The persistent effects of sports-related concussion during adolescence on sensorimotor integration

by

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Author's Declaration

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

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Abstract

A history of concussion increases the risk of subsequent musculoskeletal injury. However, the exact mechanism of the increased risk of injury remains unknown. Persistent alterations in sensorimotor control during periods of high cognitive demand may be responsible for the increased risk of musculoskeletal injuries after concussion diagnosis. The current study used short-latency afferent inhibition (SAI) to investigate persistent differences in sensorimotor circuits in individuals with and without concussion history during a cued response time task involving motor planning and modulation.

Thirty-two individuals who had participated in contact sports for at least three years as adolescents (13-18 years old) were recruited. Fourteen participants had a history of concussion, and eighteen had no history of concussion. SAI was quantified in the first dorsal interosseous muscle (FDI) during a cued finger response task. During the cued response task, participants were cued to a response finger. Cues were either valid (70% of trials) or invalid (30% of trials). To probe distinct sensorimotor circuits SAI was quantified using either posterior-anterior current for 120 μs (PA_{120}) or anterior-posterior current for 30 μs (AP_{30}) during both trial types. The novel finding of this study was that AP_{30} SAI decreased for invalidly cued, compared to validly cued, trials in those with concussion history. In contrast, AP_{30} SAI was not influenced by cue type in the no concussion history group. PA_{120} SAI was similarly reduced during invalidly cued trials across those with and without a concussion history.

These findings suggest that individuals with a history of adolescent concussion have persistent adaptations to sensorimotor integration. The specificity of the adaptation to the sensorimotor circuits recruited by AP_{30} current during invalid trials suggests that those with a concussion history can generally adapt to offset the chronic effects of their concussion except

under periods of high perceptual load. The breakdown of sensorimotor integration in these sensorimotor circuits could compromise motor execution during a period of high perceptual load and explain the increased risk of musculoskeletal injury following concussion recovery.

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List of Abbreviations

ACh - Acetylcholine

AP – Anterior-posterior

CSF – Cerebrospinal fluid

CT – Computerized tomography

cTMS – Controllable pulse parameter transcranial magnetic stimulation

D – Direct

EEG – Electroencephalography

EMG – Electromyography

ERP – Event-related potential

FDI – First dorsal interosseous

fMRI – Functional magnetic resonance imaging

GABA – Gamma-aminobutyric acid

Hx – History

I – Indirect

iTBS – Intermittent theta burst stimulation

M1 – Motor cortex

MEP – Motor evoked potential

MRI – Magnetic resonance imaging

P – Posterior-anterior

PAS – Paired associative stimulation

PPT – Purdue Pegboard test

S1 – Somatosensory cortex

SAI – Short-latency afferent inhibition

SNAP – Sensory nerve action potential

SRC – Sports-related concussion

TBI – Traumatic brain injury

tDCS – Transcranial direct current stimulation

TES – Transcranial electrical stimulation

TMS – Transcranial magnetic stimulation

VPL – Ventral posterior lateral

1.0 Introduction

Sensorimotor integration is the process by which people perceive themselves in their external environment and produce appropriate actions to navigate within that environment. Sensorimotor integration occurs via sensory afferents converging on the motor cortex, influencing the production of motor efferents and resulting in the execution of the appropriate motor actions. However, sensorimotor integration does not occur in isolation. For example, cognitive functions, such as working memory and attention, may shape sensorimotor integration by sending signals to the motor cortex. Therefore, information coming from other brain regions may also shape sensorimotor integration by altering direct and indirect afferent projections to the motor cortex.

Sports-related concussions (SRCs) are diffuse, mild traumatic brain injuries (TBIs) associated with long-term cognitive and motor deficits. On average, it takes less than a month for athletes to "recover" clinically from a concussion and return to play (McCrory et al., 2017). Current return-to-play guidelines allow athletes to return to competition in as little as six days after their suspected concussion (McCrory et al., 2017; Ontario Neurotrauma Foundation, 2022). However, emerging evidence demonstrates underlying cortical abnormalities months to years after a concussive injury. Neurophysiological abnormalities such as motor cortex dysfunction (De Beaumont, Lassonde, et al., 2007), reduced cortical plasticity (Meehan et al., 2017), and impairment of attentional mechanisms (De Beaumont, Brisson, et al., 2007) have been observed long-term in athletes with a history of SRC. Despite chronic neurophysiological differences, most athletes do not score differently from their non-concussed peers on standard cognitive neurocognitive assessments. The persistence of sub-clinical neurocognitive and

neurophysiological abnormalities suggests those with a history of SRC use compensatory behaviours that mask cognitive deficits. Cognitive functions interact with our motor systems to shape motor control and learning processes. Therefore, cognitive deficits inevitably diminish motor control. Recently, a strong relationship between a higher risk of musculoskeletal injury and a history of SRC has been demonstrated (Brooks et al., 2016; Nordström et al., 2014). One hypothesis is that the absence of clinical differences in chronic SRC is because these individuals can recruit compensatory mechanisms, such as increased recruitment of cognitive resources, to offset the chronic neurophysiological effects of the injury. Increased risk of musculoskeletal injury may be explained by periodic moments of high cognitive load where cognitive demand exceeds available resources leading to a breakdown in their compensatory strategy. Neurophysiological damage after concussion may have serious physical consequences when compensatory mechanisms break down and deficits are exposed. Little is known about the neural mechanisms of the motor skill breakdown responsible for the increased musculoskeletal injuries upon return to play.

This study used short-latency afferent inhibition (SAI), a non-invasive brain stimulation methodology, to investigate compensatory changes in sensorimotor integration in individuals with a history of SRC under varying cognitive load. SAI has previously demonstrated sensitivity to explicit, conscious, cognitive control of action as it shapes the subconscious integration of sensory afference into motor commands. Therefore, SAI is an excellent candidate to probe breakdowns of sensorimotor integration in situations of high cognitive demand in those with a history of SRC. Enhanced knowledge of cognitive-sensorimotor interactions is important for understanding the neural underpinnings of concussion, developing rehabilitation programs, and creating safer return to play guidelines.

1.1 The Sensory System, the Motor System and Sensorimotor Integration

Specialized receptors in the peripheral body tissues are responsible for transmitting signals, known as sensory afferents, about our external environment and body state to the cortex. One type of sensory receptor, known as mechanoreceptors, mediate our sense of limb position and movement. Mechanoreceptors are specialized dorsal root ganglion structures that convert mechanical forces to electrical signals that can be transmitted and interpreted by the nervous system. In the case of muscle spindle fibers (muscle length), Golgi tendon organs (muscle force), and cutaneous receptors (skin stretch), large-diameter, heavily myelinated axons quickly transmit afferent information from the receptor to the medulla via the dorsal part of the spinal cord. After decussation at the medulla, the sensory axons synapse on the ventral posterior lateral (VPL) nucleus of the thalamus, which then relays information to the primary somatosensory cortex (S1). S1 is organized somatotopically and contains Brodmann areas 1, 2, 3a and 3b. Muscle, joint and pressure sensations are relayed to areas 2 and 3a. Cutaneous receptors relay touch sensation to areas 1 and 3b. Somatotopic organization of S1 allows for the efficient distribution of relevant information to adjacent cortical structures involved in perception and action, such as the secondary somatosensory cortex, primary motor cortex (M1) and posterior parietal cortex. In particular, the sensory afferents relayed from S1 to M1 provide crucial information to determine the selection of the appropriate motor response and can also shape the plasticity of the motor cortex (Vidoni et al., 2010).

Voluntary motor responses are the result of motor efferents travelling from the brain to the body and limbs. The corticospinal tracts are the motor pathways originating from M1 that control the muscles of the limbs and trunk. The lateral cortical spinal tract is responsible for innervating the distal muscles of the upper limbs. Neurons in M1 project their axons through the

internal capsule and then through the anterior midbrain. Decussation of these axons in the medulla make up the pyramids. Then, the lateral corticospinal tract continues further down along the lateral tract of the spinal cord. The lateral corticospinal tract axons will synapse on motor nuclei in the cervical spine that supply the upper limbs and trunk. M1 has a somatotopic organization that mirrors S1. This somatotopic organization facilitates the study of M1 organization and excitability as non-invasive stimulation can be used to mimic descending output from M1 projecting to the lateral corticospinal tract to the alpha motor neurons innervating the distal muscles of the upper limb.

Sensorimotor integration is the process by which sensory afferents converge on M1 to shape efferent projections and resulting motor commands. Excitatory sensory afferents arrive in M1 from many cortical areas including S1, the premotor cortex and the supplementary motor area (Ziemann, 2020). Sensory gating is an important mechanism for streamlining task-relevant sensory information moving through the cortex and allowing for habituation to task-irrelevant stimuli (Grunwald et al., 2003). Sensory gating is the process by which relevant sensory information is passed on to secondary cortical structures, and irrelevant sensory information is held back. The gating of irrelevant sensory information is crucial in the generation of the appropriate motor commands as it allows us to efficiently process the most important sensory information in detail rather than slowly process all possible sensory information.

Sensory gating is of cortical or thalamocortical origin (Cohen & Starr, 1987) and is mediated by the prefrontal cortex and thalamic connections (Knight et al., 1999). Somatosensory gating, which can be considered an explicit type of sensory gating, involves the facilitation of relevant or irrelevant sensory inputs synapsing on the motor cortex depending on how attentional and working memory resources are voluntarily allocated. A more implicit form of sensory

gating, known as movement-related gating, inhibits re-ascending sensory inputs during voluntary motor movements (Knight et al., 1999). Movement-related gating occurs in movement-relevant muscles. Sensitivity to expected signals arriving from muscles involved in the movement is dampened and sensitivity to unexpected signals indicating the movement is not being executed as planned is heightened (Asmussen et al., 2013). Attention (explicit) can influence or override movement-related gating (implicit) depending on the strategies chosen to allocate cognitive resources to perform a task (Suzuki & Meehan, 2020). When sensory gating systems are damaged, people struggle with attentional demands and become overwhelmed with the constant onslaught of sensory input, resulting in poor decision-making (Knight et al., 1999).

Efficient sensorimotor integration is a crucial component of skilled motor movements. As with sensory gating, mechanisms mediating skilled motor behaviours work in tandem with executive functions to facilitate motor learning and adaptation. Both working memory and attention play important roles in motor learning and skilled motor performance. Explicit, conscious memory uses declarative knowledge (i.e., facts) about a learned motor skill to aid in motor production. Implicit, subconscious memory uses procedural knowledge (i.e., kinetics) about a learned motor skill to produce motor action. Explicit and implicit memory are driven by distinct neural pathways and therefore influence motor production separately. Attention is influenced by both implicit and explicit working memory. Increasing working memory load causes a reduction in the executive control of attention (Hester & Garavan, 2005). Attention is also guided by working memory, both automatically and strategically (Carlisle & Woodman, 2011). Working memory in tandem with specific attentional focus can result in varying degrees of motor skill success. Relying on an external focus of attention (i.e., performance) is more helpful than an internal focus of attention (i.e., body kinetics) in the production of motor skills

(Wulf, 2013). These strong interactions between attention and working memory demonstrate their joint influence over motor skill production and adaptation. More work needs to be done to investigate the neural underpinnings of attention and working memory as they influence motor production. A great way to investigate how attention and working memory influence motor performance is transcranial magnetic stimulation (TMS).

1.2 Transcranial Magnetic Stimulation

TMS is a non-invasive brain stimulation technique that can be used to probe or influence the excitability of neurons in the cortex. TMS induces a short, intense magnetic field in the cortex by passing an electrical current through a magnetic coil. By using a figure-eight-shaped coil, a focal output of the magnetic pulse is produced at the intersection of the two loops that make up the coil. The induced current can alter the membrane potential of a relatively focused set of neurons, resulting in their depolarization and the production of an action potential. Corticospinal neuron excitation results in the production of direct (D) or indirect, transsynaptic (I) waves. D-waves are the result of stimulating pyramidal tract neurons directly (Patton & Amassian, 1954). While electrical stimulation techniques, like transcranial electrical stimulation (TES), directly excite the axon of the pyramidal tract neurons, TMS does not act directly on the pyramidal neuron. Instead, TMS acts on the axons of interneurons that transynaptically excite the pyramidal neuron (CITE). As a result, TMS is associated with transsynaptic I-waves. The earliest I-waves generated by TMS have a latency that is ~1.5ms longer than the D-wave generated by electrical stimulation. The 1.5ms latency corresponds to the latency of action at a single synapse. TMS does not just generate a single I-wave, subsequent I-waves can appear in succession (I_2, I_3, I_4) at periods of ~1.5ms, reflective of an increasing number of synapses between the site of TMS action and the pyramidal neuron. The exact combination of I-waves

generated by a TMS stimulus depends on specific stimulation settings such as current direction and latency (Ziemann, 2020).

When placed over M1 tangentially to the scalp, the induced current can optimally stimulate motor neuron groups and elicit motor evoked potentials (MEPs) in the targeted muscle. The production of MEPs via M1 demonstrates the excitability of the corticospinal neurons. Given the somatotopic organization of M1 and focality of the magnetic field produced by the figure-eight shaped coil, we can use TMS over M1 to investigate the excitability of specific motor representations and the integrity of the motor tracts. This can be accomplished by quantifying the amplitude and latency of the resulting MEP. Preceding the TMS stimulus with some form of conditioning also allows for the assessment of intracortical and intercortical influence over corticospinal output (Hallett, 2007). For example, intracortical interneuron influence over M1 output can be assessed using paired pulses of TMS stimuli. Intercortical communication can be assessed by delivering a TMS stimulus outside of M1 followed by TMS over M1 to elicit an MEP. Paired pulses of TMS use one TMS stimulus to elicit a reference MEP while the second "conditioning" stimulus is used to capture the effect on the intracortical or intercortical neurons. The effect on these neurons is captured by how the amplitude of the reference MEP changes in the presence of the conditioning TMS stimulus. Sensorimotor integration can be assessed by preceding TMS with excitation of a peripheral sensory nerve. Using the same principles as paired pulse TMS, the peripheral stimulus can be considered the conditioning stimulus. Finally, using different TMS assessments under varying behavioural conditions allows one to assess the functional significance of the different traits assessed by the specific type of TMS assessment employed (Hallett, 2007).

Two main current directions are used during TMS: posterior-anterior (PA) current and anterior-posterior (AP) current. Their nomenclature reflects the direction of the current they induce in the brain. PA current is most used in laboratory studies and therefore, is featured most prominently in published literature. PA current evokes the largest recorded MEPs at a lower required stimulation intensity (Day et al., 1989; Hallett, 2007; Hannah & Rothwell, 2017). Previous work suggests that PA current recruits different interneuron groups than AP current. AP current produces MEPs with longer latencies than MEPs produced using PA current (Ni et al., 2011). MEP latency differences are due to PA current recruitment of earlier I waves (I_1, I_2), while AP current preferentially recruits later I waves (I_3, I_4) (Day et al., 1989; Di Lazzaro et al., 2001).

Recent technological advances have created opportunities to change the properties of the TMS stimulus used in an assessment. Current configurations can be described by their specific direction and duration settings. Conventional TMS uses a fixed TMS stimulus duration of ~72-80μs. The fixed duration recruits a mixture of interneuron groups that converge on the M1 output neuron (Sommer & Wurtz, 2008). The mix of interneurons recruited appears to capture several distinct sensorimotor groups (Hannah & Rothwell, 2017). Each group may contribute unique functional elements to skilled motor behaviour. The proposed work will use controllable pulse parameter TMS (cTMS), an innovative form of TMS (D'Ostilio et al., 2016), to better isolate these distinct sensorimotor groups and identify their specific contribution to cognitive motor control.

Recent cTMS studies have investigated four main current configurations: PA_{120}, PA_{30}, AP_{120} and AP_{30} (D'Ostilio et al., 2016; Hannah & Rothwell, 2017). Using these four current configurations has allowed investigation of both PA and AP current directions, combined with

both long and short-duration pulses. Preliminary findings demonstrate that PA_{120} and PA_{30} behave similarly, producing MEPs with almost identical latencies and amplitudes (Hannah & Rothwell, 2017). These findings suggest that conventional PA current duration recruits a single interneuron group. D'Ostilio et al. (2016) demonstrated that AP current pulse duration altered MEP latencies while PA current pulse duration did not. AP_{30} elicits MEPs with significantly longer onset latencies compared to all other pulse types (Hannah & Rothwell, 2017). The longer latency seen using AP_{30} reflects a longer, distinct route through which TMS stimulation influences the corticospinal neurons. These findings also suggest that conventional AP current duration may recruit multiple interneuron groups. Work by Hannah & Rothwell (2017) demonstrated that AP_{30} is the only current configuration that demonstrates changes to SAI when cerebellar excitability was altered using direct current stimulation ($tDCS_{Cb}$). Therefore, AP_{30} current likely has cerebellar connections in its network. The cerebellum plays a role in sensorimotor control and motor learning, suggesting its relationship with the AP_{30} current could be quite meaningful. The cerebellum uses sensory feedback to anticipate and adjust motor executions, as evidenced by poor muscular control exhibited when the cerebellum is damaged (Flament & Hore, 1986). Using the same feedforward mechanisms, the cerebellum contributes to motor learning by enhancing adaptations in body movements. The role of the cerebellum in the neural network of AP_{30} SAI could mean that AP_{30} SAI is crucial for motor correction and adaptations. This relationship needs to be considered when interpretating results.

The recruitment of different interneuron groups makes it crucial to investigate both current directions to assess specific cortical pathways that may otherwise be missed by using only one of the PA or AP currents. This study employed both PA_{120}, and AP_{30} current configurations due to the growing evidence that these two currents recruit functionally distinct

neuron pools. PA_{120} and AP_{30} currents may be sensitive to distinct elements of behaviour, such as motor preparation and movement feedback.

1.3 Short-Latency Afferent Inhibition

SAI involves preceding a TMS-induced MEP with the peripheral electrical stimulation of the corresponding afferent nerve by ~19-24ms. The 19-24ms window yields the maximum effect of the electrical stimulation on the MEP as this window approximates the time it takes for sensory afferents to reach M1 (Tokimura et al., 2000). SAI is cortical in origin with MEPs dampened by the sensory afferents converging on the corticospinal neurons on M1 at the same time as TMS stimulus is delivered (Tokimura et al., 2000). SAI inhibits late-I waves more than early I-waves, particularly when paired with AP current compared to PA current (Ni et al., 2011; Tokimura et al., 2000). The magnitude of SAI depends on the volume of the sensory afferent volley, maxing out once all available peripheral sensory fibers are recruited by the electrical stimulus (Bailey et al., 2016). Mixed median nerve afferent fibers are maximally recruited at approximately 50% of maximum sensory nerve action potential (SNAP), supporting the theory that median nerve evoked SAI beyond 50% of maximum SNAP receives contributions from antidromic motor nerve fibers (Bailey et al., 2016).

SAI is an important component of motor functioning and appears to be sensitive to movement-related gating. SAI is reduced in the task-relevant muscle(s) directly before, and during movement (Asmussen et al., 2013). In contrast, SAI is enhanced in the task-irrelevant neighbouring muscles representation during motor production (Fischer & Orth, 2011). This relationship demonstrates SAI's involvement in motor preparation. It is hypothesized that this movement-related gating promotes desired muscle contractions and suppresses predictable sensory afferents that result from the intended movement to enhance the detection of unexpected

outcomes in surrounding muscles (Suzuki & Meehan, 2020). Further evidence of SAI's involvement in motor functioning is its reduction in populations with sensorimotor deficits, such as Parkinson's disease (Nardone et al., 2013; Sailer et al., 2003).

Pharmacologically, SAI is modulated by elevated levels of gamma-aminobutyric acid (GABA), specifically $GABA_A$ receptors, and acetylcholine (ACh) (Di Lazzaro et al., 2000, 2007). In the presence of $GABA_A$ agonists, like lorazepam, SAI is reduced (Turco et al., 2018), meaning there is less suppression of MEPs induced by the conditioning stimulus. SAI is not modulated by baclofen, a $GABA_B$ agonist, suggesting that SAI is not mediated by $GABA_B$ receptors (Turco et al., 2018). Scopolamine, an ACh antagonist, causes a reduction in SAI (Di Lazzaro et al., 2005; Ziemann et al., 2015). SAI can be used in clinical settings to investigate populations with cognitive deficits. SAI is reduced in Alzheimer's, a disease known for its cholinergic deficits (Di Lazzaro et al., 2005; Nardone et al., 2008). Further, SAI is reduced in populations with mild cognitive impairments (Nardone et al., 2012). These findings suggest SAI could be a marker for cholinergic activity important for memory and other cognitive functions.

Previous work in my lab has used SAI to demonstrate that explicit, conscious, cognitive control of action shapes the subconscious integration of sensory afference into motor commands (Mirdamadi et al., 2017; Suzuki & Meehan, 2018, 2020). Mirdamadi et al. (2017) demonstrated that PA SAI and AP SAI are sensitive to different attentional demands, suggesting they recruit separate interneuron groups. AP SAI, but not PA SAI, is sensitive to perceptual demands, with a decrease in inhibition seen during higher perceptual loads. This finding suggests AP SAI may rely on attentional mechanisms within its neural network and help modulate incoming sensory information converging on M1.

SAI is also sensitive to working memory demands. Suzuki et al. (2018) first demonstrated that both AP SAI and PA SAI were sensitive to verbal working memory load when SAI decreased as verbal working memory load increased across current directions. However, in a more recent study completed in my lab, only PA SAI showed sensitivity to verbal working memory load. PA SAI increased as verbal working memory load increased (Lenizky, 2020). Both studies were conducted with conventional TMS stimulators current durations of 72 or 80μs.

As discussed earlier, current duration likely plays a role in determining the specific interneuron circuits recruited by the TMS stimulus. SAI is sensitive to current duration and produces the greatest inhibition using AP_{30} (Hannah & Rothwell, 2017). Given its sensitivity to cognitive influences, SAI is an excellent candidate to probe sensorimotor changes in people with a concussion history using alternative cognitive strategies to compensate for their injury.

1.4 Concussion Biomechanics and Symptoms

Concussions can be the result of direct head impact or accelerative/decelerative forces that send the head into motion without direct head contact. Both direct and indirect head impacts cause serious neural damage due to the movement of the brain within the skull. The brain is surrounded by a pliant cushioning layer of cerebrospinal fluid (CSF) within the rigid bone of the skull. Unfortunately, during a concussive head impact, the pliant CSF allows the brain to move within the skull, and the brain continues to accelerate even after our head has stopped moving. This acceleration inevitably causes the brain to compress against the skull. The brain compresses against and then rebounds off the skull before accelerating in the opposite direction. Then, the head decelerates, leading to a second compression as the brain collides with the opposite side of the skull. This is known as a “coup contrecoup” injury and causes further shearing of neurons and their axons. The impact of the brain against the skull causes major damage to the neural

tissues and, therefore, the underlying neurons via compression. Rotational forces can also create shearing and stretching strains in the neural tissue, further damaging neurons. Thus, the forces applied to the head and brain during a concussive impact cause global damage to the brain, damaging neurons in multiple cortical areas, not just at the site of contact. The majority of athletes with a SRC present with normal structural brain scans using traditional brain imaging tools such as magnetic resonance imaging (MRI) or computerized tomography (CT), demonstrating that concussive injuries are not localized (Borg et al., 2004; Iverson et al., 2009). Regardless of where on the head, neck, or body a concussive blow is delivered, concussions result in global damage to the neurons in the brain.

It is important to understand that a concussion is a non-localized disorder of neurophysiological damage, yet concussions are still being clinically diagnosed based on symptomology. The most common symptoms of concussion are headache, feeling in a fog, irritability, balance problems, memory problems and drowsiness (McCrory et al., 2017). However, symptoms and symptom timeline vary widely between individuals and a single symptom is not a reliable indicator of concussion. Loss of consciousness associated with a head impact may be the easiest way of guaranteeing a concussion diagnosis, but many concussive head impacts do not result in a loss of consciousness. Given that symptoms are self-reported and highly individualized, concussion diagnoses remain inconsistent.

Surprisingly, most athletes report a resolution of their symptoms and are back in sport less than one month after their concussion diagnosis (McCrory et al., 2017). The current return to play protocols after concussion use sideline pencil and paper or computerized tests administered by athletic therapists or physicians to determine if an athlete is healthy and able to continue sport participation. Sideline tests usually involve a symptom scale, where athletes with high scores

show the most severe symptoms, a cognitive battery and some neuromotor function tests (i.e.: balance). The cognitive battery usually assesses various mental faculties, such as executive functions, processing speed, verbal working memory and reaction time. Despite promising to test important cognitive faculties, the cognitive batteries used in sideline concussion tests are not mentally taxing and have not demonstrated a robust ability to differentiate between those with or without a concussion. Furthermore, if sideline tests are administered more than three days after the initial injury, they become even less sensitive to detecting concussive injuries (McCrory et al., 2017). The lack of differentiation demonstrates that sideline cognitive tests are not sensitive enough to detect subtle cognitive changes in concussed athletes compared to their healthy teammates. The lack of sensitivity could be caused by using cognitive tests that are too easy and therefore allow young athletes to compensate for their injuries via other brain mechanisms and perform well enough to pass undetected.

The inconsistency of symptom presentation, lack of clear structural damage and difficulty diagnosing concussion demonstrate a concussive injury's complex and diffuse nature. The lack of specific structural damage indicates that functional damage is the reason for sporadic symptom presentation after a concussion. The insensitivity of current return to play tests to persistent symptoms contributes to the often too-early return to sport and subsequent masking of the long-term effects of concussion. Functional changes after concussion continue to be investigated using instruments such as TMS and electroencephalography (EEG) to provide more sensitive measures to a concussive brain injury.

1.5 Neurophysiological Changes After Concussion

Both EEG and TMS studies demonstrate functional differences in those with a history of SRC compared to those without, despite being asymptomatic and well beyond the initial time of

injury. Athletes with a history of concussion have persistent changes in M1 function. The most common persistent alterations occur in measures of intracortical inhibition, such as a prolonged cortical silent period (De Beaumont et al., 2009; De Beaumont, Lassonde, et al., 2007). Athletes with a history of concussion also show reduced plasticity in M1 after intermittent theta-burst stimulation (iTBS) compared to healthy individuals (Meehan et al., 2017). Further, M1 shows reduced plasticity after paired associative stimulus (PAS) protocol, resulting in reduced motor learning due to increased $GABA_B$-mediated inhibition (De Beaumont et al., 2012). Reduced M1 plasticity impaired implicit motor learning on a serial reaction time task compared to their non-concussed peers. These findings suggest individuals with a history of concussion maintain M1 deficits years after their concussion diagnosis. Impaired motor learning and impaired motor control are dangerous for athletes to have upon return to play, as sports participation relies heavily on both skills.

Beyond persistent changes in M1, athletes with a history of concussion also demonstrate altered neurophysiological markers of cognition. The somatosensory-evoked N2, P3a and P3b event-related potentials (ERP) using EEG all suffer decreased amplitudes in asymptomatic athletes with a concussion history during an oddball task (Broglio et al., 2009; De Beaumont et al., 2009; De Beaumont, Brisson, et al., 2007). The N2 ERP is known to reflect attention to a stimulus and response inhibition. The P3a and P3b components of the P3 ERP occur just after the N2 ERP. The P3a component is related to attentional resource allocation to novel stimuli. The P3b component is related to attentional resource allocation for memory processing. Overall, asymptomatic athletes with a history of concussion demonstrate neurophysiological deficits in their ability to focus their attentional resources and process information. Attentional deficits could explain some common concussion symptoms, such as feeling in a fog or having memory

difficulties. Persistent alterations in these three ERPs suggest altered mechanisms for coping with incoming sensory afferents related to executive functions.

Both behavioural and physiological correlates of sensory gating also demonstrate differences in those with and without a history of concussion. Healthy individuals demonstrate tactile-evoked N70 ERPs that are modulated to reflect the tactile stimuli's task relevance. In comparison, athletes with a history of concussion do not show significant modulation of the N70 ERP as the stimuli's relevance to the task changes (Adams et al., 2020). Behaviourally, this manifests as less accuracy on tasks involving distractor stimuli (Adams et al., 2020). These findings suggest that individuals with a history of concussion find it difficult to focus on the stimuli in their environment that are most relevant to the task at hand. Their relevancy-based sensory gating is impaired. When incoming sensory afferents are unable to be sorted based on task-relevancy, somatosensory cortical networks become overwhelmed. Rather than passing along specific information to the next cortical area, the S1 relays most, if not all, incoming sensory information. Sensorimotor integration becomes more difficult without proper sensory gating as too many sensory axons converge on M1 simultaneously, leading to slower and poorer motor execution.

Individuals with a history of concussion demonstrate neurophysiological deficits in attentional resource allocation to incoming sensory information and M1 functioning, suggesting impaired sensorimotor integration. SAI may be an excellent way to probe altered sensory and motor functioning in those with a history of concussion that may not otherwise be detected by current sideline concussion measures.

Past work investigating SAI in athletes with a concussion history has demonstrated no significant differences between those with a concussion history and those without (Davidson &

Tremblay, 2016; Tremblay et al., 2011). The lack of significant differences seen between those with a history of concussion and those without could be due to several limitations. The aforementioned studies were conducted at rest, meaning that no behavioural component was being manipulated while SAI was assessed. At rest, individuals are not being taxed cognitively, as there is relatively little effort required to sit still. Compensatory mechanisms used by individuals with a history of concussion likely do not break down in situations of low cognitive effort, as demonstrated by their normative scores on sideline concussion tests. Therefore, when studying individuals at rest, it becomes far less likely that any significant differences would be detected between groups. Past work investigating SAI in athletes with a history of concussion was also performed using only PA current. As mentioned previously, PA SAI and AP SAI are sensitive to different cognitive influences and represent distinct interneuron networks. In the same vein, manipulation of TMS current duration has also shown the recruitment of distinct interneuron networks. The current duration has always been fixed while investigating SAI in athletes with a history of concussion. Therefore, using only PA current TMS and fixed current duration may have masked sensorimotor deficits by variable recruitment of interneuron networks across individuals.

Using SAI as a tool to investigate sensorimotor integration during a cognitive-motor task in individuals with a history of concussion could provide significant insights into the sensory and motor deficits exposed in this population in previous neurophysiological studies.

1.6 Slowed Processing Speed After Concussion

Cued response time tasks are used to investigate processing speed and efficiency, motor response times and motor response inhibition. Cued tasks are designed to prime motor responses before target stimulus onset. The priming of a motor response allows for quicker response times.

Simple (non-cued) response time tasks have longer associated response times than cued response time tasks. In a simple response time task, upon presentation of a target stimulus, participants must first process the target visually, begin higher-level processing in the adjacent cortices and use the visual information to inform their motor plan selection. However, a cued response time task eliminates the need to spend time selecting a motor response, as the appropriate motor response has already been primed thanks to the cue presentation right before the target onset. The elimination of motor response selection subsequently shaves off hundreds of milliseconds in response time. However, when a cue is misleading and does not reflect the target presented, response times and errors increase (Randall & Smith, 2011). After processing the target and realizing the primed motor response is incorrect, alternative motor responses must then be considered, from which one must be chosen and then executed. Motor plan adjustments account for the increased reaction times. The increased errors may be explained by accidental execution of the cue-primed motor response despite recognition of a different target, demonstrating a lack of motor inhibition. Increased errors may also be explained by the inappropriate selection of alternative motor plans after recognizing the invalidly cued target.

Individuals with a history of concussion have demonstrated slower response times in both simple and cued response time tasks compared to their non-concussed peers (Eckner et al., 2014; Sosnoff et al., 2007; Tommerdahl et al., 2020; Warden et al., 2001). Slowed response times suggest impaired processing speed and attentional mechanisms. Previous work using cued response time tasks in individuals with a history of concussion have only looked at response time as a behavioural measure of processing speed and have not addressed potential physiological changes in sensorimotor integration. Using a cued response time task combined with SAI could

provide a tool sensitive enough to detect underlying neurophysiological differences in sensorimotor integration between individuals with a history of concussion and those without.

1.7 Concussion and Future Musculoskeletal Injury

The dangers of the sensory and motor deficits demonstrated after concussion have real-world consequences. A growing body of evidence indicates that athletes have an increased risk of musculoskeletal injury after a concussion diagnosis. The relationship between concussion history and subsequent risk of lower extremity musculoskeletal injury has been established in professional and collegiate-level athletes (Brooks et al., 2016; Nordström et al., 2014) and high school athletes (Lynall et al., 2017). The strong relationship between concussion and increased risk of musculoskeletal injury from their concussive injury suggests a persistent underlying neurophysiological breakdown despite achieving clinical recovery.

Sensorimotor integration deficits may be at the root of the increased musculoskeletal injuries post-concussion. During a game, athletes must constantly process and navigate various gameplay scenarios in real-time. By using cues from their external environment, they must react appropriately to the game happening around them to participate and excel. Processing external environmental cues involves receiving vast amounts of sensory inputs to S1. To respond appropriately to the gameplay, athletes must then integrate relevant sensory information and input from higher-order cognitive functions as they synapse on M1. When sensorimotor integration is efficient, as seen in healthy individuals, athletes make rapid motor choices to perform as expected. After a concussion, slowed and incomplete processing of information by concussed athletes could leave them open to riskier contact situations as they attempt to execute a movement. The difference between taking a hit into the boards from an opponent and narrowly avoiding the blow comes down to milliseconds. When sensorimotor integration is inefficient,

motor performances become delayed. Without task-relevant sensory gating occurring, an influx of sensory afferents converges onto M1. Information being sent from S1 to M1 may become diluted and difficult to sort through, resulting in delayed or erroneous motor execution. Therefore, if the production of a motor response is even slightly delayed, athletes are more likely to end up in riskier situations and receive a musculoskeletal injury. As cognitive resources decline with age, those with a history of concussion will be forced to compensate for their functional damage more frequently. As compensation increases there will be a greater risk of sensorimotor integration breakdown and a greater risk of musculoskeletal injury.

If cognitive resources decline with age, we must also concern ourselves with the long-term brain health of individuals with a history of concussion. The neurophysiological differences reported in these individuals measured using TMS and EEG highlight important differences in brain health. And while athletes with a history of concussion do not seem to score differently than their non-concussed peers on standard return-to-play pencil and paper tests, it's concerning that their brain function does not return to normal. The accelerated-aging model (Broglio et al., 2012) outlines the potential long-term consequences of concussions, hypothesizing that those with a history of concussion will not experience normal aging. Individuals with a history of concussion will likely experience earlier and/or accelerated cognitive decline due to compensatory mechanism breakdown. Neurophysiological dysfunction after concussion that passes clinically undetected as a young adult will eventually be exposed as cognitive load becomes more difficult to manage as a process of aging. As they age, they will no longer be able to rely on other cortical circuits to compensate for the concussive damage. This model relies on the considerable data pointing out that concussions are not a transient injury, as well as more recent literature addressing the increased rates of cognitive deficits and Alzheimer's among

retired, aging athletes (De Beaumont et al., 2009; Guskiewicz et al., 2005). The possible long-term effects of concussions could be catastrophic. To begin designing rehabilitation strategies to help alleviate cognitive deficits in those with a history of concussion, we must try to understand the mechanisms responsible for the chronic neurophysiological changes.

By using SAI to investigate sensorimotor integration during situations involving high cognitive effort, we hope to shed light on the compensatory mechanisms at risk of breaking down for those with a history of concussion. This study used SAI to address the underlying mechanisms responsible for the increased risk of musculoskeletal injury seen after a concussion diagnosis. This study also added to our understanding of TMS current configurations and the neural networks they recruit, as this will be the first study to assess PA_{120} and AP_{30} SAI during a cued response time task in those with and without a history of concussion. Regardless of between group outcomes, we will be able to add to the literature investigating the sensitivity of these sensorimotor integration circuits to cognitive load and motor plan adjustments.

2.0 Aims & Hypotheses

This study aimed to assess persistent adaptations in sensorimotor integration following exposure to sport-related concussion (SRC). Specifically, we investigated whether young adults with a history of sport-related concussion during adolescence demonstrate differences in sensorimotor integration compared to those who played similar sports but did not have a history of concussion.

Aim 1: Investigate sensorimotor integration differences using SAI in individuals with a history of SRC compared to those without during trials that involve sensory-guided action

Hypothesis 1A: PA_{120} SAI in FDI will be greater in individuals with a history of SRC compared to those without just prior to an impending movement involving the FDI.

Hypothesis 1B: AP_{30} SAI in FDI will be similar for individuals with a history of SRC and those without just prior to an impending movement involving the FDI.

Aim 2: Investigate sensorimotor integration differences using SAI in individuals with a history of SRC compared to those without during trials with an invalid cue requiring a motor plan adaptation away from the index finger response.

Hypothesis 2A: PA_{120} SAI will increase from valid to invalid trials for those without a history of SRC, indicating efficient updating of the motor plan. In contrast, PA_{120} will show little to no change for those with a history of SRC from valid to invalid trials for those with a history of SRC.

Hypothesis 2B: AP_{30} SAI in FDI in individuals without a history of SRC will be enhanced on valid to invalid trails as the motor plan is adapted. In contrast, AP_{30} will show little to no change for those with a history of SRC from valid to invalid trials for those with a history of SRC.

3.0 Methods

3.1 Participants

Thirty-two, healthy adults (18-28 years old) who played collision or contact sport for at least three years during middle to late adolescence (13-18 years old) were recruited for this study. Examples of contact sports include hockey, football, rugby, basketball, lacrosse, and soccer. The presence or absence of a sports-related concussion history will be used to group individuals. The concussion group (n=14) consisted of participants with a self-reported, physician-diagnosed history of SRC during adolescence and were asymptomatic. All concussions were chronic as they had occurred at least 6 months prior to participation in the study. Participants with no history of sports-related concussion were used as healthy age-matched controls (n=18). Participants were excluded if they had a history of any other neurological injury/disease or had any contraindications to TMS. Only a subset of participants in the no concussion history group (n=12) and the concussion history group (n=10) were included for the AP_{30} current analyses, as we could not achieve a 1mV MEP threshold using AP_{30} current on 33% of the participants in the no history group and 29% of participants in the concussion history group. One participant had to be excluded based on their response times and accuracy on the cued response time task. They had slow and similar reaction times, as well as consistent accuracy, across both trial types suggesting they were not paying attention to the cue and were simply responding to the target.

3.2 Experimental Procedure

The study consisted of a single, 2.5 to 3-hour session in the lab. Before participants came to campus, an online meeting was scheduled using a secure platform (i.e., Microsoft Teams,

Cisco Webex). This meeting involved the administration of all baseline questionnaires that did not require in-person completion including information about participants' general characteristics and sports history. Participants were also screened for concussion history and any contraindications to TMS. All participants provided written, informed consent.

Next, a laboratory session was scheduled. Upon arrival at the lab, participants were screened for concussion symptoms using the ImPACT Post Concussion Symptom Scale. Following concussion screening, participants completed a baseline cognitive battery to assess their cognitive functioning. Once the cognitive battery was completed, TMS measures began. First, the motor cortical hotspot for the first dorsal interosseous muscle (FDI) was determined. Next, motor threshold, the TMS stimulator intensity needed to elicit an MEP of 1mV during slight FDI contraction was determined. TMS was administered while participants complete a cued reaction time task. Participants completed the cued reaction time task twice, once for each TMS current configuration (PA_{120}, AP_{30}). 30 TMS stimulations paired 50% of the time with peripheral nerve stimulation were delivered before and after completion of the cued response time task with each current configuration (PA_{120}, AP_{30}) as baseline SAI measures. The order of the current configuration was randomized between participants.

Throughout the trials, participants were asked to maintain minimal contraction of FDI, typically between 0.1 to 0.3 mV peak to peak. There were 400 total trials, split into 200 trials for each current configuration (Table 1). The 200 trials were split into 20 blocks of 10 trials. The order of PA_{120} and AP_{30} current was randomized between participants. Conditioned and unconditioned trials, as well as valid and invalid trials, were randomized throughout the 200 trials. The order of trials within each block were pseudorandomized but were consistent across each 200-trial set.

Table 1 - Breakdown of trials for PA_{120} and AP_{30} current

PA_{120} (200 trials)							
Unconditioned (100 trials)				Conditioned (100 trials)			
Valid (70 trials)		Invalid (30 trials)		Valid (70 trials)		Invalid (30 trials)	
1	2,3,4	1	2,3,4	1	2,3,4	1	2,3,4
25 trials	15 trials each	15 trials	5 trials each	25 trials	15 trials each	15 trials	5 trials each

AP_{30} (200 trials)							
Unconditioned (100 trials)				Conditioned (100 trials)			
Valid (70 trials)		Invalid (30 trials)		Valid (70 trials)		Invalid (30 trials)	
1	2,3,4	1	2,3,4	1	2,3,4	1	2,3,4
25 trials	15 trials each	15 trials	5 trials each	25 trials	15 trials each	15 trials	5 trials each

The four digits of the right hand are referred to as 1 (Index), 2 (Middle), 3 (Ring) and 4 (Little), respectively.

3.3 Baseline Cognitive Battery

The baseline cognitive battery was used to assess higher-level cognitive functioning, including working memory, attention, and reaction time. First, the Trail Making Test (Parts A & B) were administered using pencil & paper to measure psychomotor speed and executive functions. Next, the Purdue Pegboard Test was administered as part of a dual-task paradigm. Participants completed the assembly portion of the Purdue Pegboard Test (PPT) to assess neuropsychological deficits and manual dexterity. The assembly portion required participants to build and secure sets of pins, washers, and collars into pegboard holes as quickly as possible in 1 minute. Participants were also instructed to remember a set of letters while they completed the assembly portion of the task. The letter sets were either 2 letters (low load) or 6 letters (high load). Participants were asked to remember the letters as their primary focus while they completed the assembly portion of the PPT. Once finished, participants were prompted to tell the study team member as many of the letters as they could remember from the original set of letters. The PPT was administered as dual-task to assess how higher-order cognitive influences may affect motor outputs and ultimately reflect more closely the design of the TMS task. Finally, the NIH Toolbox Cognitive Battery, a computer-based task, was administered to measure attention, processing speed and working memory.

3.4 Cued Reaction Time Task

The cued reaction time task was used to investigate sensorimotor integration and motor plan changes. Participants were seated with their chin placed in a chin rest in front of a computer screen. Participants' right index, middle, ring and pinky fingers were used to respond on adjacent response keys on a keypad. Each response key corresponded to a distinct colour. The colours were red, yellow, green and blue across the keypad from left to right. Before the onset of the

trials, instructions about the task appeared on the screen. Trials began with a blank screen for 500ms, followed by the appearance of four circles for 500ms (cue). There was one circle in each of the North, South, East, and West locations on the screen. Each of the four circles was one of the four colour responses on the keypad (red, yellow, green, blue). After 500ms, the four circles disappeared from the screen, and a single, coloured circle (response probe) appeared at the centre of the screen for 1000ms. Participants were instructed to respond as quickly and accurately as possible to the response probe by pressing the corresponding key on the keypad. In 70% of trials, the circle appearing in the North (cue) was the same colour as the response probe: known as a Valid trial. On the other 30% of trials, one of the three circles in the West, East or South were the same colour as the response probe: known as an Invalid trial. Participants were told about the 70:30 split between valid and invalid trials before beginning the task and were instructed to prepare accordingly knowing this information. A 1500ms intertrial interval followed the participant's response (Figure 1).

Response time was defined as the time between response target onset and the participant response. Errors were defined as trials where the participant pressed the incorrect color button or trials where the participant failed to respond within 2000ms of the response target presentation. Accuracy was defined as the number of correct responses over the total number of trials.

3.5 Transcranial Magnetic Stimulation (TMS)

MEPs were elicited by TMS 200-275ms after the response presentation in the cued reaction time task. MEPs were recorded using LabChart 8 software in conjunction with a Quad BioAmp and PowerLab 4/26 acquisition system (AD Instruments, Colorado Springs, Colorado,

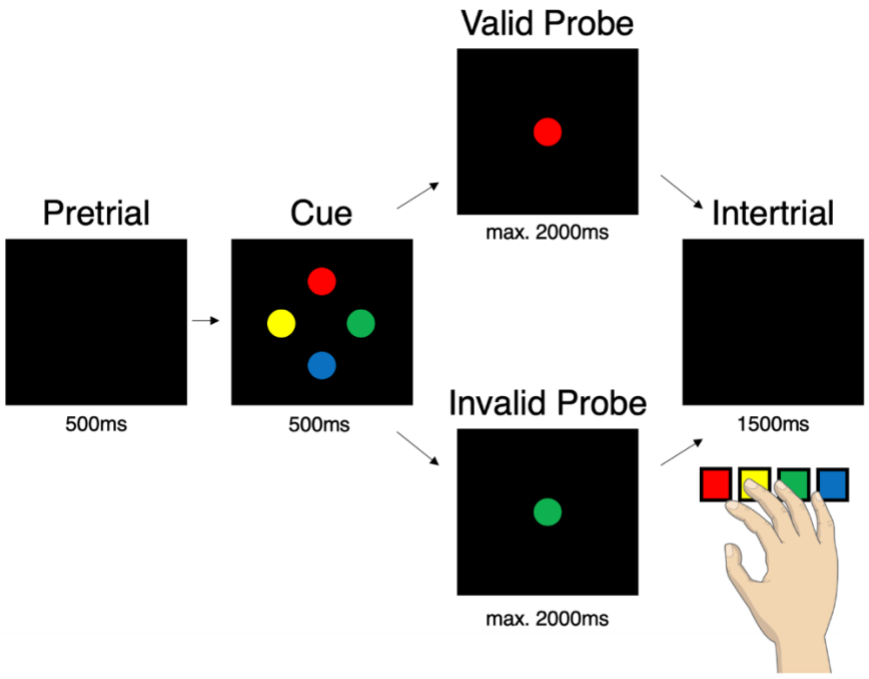


Figure 1 - Overview of the cued response time task.

USA). Surface electromyography (EMG) electrodes (Ag-AgCl) were placed over FDI using a tendon-belly montage. Surface EMG recording was triggered using a 5V TTL pulse with an epoch of -0.3 to 0.5s. During acquisition, data was amplified (x1000), digitized (x4000 Hz) and filtered (bandpass filtered 5-1000 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.

TMS was delivered using a controllable pulse parameter TMS stimulator (cTMS; Rogue Research, Montreal, Québec, Canada). Participants were seated with their arms bent and supported on a desk in front of them. The TMS coil was oriented tangentially to the scalp with the handle positioned 45° posterior to the midline. The same positioning was used for all combinations of posterior-anterior (PA_{120}) and anterior-posterior (AP_{30}) stimulation. The current direction was determined by using two distinct coils, with the only difference between the two coils being the direction of the current moving through the coil. The stimulus duration was set using the stimulator's onboard control software. For all current directions, the M-ratio was set to 0.2.

The FDI motor cortical hotspot was defined as the scalp position eliciting the most consistent response following PA_{120} stimulation. The coil's location and trajectory 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. The intensity required to elicit a MEP of ~1mV (in the absence of peripheral stimulation) was independently defined for PA_{120} and AP_{30} using the ML-PEST method (Silbert et al., 2013).

3.6 Short-Latency Afferent Inhibition (SAI)

SAI consists of preceding a TMS-induced MEP with the corresponding peripheral afferent nerve's electrical stimulation (Tokimura et al., 2000). Electrical stimulation was delivered using an DS7A constant current high voltage stimulator (Digitimer, North America LLC, Fort Lauderdale, Florida, USA). Stimulation was applied in a constant current square wave pulse with a duration of 0.2 ms, cathode proximal (Mirdamadi et al., 2017) over the median nerve at the right wrist. The peripheral electrical stimulus was set to an intensity to achieve a slight thumb twitch of 0.2mV (Abbruzzese et al., 2001). There was no peripheral electrical stimulus for the unconditioned trials, and on conditioned trials, the electrical stimulation of the median nerve preceded TMS stimulation by 21 ms. MEPs recorded during the conditioned trials were compared with MEPs elicited during the unconditioned trials. The amount of SAI was reported as a percentage of the unconditioned MEP.

$$SAI = \frac{Conditioned\ MEP\ Amplitude}{Unconditioned\ MEP\ Amplitude}\ x\ 100\%$$

3.7 Data Analysis

Statistical analyses were conducted using the R environment for statistical computing (version 4.2.1) and the following packages: "rstatix", "tidyverse", “car”, “emmeans”, “sjstats”, “lme4” and “lmerTest”. Before running any statistical tests, all data sets were tested for homogeneity of variance using Levene’s test and assumptions of normality using the Shapiro-Wilks test.

Separate (PA_{120}, AP_{30}) two-way Group (Concussion Hx, No Concussion Hx) by Trial Type (Valid, Invalid) mixed measures ANOVAs were conducted to assess response time and accuracy during the cued response task. Significant interactions were decomposed using pairwise

comparisons or simple main effects. Bonferroni corrections for multiple comparisons were employed where appropriate.

To address hypotheses 1A and 1B, changes in SAI between groups during valid index trials were assessed using two separate (PA_{120}, AP_{30}) independent samples t-test. To address hypotheses 2A and 2B, separate (PA_{120}, AP_{30}) two-way Group (Concussion Hx, No Hx) by Trial Type (Valid, Invalid) mixed measures ANOVAs were performed to assess changes in SAI during the cued response task. Significant interactions were decomposed using pairwise comparisons or simple main effects. Bonferroni corrections for multiple comparisons were employed where appropriate.

Two separate (PA_{120}, AP_{30}) linear mixed models using one categorical (Trial Type) and one continuous variable (number of concussions) were conducted to see if number of concussions was able to predict SAI values depending on Trial Type (Valid, Invalid).

Two three-way mixed measures ANOVA (PA_{120}, AP_{30}) were conducted to see if biological Sex (Female, Male) influenced SAI during the cued response task across Group (Concussion Hx, No Hx) and Trial Type (Valid, Invalid). Significant interactions were decomposed using pairwise comparisons or simple main effects. Bonferroni corrections for multiple comparisons were employed where appropriate.

4.0 Results

4.1 Participant Characteristics

Table 2 shows the means and standard deviations for general participant characteristics in the Concussion History group and the No History group.

4.2 Baseline Cognitive Tests

Independent samples t-tests or Mann-Whitney U-tests (if data were non-parametric) were run for all baseline tests for the NIH Toolbox, Trail Making Test A and B, and the Purdue Pegboard Task. The Mann-Whitney U-test investigating differences between Groups (Concussion Hx, No Hx) on the NIH Toolbox Card Sorting task, a measure of cognitive flexibility, was significant [W=66.5, p=0.0245, effsize=-0.321]. The concussion history group [*mean*±*SD*, 81.4±25.0] had significantly lower scores than the no history group [88.6±19.7] on a measure of cognitive flexibility.

All other statistical tests did not reveal any significant differences between the Concussion Hx and No Hx groups for any of the baseline measures (Table 3).

4.3 Cued Reaction Time Task Performance

A two-way mixed measures ANOVA was run to assess the effect of Trial Type (Valid Index, Invalid Non-Index) and Group (Concussion Hx, No Hx) on response time (RT). The ANOVA revealed a significant main effect of Trial Type [$F_{1,30}$=190.97, p=1.52x10^{-14}, η_p^2=0.864]. Both the simple main effect of Group [$F_{1,30}$=0.834, p=0.368, η_p^2=0.027] and Group by Trial Type interaction were not significant [$F_{1,30}$=0.053, p=0.820, η_p^2=0.002].

Table 2 - Summary of participant characteristics for Concussion History group and No History group

	Concussion Hx	**No Hx**
n	14	18
Age (years)*	22.3 ± 2.3	22.4 ± 2.4
Sex	9M, 5F	6M, 12F
Years of Contact Sport*	5.1 ± 1.2	5.4 ± 1.1
Number of Concussions*	2.0 ± 1.0	N/A

**Mean ± SD*

Table 3 – Summary of baseline measures compared across the Concussion History and No History groups with relevant statistics.

Baseline Measure	***p*-value**	**Effect Size**
Trail Making Test A	0.562	W = 0.106 (small)
Trail Making Test B	0.223	W = 0.219 (small)
NIH Toolbox: Attention	0.251	W = 0.207 (small)
NIH Toolbox: Sorting Task	0.0245*	W = -0.321 (small)
NIH Toolbox: Processing Speed	0.463	W = 0.133 (small)
Purdue Pegboard Test: Working Memory & Manual Dexterity (2 letters)	0.827	Cohen's d = -0.0786 (negligible)
Purdue Pegboard Test: Working Memory & Manual Dexterity (6 letters)	0.703	W = 0.0707 (small)

W = Wilcoxon effect size

RT was significantly increased for invalidly cued trials [*mean*±*SD*, Concussion Hx=0.667±0.077, No Hx=0.635±0.099] compared to validly cued trials [Concussion Hx=0.500±0.075, No Hx=0.473±0.123] regardless of concussion history (Figure 2).

The Shapiro-Wilk test was significant in the No Hx group data [W=0.751, p=0.00034] meaning the data violated normality. A non-parametric mixed measures ANOVA was run using Aligned Rank Transform to assess the effect of Trial Type (Valid, Invalid) and Group (Concussion Hx, No Hx) on accuracy. The ARTool (Wobbrock et al., 2011) ANOVA revealed a significant main effect of Trial Type [F=22.8, p=0.000044, η_p^2=0.432]. The main effect of Group [F=0.0267, p=0.745, η_p^2=0.000891] and the interaction of Trial Type by Group [F=0.834, p=0.368, η_p^2=0.0270] were not significant. Accuracy was significantly reduced for invalidly cued trials [Concussion Hx=93.8±3.94, No Hx=92.7±5.23] compared to validly cued trials [Concussion Hx=96.4±2.53, No Hx=97.2±2.57] regardless of concussion history (Figure 3).

4.4 Short-Latency Afferent Inhibition (SAI) – Cued Response Time Task

Table 4 in Appendix A lists the individual thresholds for each participant as a percentage of the maximum stimulator output. The mean stimulation intensities required to elicit an MEP of 1 mV using PA_{120} were 28.8±5.60 in the concussion history group and 30.3±7.12 in the no history group. The mean stimulation intensities required to elicit an MEP of 1 mV using AP_{30} were 76.5±7.70 in the concussion history group and 76.7±14.4 in the no history group.

A two-way mixed measures ANOVA was run to assess the effect of Current (PA_{120}, AP_{30}) and Group (Concussion Hx, No Hx) on PA_{120} SAI at rest. The ANOVA revealed a significant main effect of Current [F=728.5, p=3.31×10^{-17}, η_p^2=0.973]. Neither, the main effect

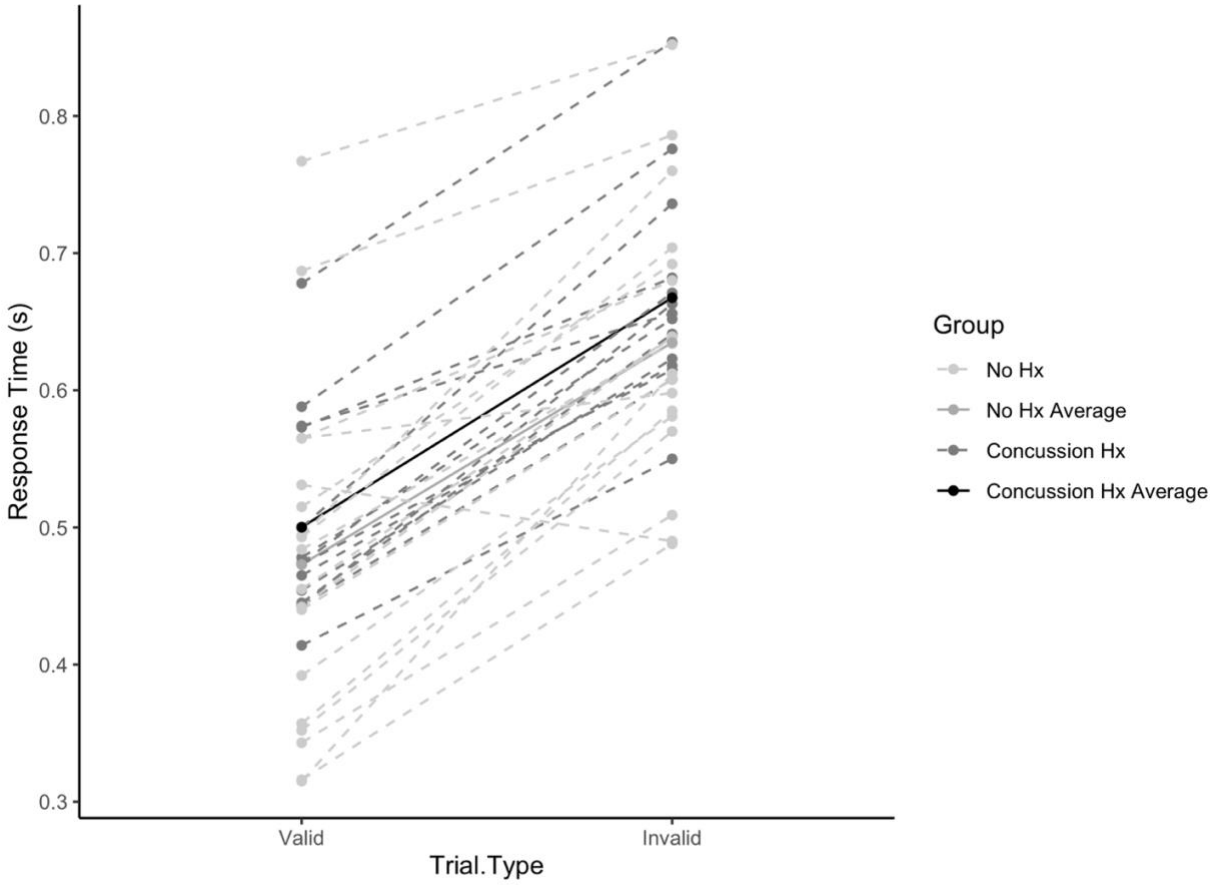


Figure 2 - Individual subject response times during Valid and Invalid trials in both the Concussion Hx and No Hx groups.

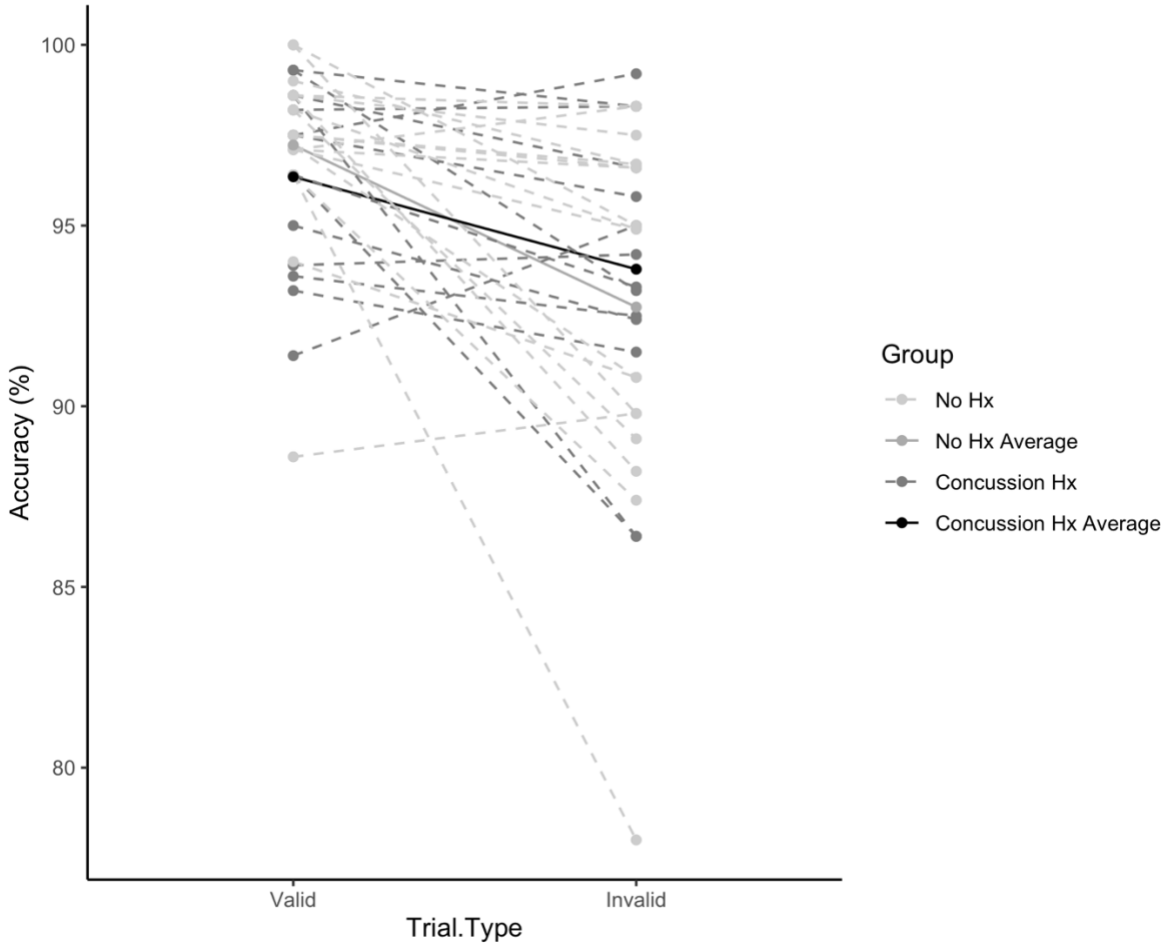


Figure 3 - Individual subject accuracy during Valid and Invalid trials in both the Concussion Hx and No Hx groups.

of Group [F=0.015, p=0.902, η_p^2=0.000773] or the interaction of Current by Group [F=0.466, p=0.503, η_p^2=0.0230] were significant. PA_{120} current [Concussion Hx=28.9±5.81, No Hx=30.2±6.92] elicited 1mV MEPs at a significantly lower threshold than AP_{30} current [Concussion Hx=77.5±7.25, No Hx=75.8±14.1], regardless of concussion history.

4.4.1 SAI – Rest

A two-way mixed measures ANOVA was run to assess the effect of Time (Pre, Post) and Group (Concussion Hx, No Hx) on PA_{120} SAI at rest. The ANOVA revealed no significant interaction of Time by Group [$F_{1,22}$=0.219, p= 0.644, η_p^2= 0.010], main effect of Group [$F_{1,22}$=0.630, p=0.436, η_p^2= 0.028] or main effect of Time [$F_{1,22}$=0.047, p=0.831, η_p^2= 0.002]. Therefore, there was no difference in PA_{120} SAI at rest between the concussion history group [Pre=57.7±24.2, Post=58.7±21.5] and the no history group [Pre=67.0±29.9, Post=64.1±21.9] regardless of time (Figure 4).

A two-way mixed measures ANOVA was run to assess the effect of Time (Pre, Post) and Group (Concussion Hx, No Hx) on AP_{30} SAI at rest. The interaction of Group by Time [$F_{1,13}$=0.458, p=0.510, η_p^2= 0.034], the main effect of Group [$F_{1,13}$=0.044, p=0.838, η_p^2= 0.003] and the main effect of Time [$F_{1,13}$=0.026, p=0.874, η_p^2=0.002] were not significant. Therefore, there was no difference in AP_{30} SAI at rest between the concussion history group [Pre=45.5±18.7, Post=49.6±26.4] and the no history group [Pre=50.9±22.5, Post=48.4.1±17.8] regardless of time (Figure 5).

4.4.2 SAI During the Cued Response Time Task

The Shapiro-Wilk test was significant in the Concussion Hx group data [W=0.859, p=0.0298] meaning the data violated normality. A Mann-Whitney U-test was run to determine if

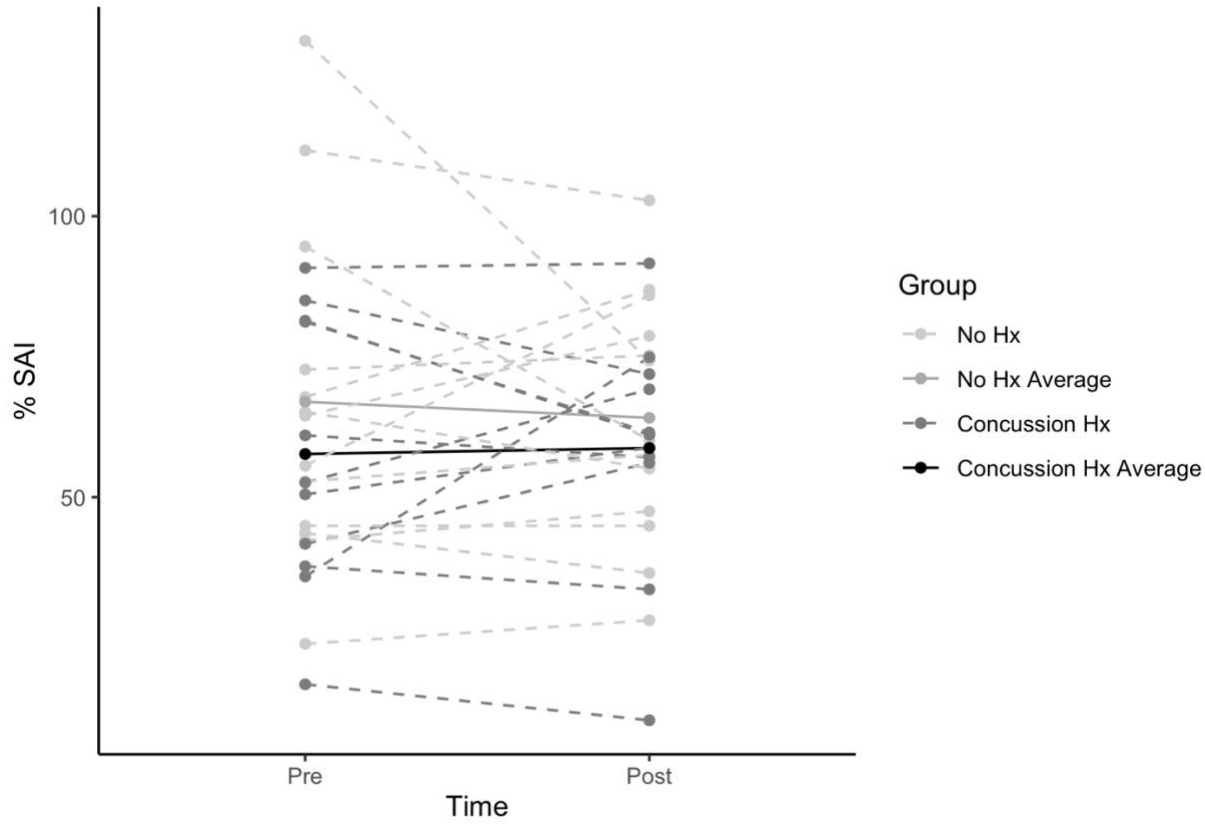


Figure 4 - PA_{120} SAI at rest Pre and Post task in the Concussion History and No History group

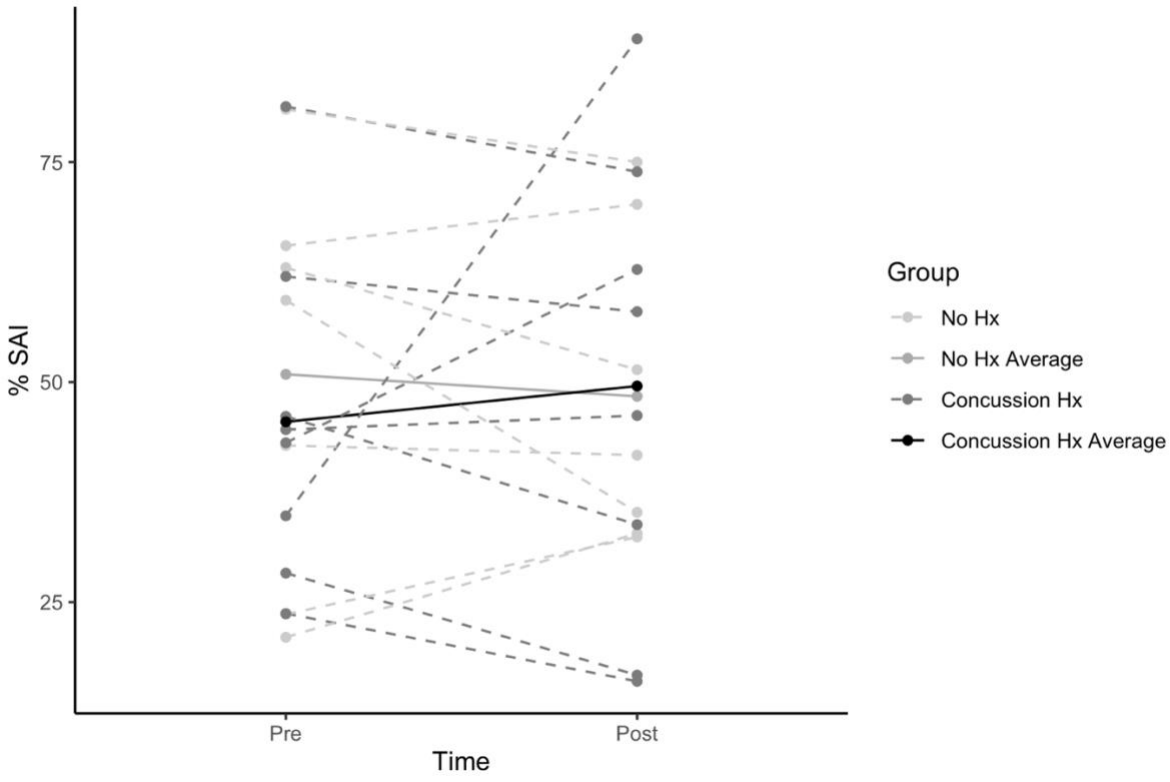


Figure 5 - AP_{30} SAI at rest Pre and Post task in the Concussion History and No History group

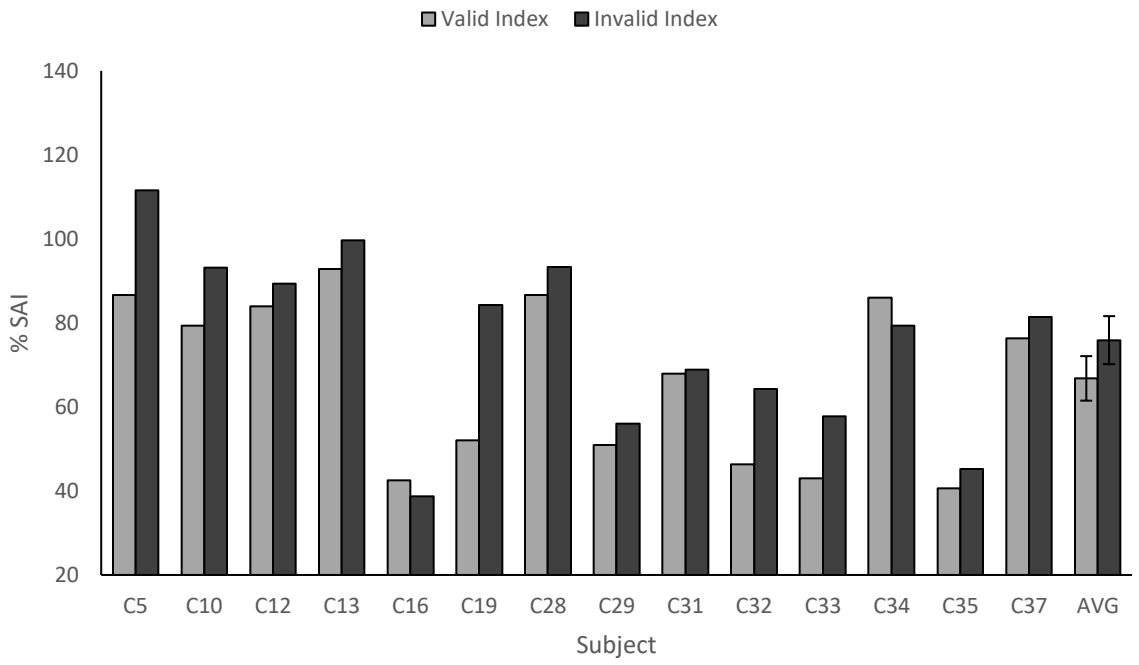
PA_{120} SAI during valid trials of the cued response time task were different in the Concussion Hx group and the No Hx group. The t-test revealed no significant difference between the groups [W=127, p=0.985, effsize=0.0470, Concussion Hx=66.8±19.8, No Hx=63.8±22.9] on valid trials (Figure 6).

An independent samples t-test was run to determine if AP_{30} SAI during valid trials of the cued response time task were different in the Concussion Hx group and the No Hx group. The t-test revealed no significant difference between the groups [t=-0.966, df=20, p=0.345, cohen's d=-0.414, Concussion Hx=44.2±18.2, No Hx=52.4±21.1] on valid trials (Figure 7).

The Shapiro-Wilk test was significant in the Concussion Hx group data [W=0.859, p=0.0298] meaning the data violated normality. A non-parametric mixed measures ANOVA was run using Aligned Rank Transform to assess the effect of Trial Type (Valid, Invalid) and Group (Concussion Hx, No Hx) on PA_{120} SAI. The ARTool ANOVA revealed a significant main effect of Trial Type [$F_{1,30}$=6.28, p=0.0179, η_p^2=0.173]. The main effect of Group [$F_{1,30}$=0.262, p=0.612, η_p^2=0.000865] and the interaction of Trial Type by Group [$F_{1,30}$=0.0240, p=0.878, η_p^2=0.000797] were not significant. PA_{120} SAI was significantly reduced for invalidly cued trials [Concussion Hx=75.9±21.4, No Hx=72.0±25.0] compared to validly cued trials [Concussion Hx=66.8±19.8, No Hx=63.8±22.9] regardless of concussion history (Figure 6).

A two-way mixed measures ANOVA was run to assess the effect of Trial Type (Valid Index, Invalid Non-Index) and Group (Concussion Hx, No Hx) on AP_{30} SAI. The ANOVA revealed a significant Trial Type by Group interaction [$F_{1,20}$=8.442, p=0.009, η_p^2=0.297]. Both the simple main effect of Trial Type [$F_{1,20}$=1.959, p=0.177, η_p^2=0.089] and Group were not significant [$F_{1,20}$=0.002, p=0.966, η_p^2=0.000098]. Decomposition of the interaction using the

A.



B.

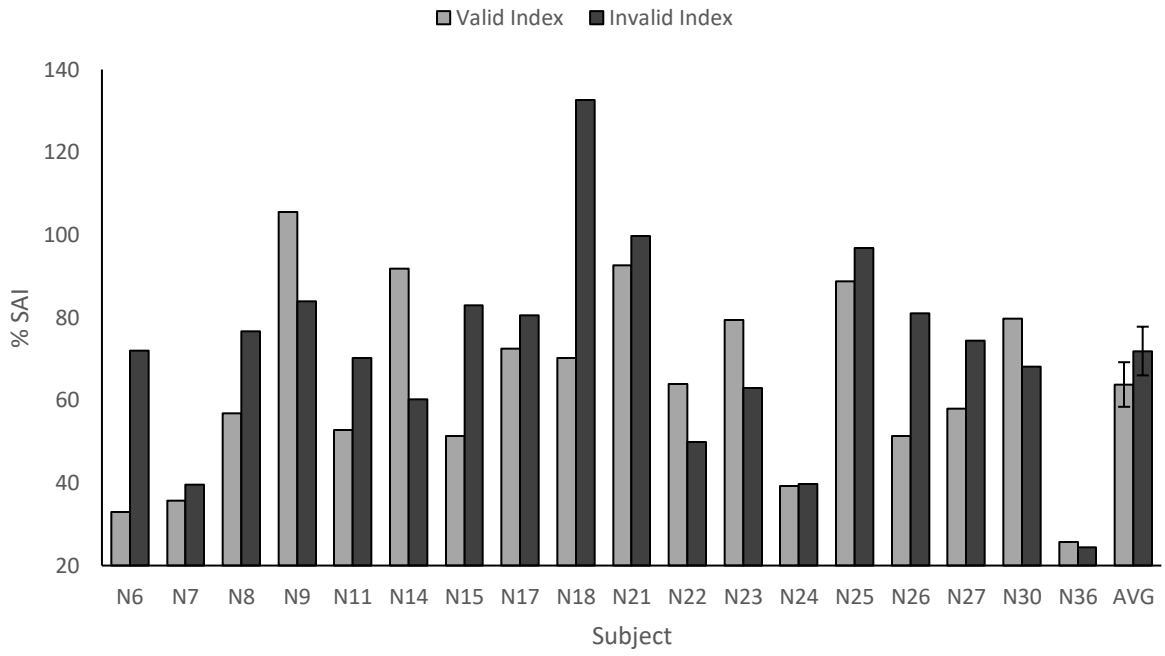


Figure 6 - Individual PA_{120} SAI values for Valid and Invalid trials. A. Individual subject data from the Concussion Hx group. Group average on far right. B. Individual subject data from the No Hx group. Group average on far right.

simple main effect of Group and revealed that AP_{30} SAI during invalid trials decreased compared to valid trials in the Concussion Hx group [$F_{1,9}$=19.7, p=0.002, η_p^2=0.686, Valid=44.2±18.2, Invalid=55.8±22.0], but there was no change in the No Hx group [$F_{1,11}$=0.851, p=0.376, η_p^2=0.072, Valid=52.4±21.1, Invalid=48.3±19.4] (Figure 7).

4.5 Post-Hoc Analyses

4.5.1 Number of Concussions as a Predictor for SAI

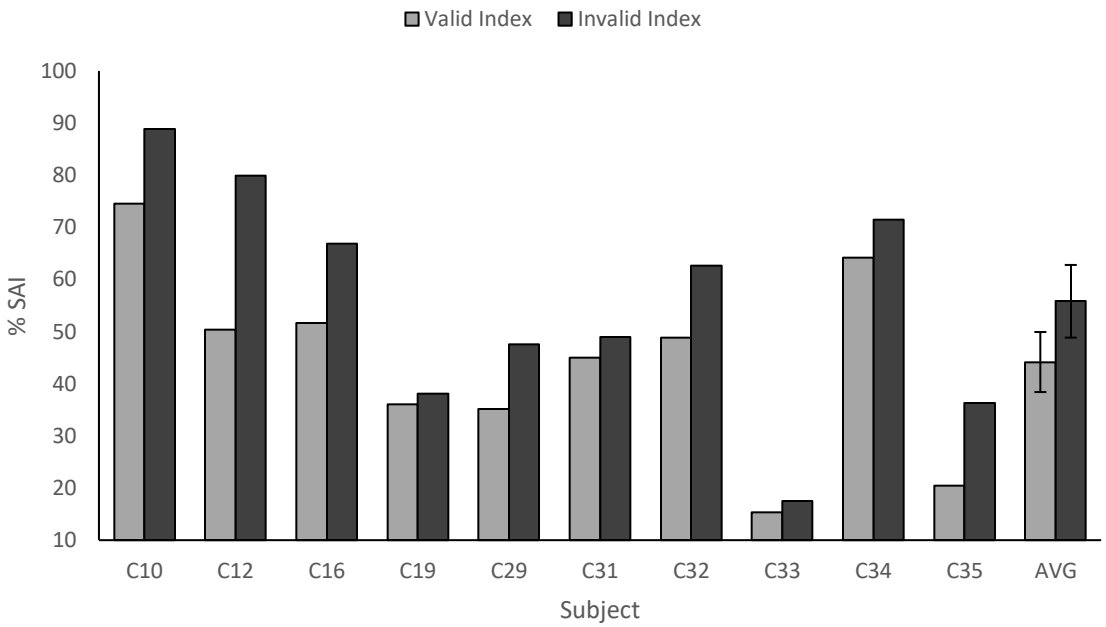
A linear mixed model was conducted to investigate the relationship between Number of Concussions and Trial Type (Valid, Invalid) and PA_{120} SAI in the Concussion Hx group. The interaction of Trial Type by Number of Concussions [$F_{1,12}$=0.246, p=0.629, η_p^2=0.02], as well as the main effects of Number of Concussions [$F_{1,12}$=1.99, p=0.1837, η_p^2=0.14] and Trial Type [$F_{1,12}$=2.79, p=0.121, η_p^2=0.19] were not significant (Appendix C).

A linear mixed model was conducted to investigate the relationship between Number of Concussions and Trial Type (Valid, Invalid) and AP_{30} SAI in the Concussion Hx group. The linear mixed model revealed a significant main effect of Trial Type [$F_{1,8}$=16.2, p=0.00381, η_p^2=0.67]. The main effect of Number of Concussions [$F_{1,8}$=0.0621, p=0.810, η_p^2=0.00771] and the interaction of Trial Type by Number of Concussions [$F_{1,8}$=3.98, p=0.0811, η_p^2=0.33] were not significant. Therefore, AP_{30} SAI was significantly reduced for invalidly cued trials compared to validly cued trials regardless of number of concussions (Appendix D).

4.5.2 Biological Sex as a Predictor for SAI

A three-way mixed measures ANOVA was run to assess the effect of Sex (Male, Female) and Trial Type (Valid Index, Invalid Non-Index) and Group (Concussion Hx, No Hx) on PA_{120}

A.



B.

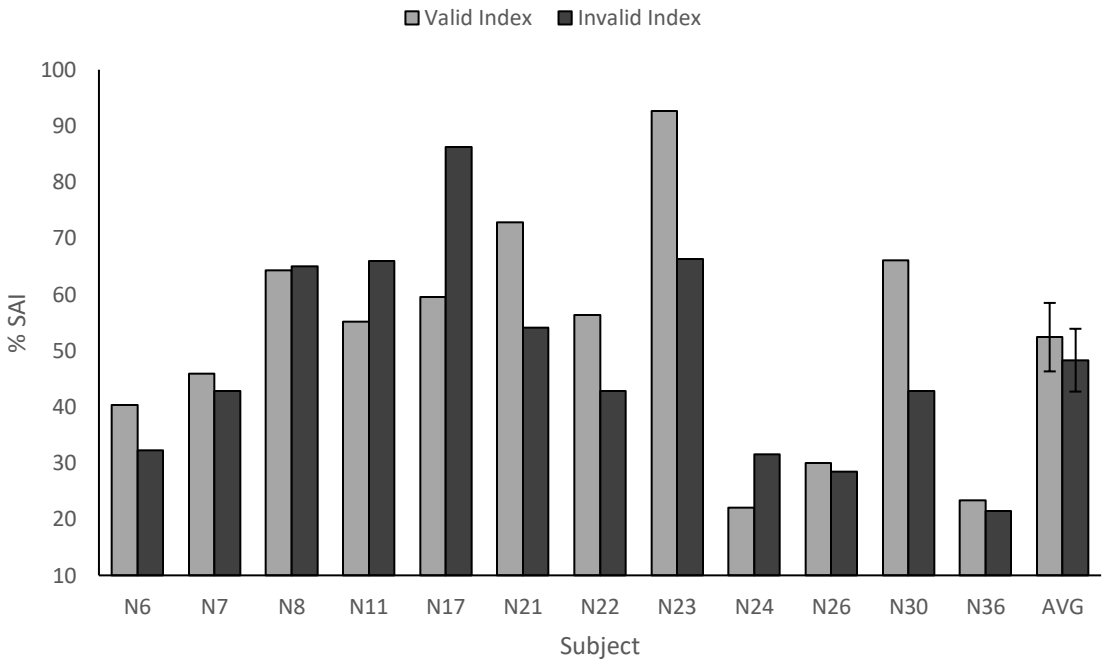


Figure 7 - Individual AP_{30} SAI values for Valid and Invalid trials. A. Individual subject data from the Concussion Hx group. Group average on far right. B. Individual subject data from the No Hx group. Group average on far right.

SAI. The ANOVA revealed only a significant main effect of Trial Type [$F_{1,28}$=6.857, p=0.014, η_p^2=0.197]. Both the simple main effect of Sex [$F_{1,28}$=0.0007, p=0.933, η_p^2=0.000256] and Group were not significant [$F_{1,28}$=0.229, p=0.636, η_p^2=0.008]. The Sex by Trial Type [$F_{1,28}$=2.281, p=0.142, η_p^2=0.075], Sex by Group [$F_{1,28}$=0.790, p=0.382, η_p^2=0.027], Group by Trial Type [$F_{1,28}$=0.021, p=0.887, η_p^2=0.000733] and Sex by Group by Trial Type [$F_{1,28}$=0.017, p=0.896, η_p^2=0.000622] interactions were not significant. These results are consistent with our original two-way mixed measures ANOVA to address the main hypotheses and we can therefore conclude that biological sex did not significantly influence PA_{120} SAI. The simple main effect of Trial Type has been previously decomposed.

A three-way mixed measures ANOVA was run to assess the effect of Sex (Male, Female) and Trial Type (Valid Index, Invalid Non-Index) and Group (Concussion Hx, No Hx) on AP_{30} SAI. The ANOVA revealed only a significant interaction of Trial Type by Group [$F_{1,18}$=7.38, p=0.014, η_p^2=0.291]. The simple main effect of Sex [$F_{1,18}$=0.487, p=0.494, η_p^2=0.026], Trial Type [$F_{1,18}$=1.52, p=0.234, η_p^2=0.078] and Group were not significant [$F_{1,18}$=0.032, p=0.859, η_p^2=0.002]. The Sex by Trial Type [$F_{1,18}$=0.000048, p=0.995, η_p^2=0.00000267], Sex by Group [$F_{1,18}$=0.432, p=0.519, η_p^2=0.023] and Sex by Group by Trial Type [$F_{1,18}$=0.193, p=0.665, η_p^2=0.011] interactions were not significant. These results are consistent with our original two-way mixed measures ANOVA to address the main hypotheses and we can therefore conclude that biological sex did not significantly influence AP_{30} SAI. The interaction between Group and Trial Type has been previously decomposed.

Figures depicting the spread of this data can be found in Appendices D and E.

5.0 Discussion

This study used SAI to investigate persistent adaptations in distinct sensorimotor circuits following exposure to SRC. The main finding was that young adults that had a sports-related concussion history from their adolescence demonstrated long-term changes in sensorimotor integration when presented with unexpected stimuli compared to young adults who also competed in contact sports but had no concussion history. Specifically, this finding was demonstrated in AP_{30} sensorimotor circuit.

This study's first objective was to investigate changes in sensorimotor integration in individuals with a concussion history during simple, validly cued trials. The finding that PA_{120} SAI was similar during valid trials across groups suggests that a history of adolescent concussion does not persistently alter sensorimotor integration during motor preparation. We had anticipated more PA SAI in the concussion history group because past work demonstrated that individuals with a concussion history have difficulty coping with working memory and attentional demands (Broglio et al., 2009; De Beaumont et al., 2009). Therefore, we hypothesized we would see greater inhibition in the concussion history group as they would less efficiently filter through incoming sensory information while being taxed cognitively. However, our study showed that integration of sensory afference arriving at motor cortex had a similar effect on the FDI muscle response during valid trials. This finding implies that sensory afference was gated efficiently by the concussion history group, likely because they were not being taxed enough to need to rely on alternative strategies and cognitive resources.

Consistent with our hypotheses, we found that AP_{30} SAI was similar across groups during valid trials. We expected to see this result because of AP_{30} SAI sensitivity to cerebellar influence (Hannah & Rothwell, 2017) and perceptual load (Mirdamadi et al., 2017). The relationship

between the AP_{30} circuit and the cerebellum suggests a sensitivity to motor plan changes. During valid trials, participants did not need to adjust their programmed motor response or process any new perceptual information. Therefore, the finding that AP_{30} SAI was similar across groups during valid trials could be reflective of AP_{30} circuit's irrelevance during trials that require no motor plan modulation. The amount of AP_{30} SAI seen in both groups is therefore likely a reflection of common sensory input about the planned movement as seen in PA_{120} circuit.

This study's second objective was to investigate changes in sensorimotor integration in individuals with a concussion history from valid trials to invalid trials involving a motor plan change. Changes across valid and invalid trials were used to explore brief instances that increase processing load for an unexpected outcome in the environment. Increases in processing load may tax cognitive resources and create brief breakdowns in sensorimotor integration. Breakdowns in sensorimotor integration could in turn explain the increased risk of musculoskeletal injury.

AP_{30} SAI across cue type was differentially impacted by concussion history. AP_{30} SAI decreased from valid to invalid trials in participants with a concussion history. Meanwhile, there was no significant change from valid to invalid trials in participants with no concussion history. These results may suggest that individuals with a concussion history are particularly sensitive to changes in perceptual load. Previous work in our lab has demonstrated that AP SAI is reduced under periods of high perceptual load (Mirdamadi et al., 2017). Adams et al. (2020) showed that individuals with a concussion history struggle to process perceptual information efficiently and do not modulate their attention based on task relevancy. By processing task irrelevant stimuli, individuals with a concussion history may be processing far more information than is necessary or typical. Recent work investigating the relationship between attention and cerebellar influence over AP circuit demonstrated that during high attentional load SAI is reduced, but after

cerebellar iTBS SAI is enhanced during high attentional load (Mirdamadi & Meehan, 2022). The working hypothesis for the relationship between attentional and cerebellar influence is that their mutual suppression of AP SAI kickstarts a homeostatic mechanism that boosts neuronal response to maintain sensorimotor function. The homeostatic mechanism in turn enhances sensory afferent projection to the motor cortex, resulting in enhanced levels of SAI. Keeping this hypothesis in mind, the reduction in AP_{30} SAI during periods of high perceptual load we observed in the concussion history group may suggest that they are relying heavily on their attentional mechanisms to process perceptual load and may be leaning less on cerebellar inputs to guide their motor plan modulation.

We had originally anticipated seeing an increase in AP_{30} SAI in the no history group reflecting efficient motor plan changes. This is due to past work demonstrating AP_{30} circuit's sensitivity to cerebellar influence (Hannah & Rothwell, 2017) suggests it may play a role in movement modulation. As well, recent work by Aberra et al. (2020) suggests that PA and AP currents may preferentially recruit neurons in specific motor regions. PA current may preferentially recruit layer 5 pyramidal neurons located in the rostral central sulcus, while AP current may recruit neurons in the premotor cortex. Therefore, AP current stimulation over M1 likely activates neurons in a network that receives input from the cerebellum and premotor cortex. There is a vast amount of literature suggesting that the cerebellum and premotor cortex play critical roles in motor adaptation and motor learning (Hardwick et al., 2015; Hashimoto et al., 2010; Manto et al., 2012). Given the nature of these brain regions and their relationship with AP current, AP current may be sensitive to motor plan changes. The no concussion history group did not demonstrate any significant changes in AP_{30} SAI from valid to invalid trials. The overlapping relationship between attention and cerebellar influence on AP sensorimotor circuits

may help to explain this finding. Motor plan modulation requires feedback from the cerebellum as well as attentional control. It is possible that the no concussion history group was better able to control changes in sensory feedback in the AP_{30} circuit during motor plan modulation by relying on attention and cerebellar influence more evenly.

PA_{120} SAI decreased significantly from valid to invalid trials in both groups. This finding was the opposite of what we had hypothesized based on principles of movement-related gating. We had expected to see an increase in SAI from valid to invalid trials as the motor response shifts from the index finger to one of the other fingers on the hand (Asmussen et al., 2013; Cho et al., 2016; Fischer & Orth, 2011). We hypothesized an increase in SAI when shifting the motor plan away from the index finger would reflect the typical increase in sensory afference reaching M1 seen in surrounding muscles uninvolved in an impending movement. These studies reported reduced SAI just before the movement onset when the muscle was at rest. Although we also assessed SAI just prior to movement onset, our participants were already required to maintain a slight tonic contraction of the target FDI muscle to facilitate the TMS assessment. Little is known about how a steady, tonic contraction before muscle movement onset may affect movement-related gating and SAI. Attention has been shown to modulate movement-related gating. When maintaining an internal focus of attention on the index finger, typical SAI reduction at movement onset was of greater magnitude (Suzuki & Meehan, 2020). It is possible that the instruction to maintain a slight tonic contraction during our task may have promoted an internal focus of attention on the index finger. Movement-related gating principles would dictate an increase in SAI in the index finger during invalid trials when it is no longer the movement-impending finger. Despite switching fingers to respond to invalid cues, participants' focus might have remained on their index finger. Maintaining focus on their index finger may have resulted

in a continued reduction in SAI as if the index finger was still a movement-impending finger. Promoting an internal focus of attention on the index finger may have accidentally created a situation with two fingers requiring impending movements, therefore reversing the expected sensory afferent influence on M1 that we had expected.

Alternatively, our results could be explained by the working hypothesis that PA SAI may be sensitive to motor command planning and preparation (Suzuki & Meehan, 2020). During valid trials, participants were required to prepare a motor plan for their index finger and upon presentation of the response target, were able to maintain the original motor plan and then initiate the response with their index finger. During invalid trials, participants prepared a motor plan for their index finger after seeing the cue but were then forced to change their motor plan to a different finger upon the identification of the response target. Switching the motor plan from one finger to another finger would require a change in sensory processing to reflect the new motor plan for the chosen impending finger. The decrease in PA_{120} SAI from valid to invalid trials may reflect a sensitivity to updating of the motor plan.

High accuracy across groups for both trial types suggests that both groups were successful in the adaptation of their motor plans. However, results of our statistical tests of response time demonstrated a moderate effect size of group. This suggests that for both valid and invalid trial types, the concussion history group had slower response times. Therefore, the high accuracy in the concussion group may come at the cost of slower response time. One possible explanation for the slower reaction times of the concussion history group may be increased difficulty in processing perceptual load. If processing simple stimuli and changing stimuli requires more cognitive effort, then the resulting motor plan changes could take longer and be reflected in slower response times. These behavioural results provide further evidence that

individuals with a concussion history are processing perceptual load differently than those with no history of concussion.

While the results of our post-hoc analyses addressing the relationship between number of concussions sustained and changes in SAI did not reveal any significant findings, we did see moderate to large effect sizes that should be addressed. The interaction between number of concussions and trial type for AP_{30} SAI had a large effect size. The number of sustained concussions negatively correlated with AP_{30} SAI across trial types, indicating that individuals with a higher number of concussions showed less of a reduction in SAI from valid to invalid trials. By showing less of a reduction, participants with more concussions looked more similar to the no history group. This finding suggests that a larger number of concussions results in somewhat of a "return to normal" with similar amounts of SAI to individuals with no concussion history. However, it is more likely that this finding might reflect a breakdown of compensatory mechanisms involving attention. When no longer able to use attentional adaptations, there would be no attentional-cerebellar interactions. Lack of attentional-cerebellar interaction would keep amounts of SAI closer to what was demonstrated in situations of higher perceptual load for individuals with no concussion history. However, this does not mean individuals with a greater number of concussions are neurophysiologically the same as individuals with no concussion history. While not statistically significant, these effect sizes suggest we are slightly under powered to detect a potential magnitude effect of number of sustained concussions on changes in sensorimotor integration.

The results of the three-way mixed ANOVA revealed that biological sex did not influence changes in SAI across groups and trial types. These findings were not surprising as we had not designed this study with biological sex analyses in mind. The number of males and

females in our concussion history and no history groups were not evenly matched. SAI has not previously been linked to sex-based differences and literature surrounding sex-based differences in cognitive deficits and recovery after concussion has been mixed (Merritt et al., 2019).

The results of the baseline cognitive tests showed a significant difference in cognitive flexibility between the concussion history group and the no concussion history group. However, after looking at the individual data for this task, there is one participant whose score is quite substantially lower than the rest of the cohort. It is more than likely that this participant's data is skewing the results of this baseline cognitive test in particular. On all other cognitive domains this participant scored similarly to their peers. It is possible that they misunderstood the instructions and did not do the test properly.

No other baseline tests demonstrate any significant differences between the concussion history group and the no history group. This result is as expected as we were not anticipating typical baseline concussion measures to be difficult enough to expose cognitive deficits masked by compensatory mechanisms. Therefore, despite the neurophysiological differences, on simple measures of cognitive functioning our groups performed the same. It is not unusual for individuals with a concussion history to be clinically undetected by cognitive tests (Broglio et al., 2006). It is also not the first time that individuals with a concussion history have performed the same as their healthy peers on cognitive tests and then demonstrated clear neurophysiological differences (Pontifex et al., 2009). Our study suggests that simple cognitive tests do not help to discriminate long-term brain changes in young adults with a concussion history from those with no history. Further neurophysiological testing is required to detect subtle, long-term changes in the brain of those with a concussion history.

Another important result of our study was that pre-task and post-task measures of PA_{120} and AP_{30} SAI were not different between the groups. We were not expecting to see differences in SAI at rest across the groups because resting does not require any cognitive effort. Our working theory is that individuals with a concussion history only breakdown under periods of high cognitive load. Therefore, in situations of low cognitive load, we anticipate the concussion history group would have similar results to individuals with no concussion history. The pre- and post-task SAI measures were taken while participants kept their eyes on a fixation cross on the screen and maintained a slight contraction in their index finger. During these measures, participants were not performing a task. In contrast, participants were processing perceptual information and planning and executing motor responses while performing the cued response time task. SAI was only sensitive to group differences when participants were performing a task requiring motor plan modulations and changes in perceptual load. This is an important consideration when using SAI to probe sensorimotor circuits in concussed populations. It is crucial that we study concussed populations while they are performing a cognitive task to accurately measure differences in sensorimotor integration and other neurophysiological phenomena.

6.0 Limitations

The current study has several limitations that need to be considered. First, the current study only investigated two sensorimotor circuits (PA_{120} and AP_{30}). The choice to investigate only PA_{120} and AP_{30} was made because past work suggests the AP_{30} circuit is functionally distinct from the PA120 circuit as well as other quantifiable sensorimotor circuits, that have similar responses as the PA_{120} circuit. However, cTMS is a relatively new technique and research is limited. The assumption that the other circuits recruited by PA_{30} or AP_{120} current would behave like the circuit recruited by PA_{120} current may be incorrect. It has been hypothesized that AP_{120} current may recruit a mix of neurons that are recruited by PA_{120} and AP_{30} current, respectively (Hannah & Rothwell, 2017). AP_{120} current behaves more similarly to PA_{120} current overall, with more similar MEP latencies and sensitivity to different stimuli, like cerebellar stimulation (Hannah & Rothwell, 2017). Recent work in our lab has also demonstrated that PA_{120} and AP_{120} recruit neurons similarly during working memory tasks. Regardless of the similarities between PA_{120} and AP_{120} current, work using these current parameters is still novel and exploratory. We acknowledge that we may be missing out on a distinct sensorimotor loop by not including AP_{120} current in this study. More research needs to be conducted using all current parameters to better understand their individual recruitment of neural networks.

Another limitation of this study was not including a third group of individuals who had not competed in contact sports and did not have a concussion history. It is possible that our no concussion history group may not be truly typical given their repetitive exposure to subclinical head impacts through participation in contact sport. Therefore, it would have been helpful to have a third group of athletes with no concussion history and no participation in contact sport to tease apart any effects of subclinical impacts. If our no history group's results were similar to our

non-contact sport group, we could conclude that their physiological results were most likely typical. However, if there was a difference in the results between the no history group and the non-contact sport group, we may have been sensitive to potential changes in neurophysiological functioning from subclinical head impacts from contact sport participation. Our study assumes that our no history group performs typically.

Along the same lines, the variability seen in the direction of change in SAI between valid and invalid trials in our no history group needs to be addressed. The change in both PA_{120} and AP_{30} SAI across trial type in our concussion history group was quite consistent. However, for both PA_{120} and AP_{30} SAI in our no history group there were few participants who showed quite drastic changes in SAI in the opposite direction from the group. Particularly in the AP_{30} no history data, there is quite a mix of directional change. It is possible that some of the individuals in our no concussion history group may have previously had a concussion but were unaware. It is also possible that some of the participants were exposed to enough subclinical head impacts that have caused long-term brain changes. This may have slightly changed the outcome of our results, particularly for AP_{30} SAI.

A third limitation of this study was the need to use a slight contraction of the FDI muscle. The slight contraction was required to lower motor threshold and increase the probability that required PA and AP stimulus intensities to elicit the required motor evoked responses would be within the stimulator's capacity. Typically, it is more difficult to recruit afferent muscle projections via AP_{30} current at rest due to its short pulse duration and the direction of the induced magnetic field. Sometimes even with a slight contraction it is not possible to recruit enough afferent projections via AP_{30} current to threshold to 1mV. However, a slight contraction is still currently the best option for increasing the chances of being able to get a 1mV threshold with

AP_{30} current. Previous research using a slight contraction of the FDI muscle has only been done while the participant is otherwise at rest and not performing a task. However, having participants maintain a slight contraction does increase the difficulty of relating our results to past work using only PA current elicited by traditional TMS stimulators since these studies are conducted with the muscle at rest. While the contraction did not interfere with participants' abilities to respond to the task, it did change their locus of attention. Participants were forced to pay attention to the contraction of their FDI muscle while simultaneously paying attention to the task. It is possible that the splitting of their attention unknowingly caused somewhat of a dual task paradigm. As well, it is not currently known how exactly a sustained, slight contraction affects SAI, so we can't be sure if there would be any differences in neurophysiological response during this task with no contraction.

A final limitation of the study was that given our sample size we did not have large groups of each biological sex to use for comparisons. This resulted in us being under powered to detect any sex-based differences that may have been present. Although our effect sizes in our comparisons of biological sex and SAI were negligible, we cannot be certain that differences across biological sex would not be present with a larger cohort. As well, smaller groups of biological sex made it difficult to control across sport types. Due to societal influence over sporting rules, certain sports cannot be considered to have equivalent exposure to body contact across the sexes. For example, the rules around contact in men's football, lacrosse or hockey cannot be equated to the rules around contact in the same women's sports. In men's football, lacrosse and hockey, players are allowed to accelerate into other players head-on and collide. In women's flag football, lacrosse and hockey, players are allowed to use their bodies to push another player off the ball/puck or hold them against the boards, but they cannot accelerate head-

on into another player to stop them. This disparity in sport rules makes a large difference in how many head impacts a player may be exposed to while practicing or competing in the sport. While we did our best to match our participants based on sex and sport, it is possible that sport rule differences based on biological sex may have influenced the differences that we saw between our groups.

7.0 Potential Implications

The long-term sensorimotor integration changes seen in our study are of even further interest when we consider them in the context of the accelerated aging model of the brain after mTBI. The accelerated aging model suggests that cognitive deficits after mTBI are concealed by compensatory mechanisms that may be exposed as the brain ages (Broglio et al., 2012). Typical maturation with age is characterized by natural declines in motor and cognitive functioning. For example, as people age, they typically experience a gradual decline in processing speed, reaction time, sensation, contextual memory and more (Fozard et al., 1994; Kensinger, 2009). Atrophy of the motor cortical regions is also observed and may be related to balance, gait and coordination deficits in aging adults (Seidler et al., 2010). Frighteningly, a pattern of accelerated decline is emerging in the literature with converging evidence that cognitive and motor deficits are exacerbated in older adults with a concussion history (De Beaumont et al., 2009; Guskiewicz et al., 2005). In this study, we demonstrated significant sensorimotor integration deficits present in young adults with a concussion history. If the accelerated aging model is accurate, it is possible that older adults with a concussion history may demonstrate this same pattern of results more drastically. As well, the cognitive and motor decline is not guaranteed to be linear. As individuals with a concussion history age, they may begin a steep, exponential decline in sensorimotor integration abilities. Rapid and early cognitive decline could have devastating effects on health and quality of life.

Another way that the long-term neurophysiological changes in those with a concussion history may be exacerbated is during a more difficult task. The task used in this study was simple and had a relatively low perceptual and executive load. In a task that has more perceptual demands or demands the use of more working memory capacity, it is possible that these

sensorimotor integration differences may be magnified. Previous EEG studies conducted in healthy young adults that required increased working memory demands resulted in a consistent change in magnitude relative to the working memory load, whether it be an increase in frontal theta activity (Jensen & Tesche, 2002) or a decrease in alpha activity (Gevins et al., 1998). Studies on perceptual load in healthy young adults have shown similar results, with the magnitude of their effect being reflective of the perceptual load size (Handy & Mangun, 2000; Lavie et al., 2009). In a recent study in our lab, PA SAI increased in accordance with increasing verbal working memory load (Lenizky, 2020), suggesting that the magnitude of change in SAI can be influenced by specific cognitive load. They also demonstrated that response time increases significantly as working memory load increases. All these findings suggest that on a task requiring more executive or perceptual processing, neurophysiological changes are more pronounced. In the present study, we are already seeing sensorimotor integration differences in those with a concussion history on a simple cued task. This raises concerns for what the magnitude of difference in SAI may be on a more complex task.

It is important to consider the behavioural implications of increased task difficulty as well. While our task did not result in an eventual breakdown of task performance, it is likely a harder task would. Previous work has also demonstrated that response time increases as working memory load increases (Lenizky, 2020). Therefore, the small to moderate effect of increased response time we see in our concussion history group would likely reach significance on a harder task, which could have major implications in sports performance. Accelerated sensorimotor integration deficits and slower reaction times have major consequences for the aging population. As individuals with a concussion history age, they will be at an even greater risk of injury due to motor production delays or breakdown.

8.0 Future Directions

As mentioned in the discussion, there are multiple avenues for future research in long-term sensorimotor integration changes in individuals with a concussion history. Further research in this area could help provide more precise answers about the long-term impacts of adolescent concussion and how young adults may be masking cognitive deficits.

A first step would be to conduct a study using a task that requires similar motor response selection but requires more executive or perceptual processing. This would be important research to see if the magnitude of the effects seen in this study are exacerbated in more complex scenarios. As well, if the task focused more singularly on taxing perceptual load or executive load, rather than a combination of multiple faculties, it could help to further pinpoint exactly how sensorimotor circuits are being influenced by cognitive demands. Performing a study with a more directed task could serve to better understand the exact cognitive functions affected after a concussion.

Future work should include all possible TMS current configurations during a similar study of sensorimotor integration. Including the use of PA_{70}, PA_{30}, AP_{120} and AP_{70} SAI would allow the investigation of potentially six distinct sensorimotor loops. It is possible that other sensorimotor integration differences are present in those with a concussion history, but we were unable to probe them using only PA_{120} and AP_{30} current. Understanding all the neurophysiological differences in individuals with a concussion history would be beneficial to understanding potential mechanisms for the increased risk of musculoskeletal injury.

Future work should also include a third group of individuals who participated in non-contact sports and have no concussion history, as discussed in the limitations. This would allow for the establishment of a truly typical neurophysiological “baseline”. Having never been

exposed to clinical or subclinical head impacts, a non-contact, no concussion history group would provide another control group to tease out any possible effects of subclinical impacts. By including a group with no exposure to subclinical head impacts it would be possible to draw conclusions about what physiological differences can be independently associated with concussion diagnosis and exposure to subclinical impacts, respectively.

Finally, studies of sensorimotor integration should also be performed in older adults with a concussion history from their adolescence/early adulthood. A cross sectional study performed across the lifespan could capture data points from adults across a broad range of ages (e.g., 18-80 years old) and could examine sensorimotor integration changes over time. Given what the literature about accelerated aging is suggesting and considering how many kids are diagnosed with a concussion annually, it will be crucial to investigate neurophysiological changes over time in individuals with a concussion history. Likely, the effects seen in this study would be exacerbated with age as cognitive resources decline. Being able to quantify these neurophysiological changes would help to support our understanding of the aging brain and how we may be able to help prevent accelerated and long-term brain changes. It would once again be important to include other control groups to differentiate what changes can be considered typical age-related changes and what changes may be a result of accelerated-aging due to concussion history.

9.0 Conclusion

The current study expands on the literature surrounding long-term implications of sports-related concussions in early life. Our results show differences in sensorimotor integration between young adults with a concussion history in adolescence when dealing with unexpected stimuli compared to young adults with no history of concussion. The AP_{30} sensorimotor circuit was selectively sensitive to this difference. AP_{30} SAI decreased from valid to invalid trials in the concussion history group, while the no history group did not demonstrate changes in AP_{30} SAI across trial types. Given AP_{30} circuits relationship to attention and cerebellar functioning, results of our study suggest individuals with a concussion history may be more sensitive to high perceptual load during periods of motor plan modulation.

These findings suggest that individuals with a concussion history may have a harder time integrating sensory information under higher perceptual load than individuals with no concussion history. This could be one potential mechanism to explain the increased risk of musculoskeletal injury after a concussion diagnosis. Difficulties processing perceptual load could have major implications for sensorimotor integration abilities, particularly in the context of sport performance. Sport performance relies heavily on quick and skilled motor execution. Sensorimotor integration deficits may delay motor production or result in erroneous motor actions. Continued investigation of long-term sensorimotor integration changes after concussion diagnosis will be important to determine the underlying mechanism for the increased risk of musculoskeletal injury.

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Appendices

Appendix A

Table 4 - cTMS threshold values for both current directions for each subject

Subject	**Group**	**PA_{120} Threshold**	**AP_{30} Threshold**
C5	Concussion Hx	35.5	N/A
C10	Concussion Hx	33.5	N/A
C12	Concussion Hx	24	78
C13	Concussion Hx	34	N/A
C16	Concussion Hx	25.5	76
C19	Concussion Hx	26.5	73
C28	Concussion Hx	23	68
C29	Concussion Hx	27	84
C31	Concussion Hx	29	88
C32	Concussion Hx	20.5	70
C33	Concussion Hx	23.5	74
C34	Concussion Hx	29	75
C35	Concussion Hx	32	89
C37	Concussion Hx	41.5	N/A
N6	No Hx	29	95
N7	No Hx	30.5	77
N8	No Hx	21.5	55
N9	No Hx	32	N/A
N11	No Hx	31.5	85
N14	No Hx	34.5	N/A
N15	No Hx	31	N/A
N17	No Hx	27	73
N18	No Hx	32.5	N/A
N21	No Hx	29.5	86
N22	No Hx	28	66
N23	No Hx	32	92
N24	No Hx	21.5	65
N25	No Hx	47	N/A
N26	No Hx	27.5	85
N27	No Hx	43.5	N/A
N30	No Hx	19	51
N36	No Hx	25.5	80
Average±STD	Concussion Hx	28.8±5.60	76.5±7.70
Average±STD	No Hx	30.3±7.12	76.7±14.4

Appendix B

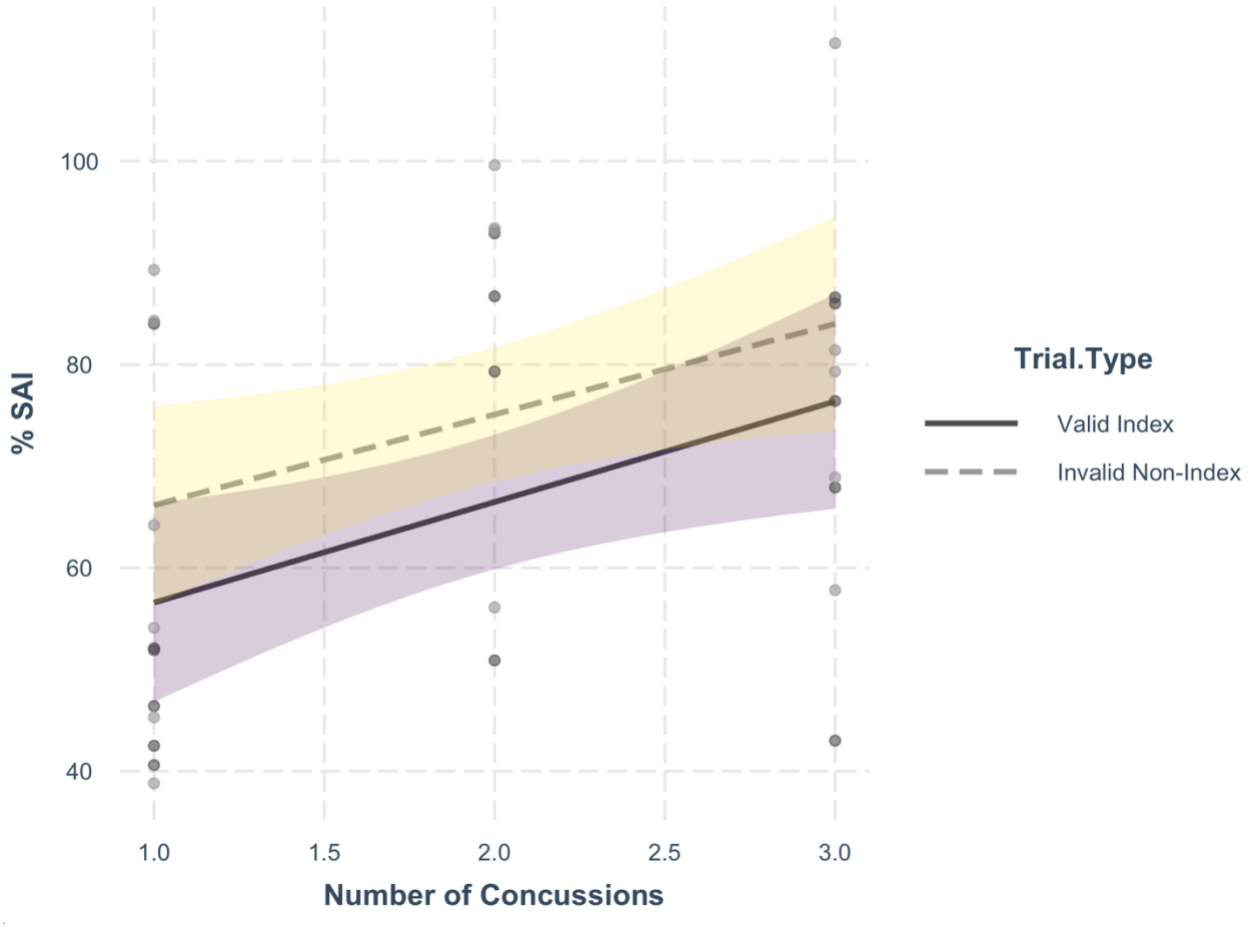

Figure 8 - Plot of linear mixed model investigating the relationship between number of sustained concussions and PA_{120} SAI for Valid and Invalid trials.

Appendix C

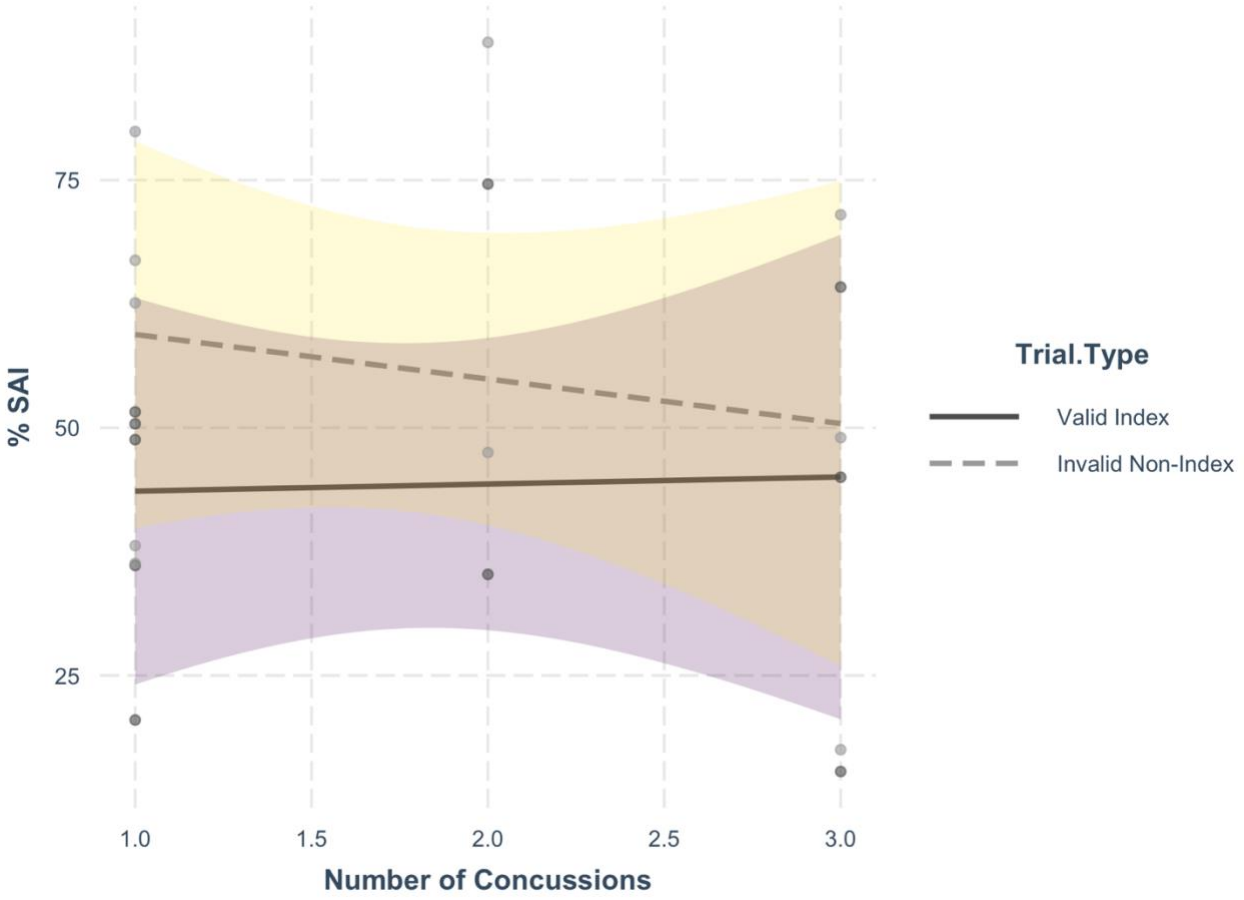

Figure 9 - Plot of linear mixed model investigating the relationship between number of sustained concussions and AP_{30} SAI for Valid and Invalid trials.

Appendix D

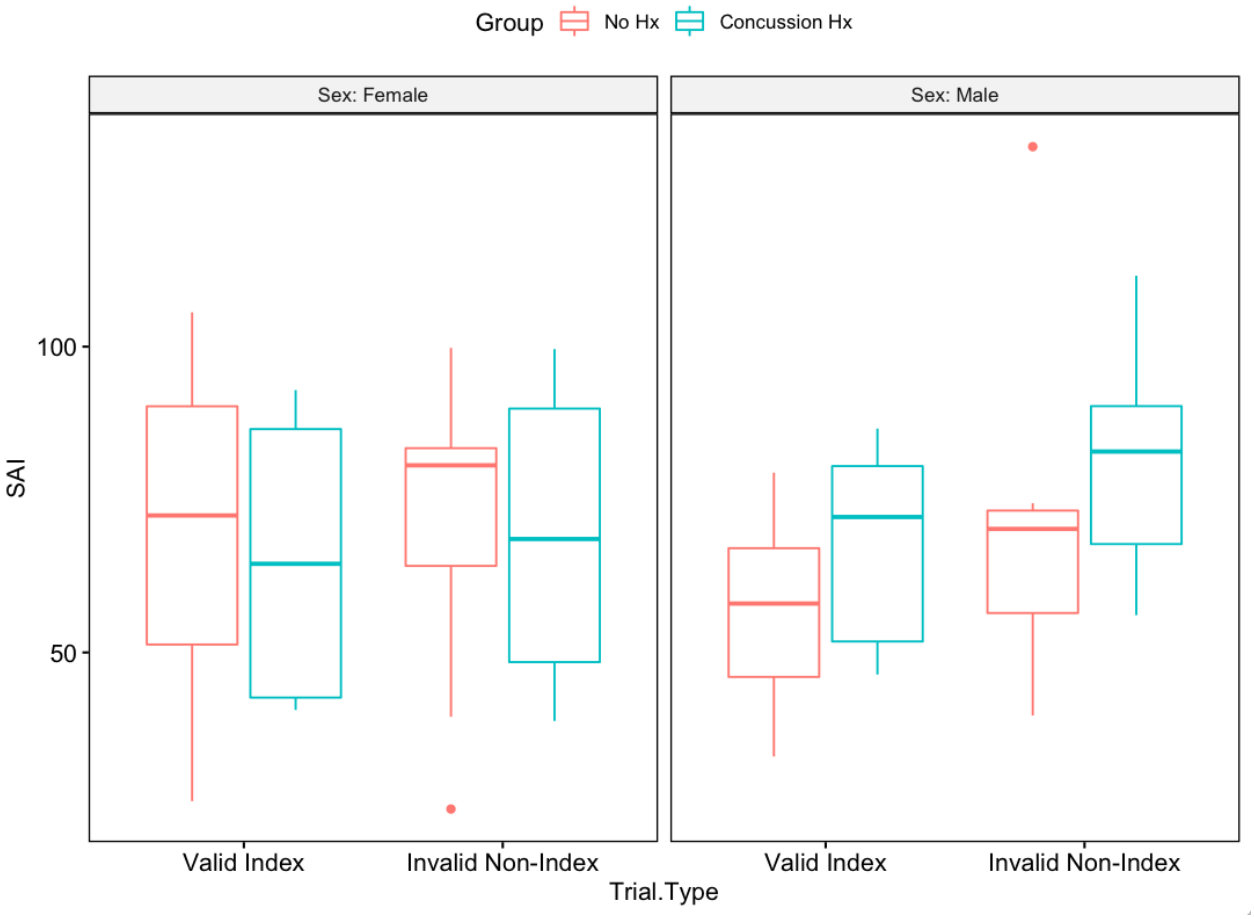

Figure 10 – PA_{120} SAI values for Valid and Invalid trials across groups plotted by biological sex.

Appendix E

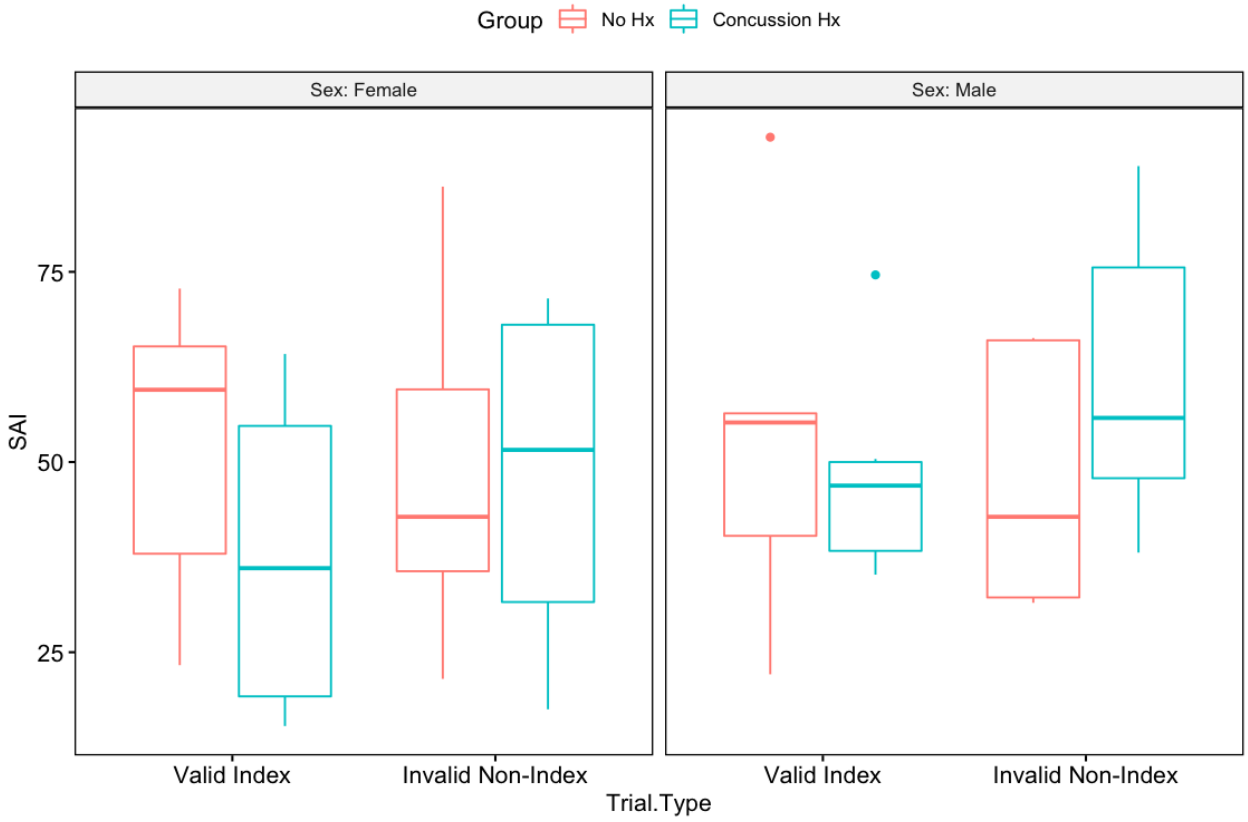

Figure 11 – AP_{30} SAI values for Valid and Invalid trials across groups plotted by biological sex.