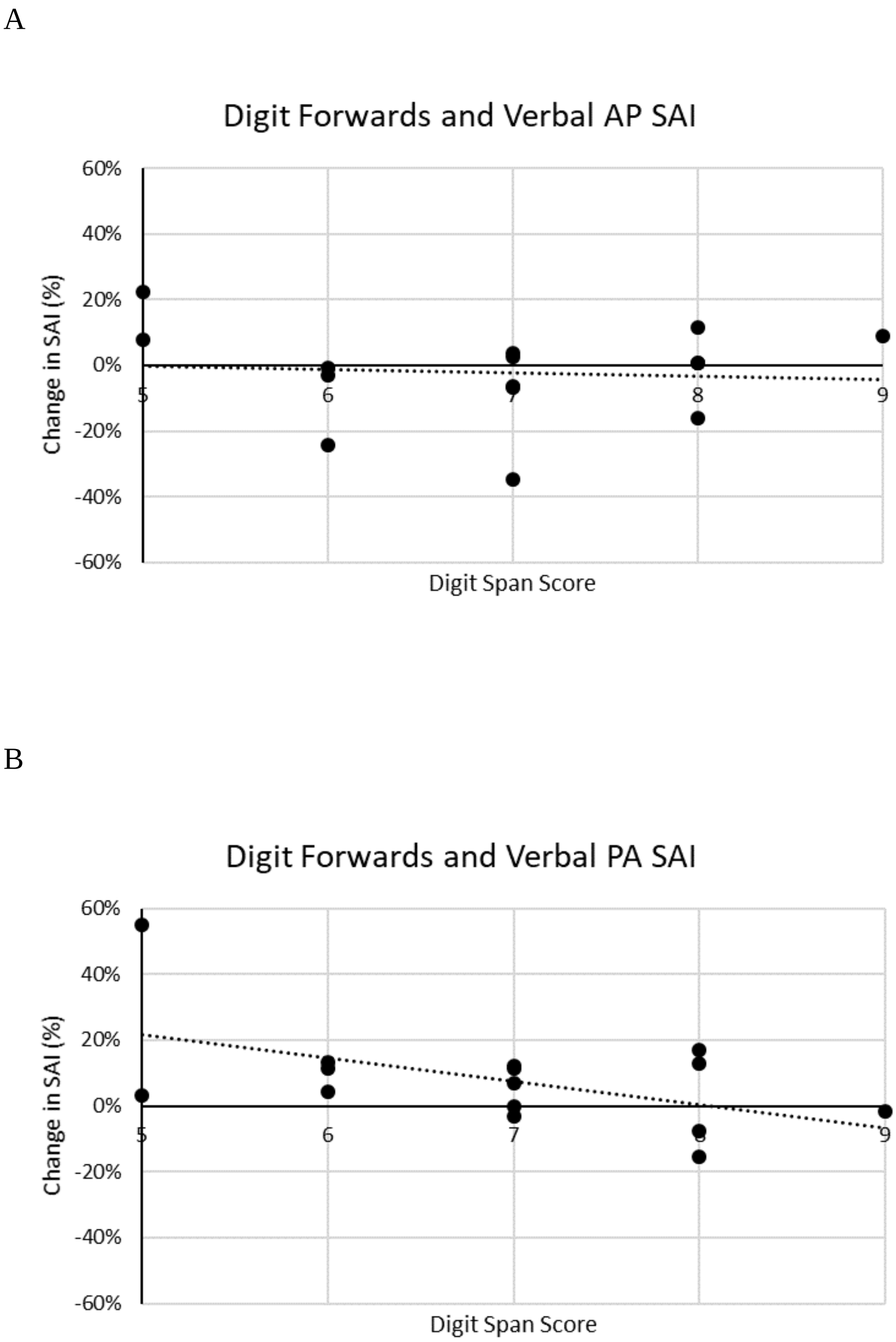
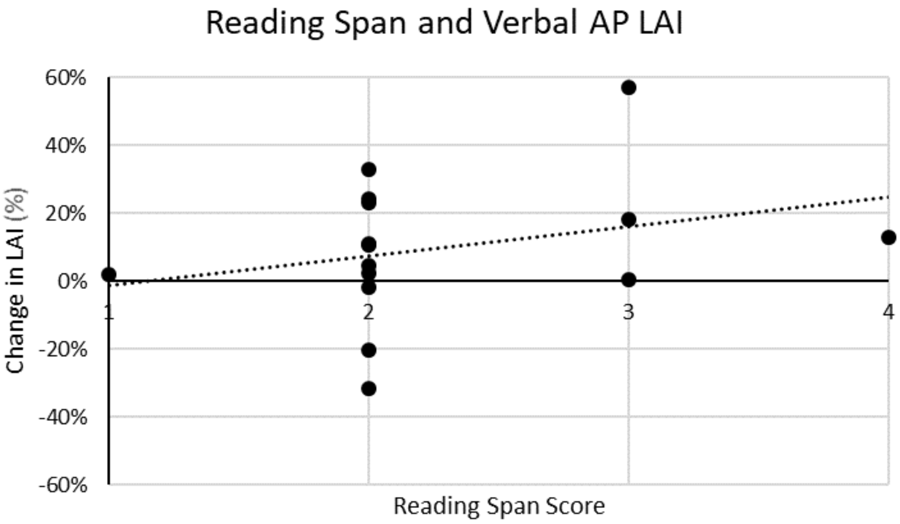


Figure 33 - Relationship between Digit Span Forwards score and the change in both AP (A) and PA (B) LAI within the verbal task

A



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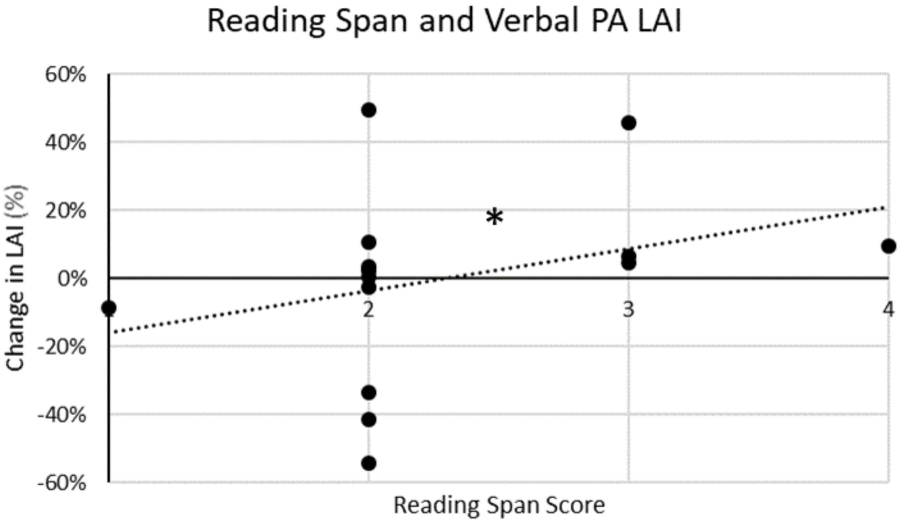

Figure 34 - Relationship between Reading Span score and the change in both AP (A) and PA (B) LAI within the verbal task