The effect of concussion history on relevancy-based gating of visual and tactile stimuli

by

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Author's Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Statement of Contributions

I declare that I contributed the majority of the research design, data collection, data analysis, and data interpretation for Chapters 2 through 4, and all writing of the thesis. Dr. Richard Staines was the primary co-author on all published manuscripts which were derived from this thesis. Dr. Christina Popovich contributed to data collection and manuscript review for Chapter 2 and Danielle Andrew contributed to data collection for Chapter 3.

Abstract

At the cortical level, incoming sensory inputs are subject to interruption as they are transmitted to modality-specific cortical areas, in order to prevent excessive processing of task-irrelevant sensory information and aid in planning appropriate responses. This interruption of stimulus transmission is known as sensory gating, and it is an important component of attentional orienting: effective gating allows attention to be oriented only to stimuli which are task-relevant. Concussion is a condition in which attentional orienting processes appear to be disrupted, but the details of this disruption and its underlying mechanisms are unknown. The experiments contained within this thesis address questions related to the effects of concussion on sensory processing. This thesis aimed to characterize the electrophysiological and behavioural correlates of attentional orienting and sensory gating on a sensory selection task; to build an understanding of the cortical mechanisms involved in sensory selection under conditions of varying task-relevance and in the presence of distractor stimuli; and to address the clinical hypothesis that a history of concussion injury leads to problems gating irrelevant sensory information out of the processing stream. The results provide insight into the process of sensory gating based on task-relevance, the top-down and bottom-up factors that modulate attentional orienting, the cortical networks involved, and the disruption to these processes that can occur with concussion.

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List of Abbreviations

ANOVA	Analysis of variance
ATP	Adenosine triphosphate
BA	Brodmann's area
BOLD	Blood oxygen level dependent
CSP	Cortical silent period
cTBS	Continuous theta burst stimulation
DLPFC	Dorsolateral prefrontal cortex
DTI	Diffusion tensor imaging
EEG	Electroencephalography
EP	Evoked potential
ERP	Event-related potential
ERP	Event-related potential
fMRI	Functional magnetic resonance imaging
Hx	History
ICF	Intracortical facilitation
LICI	Long intracortical inhibition
MEP	Motor-evoked potential
MRI	Magnetic resonance imaging
MT	Motor threshold
mTBI	Mild traumatic brain injury
PET	Positron emission topography
PFC	Prefrontal cortex
SD	Standard deviation
SEP	Somatosensory evoked potential
SI	Primary somatosensory cortex
SICI	Short intracortical inhibition
SII	Secondary somatosensory cortex
TMS	Transcranial magnetic stimulation
TPJ	Temporoparietal junction
TRN	Thalamic reticular nucleus

Chapter 1: Background

1.1 Organization and General Objectives of Thesis

This thesis is organized into five chapters. Chapter 1 outlines the general objective of the thesis, followed by a review of literature related to attention and concussion. Chapters 2 through 4 detail the rationale, hypotheses, methods, results, and discussion of the individual studies which make up the thesis. Chapter 5 includes a general discussion of the findings of this thesis, its limitations, and directions for future study.

This thesis had three main aims underlying the study design and hypotheses. The first was to characterize the electrophysiological and behavioural correlates of attentional orienting and sensory gating on a sensory selection task. There is a much more thorough understanding in the literature of multi-sensory integration than of sensory selection at present; previous studies have established a complex interplay between sensory integration and attentional orienting [1–3]. It stands to reason that sensory selection may also be deeply connected to both top-down and bottom-up attentional orienting processes, but this has not been studied in detail to date. Expanding what is known about the process of sensory selection, as well as how it relates to attentional orienting, forms the foundation of this thesis. The second aim of this thesis was to build an understanding of the cortical mechanisms involved in sensory selection under conditions of varying task-relevance and in the presence of distractor stimuli. The prefrontal cortex, as part of a neural network which also includes the thalamus and thalamic reticular nucleus, is involved in mediating various attentional processes. Patients with prefrontal cortical lesions show selective loss of attenuation of cortical responses to unattended stimuli and are less able to inhibit task-

irrelevant information, suggesting that the prefrontal cortex plays a significant role in sensory selection processes [4–6]. The role of the PFC in modulating cortical and behavioural responses during a sensory selection task was probed as part of this thesis, as an understanding of these mechanisms is the first step to assigning meaning to changes observed when this task is used in a clinical population. The third overall aim of this thesis was to use the knowledge gained from the first two studies to address the clinical hypothesis that a history of concussion injury leads to problems gating irrelevant sensory information out of the processing stream. Concussion has been associated with electrophysiological changes in working memory [7] and in visuospatial attention in general [8], but the effect of concussion on relevancy-based gating has not yet been established. The clinical presentation of patients suggests that inhibiting responses to irrelevant or distracting stimuli may be a problem, but establishing that cortical processing is altered and understanding the cortical mechanisms underlying this physical presentation is a critical first step in all other concussion research, from designing effective assessment tools and rehabilitation protocols, to making decisions about injury prevention, prognosis and recovery.

1.2 Concussion

Definition and incidence

Concussion is a type of traumatic brain injury which leads to neurological dysfunction as a result of impulsive force being transmitted to the brain [9,10]. Although concussions occur in many contexts, including sports, motor vehicle collisions, and falls, much of the research on concussion to date has examined athletic populations and focused

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on returning athletes to play. Currently, no diagnostic tests or criteria exist to objectively diagnose concussion, so medical professionals rely on patients to accurately self-report their symptoms; since athletes tend to be motivated to under-report symptoms in order to minimize a loss of playing time, reports of concussion incidence likely underestimate reality [11]. However, an examination of one men's and one women's hockey team over a Canadian Interuniversity Sport season found that 10.7 concussions per 1000 athletic exposures were sustained during regular season play, and 11.76 per 1000 athletic exposures during the playoff season [12].

A note about terminology: The terms concussion and minor traumatic brain injury (mTBI) are occasionally used interchangeably in academic and medical literature, but by strict definition, they are not the same injury. The term mTBI covers many types of brain injuries caused by trauma, including but not limited to concussion. For this research program, the term concussion will be used in its strict definition for all original work. When referencing research performed by other groups, the terminology used in the source articles will be reproduced here.

Neurochemical cascade of concussion

The transmission of biomechanical force to the brain initiates a cascade of cellular changes which have become known as the neurochemical cascade of concussion. This cascade begins when force imparted to the brain causes axonal stretching or shearing in diffuse regions [10]. As a result, neuronal cell membranes are disrupted, causing an efflux of intracellular potassium ions and depolarizing neurons [10]. This depolarization causes the release of excitatory neurotransmitters, mainly glutamate, opening ligand-gated

potassium channels and resulting in the release of more potassium in a feedback loop of depolarization [10,13]. At the same time, the cells experience an influx of extracellular calcium ions and greater demand is placed on the ATP-dependent sodium-potassium pump to restore ionic balance [10,13]. This depletes the cell's ATP reserves and leads to an energy crisis with demand outstripping supply [10]. Glycolysis occurs in an attempt to compensate for the energy deficit, which is quick but inefficient and leads to an increase in intracellular lactate concentration; evidence from positron emission tomography (PET) scans confirms this period of hyperglycolysis in humans [10]. Cerebral blood flow, which is usually highly coupled to glucose metabolism, becomes uncoupled, and cerebral hypoperfusion results over several days; initially, this is due to hyperemia, then to vasospasm, and finally to decreased cerebral blood flow [10]. The result is a subacute period of suppressed neural metabolism during which the brain must rely on alternate fuel sources [10].

Effect of concussion on cortical processes

The changes in cellular function initiated by a force transmitted to the brain are well-documented and presumed to be the cause of the signs and symptoms of concussion, but the mechanisms involved are not yet understood. For example, questions remain about why the clinical presentation of concussion varies so widely between patients, or why some patients recover while others do not. Does the injury affect all cortical or subcortical networks equally? How can we explain the wide array of symptoms associated with concussion? Despite increased research and media interest in concussion, there remains a lack of understanding of the neural mechanisms underlying the physical presentation of

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the injury; however, understanding of the neural mechanisms underlying how concussion impairs function and communication within and between cortical networks is essential to understand the clinical presentation of the injury, make effective prognostic and return to play decisions, and design effective diagnostic and treatment tools.

Since concussion represents an impairment in function without any evidence of structural change, traditional medical imaging techniques have not been useful in understanding the details of the injury. However, there is a growing body of literature showing that changes are apparent on non-traditional, non-structural neuroimaging tests, which may be useful in solidifying the neural mechanisms of concussion's clinical presentation.

Functional magnetic resonance imaging (fMRI) has become widely used in many clinical and cognitive neuroscience studies, including studies of changes after concussion [14]. It is currently the dominant paradigm for assessing changes in brain physiology and making links to human behaviour [14] which makes it an excellent choice in concussion research, where the symptoms and behavioural effects are well-documented, but the neural mechanisms are not yet well-understood. The basis of fMRI is the blood-oxygen level dependent (BOLD) signal, a ratio of oxyhemoglobin to deoxyhemoglobin in a neural area [14,15]. An increase in neuronal activity within a brain area leads to an increase in local blood flow, reducing local concentrations of deoxyhemoglobin and leading to a relatively higher concentration of oxyhemoglobin, and thus an increased BOLD signal [15,16]. The BOLD signal is therefore an indirect index of neuronal firing [14,15]. Disruptions in the BOLD signal have been shown during a variety of tasks in patients after

concussion. Patients with more severe concussion symptoms have shown increased BOLD

signal intensity on working memory and attention tasks than less-symptomatic patients,

and patients have been found to have increased BOLD signal at a lower working memory

load when compared to controls [17]. In addition, at the highest working memory load, the

patient group showed increased cortical activity outside of the working memory network,

specifically in the posterior parietal cortex, parahippocampal gyrus, and posterior cingulate

gyrus [17]. Symptom severity has also been linked to differential activation patterns on

fMRI during working memory tasks, and more symptomatic patients in the acute post-

injury phase recruited more cognitive resources than less symptomatic patients [18]. A

study examining working memory and attention tasks found no differences on fMRI

between controls and patients six months post-concussion [19]. This can be interpreted as

evidence of neurochemical and neurophysiological recovery; however, there is

considerable heterogeneity inherent among samples of participants after concussion, with

differences in factors such as number of injuries or age at time of injury, which complicates

interpretation of differing results.

Other studies of cortical network changes after concussion have utilized diffusion

tensor imaging (DTI). DTI is an advanced, MRI-based technique that generates images by

measuring water molecule diffusion within brain white matter tracts [20]. The signal

generated is a measure of the relative directionality of water diffusion in axons, known as

fractional anisotropy (FA) [20]. Certain tissue structures and characteristics can restrict the

motion of these molecules, and in the brain, myelinated fibres organized into long tracts

allow diffusion to occur more easily along the tract than perpendicular to it [15,20]. FA is

used as a marker of white matter integrity, making it a good tool to investigate white

matter abnormalities after concussion [20]. Alterations in diffusivity measures on DTI have

been found in athletes after concussion, but also in non-concussed athletes participating in

contact sport. Chamard *et al.* found lower levels of FA in the segment of the corpus

callosum projecting to the primary motor cortex in female athletes after concussion, as well

as diffusivity changes suggesting altered cellular integrity in other major white matter

tracts [21]. In contrast, Koertke *et al.* found an increase in diffusivity measures in major

white matter tracts when non-concussed athletes were compared before and after one

hockey season [22]. These authors suggest that these increases in diffusivity measures may

indicate such white matter abnormalities as thinning of the myelin sheaths or changes to

the axons themselves [22]. Even in the absence of diagnosed concussion, significant

changes were found in diffusivity measures, which suggests that either DTI is very sensitive

and able to pick up sub-clinical cortical changes which may not be functionally relevant, or

that even without a symptomatic concussion, contact sports such as hockey have the

potential to induce short- or long-term changes to white matter tracts.

Transcranial magnetic stimulation (TMS) has also been used to investigate changes

in neurophysiological function after concussion. TMS uses a magnetic field applied

externally to the skull to induce electrical currents in conductive neural tissue; when

applied over the motor cortex, a motor-evoked potential (MEP) in a target muscle can be

recorded on electromyography (EMG) [23]. There are several TMS measures which can be

used to quantify corticospinal excitation or inhibition: motor threshold (MT), which is the

lowest stimulus intensity required to produce a detectable MEP; the MEP waveform

observed on EMG, which reflects the excitability of the motor cortex; and the cortical silent

period (CSP), which is quantified as the length of time that EMG activity is absent following

the MEP [23]. Paired pulse TMS protocols, which deliver a conditioning stimulus either above or below threshold, followed by a secondary test stimulus, can also measure short or long intracortical inhibition (SICI or LICI) or intracortical facilitation (ICF), all of which reflect interneuron activity [23,24]. Populations after concussion have been shown to demonstrate increased CSP, while other measures including MEP amplitude, SICI, and ICF remained unchanged [23]. This may be indicative of increased cortical inhibition after the injury, as the CSP is thought to be generated mainly by activation of motor cortex inhibitory neurons and mediated by GABA-B activity [23]. Studies using TMS have also found abnormal plasticity measures acutely after concussion. A case-control study found increased ICF at two and six weeks after injury, and decreased LICI after two weeks which had returned to normal at the six-week time period [25]. A review article found no consensus on the effect of concussion on these and other paired-pulse measures [24], suggesting that further study is required, especially to understand how cortical plasticity changes as patients recover from concussions.

EEG is also commonly used to study cortical excitability changes after concussion. Electrophysiological measures, specifically event-related potentials (ERPs), have been used to gain insight into changes in working memory, attention, and motor function in athletes who have sustained concussions [7,26–30], and considerable evidence has been found to show persistent changes in neurophysiological indices of higher-order cognition, even in athletes who have long since returned to sport [29]. Alterations in several ERPs have been demonstrated after concussion, and these may be helpful in characterizing the associated changes in attention, working memory, and other neural processes. The P300, or P3, ERP waveform is used in the study of working memory because its latency indexes the time

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required to classify a stimulus, independent of other related processes such as behavioural response time [26]. The P300 response can be further subdivided into P3a and P3b component waveforms, which provide insight into specific aspects of working memory. The P3a is induced by infrequent and novel stimuli, and is thought to be associated with frontal lobe functional efficiency, especially related to attending to novel stimuli, while the P3b indexes memory updating and the orientation of attention [7,27]. Work by Baillargeon *et al.* examined P3a and P3b amplitude and latency changes to determine whether concussion outcomes differ by age [7]. They found that participants of all ages displayed reductions in P3b amplitude post-concussion, but this was most pronounced in adolescents, and found no changes in P3a responses in any age group [7]. The P3b is associated with the attentional resources available to update working memory, and the attenuation in the amplitude of this component corresponded to the adolescents' scores in the standard neuropsychological tests of working memory, which were also significantly lower than age-matched controls [7]. The authors explained the differential pattern of attenuation between P3a and P3b as being related to the difficulty of the task: since P3a involves more automatic processes and P3b solicits more attentional resources, they surmise that the more complex neuropsychological processes related to P3b generation were preferentially impacted in their population [7]. Another EEG waveform, the sustained posterior contralateral negativity (SPCN), was used to examine the cumulative effect of multiple concussions. The SPCN is thought to index the capacity of visual working memory during visual tasks, as it is modulated by the number of items a person is required to hold in working memory during visual working memory tasks [30]. Significant attenuation of the SPCN amplitude was found in participants with three or more concussions, as

compared to controls or those with only one or two concussions [30]. This adds to evidence that athletes who have sustained more concussions experience disproportionately worse outcomes. However, this study found no significant difference between groups in the number of items they could hold in working memory, indicating that the function of athletes' working memory was not impaired by a history of three or more concussions, despite the neurophysiological differences [30].

1.3 Attentional orienting

Neural attentional network

In order to effectively interact with the external environment, attention must be oriented and re-oriented in response to external cues or an individual's internal state. This orienting relies on a cortical and subcortical network involving the prefrontal cortex, the thalamus, and the thalamic reticular nucleus (TRN). The role of each of these in relation to attentional processes will be discussed in detail.

Prefrontal Cortex

The prefrontal cortex (PFC) is located in the frontal lobe, anterior to the premotor cortex and supplementary motor area, corresponding to Brodmann's areas 8-11 and 44-47. It is considered a hetermodal association area, with extensive cortical and subcortical connections [31]. As a result of its connections to multiple sensory and multimodal cortical areas, as well as the complex integrative functions it performs, the PFC has been implicated in many higher-order integrative processes. The connectivity of the PFC involves it in the processing of information from sensory integration areas and the performance of abstract

intellectual functions [4]. The lateral and mid-dorsal areas of the PFC link to the sensory

cortices, receiving inputs in response to visual, somatosensory, and auditory stimuli from

the occipital, temporal, and parietal lobes [31]. Additionally, some areas of the PFC also

receive converging inputs from multiple sensory modalities, or from areas that themselves

perform multimodal convergence [31]. The dorsal portion of the PFC has connections with

the motor system: Brodmann's area 46 connects to the supplementary motor cortex, the

pre-supplementary motor cortex, the rostral cingulate gyrus, the premotor cortex, the

cerebellum, and the superior colliculus [31]. The role of the PFC in the modulation of

sensory stimulus processing relies heavily on these connections.

The prefrontal cortex, in particular the dorsolateral portion (DLFPC), plays an integral

role in attenuating cortical responses to unattended or task-irrelevant stimuli. Studies have

found that patients with PFC lesions show selective loss of attenuation of cortical responses

to unattended somatosensory and auditory stimuli [4,5]. Normally, the PFC exerts an

inhibitory influence on excitability in sensory cortices, and PFC lesions appear to cause

selective loss of this control. Knight, Scabini & Woods [5] relate this disruption in cortical

function to the functional deficit in orienting to novel events seen in patients with PFC

lesions. It is understood that patients with PFC damage are less able to inhibit task-

irrelevant information [6], a behavioural manifestation which can also be observed in

patients after concussion. This leads to questions about how concussion impacts prefrontal

cortical networks and sensory gating processes in general.

The prefrontal cortex also plays a key role in the gating process, particularly for early

inputs [5]. Work using auditory evoked potentials has found selective enhancement in

patients with PFC lesions, regardless of whether the stimuli were presented in the ear

ipsilateral or contralateral to the PFC lesion [5]. The authors argue that the enhancement was due to a loss of PFC inhibition on the primary auditory cortex [5]. This is clinically relevant, as a loss of gating control over incoming stimuli could lead to "flooding" by irrelevant sensory inputs [5]. However, Knight, Scabini and Woods [5] found that the patients they examined performed as well as controls when orienting accuracy was compared. They argue that this was due to the unilateral nature of the lesions and the ability of the intact PFC to exert modulatory effects on both hemispheres [5].

The connectivity of the PFC to many other brain regions, specifically the visual, auditory, and association cortices, allows it to provide inhibitory and excitatory control over various cortical and subcortical regions, and to gate incoming inputs from other regions [6]. The "distractibility hypothesis of prefrontal function" has been used to explain impaired gating in the sensorimotor or cognitive processes of patients with PFC lesions [6]. An impairment in stimulus gating may lead to sensory or cognitive flooding, rendering a person unable to pick out task-relevant stimuli. The PFC plays a central role in attending to external events, and impairments in sensory inhibition, selective or sustained attention, and novel event detection are related to PFC damage [4,6]. By combining an ability to gate sensory inputs according to relevance with its extensive connections to other cortical and subcortical areas, the PFC is able to play an integral role in gating unattended stimuli.

Effects of Concussions on the Prefrontal Cortex

There is some evidence that concussions have a detrimental effect on prefrontal cortical function. Neurometabolic differences have been found in the dorsolateral prefrontal cortex (DLPFC) between concussed and control athletes at acute (five days) and chronic (six month) time points post-injury [32]. Specifically, decreased ratios of N-

acetylaspartate to creatine/phosphocreatine were shown in the concussed participants, which had not returned to control levels even six months post-injury [32]. It was not clear, however, whether these neurometabolic changes in the DLPFC were responsible for the symptoms of the injury or simply a long-term consequence of concussion [32]. Other work examining cortical activation patterns found that after mTBI, patients had increased activation outside of shared regions of interest on fMRI, with the injured group showing increased BOLD signal in the DLPFC during the encoding phase of a spatial navigation working memory task [33]. This change in BOLD signal correlated with decreased diffusivity measures on DTI, but no significant differences in white matter integrity were found between the groups [33]. Taken together, these results suggest that processes mediated by the DLPFC are impaired by concussion, but the mechanisms underlying the impairment are not clear.

The Thalamus

The thalamus is one of the major subdivisions of the diencephalon, located at midline and deep to the cortex. It consists of two symmetrical halves, each composed of multiple thalamic nuclei. The thalamus represents a relay point in the pathway of sensory information from the periphery to cortical sensory regions. It has been conventionally viewed in light of its function in sensory perception, and presumed to play only a minor modulatory role in the processing of sensory information [34]. However, studies of the connections between the thalamus and other brain areas suggest that it is involved to a greater extent in sensory perception, as well as in initiating motor responses to sensory stimuli. There is evidence that the thalamus provides a means of connecting sensation with

action and perception, positioning the thalamus as a potential key player in the process of determining which sensory inputs are relevant to a task of interest.

The thalamus is able to affect motor output by a process of corollary discharge [34–37]. Axons afferent to the thalamus are branched, with one branch continuing to the thalamus and the other extending to motor or premotor centres, such as other areas of the brain or the spinal cord, making messages relayed by the thalamus to the cortex copies of motor instructions [34–37]. This supports a close link between perception and motor action, rather than a view that perceptual processing is an independent activity [37]. The thalamus is able to monitor outputs from all cortical areas and from its own relays, and send messages representing instructions for motor activity to lower centres, which can contribute to higher cortical functions and perceptual processing [34,37]. Similarly, sensory processing cannot be viewed as a purely intracortical process. The thalamus also provides a close link between sensory messages afferent to the cortex for processing and motor messages afferent to motor centres [37]. Sensation, action, and perception are inextricable, and the thalamus is central: sensation is not useful without corresponding motor action, and motor responses are more useful when they can be stored in memory to inform future perceptual processes [37]. When information is properly gated, only the task relevant items reach the thalamus, ensuring that motor outputs are relevant to goals or task demands.

The Thalamic Reticular Nucleus

Surrounding the thalamus is a structure known as the thalamic reticular nucleus (TRN). It forms a thin sheet around the dorsal and lateral surfaces of the thalamus, medial

to the internal capsule and directly in the path of axons linking the thalamus and the cerebral cortex. Reticular neurons project to synapse in the thalamus, and corticothalamic and thalamocortical neurons pass through the TRN and give off collaterals to innervate TRN cells [35,37]. These reticulothalamic cells are GABAergic, or inhibitory in their actions. Thalamic afferents to the TRN are glutamatergic, or excitatory, as are the corticothalamic and corticoreticular axons [35,37,38]. This allows a fine balance of excitation and inhibition in the thalamic relay: an indirect, transreticular corticothalamic pathway inhibits thalamic relay cells, while a direct corticothalamic pathway is excitatory [37]. The TRN can also act on corticocortical pathways, but the difference between a direct corticocortical pathway and an indirect one which includes the TRN is unknown [37].

The balance of excitation and inhibition in thalamic relays is important to the function of the TRN, but the TRN is only able to exert its effects because it is interconnected with so many other brain regions. The TRN is roughly divided into sectors, with each sector corresponding to a thalamic nucleus or group of nuclei and one or several areas of cortex [36,39]. The TRN acts as an inhibitory intermediary or modulator between its associated thalamic nuclei and cortical areas [36]. When it is acting on relays between the thalamus and prefrontal cortex, it can downregulate the gating of early somatosensory information normally done by the PFC. More research is required, but it is likely that the pattern of organization of thalamocortical circuits in the TRN relates to the ability of the TRN to act on these and other pathways [36]. Detailed examination of the differences in auditory, visual, and somatosensory pathways through the TRN indicates that each has different patterns of connection to the thalamus, but in all cases, the inclusion of the TRN in the pathway between the cortex and the thalamus allows for inhibitory modulation of thalamic activity

[36]. In turn, these axons running from the thalamus to the cortex or to lower motor centres send branches to the TRN along the way [39]. These messages may be related to sensory inputs or instructions for motor actions. The connectivity of the TRN allows for activity in any sector of the reticular nucleus to be influenced by inputs from different cortical areas and thalamic relays, and the inhibitory inputs the TRN sends to the thalamus will modulate many thalamocortical relays [39]. As messages pass through the thalamus, they are modified by inputs from the cerebral cortex, brainstem, and TRN according to attentional needs [37]. Inputs from the prefrontal cortex may relate to gating decisions made about early somatosensory inputs, which can be compared to other inputs. The influence of the TRN on the thalamus is inhibitory, downregulating or dampening its outputs. The brainstem may provide pain or temperature information. All of these will be combined, and will modulate the thalamic efferent signals.

Evidence shows that patients with lesions of the TRN usually have some form of neglect, which supports the hypothesis that the TRN is involved in attentional processes [35]. This key role in selective attention is likely due to the anatomical position of the TRN, between the neocortex and thalamus, and its ability to control thalamic activity via inhibition and disinhibition [35]. In light of the capacity of the thalamus to copy motor instructions from related sensory information and pass that information through the TRN, the ability of the TRN to influence the transfer of multi-modal information as required by real-time brain processing may make it a major player in gating sensory information by task-relevance. The TRN is able to modify sensory inputs and motor outputs via its inhibitory influence on the thalamus and influence how this information is transmitted based on the environmental context. The roles of the TRN and the thalamus are

inextricably linked, and both are vital to an organism's successful gating of sensory stimuli based on covert or overt attention.

In summary, a considerable body of evidence supports the coordination of the PFC, thalamus, and TRN in modulating sensory inputs, resolving conflict between these inputs, and as a communication network between various remote brain regions. This relies on reliable detection of stimuli, and timely recognition of which stimuli are most relevant and worthy of response. This thesis aims to understand the electrophysiology associated with sensory gating and selective attention, and how these processes are altered by concussion, in order to begin to probe the role of the prefrontal cortex and its associated connections to explain this impairment and to understand how it affects behavioural and neurophysiological outcomes.

Top-down and bottom-up orienting of attention

Attention can be voluntarily directed or involuntarily captured. Broadly, these attentional orienting processes are referred to as top-down or bottom-up. Top-down orienting directs attention voluntarily toward a general location, a sensory modality, or a specific stimulus, in accordance with goals or task demands or an individual's memories or internal state [1–3,40]. Attention can also be captured by a stimulus, regardless of the relationship of the stimulus to the goal or task at hand. This is known as bottom-up orienting or stimulus-driven selection, and it occurs independently of voluntary control, depending on the visual, spatial, or temporal properties of the stimulus itself, as well as the salience of stimuli [1,2]. Because these two processes are not mutually exclusive, attention and stimulus processing are inter-related. The integration of two or more related stimuli,

known as multisensory integration, has been the subject of considerable research, and multisensory integration is understood to be both linked to and modulated by attention. The process of inhibiting sensory inputs, termed sensory gating, is less well-understood. This research program utilizes a sensory gating task to probe changes in neurological function after concussion.

Sensory gating

Sensory gating refers to the inhibition of sensory information transmission at some point between the periphery and cortical receptive zones and is thought to protect higher cortical centres from being overwhelmed with irrelevant information [41–52]. This interruption in sensory stimulus transmission can occur in response to movement, or as a result of changes in task demands. While both will be discussed, gating based on the shifting task-relevance of stimuli was the focus of this research program.

Movement-Based Gating

Several studies have shown decreased amplitudes of somatosensory evoked potentials when these potentials were delivered during active and passive movement. Rushton, Rothwell and Craggs [53] observed decreased amplitude of a P45-N55 somatosensory evoked potential (SEP) during conditions of active and passive finger movement, but no effect of movement on the earlier N20-P30 complex. In contrast, Abbruzzese *et al.* [54] found active and passive finger movement to significantly decrease the amplitude of the N20-P25 SEP. Jones, Halonen and Shawkat [55] also found decreased SEP amplitudes during active and passive thumb movement, but included a condition which evoked the SEP simultaneously with the passive movement, in order to probe the role of cutaneous muscle and join receptor afferent information in the gating process. This

revealed that muscle and joint receptor afferents were not the sole source of gating information, as gating occurred normally during this experimental condition despite the receptor afferent information being unable to reach the cortex by the time the SEP was delivered [55]. While active and passive movement have an influence on early somatosensory stimulus processing, the timing and mechanisms associated with this modulation are unclear.

Relevancy-Based Gating

Gating can also occur in response to goals or task demands. In the literature, different experimental designs variously manipulate task demands or stimulus relevance. Staines, Brooke and McIlroy examined how leg movement influenced SEP amplitudes, and found an effect of task-relevance [56]. They found that SEP amplitudes evoked from both cutaneous and deep nerve fibres were gated, or decreased in amplitude, during passive movement, but when cutaneous information was made relevant to the experimental task, the SEPs evoked from the cutaneous sural nerve were selectively released from this gating [57]. Conversely, when proprioceptive information was made task-relevant, SEPs from the sural nerve were attenuated and those generated by stimulating the deeper tibal nerve, which innervates muscle tissue and associated proprioceptive organs, were released from attenuation [57]. This covert attention shift selectively gated the task-irrelevant stimulus, but left the cortical responses to the attended and relevant stimulus unchanged. Staines *et al.* also found SEPs and H-reflexes to be attenuated during a simple passive movement task, but showed that the SEP was increased when the movement information became task-relevant [58]. Similarly, work by Brown *et al.* demonstrated movement related gating by showing decreased amplitudes of the N19-P25 cortical potential generated by median

nerve stimulation during passive wrist movement, and increased amplitude of this potential when the contralateral hand was required to track the passive movement [59]. In both cases, these shifts in relevance are examples of covertly shifting attention, and resulted in an increase in cortical excitability when attention was directed to the stimulated body part.

Sensory gating and concussion

Gating of sensory stimuli is worthy of investigation after concussion, as the process of gating subserves an individual's ability to orient attention, and attention has been shown to be impaired by concussion. Visuospatial attention, the act of directing visual attention to a particular spatial location, can be divided into alerting, orienting, and executive components [8]. The alerting component is responsible for sustaining arousal throughout a continuous task; the orienting component facilitates attention shifting between spatial locations in order to optimize processing speed for detecting targets that appear in that location; and the executive component of attention is involved in resolving conflict and switching between tasks requiring different responses [8]. Minor traumatic brain injuries (mTBI) have been shown to significantly impair the executive component of attention when assessed using the Attentional Network Test [8]. The orienting component was also found to be slightly impaired, and the alerting component was unaffected; there was also no difference in error rates between the concussed and control groups [8]. The executive component of this test was most applicable to the task used in the first three studies of this thesis, as it is understood to assess the ability of the test-taker to select relevant information and ignore irrelevant stimuli to produce appropriate responses [8]. Participants with mTBI were less able to disregard the irrelevant distractor stimuli during

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incongruent trials, which resulted in slower reaction times, particularly when comparing accurate to inaccurate trials [8]. Impairment of the executive component of attention in the injured participants did not recover during their one-month study period, suggesting that the brain regions responsible for this function may be particularly susceptible to injury or may take more time to resolve than brain regions related to other components of attention [8].

Gating impairment after concussion has been demonstrated using a battery of neuropsychological tests and structured interviews to assess attention, executive function, learning, and memory [52]. In a group of 182 patients with persistent concussion symptoms, 60% had scores which indicated sensory gating anomalies [52]. Kumar *et al.* also reported that deficits in sensory gating could explain 60% of the variance in self-reported symptoms, even controlling for scores on neuropsychological tests [52]. Sensory gating impairment may disrupt basic information processing, and these authors suggest that concussion symptoms are a result of sensory gating deficits [52].

The studies by Kumar *et al.* [52] and Halterman [8] provide justification for the examination of sensory gating and attention after concussion in this thesis. The studies of this research program aim to examine cortical as well as behavioural responses to sensory selective attention tasks in order to understand the neurophysiology underlying the mechanisms of sensory gating, and how these mechanisms may be affected by concussion.

1.4 Conceptual Model of Thesis and Specific Research Questions

The aims and objectives of this thesis are summarized in a conceptual model, presented here. This model will be repeated and adapted in each of the thesis chapters.
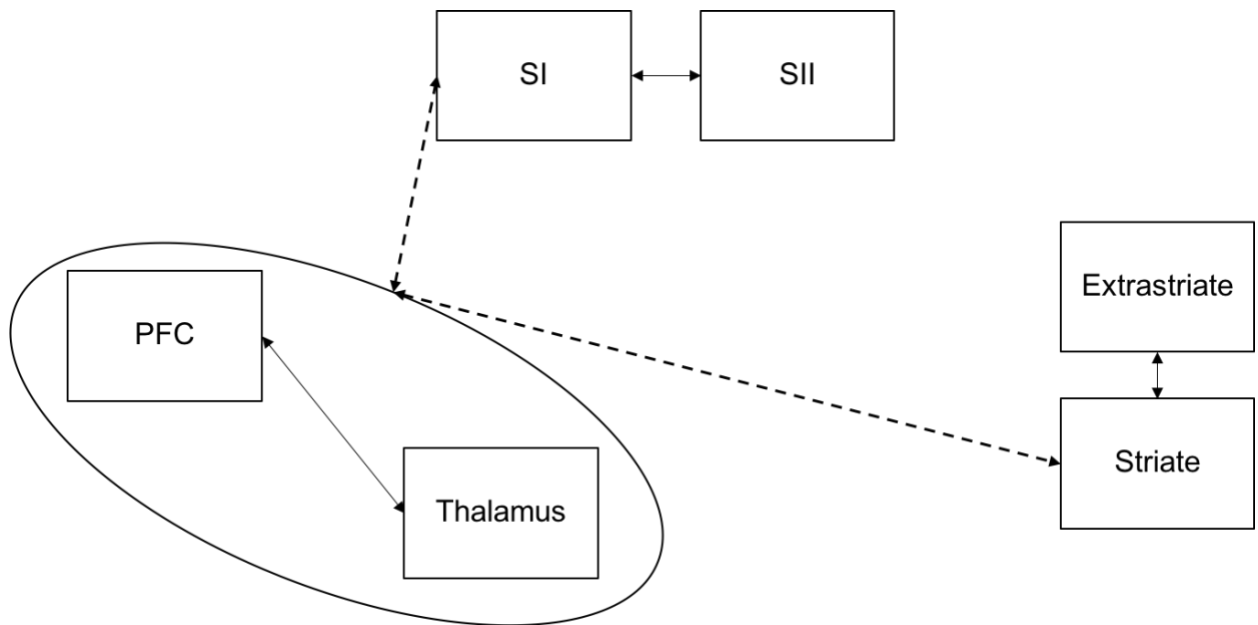
Figure 1.1: Conceptual model of thesis

This thesis aims to define the connection between sensory gating, an attentional orienting function, and the cortical representation of specific sensory stimuli. In the model, the cortical attentional system is indicated represented by the oval containing the interconnected PFC and Thalamus; primary and secondary somatosensory cortices are denoted by the boxes labelled SI and SII, respectively; and the visual processing areas are indicated by the boxes labelled Striate and Extrastriate.

More specifically, the first study of this research program sought to answer two research questions:

1. How are early modality-specific cortical representations of visual and tactile stimuli affected based on the task-relevance of stimuli?

    It was hypothesized that modality-specific cortical representations of both visual and tactile stimuli would be attenuated when the evoking stimuli were task-irrelevant.

2. How does the presence of a simultaneous irrelevant distractor stimulus in another sensory modality modulate early modality-specific cortical responses to visual and tactile stimuli? Is there a behavioural consequence to this on a sensory grading task?

    It was hypothesized that a task-irrelevant distractor stimulus would be gated out of the processing stream, and therefore not affect cortical or behavioural responses to a simultaneous task-relevant stimulus.

Building on the results of the first study, the second study of this thesis was designed to address the following research questions:

3. What role does the prefrontal cortex play in modulating early modality-specific cortical representations of visual and tactile stimuli based on task-relevance?

    It was hypothesized that inhibiting prefrontal cortical function would inhibit task-relevancy based gating of cortical responses to both visual and tactile stimuli, such that relevant and irrelevant stimuli evoked responses of similar amplitude.

4. Does attenuating activity in the prefrontal cortex have an effect on accuracy during a

sensory grading task?

> *It was hypothesized that attenuating prefrontal cortical activity would disrupt*
>
> *gating of task-irrelevant distractors, leading to decreased accuracy when*
>
> *grading simultaneous task-relevant stimuli.*

Clinical experience suggests that attentional orienting and gating of irrelevant stimuli may be impaired by concussions. With an improved understanding of sensory gating under conditions of varied task-relevance, as well as the associated mechanisms, the third study of this thesis sought to address the following questions:

5. Is a history of concussion associated with changes in the early modality-specific cortical representations of visual and tactile stimuli under conditions of changing stimulus relevance?

   > *It was hypothesized that concussion history would disrupt top-down*
   >
   > *attentional orienting such that participants with a history of concussion would*
   >
   > *be less able to modulate cortical responses to visual and tactile stimuli based on*
   >
   > *task-relevance.*

6. Is a history of concussion associated with changes in early modality-specific cortical representations of visual and tactile stimuli when these are presented simultaneously with an irrelevant cross modal distractor? Is there a behavioural consequence of distractor presentation on a sensory grading task requiring shifting attention and suppression of responses to task-irrelevant stimuli?

   > *It was hypothesized that the disruption in relevancy-based gating in those with*

a history of concussion would lead to decreased ERP amplitudes to task-

relevant stimuli when a distractor is presented concurrently. It was also

hypothesized that sensory grading accuracy in the presence of distractor

stimuli would be negatively affected in the group with concussion history, due

to the anticipated disruption in early relevancy-based gating in this group.

Chapter 2: Study 1- Gating at early cortical processing stages is associated with changes in behavioural performance on a sensory conflict task

Adams MS, Popovich C & Staines WR. (2017). Gating at early cortical processing stages is associated with changes in behavioural performance on a sensory conflict task. *Behavioural Brain Research*, (317) 179-187.
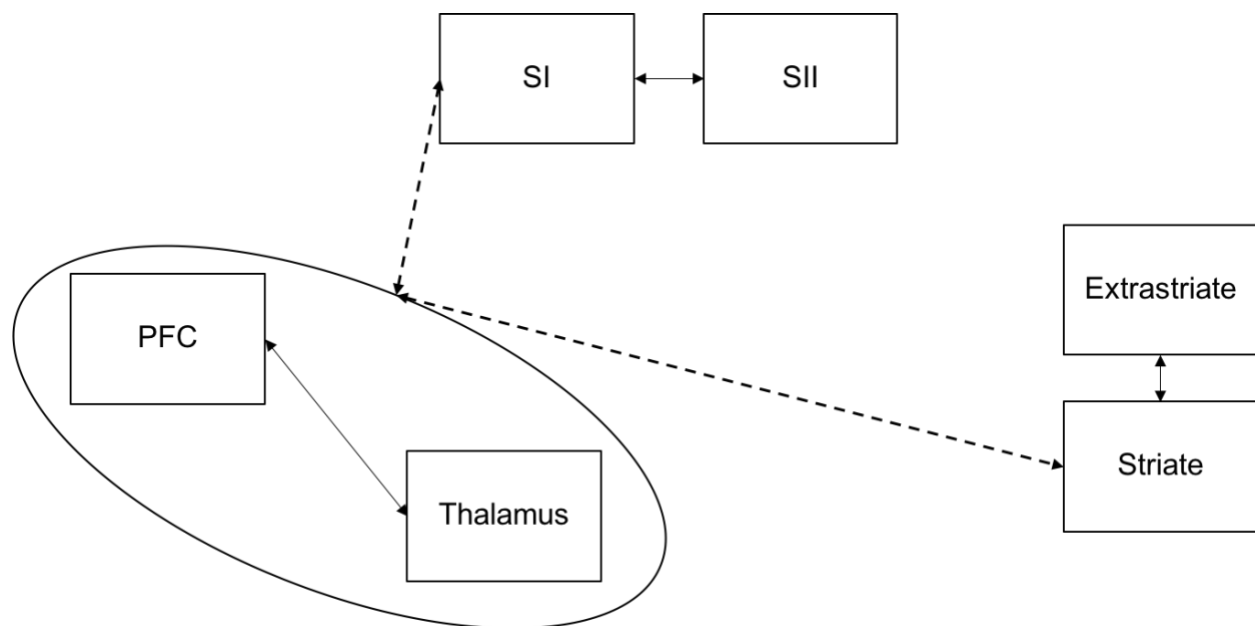

Figure 2.1: Conceptual model of study 1 design.

Study 1 was designed to probe the influence, represented by dashed lines, of manipulating task relevance and presenting distractor stimuli on cortical responses to discrete visual and tactile stimuli.

Crossmodal sensory processing refers to the influence a stimulus in one sensory modality can have on the processing of other stimuli in another modality. Based on task requirements, these stimuli may be integrated or converge with one another. This is known as crossmodal sensory integration, and results in a different cortical response than if one was presented alone [41]. Research has shown that crossmodal integration can facilitate sensory processing, as integration of two relevant stimuli allows for a more coordinated interpretation of the external environment. This is demonstrated experimentally by improved reaction times [42,43], and better detection of weak stimuli [44]. There is evidence that these crossmodal sensory interactions can occur early in the processing stream, in areas traditionally thought to be unimodal [41,45–48]. It is postulated that this crossmodal effect occurs between stimuli from the same source, which would likely not elicit a strong response in isolation [41]. Evidence also shows that the crossmodal effect is enhanced when stimuli are task-relevant; this is known as top-down modulation [48,49].

In contrast, when task demands deem one of two or more simultaneously presented stimuli to be task-irrelevant, the irrelevant stimulus is often suppressed or filtered out of the processing stream. This is known as sensory gating, a term which refers to the inhibition of sensory information as it travels from the periphery to the cortex [50–52]. Gating is thought to protect higher cortical centres from being overcome with irrelevant incoming information [52], and can occur via multiple mechanisms. For example, bottom-up gating can occur during active or passive movement[53–55,57,59,60]. Top-down inhibition of ascending sensory information has also been shown due to the influence of the primary motor cortex or the prefrontal cortex (PFC) [4,6,55,61,62]. Since attention has

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been shown to affect the integration of multiple crossmodal sensory inputs when both stimuli are task-relevant, it may play a role in top-down gating of task-irrelevant information as well. There is much evidence supporting the involvement of the PFC in inhibiting task-irrelevant stimuli during behavioural tasks. A review by Knight et al, [6] details behavioural and electrophysiological evidence from patients with prefrontal cortical lesions exhibiting significant impairments in sustaining attention, as well as inhibiting irrelevant sensory stimuli. It is well understood that the PFC plays an important role in sustaining attention and may also play a role in sensory gating.

The objective of the current study was to understand how attentional gating affects cortical processing of visual and tactile stimuli at early stages of modality-specific processing. Specifically, the study aimed to understand how early somatosensory and visual processing is altered based on whether a stimulus is attended or unattended, when a simultaneous distractor is presented in a different sensory modality, and the effect of an unattended distractor stimulus on behavioural performance. Therefore, the present research was designed to test three main hypotheses. The first was that early modality-specific (visual and tactile) cortical responses would be diminished when attention was directed away from the modality being tested. The second hypothesis was that early cortical responses to task-relevant sensory stimuli would remain unchanged whether those stimuli were presented alone or simultaneously with a task-irrelevant distractor in the other sensory modality. This was based on the first hypothesis, that the distractor stimulus would be effectively gated out of the processing stream at an early stage. The final hypothesis of this study was that participants' ability to accurately grade the amplitude of visual or tactile stimuli would be consistent whether these stimuli were presented alone or

simultaneously with a task-irrelevant crossmodal stimulus, again reflecting the cortical gating effect postulated in the first hypothesis.

2.2 Methods

Participants

Electroencephalographic (EEG) and behavioural data were collected from thirteen healthy volunteers (8 female, 5 male), aged 19-28. Participants had no history of brain injury, substance abuse, psychoactive drug treatment, or other neurological disease or impairment. All experimental procedures were approved by the University of Waterloo's Office of Research Ethics, and all participants provided informed consent to participate.

Experimental Paradigm

The experimental task required subjects to use a pressure-sensitive bulb to approximate the amplitude of discrete visual and tactile stimuli using a graded motor response. The stimuli were presented either in isolation, as unimodal vibrotactile (T) or visual stimuli (V), or simultaneously, as crossmodal visual and tactile stimuli (VT). A single trial consisted of either a visual, tactile, or crossmodal stimulus presentation. Experimental blocks contained 54 stimuli each presented for 500 ms, with 2.5 s between trials, so that each block lasted approximately three and a half minutes. The experimental design consisted of fifteen blocks of trials divided among three attentional manipulations (five blocks each) that were randomized across participants. Participants were instructed to attend to, and produce a force-graded response approximating the amplitude of: 1) only the tactile stimulus presented either unimodally (T(T)) or crossmodally (T(vT)); 2) only

the visual stimuli presented either unimodally (V(V)) or crossmodally (V(Vt)); or 3) the combined crossmodal stimuli (VT).

Each participant was seated comfortably for the duration of the experiment. They fixed their gaze on a computer screen for all blocks, and rested the palmar surface of the second digit of the left hand on a device which delivered vibrotactile stimuli. Participants judged the amplitude of the stimulus type they were instructed to respond to, or track, for that block: either tactile alone, visual alone, or crossmodal, and made a graded motor response by squeezing a pressure-sensitive rubber bulb with their right hand. When responding to tactile stimuli, subjects were asked to apply enough force to the pressure-sensitive bulb to approximate the vibration amplitude of each tactile stimulus presented. They were asked to do this each time a tactile stimulus was presented, whether it was presented alone or in combination with a visual one. The visual condition was similar, with subjects applying force to the bulb to correspond to the height of a bar appearing on the computer screen, regardless of whether or not a tactile stimulus accompanied it. When responding to both visual and tactile stimuli, participants were asked to add the height of the visual stimulus and the amplitude of the tactile stimulus and apply a corresponding force to the pressure-sensitive bulb representing the summation. To ensure force output on these combined trials never exceeded an individual's maximum capacity, no single stimulus required a squeeze of more than 25% of the participant's maximum force output and combined responses never exceeded 50%.

The experimental trials were preceded by a training session, which lasted approximately 5 minutes. In the training session, two bars were presented on the computer screen: a blue bar, controlled by the participant squeezing the pressure bulb, and a yellow

one which varied randomly in height. The objective was for subjects to match the blue bar

to the height of the yellow bar by applying a graded force to the pressure bulb. The blue bar

provided visual feedback to teach participants how to use the bulb to grade the visual

stimuli. At the same time, the amplitude of the vibrotactile stimulus applied to the subject's

finger varied proportionally to match the force applied to the bulb. In this way, the training

program connected the visual and vibrotactile stimuli through the means of the pressure-

sensitive bulb. During the experimental task, the blue response bar was absent, depriving

participants of feedback about the accuracy of their grading performance, and the

amplitude of the vibrotactile stimuli varied independently of the visual stimuli.

Stimuli

The target visual stimuli were yellow bars (6 cm wide) which appeared in the center

of a black computer screen. The bar was visible for 100 ms and appeared at randomized

heights on the screen, representing different amplitudes of visual stimuli. Vibrotactile

stimuli were presented to the second digit of the left hand using a custom-made

vibrotactile device. These stimuli were created by the conversion of digitally-generated

waveforms to analog signals (DAQCard 6024E, National Instruments, Austin, TX) and

amplifying the signal (Bryston 2BLP, Peterborough, Ontario, Canada) using a custom

program written in LabVIEW (version 8.5; National Instruments). Variations in the

amplitude of the voltage driving the vibrotactile device resulted in proportional changes in

the tactile stimulus applied to the finger. The amplitude of each vibration was constant

within a trial and varied randomly between trials. The average stimulus amplitude across

all trials including a tactile stimulus did not differ between the experimental conditions.

The frequency of the vibration was held constant at 25 Hz. In order to prevent auditory

perception of the vibrotactile stimuli, participants wore earbud headphones during the experiment which delivered white noise throughout the training and experimental tasks (White Noise Ambience Lite, Logicworks version 2.02, Apple App Store).

Data acquisition and recording parameters

Behavioural data were recorded using a custom program written in LabVIEW (version 8.5, National Instruments, Austin, TX). Participants applied force to the pressure-sensitive bulb that caused air to move through a rubber tube in a closed system, leading to a pressure change that was measured by a pressure sensor and converted to a voltage. There was a linear relationship between the pressure measurement and the voltage produced.

EEG data were recorded from 32 electrode sites (32 channel Quik-Cap, Neuroscan, Compumedics, NC, USA) in accordance with the international 10-20 system for electrode placement and referenced to the linked mastoids. Impedance was maintained < 5kOhms. EEG data were filtered (DC-100 Hz) and digitized at 500 Hz (Neuroscan 4.5, SynAmps2, Compumedics, NC, USA). Data were then saved for subsequent analysis, which began with epoching and visual inspection for artifacts (i.e. blinks, muscle contractions, eye movements). Epochs were 600 ms in length, beginning 100 ms before stimulus onset, and contaminated epochs were eliminated before averaging. A total of 90 trials per participant were collected for each stimulus type, and after contaminated trials were eliminated, the final trace for each experimental condition consisted, on average, of 62 artifact-free epochs.

Event-related potentials (ERPs) were averaged to the onset of each stimulus relative to a 100 ms pre-stimulus baseline. Somatosensory ERPs were measured from participant

averages for all trials of a particular condition. Mean ERP amplitudes and latencies were computed for each subject within specific time windows centred around the post-stimulus latencies of early somatosensory and visual ERP components: somatosensory - P50 (45-75 ms), N70 (60-80 ms), P100 (80-120 ms), N140 (125-175 ms); visual - P1 (125-175 ms), N1 (180-220 ms) and P2 (225-285 ms). Based on the distribution, amplitude and latency of each potential was measured from electrode sites corresponding to scalp locations showing maximum voltage during the corresponding latency window. All amplitudes were measured as raw voltage relative to the pre-stimulus baseline.

Data analysis

Behavioural analysis

Behavioural data were analyzed by comparing the amplitude of the target stimulus to the amplitude of the response created by the participant squeezing the pressure-sensitive bulb. The percent difference between the target stimulus amplitude and the participant's response amplitude was calculated. A two-way repeated measures ANOVA with attention instruction and distractor status as within subject factors was conducted to assess statistical differences in accuracy when the stimuli were presented alone or with the distractor. Although the crossmodal condition was collected, with participants asked to integrate the visual and tactile stimuli, the behavioural accuracy of this condition was not relevant to the main focus of this paper. ERP responses to the crossmodal stimuli condition are reported, however, the focus of the present research was on understanding how an irrelevant distractor stimulus was gated out of the processing stream, which was tested when subjects were attending to only one of two simultaneously presented stimuli.

Therefore, the grading accuracy of the crossmodal integration task was excluded from behavioural analysis.

ERP analysis

For all ERP analysis, potentials were calculated as peak-to-peak amplitudes between the peak of interest and the preceding potential of opposite polarity. To test the hypothesis that early somatosensory and visual ERPs would be modulated by task demands and the presence or absence of crossmodal stimuli, a two-way repeated-measures ANOVA was carried out on the amplitude of each potential with attention requirement (three levels: grade tactile, grade visual, or integrate crossmodal stimuli) and stimulus (two levels: tactile or visual alone, or simultaneous visual and tactile) as within-subject factors. Since attention has been shown to modulate tactile ERPs at an early stage of cortical processing [48,63], pre-planned contrasts were conducted on the amplitude of the P50 and N70 ERPs. Specifically, these contrasts tested two hypotheses: that the presentation of an attended stimulus would result in a significantly larger ERP than when the same stimulus was presented in its unattended condition; and, that the presentation of an attended stimulus would result in an ERP of the same amplitude regardless of whether or not an unattended "distractor" stimulus was simultaneously presented. A pre-planned contrast was also used to test the hypothesis that attending to crossmodal stimuli would result in increased amplitude of the early somatosensory ERPs of interest. While not central to the current work, this hypothesis was used to compare the results of this study to previous research from this laboratory [48,49,63].

Secondary analysis of previous research findings

Analysis of N70 potentials was completed on data previously collected by this lab group. The initial analysis of this data was reported in Popovich and Staines (2014) and

compared P50 and P100 amplitudes across three sensory conditions. The conditions were as follows: two tactile stimuli presented sequentially (TT), one visual and one tactile stimulus presented simultaneously (VT), and a visual stimulus presented 100 ms before the tactile stimulus (VTd). This study found that the P50 and P100 amplitudes were largest in the VTd condition, and smallest in the TT condition. For comparison purposes, Popovich and Staines' [48] TT condition was analogous to the presentation of tactile stimuli during the attend tactile condition in the present work, and their VT condition was analogous to the task requiring participants of the present study to integrate simultaneous crossmodal stimuli. Re-examining this data with a focus on the N70 potential allowed assessment of how the attentional state affected N70 modulation, as in one experimental design, the task instructions meant that the two sensory stimuli provided conflicting information, and in the other, both sensory stimuli were relevant to guide the motor task. The N70 ERPs were extracted as P50-N70 peak-to-peak amplitudes and compared using a one-way repeated measures ANOVA (factor: condition – TT, VT, VTd).

2.3 Results

Behavioural performance

A two-way repeated-measures ANOVA was conducted with within subject factors as previously described. A significant interaction effect was observed between attention instruction and distractor status ($F_{1,12}$=11.74, p=0.005). Pre-planned contrasts revealed that subjects' responses when asked to grade the tactile stimuli were significantly closer to the ideal responses ($F_{1,12}$=13.24, p=0.003) when no distractor was present than with the

visual distractor (Figure 2.2a). The presence of a tactile distractor did not affect

performance during the visually-guided task condition ($F_{1,12}=1.46$, p=0.25, Figure 2.2b).
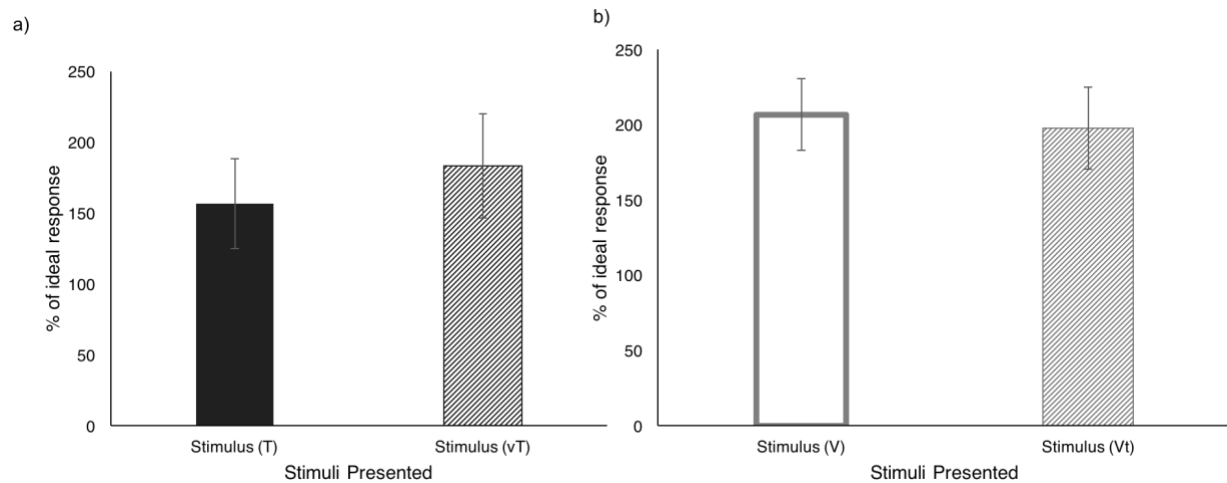
Figure 2.2: Accuracy of grading stimuli with and without a crossmodal distractor

a) Accuracy of grading tactile stimuli with and without a visual distractor

Percent of ideal response during tactile-guided grading task. Response to individual tactile

stimuli (solid black bar) was significantly closer to ideal than when an unattended visual

stimulus was simultaneously presented (striped black bar) (* indicates significant to p<0.05). In

both cases, participants were attending to and grading only the tactile stimuli.

b) Accuracy of grading visual stimuli with and without a tactile distractor

Percent of ideal response during visually-guided grading task. Response to individual visual

stimuli (open gray bar) was not significantly different than when a tactile stimulus was

presented concurrently (striped gray bar). In both cases, participants were attending to and

grading only the visual stimuli.

Event-related potentials

Figure 2.3a shows grand average traces of tactile ERPs at electrode CP4. Of the thirteen participants from whom data was collected, two were lacking discernable peaks for both the P50 and N70 ERPs of interest, leaving eleven participants for data analysis. The grand average traces are constructed from the responses of these eleven participants to the presentation of tactile stimuli.
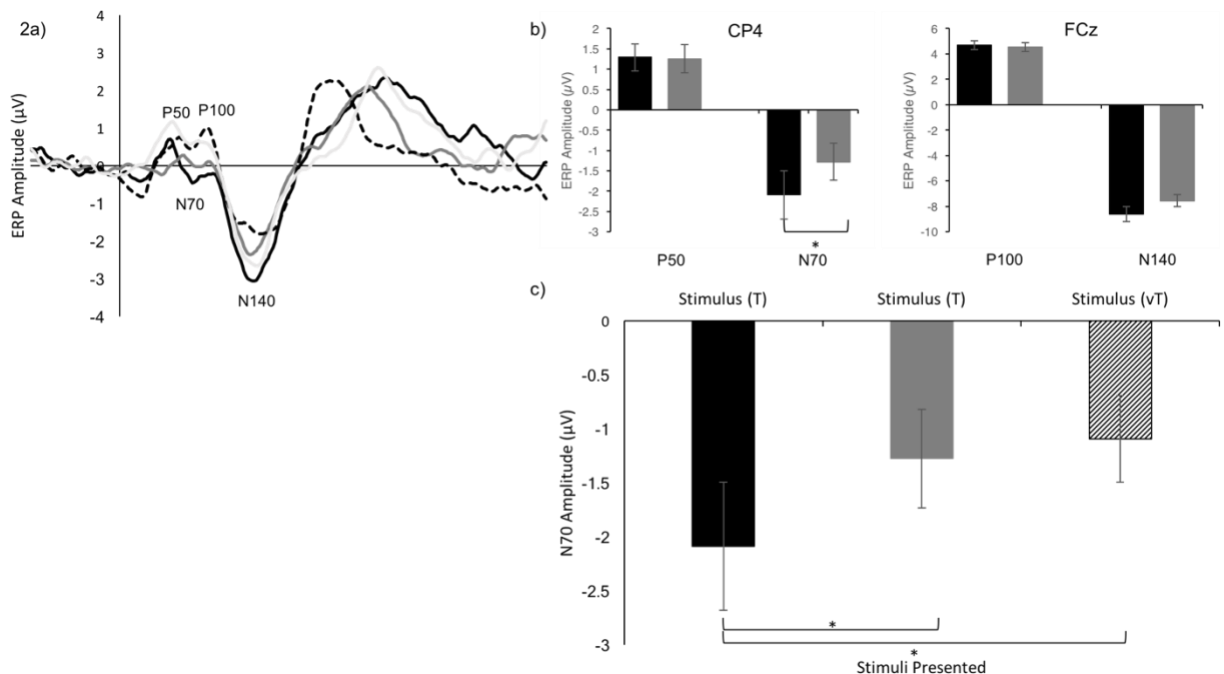
Figure 2.3: Tactile-evoked ERPs

a) Grand average waveforms (n=11) generated in response to tactile stimuli when subjects were instructed to attend to tactile (black), visual (dark gray) and crossmodal (light gray) stimuli. The solid lines were generated when participants were presented with unimodal tactile stimuli, while the dashed line indicates a visual distractor was simultaneously presented. ERP components of interest are labeled on the trace for electrode site CP4.

b) ERP amplitudes to tactile stimuli when participants were attending to tactile stimuli (black bars) and when they were attending to visual stimuli (gray bars). In all cases, the stimulus presented was tactile. N70 amplitude to tactile stimuli was significantly higher when participants were instructed to attend and respond to tactile stimuli than when they attended and responded to visual (* indicates significant to p<0.05). There was no significant difference based on attended modality for the P50, P100, or N140 potentials

c) N70 amplitude to tactile stimuli when attending to tactile stimuli (solid black bar), to tactile stimuli when attending to visual (solid gray bar), and to attending to tactile stimuli when they were presented with a simultaneous, task-irrelevant visual distractor (striped black bar). The N70 was significantly attenuated when attention was directed toward visual stimuil and in the presence of the visual distractor (* indicates p<0.05).

The amplitude and latency of the P50 potential was calculated from the eleven participants who demonstrated a clear P50 component (mean latency 58.4 +/- SE 1.1 ms). The P50 potential was maximal at electrode CP4 overlying contralateral somatosensory cortex, and analysis was conducted using the potentials from this electrode. The P50 was generated by tactile stimuli and not observed in response to unimodal visual stimuli. The two-way repeated measures ANOVA showed no significant interaction between stimulus and attention ($F_{2,58}$=0.30, p=0.74), and no significant main effects of stimulus type ($F_{1,58}$=0.15, p=0.70) or attention instruction ($F_{2,58}$=0.31, p=0.74). Pre-planned contrasts showed no significant differences in P50 amplitudes to tactile stimuli when subjects: attended to tactile versus visual stimuli ($F_{1,58}$=0.20, p=0.66; Figure 2b), attended only to tactile stimuli versus simultaneous crossmodal stimuli ($F_{1,58}$=0.29, p=0.59), or when

attention was held constant to tactile stimulation and subjects were presented with unimodal or crossmodal stimuli ($F_{1,58}$=0.22, p=0.64).

EEG tracings demonstrated a clear N70 component (mean latency 78.7 +/- SE 1.1 ms) in response to vibrotactile stimuli. The N70 was maximal at CP4, overlying contralateral somatosensory cortex, and statistical analysis was conducted using the potentials from this electrode. It was not observed in response to visual stimuli, supporting the idea that, like the P50 component, the N70 represents primary somatosensory cortical processing [49,64]. The two-way repeated measures ANOVA results showed a trend towards a significant interaction effect between stimulus type and attention requirement ($F_{2,58}$=2.92, p=0.06). There were no significant main effects of stimulus type ($F_{1,58}$=2.00, p=0.16) or attention instruction ($F_{2,58}$=0.63, p=0.54) observed. This indicated that the effect of the stimulus type was dependent on the attention instruction given. Pre-planned contrasts found that N70 amplitudes to tactile stimuli were significantly larger when subjects were attending and responding to tactile stimuli than when they attending and responding to visual ($F_{1,58}$=5.32, p=0.02; Figures 2.3b and c). The second contrast tested the difference between ERP responses to attended unimodal tactile stimuli and attended simultaneous crossmodal stimuli, and found no significant difference based on this attentional shift ($F_{1,58}$=2.22, p=0.14). The third contrast tested the effect of the stimulus being presented. N70 amplitudes were significantly larger when subjects were presented with unimodal tactile stimuli as compared to crossmodal stimuli ($F_{1,58}$=7.31, p=0.009), in cases where participants were attending and responding only to tactile stimuli (Figure 2.3c).

EEG tracings collected from all subjects demonstrated P100 and N140 components (mean latencies P100: 101.2 +/- SE 1.4 ms; N140: 149.5 +/- SE 2.2 ms) in response to vibrotactile stimuli. Both were distributed bilaterally at parietal electrode sites and were maximal at electrode FCz, therefore analysis of P100 and N140 was conducted at this electrode. Two-way repeated measures ANOVAs showed no main effect of attention for P100 ($F_{1,59}$=0.41, p=0.52) but trended toward significance for N140 ($F_{1,60}$=3.60, p=0.06). There was no significant main effect of attention instruction (P100: $F_{2,59}$=1.77, p=0.18; N140 $F_{2,60}$=0.53, p=0.59) nor a significant interaction effect for either potential (P100: $F_{2,59}$=1.64, p=0.20; N140: $F_{2,60}$=0.46, p=0.63 Figure 2b).

Figure 2.4a shows a grand average trace of the ERPs generated in response to visual stimuli. All peaks (P1, N1, and P2) were observed in all experimental participants. The figure depicts the ERPs that occurred in response to visual stimuli when subjects directed attention toward and away from visual input.
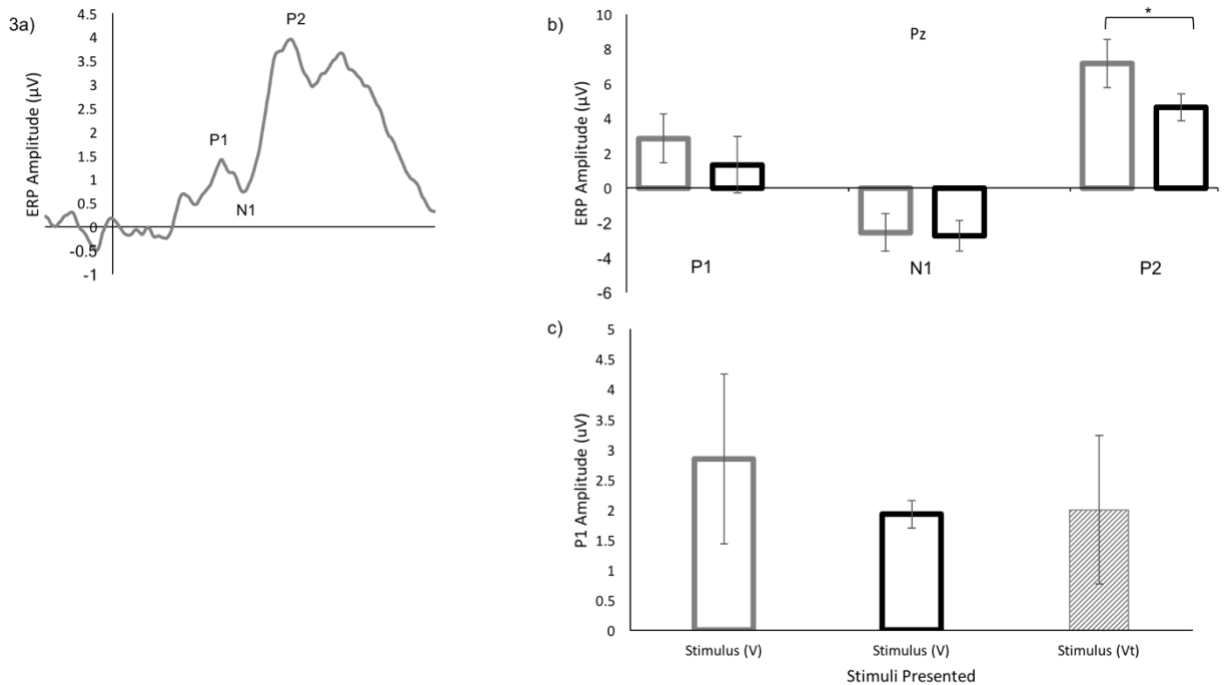
Figure 2.4: Visually-evoked ERPs

a) Grand average waveforms (n=13) generated in response to visual stimuli when subjects were instructed to attend to these stimuli. ERP components of interest are labelled on the trace for electrode site Pz.

b) Amplitudes of visually-evoked ERPs when participants were attending to visual stimuli (open gray bars) and when they were attending to tactile stimuli (open black bars). There was no significant difference in P1 or N1 amplitude whether the visual stimuli were attended or unattended. P2 amplitude to tactile stimuli was significantly smaller than that generated in response to visual stimuli (* indicates significant to p<0.05).

c) P1 amplitude to visual stimuli alone when attending to visual stimuli (open gray bar bar), to visual stimuli when attending to tactile stimuli (open black bar) and to visual stimuli with a simultaneous, task-irrelevant tactile stimulus when attending to visual stimuli (striped gray bar).

There was no significant difference in P1 amplitude whether visual stimuli were attended or unattended, nor in the presence of an unattended tactile distractor.

All subjects demonstrated three clear ERP components in response to visual stimuli, labelled P1 (mean latency 152.4 +/- SE 2.1 ms), N1 (mean latency 192.3 +/- SE 2.3 ms), and P2 (mean latency 255.5 +/- SE 3.5 ms). All were maximal at electrode Pz, distributed bilaterally, and not observed in response to tactile stimuli. Two-way repeated measures ANOVAs were performed with inverse transformations required to uphold the assumption of normality for P1 and N1 analysis. Results showed no significant interaction between stimulus and attention for either the P1 or N1 (P1: $F_{2,60}$= 0.13, p=0.88; N1: $F_{2,60}$=1.18, p=0.31), and no significant main effect of stimulus type (P1: $F_{1,60}$=0.41, p=0.52; N1: $F_{1,60}$=0.67, p=0.42; Figures 2.4b and c). Attention instruction showed a trend toward significance for the P1 potential ($F_{2,60}$=3.01, p=0.06; Figures 2.4b and c) but was not significant for the N1 potential ($F_{2,60}$=0.51, p=0.61; Figure 2.4b). A significant interaction effect was found for P2 ($F_{2,60}$= 17.78, p<0.0001). This interaction effect was explored with a post-hoc Tukey test, which found that the P2 potential was significantly larger (p<0.05) when participants were attending to visual stimuli than when they were attending to tactile stimuli (Figure 2.4b).

Secondary analysis of previous research findings

As described previously, a secondary analysis of previous research findings was conducted for comparison with the data generated by this experiment. All twenty participants in this experiment demonstrated an N70 component (mean latency 80 ms +/- SE 1.7 ms) which was maximal at electrode CP4. For the re-analysis of this data, the N70

potentials generated by the twenty participants in this experiment were compared between the same three conditions, all requiring attention to the tactile stimuli. N70 amplitudes were not significantly different between the three conditions ($F_{2,24}=0.86$, p=0.44; Figure 2.5).
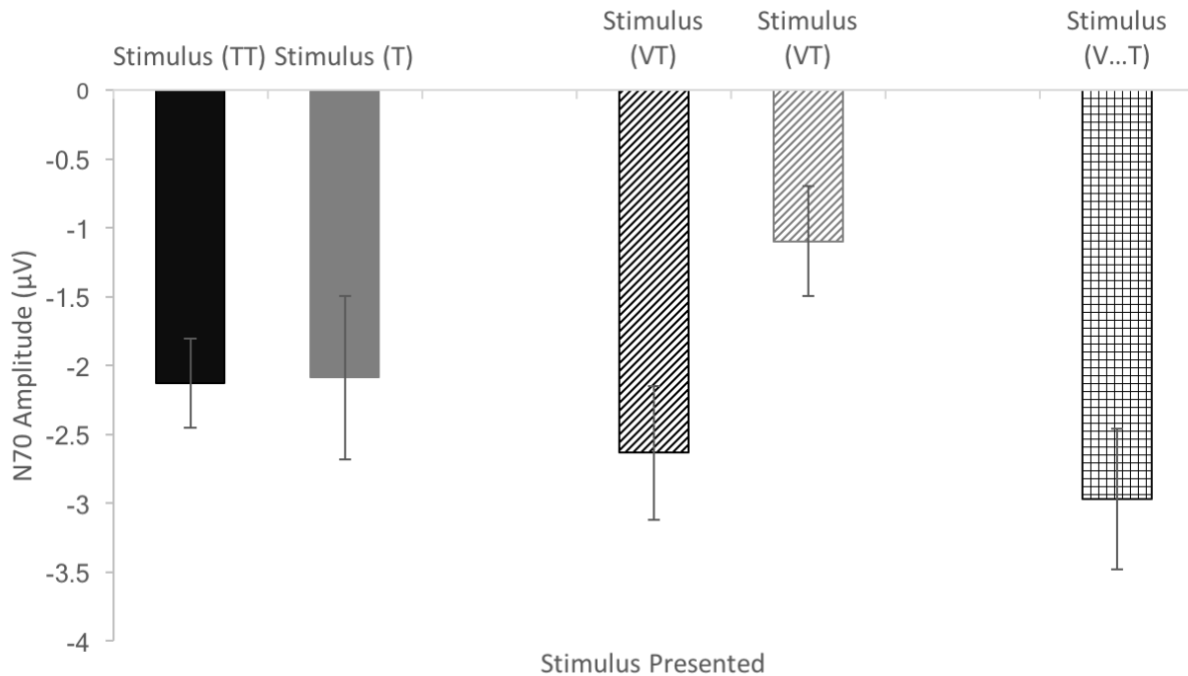
Figure 2.5: N70 amplitudes from secondary data analysis

N70 amplitudes at CP4 to tactile stimuli when subjects were instructed to attend to and summate crossmodal (visual and tactile) stimuli. The black bars represent data collected as part of a previous study [48] and gray bars represent the data collected as part of the current research. There was no significant difference in N70 amplitude when crossmodal stimuli was presented when the task required participants to combine stimuli, rather than select between them as in the present study. The solid bars represents two simultaneous tactile stimuli in Popovich and Staines [48] and one tactile stimulus in the current experiment; the striped bars

represent simultaneous crossmodal stimuli; and the checkerboard patterned bar represents

crossmodal stimuli separated by 100ms (visual presented first), a condition only present in

Popovich and Staines [48].

2.4 Discussion

These results demonstrate that early modality-specific somatosensory cortical areas are gated at an early stage by sustained attention. The present study examined three main hypotheses: that early ERPs to visual and tactile stimuli would be suppressed when the stimuli were not attended; that early ERP amplitudes would remain unchanged whether or not an unattended distractor stimulus was presented concomitantly with an attended, task-relevant stimulus; and that gating unattended stimuli would ensure that these distracting stimuli did not detract from performance on a sensory-guided motor task. It was shown that, as hypothesized, attention had an effect on early somatosensory ERP amplitude, but this effect was not consistent between the two sensory systems examined in this work. N70 amplitudes to attended tactile stimuli were larger than when the same tactile stimulus was not attended. However, this was the only somatosensory ERP that was modulated in this study, and early visual ERPs also were not affected by attention. Notably, the later visual P2 amplitude did show an effect of attention, being significantly greater in amplitude when attending to visual stimuli.

This finding is similar to the results of a study by Eimer and Driver [65]. They examined ERPs elicited in response to visual and tactile stimuli presented at attended and unattended spatial locations. This study found that spatial location only affected tactile ERP

amplitude when these stimuli were task-relevant, but that visual ERPs were modulated by location of attention regardless of their task-relevance. Both Eimer and Driver [65] and the present study suggest that tactile stimuli are effectively gated out of the processing stream when task-irrelevant, but that visual stimuli are subjected to a different modulation process. Attentional modulation of early visual ERPs has been shown previously, but in tasks which require trial-by-trial attentional shifts [66,67]. However, in experimental designs requiring attention to be sustained for blocks of successive trials, as in this study, P1 and N1 were not affected by attention switching, and ERP modulations were observed approximately 200 ms after stimulus presentation [68]. This delay in modulation corresponds with the timing of the modulations recorded in this study, and suggests that effects on early visual ERPs are more specific to rapid switches of attention rather than to attentional change in general.

This study also utilized tactile and visual stimuli to assess the effectiveness of the attentional system in suppressing non-attended sensory information that is not relevant for a sensorimotor task. When a tactile distractor was present, the visual ERPs P1, N1 and P2 were not significantly different than when the tactile distractor was absent. In contrast, a visual distractor had a significant effect on the early somatosensory N70 ERP. When the visual distractor was present during a tactile-guided task, the N70 amplitude was significantly smaller than when the task was completed without the distractor (Figure 2c). This EEG analysis was supported by an examination of participants' accuracy in grading attended stimuli when distractors were present. As hypothesized, the changes in cortical processing corresponded with participants' behavioural performance. Since somatosensory stimuli were effectively gated by attention and did not modulate early

visual ERPs during the visual grading task, visual tracking accuracy was not diminished by the presentation of a tactile distractor. Conversely, since visual stimuli were not effectively gated by attention at early processing stages and did significantly decrease early tactile ERP amplitudes, performance was significantly less accurate during tactile grading when a visual distractor was present.

The most notable result from this study is the connection between modality specific sensory potentials and behavioural performance on a task of interest. When used as distractors, unattended somatosensory stimuli did not influence the ERP response to the stimulus of interest, nor did they impact the behavioural response to the attended stimulus. This connection between ERP amplitude and behavioural performance as a result of attention is strengthened by the different modality-specific modulation patterns shown in the results of this experiment, with early attention-based gating occurring in response to unattended somatosensory stimuli but not in response to unattended visual stimuli. A study by Taylor-Clarke *et al.* [64] also made a connection between ERP modulation and behavioural performance. They asked participants to judge whether single or double-tap tactile stimuli were delivered to their forearms, and examined the effect of adding simultaneous task-relevant or task-irrelevant visual stimuli on the N80 ERP. This N80, a negativity generated approximately 80 ms after onset of somatosensory stimuli, corresponds to the N70 examined in this present work [69]. Taylor-Clarke *et al.* [64] found the N80 to be significantly larger in amplitude when simultaneous visual stimuli were task-relevant; the present study found decreased N70 amplitudes when simultaneous visual stimuli were task-irrelevant and attention was directed elsewhere. In addition, Taylor-Clarke's group found increased N80 ERP amplitude correlated to improved tactile acuity,

while in the present study, decreased N70 amplitude was correlated with decreased task accuracy. These experiments used fundamentally different task demands, with stimuli acting as informative in Taylor-Clarke's work or distracting in the present study, but the connection between early cortical change, represented by N70/80 modulation, and behavioural change is maintained.

The current study adds to the body of literature regarding early modality-specific gating in the somatosensory domain. In a study by Bolton and Staines [70] participants were required to attend to tactile stimuli delivered to one of two fingers. Stimuli differed between targets and distractors, and participants were required to count target stimuli, rather than make a specific motor response. Notably, no differences were found in early (P50 and N70) ERPs based on which finger was attended, although the P100, N140, and LLP potentials were significantly larger when the finger was attended to than when it was not [70]. This change in amplitude in response to shifting attention is similar to what was found at the N70 potential in this current study. There are two possible reasons for the difference in the timing of attentional modulation between Bolton and Staines and the present study. One is the difference in task requirements, specifically in the involvement of the motor system. In the present task, the sensory information was used to make a decision about how hard to squeeze a pressure bulb, so was interpreted and acted upon differently than in the previous study, in which the perceived tactile targets were counted. It is possible that the motor component of the present task made the tactile information more valuable, and thus susceptible to attentional upregulation at an earlier stage, reflected in the modulation of an earlier ERP, N70 instead of P100. In support of this point, other studies using sensory-guided tasks have shown modulations early in the processing

stream, either at other early cortical potentials besides N70 [63], or of the primary

somatosensory cortex more generally [71]. The second difference between the task used in

this current study and the one used by Bolton and Staines [70] was the specific attentional

requirement. Herrmann and Knight focus on the concept of within-modality switches of

attention, but also note that cross-modality switches likely involve different attentional

mechanisms [72]. The task used in Bolton and Staines [70] required participants to

perform within-modality attention switches – between tactile stimuli delivered to

disparate spatial locations. In contrast, the task used in the present experiment required

participants to perform between-modality attention switches. Since it is understood that

different attentional mechanisms underlie these different types of switches, it is possible

that the associated patterns of ERP modulation may reflect these differences.

Unlike in previous studies [48,49,63] the present work did not show attention-

based modulation of the P50 and P100 potentials. A possible explanation for this also

relates to the task differences between the present study and other experimental designs.

In the present analysis, the instruction to participants when visual and tactile stimuli were

presented simultaneously was to attend and respond to only one of the two stimuli in the

pair, although a separate block of trials was completed for comparison with data from

previous work, with participants asked to summate these two stimuli. In the works cited

above, participants were required to respond by combining responses to simultaneously

presented stimuli. The act of combining the two crossmodal stimuli seems to have the

effect of modulating P50 and P100 and leaving N70 unchanged. In contrast, the instruction

to attend to only one of a pair of stimuli appears to specifically change N70 amplitudes and

not P50 or P100. Both P50 and N70 potentials are hypothesized to be generated in the

primary somatosensory cortex (S1), and studies have shown that both are modulated by the prefrontal cortex (PFC) [4,73]. The differential modulation highlighted by the present research seems to argue that different neuronal populations within S1 are responsible for generating these ERPs, or that the PFC acts differently on these disparate representations. Other studies comparing somatosensory evoked potentials (SEPs) between individuals with PFC damage and healthy controls showed that selected early SEP components (P26 and N67) were enhanced in those with damage to the PFC [4]. The N70 potential was also enhanced following inhibitory cTBS applied to the prefrontal cortex [73]. These components are also understood to be generated in somatosensory cortices: somatosensory area 1 or 2 for the P26, and the somatosensory association cortex for the N67/ N70 [4]. The PFC, with relays through higher-order thalamic nuclei, normally acts tonically to gate or suppress early somatosensory cortex excitability. Inhibition by cTBS or damage to the PFC disrupts its inhibitory influence, leading to SEP enhancement [4,73]. Since the somatosensory gating observed in the present study also occurred at an early processing stage, the role of the PFC should be tested in this attention-related gating.

Consistent with previous work, this study found that modality-specific visual potentials are affected by attention at a later stage than modality-specific somatosensory potentials [6,68]. Previous work has examined an N170 potential, which occurs at a similar post-stimulus latency as the N1 reported in the present study, and also in response to visual stimuli [6]. Attention-related effects have been reported on the N170, and these effects were attenuated in patients with damage to the dorsolateral prefrontal cortex (DLPFC) [74]. It is not clear why the N1 did not show any attentional modulation in the present study; however, previous work showing attentional effects on the N170 used an

oddball-like task, as opposed to the selection task used in the present work. As discussed previously, since the attentional demands of a task – sustaining or shifting attention – can influence visual ERPs, so it is conceivable that the differences in task requirements may play a role in the N170/N1 modulation differences as well.

The re-analysis of N70 data from Popovich and Staines [48] leads to the hypothesis that the N70 modulation observed during the present study is specific to a selective attention or gating task instruction. Since no modulation of this potential was observed by Popovich and Staines, it can be concluded that the simple presence of crossmodal stimuli do not affect the N70 amplitude, and that the N70 is not modulated when participants are asked to utilize two stimuli to formulate their responses. It is therefore conceivable that the effect on N70 seen during the present study is specific to the gating task used here. If this is borne out by further experimentation, N70 may be useful as a marker of effective gating of tactile stimuli, making it applicable in future work examining pathological states in which impairment in attention-based gating is suspected.

The generalizability of these results to daily life is limited because the task is less functional than many activities of daily living. Generally, sensory environments are more complex than just two stimuli, and task requirements vary widely and switch often, particularly in a culture where technology is so pervasive. However, the task studied in the present experiment reproduces the basic sensorimotor gating function performed in many daily activities, and represents a starting point to studying more complex tasks and environments. Future studies can build upon the work presented here by testing N70 as a marker of tactile gating. The finding that visual stimuli act as a more effective distractor, both electrophysiologically and behaviourally, because they are gated out of the processing

stream at a later point, suggests that impairments in gating may be testable with a protocol such as this. It would also be of interest to test this gating effect using a different combination of sensory stimuli, to see if the gating effect on the tactile N70 is preserved with other stimuli. As mentioned previously, probing the role of the PFC in this gating effect would provide insight into the mechanisms responsible for this attention-related gating.

2.5 Conclusion

This study clearly demonstrates how attention acts as a gate to inhibit irrelevant stimuli, and highlights the differences in the timing of this gating between visual and tactile stimuli. It also connects these electrophysiological changes to task performance when visual and tactile stimuli were used as unattended distractors. The latencies at which the gating occurred determined the potential of stimuli for distraction – if gated out at an early stage, as the tactile stimuli were, ERP changes and behavioural performance were preserved when distracting stimuli were present. However, if gating occurred too late, as with the visual stimuli, attention could not be directed just to the stimuli of interest, so the distractor decreased both the ERP amplitudes and the accuracy of grading of the stimulus of interest.

Based on the conclusions of study 1, the conceptual mechanistic model can be updated as follows:
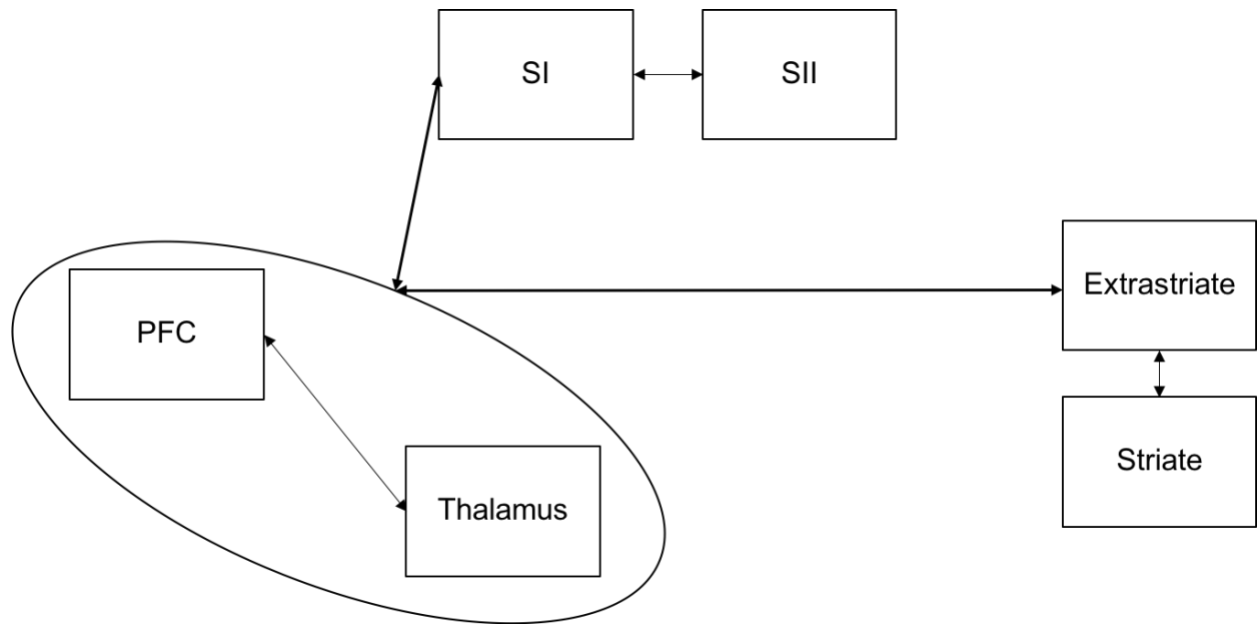
Figure 2.5: Conceptual model of study 1 findings

Study 1 showed that relevancy-based gating has an influence on early processing of somatosensory stimuli, with changes to the N70 ERP generated in primary somatosensory cortex. It also showed that the influence of varying task relevance exerted modulatory effects on visually-evoked ERPs with much longer latencies, likely generated in extrastriate areas. The model, therefore, now includes solid lines connecting the attentional nodes to the appropriate sensory-specific cortical regions.

Chapter 3: Study 2- The role of the prefrontal cortex in relevancy-based gating of visual and tactile stimuli
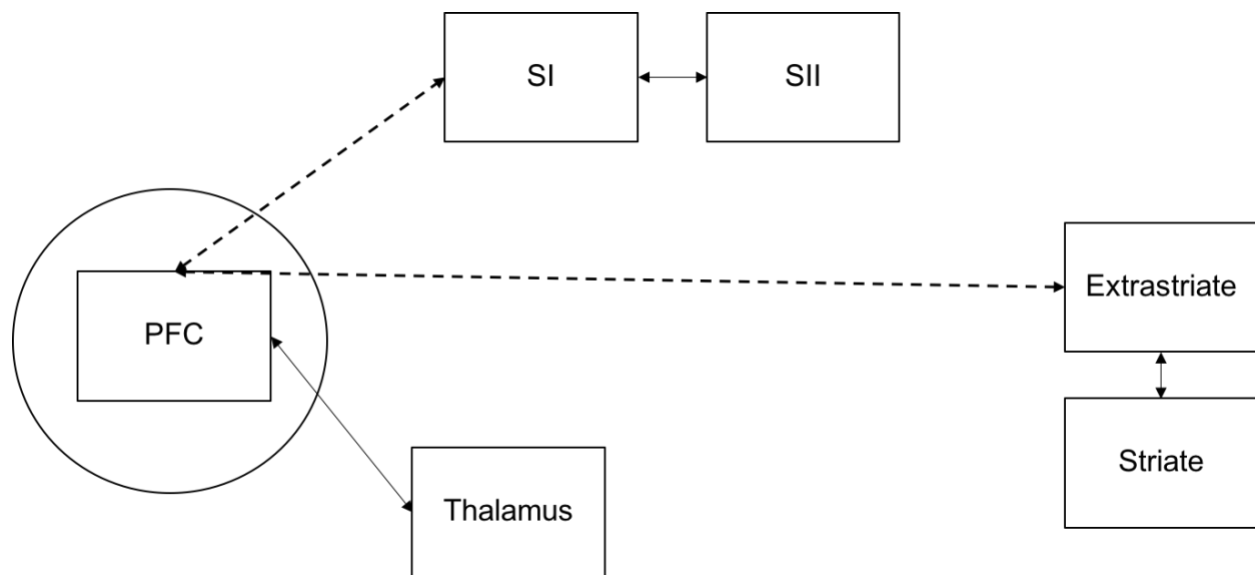
Figure 3.1: Conceptual model of study 2 design

Study 2 built on the results of study 1by looking more closely at one of the nodes of the cortical attentional system. Study 2 was designed to probe the contribution of the PFC to the top-down modulation of somatosensory- and visually-evoked ERPs by task relevance, indicated by dashed lines connecting these components of the diagram.

3.1 Introduction

Attention involves various mechanisms to allocate processing resources toward particular stimuli [1] and influence how the wide variety of sensory inputs encountered in daily life are synthesized and organized. Attention may be voluntarily oriented toward a

general location, a sensory modality, or a specific stimulus, in accordance with goals or task demands is referred to as top-down orienting [1–3,40]. Attention may also be captured by a stimulus, in a process known as bottom-up or stimulus-driven orienting; bottom-up orienting occurs independent of voluntary control, depending on the salience of a stimulus, as well as its visual, spatial, or temporal properties [1,2]. Multisensory integration is understood to be both linked to and modulated by attention, but multisensory processing also requires inhibition of some inputs; this is termed sensory gating and is the focus of the present research. Sensory gating refers to the inhibition of incoming sensory information travelling from the periphery to the cortex, and is thought to protect higher cortical centres from being overwhelmed with irrelevant information [41–52]. Sensory gating can occur in response to movement [53–55,57,59,60] or in response to top-down attention, with task-irrelevant stimuli being gated out of the processing stream.

There is literature suggesting that the prefrontal cortex (PFC) is involved in inhibiting top-down attentional processes, including evidence from patients who have sustained damage to the PFC showing impairments in inhibiting cortical responses to irrelevant stimuli [4,6,55,61,62]. In a previous experiment by this lab group, it was hypothesized that top-down attention was responsible for modulating the modality-specific cortical responses to task-relevant and -irrelevant stimuli [75]. The present experiment was designed to test this hypothesis by measuring cortical responses to relevant and distracting visual and tactile stimuli under conditions of normal and downregulated prefrontal cortical activity.

The prefrontal cortex (PFC) has been shown to play a role in top-down sensory gating of several stimulus types and under various conditions of attention, movement, or task-

relevance. In general, the prefrontal cortex has an inhibitory influence on cortical and subcortical regions including the primary somatosensory cortex [5]. Increased early-latency (26-34 ms) ERP amplitudes generated by auditory stimuli have been shown in patients with PFC damage, attributable to the loss of this tonic inhibition [5]. Evidence of early gating of sensory inputs has been shown in the temporo-parietal and prefrontal regions, with these areas contributing to attenuation of P50 responses to irrelevant auditory stimuli [76]. Grunwald *et al.* (2003) suggest that gating is a multi-step process, with the prefrontal and temporo-parietal cortices contributing to early gating and increased hippocampal activity involved in gating later than 250 ms after stimulus presentation. Impairments in gating lead to flooding by irrelevant stimuli, which in turn can lead to decreased performance on experimental tasks. Patients with prefrontal cortical lesions have shown decreased ability to use contextual information when target stimuli were preceded by random or predictive stimuli as well as slower reaction times on these tasks [77]. Patients with PFC lesions have also shown increased amplitudes of early somatosensory evoked potentials (SEPs) as well as behavioural deficits related to increased distractibility, decreased attention capacity, and habituation of novelty detection mechanisms [4,5]. This evidence makes the PFC a primary target when trying to understand the mechanisms underlying sensory gating and the distracting effect of sensory stimuli. In order to understand the role of the PFC and the mechanisms underlying sensory gating, the present experiment used continuous theta burst stimulation (cTBS) to modulate excitability in the PFC. CTBS has been shown to safely and effectively suppress cortical excitability in a number of brain regions such as the primary motor cortex the premotor cortex [78] and the prefrontal cortex [59,70,79].

Task-relevance was also manipulated in this experiment as it is an important top-down modulator of attention and appears to be a driver of sensory gating. When stimulation of cutaneous motor nerves in the lower limb was relevant to a task, only somatosensory evoked potentials (SEPs) generated by stimulating a motor nerve were attenuated; cutaneous nerve SEPs were unchanged [57]. Similarly, when proprioceptive information was task-relevant, motor nerve SEPs were unaffected but cutaneous nerve SEPs were attenuated [57]. This was also shown in the upper limb, with task-relevancy effects demonstrated on early SEPs generated by median nerve stimulation [59]. Gating of sensory event-related potentials (ERPs) has also been demonstrated. When vibrotactile stimuli were presented to left, right, or both hands, the ones which were task-relevant produced increased BOLD activity on fMRI in the contralateral primary somatosensory cortex, and decreased BOLD activity in the ipsilateral primary somatosensory cortex [71]. When examining tactile and visual stimuli using electroencephalography (EEG), task-irrelevant tactile stimuli were found to be attenuated at an early stage of processing, while task-irrelevant visual stimuli were attenuated much later [75]. There was also a significant effect on task accuracy in a sensory grading task when these stimuli were presented as unattended distractors: visual distractors significantly impaired accuracy during tactile grading, while tactile distractors had no significant effect during visual grading [75]. This was hypothesized to occur because the tactile stimuli, but not the visual ones, were subject to gating in response to top-down attention: when the tactile stimuli were task-irrelevant distractors, they were gated out of the processing stream at an early stage, and did not affect task accuracy. However, the effects of top-down attention were exerted much later in the visual domain, so visual stimuli remained longer in the processing stream, with a

corresponding cost to task accuracy. It was suspected that top-down attentional mechanisms involving the PFC were responsible for the suppression of tactile-evoked N70 and visually-evoked P2 cortical responses when the evoking stimuli were unattended, and testing these mechanisms is the aim of the present study. The hypothesis of the present experiment is that transiently suppressing prefrontal cortical activity, and therefore also impairing top-down allocation of attention and associated sensory gating, will lessen the attenuation of the somatosensory-evoked N70 and the visually-evoked P2 cortical responses to task-irrelevant stimuli. It is also hypothesized that this loss of top-down gating of task-irrelevant distractor stimuli will decrease accuracy on a cross modal sensory grading task.

3.2 Methods

Participants

EEG and behavioural data were collected from fourteen healthy volunteers (8 female, 6 male) aged 23-33 years. Participants had no history of brain injury, neurological illness or impairment, substance abuse, psychoactive drug treatment, or concussion. All procedures were approved by the University of Waterloo's Office of Research Ethics, and all participants provided informed written consent to participate.

Experimental Design

The experimental task required participants to approximate the amplitude of discrete visual and tactile stimuli by applying a graded motor response to a pressure-sensitive bulb. The stimuli were presented either in isolation, as unimodal tactile (T) or visual (V) stimuli,

or simultaneously, as crossmodal visual and tactile stimuli (VT). A single trial consisted of tactile, visual, or dual stimulus presentation. Experimental blocks lasted for approximately three and a half minutes, and contained 54 stimuli each presented for 500 ms, with 2.5 s between trials. The experimental design consisted of ten to twelve blocks of trials divided among two attention manipulations, with five to six blocks per manipulation presented in random order. Participants were required to attend, and produce a force-graded response, to approximate the amplitude of tactile stimuli (presented as unimodal or crossmodal) during the tactile attention blocks, and visual stimuli (presented as unimodal or crossmodal) during the visual attention blocks. After collection of 5-6 randomized blocks, cTBS was applied to the PFC, and then an additional 5-6 randomized blocks of the experimental task were collected.

CTBS was applied with a MagProx100 stimulation unit (MagVenture, Alpharetta, GA, USA) using a figure-8 coil (MCF-B65). Stimulation intensity was set based on a participant's active motor threshold (AMT), the minimum single pulse intensity required to produce a motor-evoked potential greater than 200 µV (peak to peak) in 5 out of 10 consecutive trials while subjects held approximately 10% of the maximum voluntary contraction of the first dorsal interosseous muscle. Next, using an intensity of 80% of AMT, cTBS was applied over the location of the right prefrontal cortex (PFC), with the coil positioned over the F4 electrode site [70]. Stimulation settings replicated those reported by Huang *et al.* [78] and consisted of 600 pulses applied in bursts of three stimuli at 50Hz repeated at a 5Hz frequency, for a total of 40 s of stimulation.

Each participant was seated comfortably for the duration of the experiment. They fixed their gaze on a computer screen for all blocks, and rested the palmar surface of the second digit of the left hand on a device which delivered vibrotactile stimuli. Participants judged the amplitude of the stimulus type they were instructed to respond to, or track, for that block: either tactile alone, visual alone, or crossmodal, and made a graded motor response by squeezing a pressure-sensitive rubber bulb with their right hand. When responding to tactile stimuli, participants were asked to apply enough force to the pressure-sensitive bulb to approximate the vibration amplitude of each tactile stimulus presented. They were asked to do this each time a tactile stimulus was presented, whether it was presented alone or in combination with a visual one. The visual condition was similar, with participants applying force to the bulb to correspond to the height of a bar appearing on the computer screen, regardless of whether or not a tactile stimulus accompanied it. No single stimulus required a response force greater than 25% of the average maximum voluntary contraction (MVC) of an age-matched participant group.

The experimental trials were preceded by a training session, which lasted approximately 5 min. In the training session, two bars were presented on the computer screen: a blue bar, controlled by the participant squeezing the pressure bulb, and a yellow one which varied randomly in height. The objective was for participants to raise the blue bar to the height of the yellow bar by applying a graded force to the pressure bulb. The blue bar provided visual feedback to teach participants how to use the bulb to grade the visual stimuli. At the same time, the amplitude of the vibrotactile stimulus applied to the subject's finger varied proportionally to match the force applied to the bulb. In this way, the training

program connected the visual and vibrotactile stimuli through the means of the pressure-sensitive bulb. The blue response bar was absent during the experimental trials, depriving participants of feedback about the accuracy of their grading performance, and during experimental trials, the amplitude of the vibrotactile stimuli varied independently of the visual stimuli.

Stimuli

The target visual stimulus was the yellow bar (6 cm wide) used in the training task which appeared in the center of a black box presented on a black computer screen. The bar was visible for 500 ms and appeared at randomly-varying heights within the box. Tactile stimuli were presented to the second digit of the left hand using a custom-made vibrotactile device. These stimuli were created by the conversion of digitally-generated waveforms to analog signals (DAQCard 6024E, National Instruments, Austin, TX) and amplifying the signal (Bryston 2BLP, Peterborough, Ontario, Canada) using a custom program written in LabVIEW (version 8.5; National Instruments). Variations in the amplitude of the voltage driving the vibrotactile device resulted in proportional changes in the tactile stimulus applied to the finger. The amplitude of each vibration was constant within a trial and varied randomly between trials. The average stimulus amplitude across all trials which included a tactile stimulus did not differ between the experimental conditions, and the frequency of the vibration was held constant at 25 Hz. In order to prevent auditory perception of the vibrotactile stimuli, participants wore earbud headphones during the experiment which delivered white noise throughout the training and experimental tasks (White Noise Ambience Lite, Logicworks version 2.70, Apple App Store).

Data acquisition and recording parameters

Behavioural data were recorded using a custom program written in LabVIEW (version 8.5, National Instruments, Austin, TX). Participants applied force to the pressure-sensitive bulb that caused air to move through a rubber tube in a closed system, leading to a pressure change that was measured by a pressure sensor and converted to a voltage. There was a linear relationship between the pressure measurement and the voltage produced. EEG data were recorded from 32 electrode sites (32 channel Quik-Cap, Neuroscan, Compumedics, NC, USA) in accordance with the International 10–20 System for electrode placement and referenced to the linked mastoids. Impedance was maintained less than 5 kΩ. EEG data were collected with a DC–200 Hz filter and digitized at 500 Hz (Neuroscan 4.5, SynAmps2, Compumedics, NC, USA). Data were then saved for subsequent analysis, which began with epoching, followed by baseline correction to the pre-stimulus interval. Epochs were 600 ms in length, beginning 100 ms before stimulus onset, and epochs contaminated by blinks, muscle contractions, or eye movements were eliminated by visual inspection before averaging. Between 90 and 108 trials per participant were collected for each stimulus type, and after contaminated trials were eliminated, the final trace for each experimental condition consisted of, on average, 69 artifact-free epochs per condition.

Data analysis

EEG analysis

For all ERP analysis, potentials were calculated as peak-to-peak amplitudes between the peak of interest and the preceding potential of opposite polarity. To test the hypothesis that top-down attentional gating mediated by the prefrontal cortex was an integral

contributor to the modulation of early somatosensory ERPs by attention, a three-way

repeated measures ANOVA was carried out on the amplitude of each potential, with

attention instruction (T, V), stimulus presented (T, V), and cTBS status (pre, post) as

within-subject factors. Data sets were tested for normality to validate the use of parametric

tests, and transformed when necessary to uphold the assumptions of the ANOVA model.

Since attention has been shown to modulate the tactile N70 ERP [75], and the prefrontal

cortex was hypothesized to drive this modulation, pre-planned contrasts were conducted

on the amplitude of the N70 ERPs before and after cTBS. Specifically, these contrasts tested

two hypotheses: that before cTBS, a relevant tactile stimulus would result in a significantly

larger N70 than an irrelevant tactile stimulus, and that this effect would be abolished after

cTBS to the prefrontal cortex; and that presenting a simultaneous irrelevant visual stimulus

would result in a smaller N70 than a lone tactile stimulus, and this would not be affected by

the application of cTBS to the prefrontal cortex.

Behavioural analysis

Behavioural data were analyzed by comparing the amplitude of the target stimulus to

the amplitude of the response created by the participant squeezing the pressure-sensitive

bulb. The response was compared to the amplitude of the target stimulus to calculate a

percentage of the ideal response, but the difference between ideal and actual response was

not the focus of the present experiment. Since the hypothesis was that presenting a

distracting stimulus would impair accuracy when compared with the undistracted

condition, a cost score was calculated by dividing the percent ideal response during the

distracted condition by the percent ideal response from the undistracted condition and

multiplying by 100. This was then subtracted from a potential maximal score of 100 to

obtain the cost of presenting the distractor. This was done for both the visual and tactile grading conditions, and T-tests were used to compare how cTBS affected the cost of a distractor on grading in each modality.

3.3 Results

Event-related potentials

Figure 3.2a shows grand average traces of tactile ERPs at electrode CP4 for all fourteen participants who participated in this study.
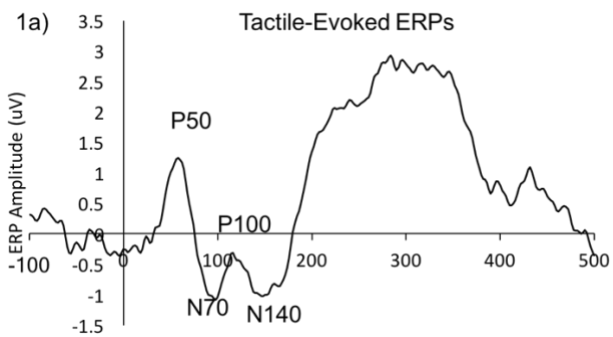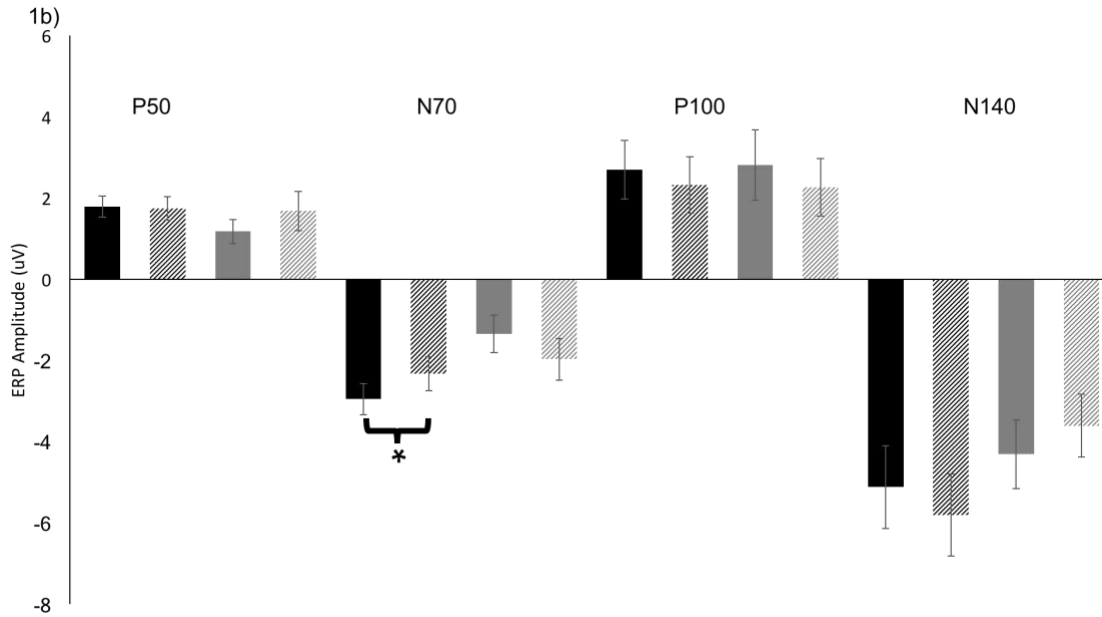

Figure 3.2: Tactile-evoked ERPs

a) Grand average waveform (n = 14) timelocked to tactile stimuli, generated when participants were presented with unimodal tactile stimuli. ERP components of interest are labelled for electrode site CP4.

b) ERP amplitudes to tactile stimuli when tactile stimuli were task-relevant (solid bars) and when they were irrelevant (striped bars). Data collected before cTBS was applied is shown in black, and after cTBS is shown in gray. P50 and N70 amplitudes were measured at electrode CP4, P100 and N140 amplitudes were measured at FCz. There was a significant difference in N70 amplitude when the evoking stimuli varied in task-relevance, but only in the pre-cTBS condition(* indicates significant to p < 0.05; error bars indicate standard error).

1c)
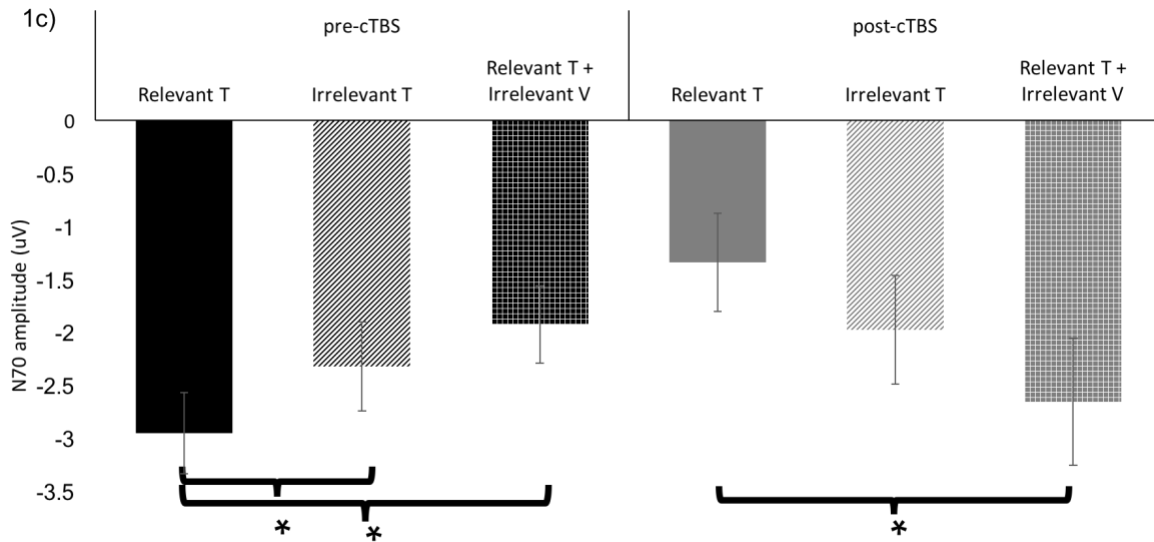
c) N70 amplitude to tactile stimuli when the evoking stimuli were relevant (solid bars), when they were irrelevant (striped bars), and when they were presented with a simultaneous irrelevant distractor (hatched bars). Data collected before cTBS was applied is shown in black, and after cTBS is shown in gray. Before cTBS, the N70 was significantly attenuated when tactile stimuli were task-irrelevant as well as when they were presented with simultaneous distractors (* indicates p < 0.05; error bars indicate standard error). After cTBS, N70 amplitudes were attenuated such that there was no difference when the evoking stimuli varied in task-relevance, but there was a difference when a simultaneous distractor was present.

The P50 potential (mean latency 57.6 +/- SE 0.79 ms) was maximal at electrode CP4 overlying contralateral somatosensory cortex, and analysis was conducted using the potentials from this electrode. The P50 was generated by tactile stimuli and not observed in response to unimodal visual stimuli. The three-way repeated measures ANOVA showed no significant interaction effects (cTBS, stimulus, and attention: $F_{1,86}=0.82$, p=0.37; cTBS

and stimulus: $F_{1,86}=1.28$, p=0.26; attention and stimulus: $F_{1,86}=0.12$, p=0.73; cTBS and attention: $F_{1,86}=0.16$, p=0.69). Main effects also did not reach statistical significance (cTBS: $F_{1,86}=0.25$, p=0.62; attention: $F_{1,86}=1.57$, p=0.21; stimulus: $F_{1,86}=0.24$, p=0.63)(Figure 3.2b).

EEG tracings demonstrated a clear N70 component (mean latency 81.7 +/- SE 1.6 ms) in response to vibrotactile stimuli but not to visual stimuli. The three-way repeated measures ANOVA showed a significant interaction between cTBS and stimulus type ($F_{1,87}=13.87$, p=0.0003) but no other significant interactions (cTBS, stimulus, and attention: $F_{1,87}=2.15$, p=0.15; stimulus and attention: $F_{1,87}=0.04$, p=0.85; cTBS and attention: $F_{1,87}=1.72$, p=0.19). There were also no significant main effects found (cTBS: $F_{1,87}=0.36$, p=0.55; attention: $F_{1,87}=0.32$, p=0.57; stimulus: $F_{1,87}=0.51$, p=0.48). In order to explore the significant interaction between cTBS and stimulus type on N70 amplitude, two separate two-way ANOVA analyses were conducted. One used the N70 amplitude values collected in the baseline condition, prior to the application of cTBS data set, and the other used the post-cTBS data set. Testing across levels of cTBS was chosen as it relates to the main hypothesis of the present study, that cTBS to the PFC will affect modulation of sensory-evoked potentials. In the analysis of N70 values collected before cTBS was performed, there was no significant interaction between attention and stimulus type ($F_{1,38}=1.37$, p=0.25), and no significant main effect of attention ($F_{1,38}=3.07$, p=0.09). There was, however, a significant main effect of stimulus type ($F_{1,38}=7.06$, p=0.01), indicating a significant difference in N70 amplitude when tactile stimuli were presented alone as compared to with a simultaneous visual stimulus. Pre-planned contrast found that N70 amplitudes to tactile stimuli were significantly larger when subjects were attending and responding to tactile stimuli than when they attending and responding to visual ($F_{1,38}=4.17$, p=0.05), and

that N70 amplitudes were significantly larger when subjects were presented with unimodal tactile stimuli as compared to crossmodal stimuli in cases where participants were attending and responding only to tactile stimuli ($F_{1,38}=7.15$, p=0.01). After cTBS was conducted, there was no significant interaction between attention and stimulus type ($F_{1,38}=1.34$, p=0.25), and no significant main effect of attention ($F_{1,38}=0.31$, p=0.58). There continued to be a significant main effect of stimulus type in the post-cTBS data ($F_{1,38}=9.46$, p=0.004)(Figure 1b). Pre-planned contrasts, described previously, showed that the focus of attention did not have a significant effect on N70 amplitude ($F_{1,38}=1.48$, p=0.23), and that N70 amplitudes were larger in response to lone tactile stimuli as compared to tactile stimuli with a concurrent visual distractor ($F_{1,38}=8.97$, p=0.005) (Figure 3.2c).

EEG tracings collected from all subjects demonstrated P100 and N140 components (mean latencies P100: 106.3+/- SE 1.1 ms; N140: 158.0 +/- SE 1.2 ms) in response to vibrotactile stimuli. Both were distributed bilaterally at parietal electrode sites and were maximal at electrode FCz, therefore analysis of P100 and N140 was conducted at this electrode. A three-way repeated measures ANOVA of P100 data showed no significant interaction effects (cTBS, attention, and stimulus type: $F_{1,13}=0.63$, p=0.44; attention and stimulus type: $F_{1,13}=1.3$, p=0.27; cTBS and stimulus type: $F_{1,13}=1.43$, p=0.25; cTBS and attention: $F_{1,13}=0.01$, p=0.91), nor any significant main effects (cTBS: $F_{1,13}=0.63$, p=0.44; attention: $F_{1,13}=0.08$, p=0.79; stimulus type: $F_{1,13}=0.17$, p=0.69). A three-way repeated measures ANOVA of N140 amplitudes showed a significant interaction between cTBS and attention ($F_{1,13}=11.30$, p=0.005). There were no other significant interaction effects (cTBS, attention, and stimulus type: $F_{1,13}=0.01$, p=0.91; attention and stimulus type: $F_{1,13}=0.21$, p=0.66; cTBS and stimulus type: $F_{1,13}=3.69$, p=0.08). Since the effect of cTBS marked the

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comparison central to the hypothesis of this experiment, two separate two-way ANOVAs were conducted to investigate the significant interaction between cTBS and attention, with the data set divided by cTBS status, as stated previously. An inverse transformation was required to uphold the assumption of normality. The pre-cTBS N140 amplitude comparisons showed no significant main effects (stimulus type: $F_{1,13}=0.94$, p=0.35; attention: $F_{1,13}=0.94$, p=0.35) and no significant interaction between attention and stimulus type ($F_{1,13}=1.09$, p=0.32). In the two-way ANOVA conducted of the N140 amplitudes generated after cTBS was applied to the PFC, there was a trend toward a significant interaction between attention and stimulus type ($F_{1,13}=4.03$, p=0.07), but no significant main effects of stimulus type ($F_{1,13}=3.38$, p=0.09) or attention ($F_{1,13}=0.23$, p=0.64) (Figure 3.2b).

Figure 3.3a shows a grand average trace of the ERPs generated in response to visual stimuli. All peaks (P1, N1, and P2) were observed in all experimental participants. The figure depicts the ERPs that occurred in response to visual stimuli when subjects directed attention toward and away from visual input.
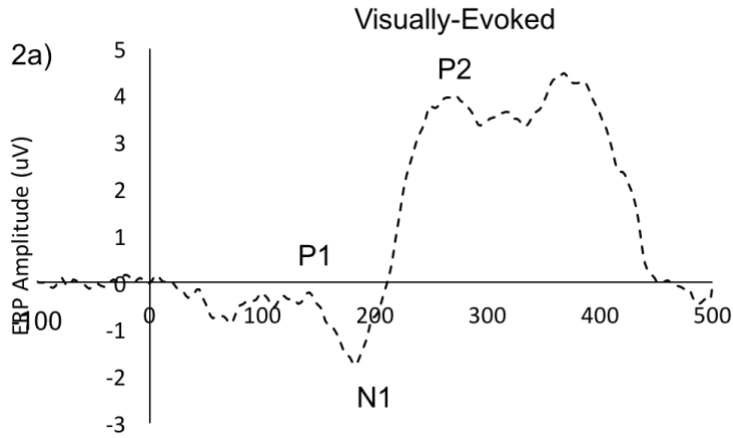
Figure 3.3: Visually-evoked ERPs

a) Grand average waveform (n = 14) generated in response to visual stimuli when subjects were instructed to attend to these stimuli. ERP components of interest are labelled on the trace for electrode site Pz.
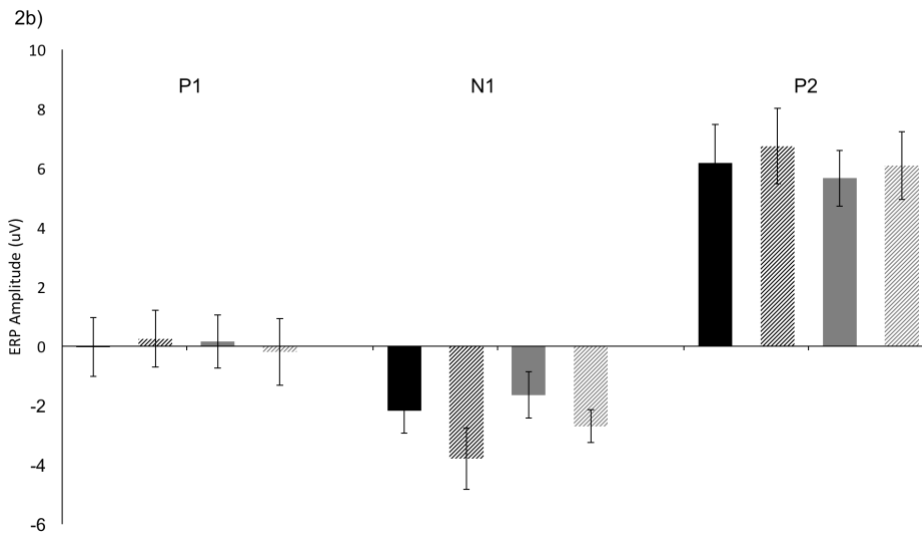
b) Peak-to-peak amplitudes of visually-evoked ERPs, collected from electrode Pz when visual stimuli were task-relevant (solid bars) and when they were irrelevant (striped bars). Pre-cTBS data is presented in black; post-cTBS data is presented in gray. There were no significant

amplitude differences when visual stimuli varied in task-relevance, either before or after cTBS to

the PFC. (Error bars denote standard error).
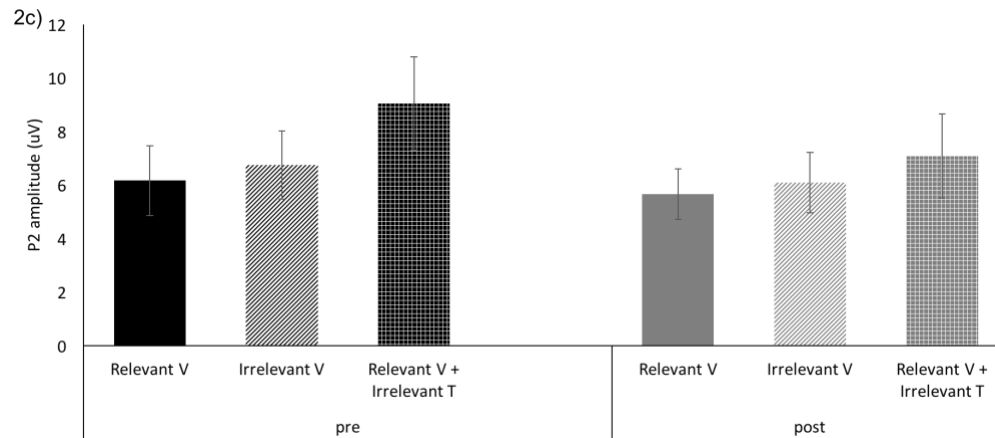
c) P2 amplitude when the evoking visual stimuli were relevant (solid bars), when they were

irrelevant (striped bars), and when they were presented with a simultaneous irrelevant tactile

distractor (hatched bars). Data collected before cTBS was applied is shown in black, and after

cTBS is shown in gray. There were no significant differences in P2 amplitude between any of the

conditions, either before or after cTBS. (Error bars denote standard error).

All subjects demonstrated three clear ERP components in response to visual stimuli, labelled P1 (mean latency 137.5 +/- SE 1.4 ms), N1 (mean latency 182.5 +/- SE 1.8 ms), and P2 (mean latency 254.8 +/- SE 2.0 ms). All were maximal at electrode Pz, distributed bilaterally, and not observed in response to tactile stimuli.

Three-way repeated measures ANOVAs were performed on the visually-evoked P1 potential. There was a significant interaction between attention and stimulus type ($F_{1,13}$=6.34, p=0.03), but no other interactions reached significance (cTBS, attention and

stimulus type: $F_{1,11}=0.41$, p=0.53; cTBS and attention: $F_{1,13}=0.29$, p=0.60; cTBS and stimulus type: $F_{1,13}=0.62$, p=0.45). Main effects were also not significant (stimulus type: $F_{1,13}=0.34$, p=0.57; attention: $F_{1,13}=0.32$, p=0.58; cTBS: $F_{1,13}=1.21$, p=0.29). Multiple post-hoc tests were conducted to explore the significant interaction between attention and stimulus type, including two-way ANOVAs with the data divided by cTBS, attention, or stimulus type. All failed to reach significance (p<0.05), and as such, the significant interaction between attention and stimulus type found for the P1 potential in the three-way ANOVA was not afforded further consideration (Figure 3.3b).

A three-way repeated measures ANOVA of the N1 ERP found a significant interaction between attention and stimulus type ($F_{1,13}=6.40$, p=0.03). There were no significant interactions between other factors (cTBS, attention, and stimulus type: $F_{1,12}=3.55$, p=0.08; cTBS and stimulus type: $F_{1,13}=0.95$, p=0.35; cTBS and attention: $F_{1,13}=1.40$, p=0.26), nor any significant main effects (cTBS: $F_{1,13}=3.83$, p=0.07; attention: $F_{1,13}=1.39$, p=0.26; stimulus type: $F_{1,13}=0.27$, p=0.61). The significant interaction between attention and stimulus type was explored, as with the P1 data, using two-way ANOVAs with the data divided by each factor in turn. All failed to reach significance (p<0.05), and as such, the significant interaction between attention and stimulus type found in the three-way ANOVA analysis of N1 amplitudes was not afforded further consideration (Figure 3.3b).

A three-way repeated measures ANOVA of the P2 ERP was conducted using a logarithmic transformation to uphold the assumption of normality. The analysis found no significant interaction effects between any factors (cTBS, attention, and stimulus type: $F_{1,13}=0.03$, p=0.87; attention and stimulus type: $F_{1,13}=1.31$, p=0.27; cTBS and stimulus type:

$F_{1,13}$=0.92, p=0.35; cTBS and attention: $F_{1,13}$=0.05, p=0.82). There was a trend toward a significant main effect of stimulus type ($F_{1,13}$=4.36, p=0.06), but no significant main effect of attention ($F_{1,13}$=0.24, p=0.63) or cTBS ($F_{1,13}$=0.47, p=0.50) (Figure 3.3b).

Behavioural performance

Independent T-tests were conducted within each sensory modality to test the change in accuracy caused by a distractor, before as compared to after cTBS to the PFC (Figure 3.4). For tactile grading, there was a trend toward a significant difference (t(13) = -1.56 ; p= 0.07) when comparing the cost of a visual distractor pre-cTBS (M = 8.97; SD = 6.63) to the cost post-cTBS (M = 47.98; SD = 93.37). For visual grading, cTBS did not significantly affect the cost of presenting a tactile distractor (t(26) = -0.26; p = 0.4; pre-cTBS M = 4.40, SD = 6.63; post-cTBS M = 4.78, SD = 3.61).

3)
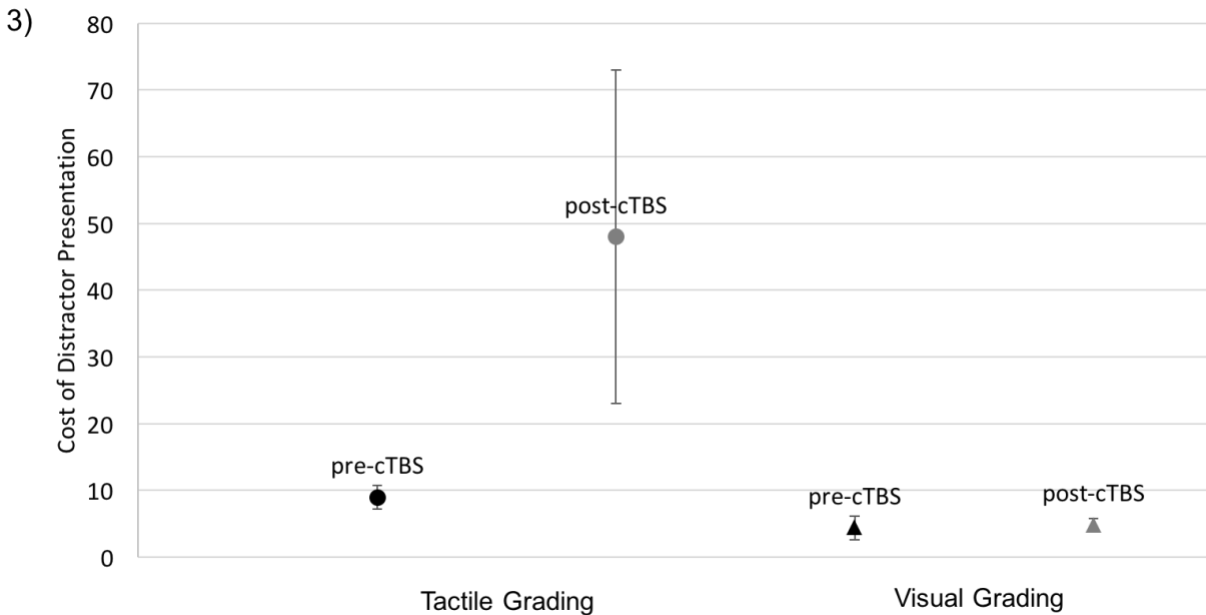
Figure 3.4: Cost of presenting a simultaneous distractor.

Accuracy cost when target stimuli are presented with simultaneous distractors, for both tactile (circles) and visual (triangles) targets. Black markers represent data collected before cTBS application; gray markers represent post-cTBS performance. There was a trend toward a significantly increased distractor cost during tactile grading after cTBS to the PFC (p = 0.06), but cTBS to the PFC did not affect the cost of presenting a tactile distractor during visual grading. (Error bars denote standard deviation).

3.4 Discussion

This study demonstrates that the tactile-evoked N70 ERP is modulated by attention in a top-down manner, and that this effect is subserved by prefrontal cortical activity, providing insight into the mechanism underlying the modulation of early modality-specific somatosensory cortical excitability by attention described in Adams, Popovich & Staines

[75]. The hypothesis that the PFC is a key player in the top-down attentional modulation of the somatosensory N70 potential was supported by the findings of the present study: the data collected before the application of cTBS replicated the findings of the previous research, with a smaller N70 amplitude generated to unattended than to attended tactile stimuli, and down regulating PFC activity through the use of cTBS abolished any difference in N70 amplitude between the two attention conditions. Prior to this experiment, it was hypothesized that the PFC would mediate top-down attention processes involved in attenuating cortical responses to task-irrelevant stimuli. The expectation, therefore, was that down regulating the excitability of the PFC would eliminate the amplitude difference in N70 responses to task-relevant and -irrelevant stimuli by increasing the amplitude of responses to distractor stimuli. An examination of the data from the present work shows that the lack of difference in N70 amplitude between the attended and unattended somatosensory stimuli after cTBS may be driven more by an attenuation of cortical excitability in response to task-relevant tactile stimuli than by a loss of inhibition of responses to the task-irrelevant stimuli. These data support the conclusion that cTBS to the DLPFC diminishes N70 responses to the attended as well as the unattended conditions.

The effect of cTBS on increasing N70 responses to task-relevant tactile stimuli is consistent with effects which, while not explicitly reported by other authors, can be extrapolated by examining grand average traces. Bolton and Staines [70] studied the effect of cTBS to the dorsolateral prefrontal cortex (DLPFC) on cortical responses to attended or unattended tactile stimuli delivered to two digits. They showed that tactile stimuli produced significantly larger P100 peak amplitudes when they were task-relevant than when they were not, and that this effect was abolished after cTBS to the DLPFC [70]. In

these grand average traces, a negativity occurred approximately 70 ms post-stimulus. Visual inspection suggests that this peak was smaller when evoked by task-relevant tactile stimuli after cTBS, as compared to before. These N70 amplitudes to task-irrelevant tactile stimuli were also reduced by cTBS to the DLPFC, but like in the present study, this effect was less dramatic. Similarly, examination of grand average traces reported by Brown *et al.* [59] suggests that the DLPFC plays a role in facilitating early responses to task-relevant somatosensory stimuli. Since these authors examined SEPs instead of tactile-evoked ERPs, the grand average traces reproduced in Brown *et al*. [59] show a negativity slightly earlier than the N70 reported in the present research, but visual inspection of this data also suggests that the amplitude of this negativity is diminished after cTBS to the DLPFC, as compared to their rest condition [59]. In neither of these cases did the modulation of N70 reach statistical significance, which is in contrast to the results presented in the current study. This is likely a result of differences in task demands between the present study and these experimental designs. The present study presented stimuli in two different sensory modalities and asked participants to attend and respond to just one at a time; in the study by Bolton and Staines [70], the stimulus modality didn't change, but the attended location did, and in Brown *et al.* [59], SEPs were evoked by median nerve stimulation during rest, task-relevant, and task-irrelevant movement conditions. The act of switching attended location, not attended sensory modality, seems to have the effect of modulating P100 and leaving N70 unchanged [70], while changing task demands appears to modulate early but not later SEPs [59]. In contrast, the instruction to attend to only one of a pair of cross-modal stimuli appears to specifically change N70 amplitudes and not the later P100. In both cases, decreasing prefrontal cortical activity had the effect of decreasing the attention

effect on the potential that was specifically modulated by the differing experimental designs.

In addition to confirming that, as hypothesized, N70 was modulated by top-down attentional circuits involving the PFC, this study also demonstrated a bottom-up attentional effect on N70 amplitude which was independent of PFC activity. Both before and after cTBS was applied, the amplitude of the tactile-evoked N70 was different when tactile stimuli were presented with a simultaneous visual distractor than when presented alone. Prior to the application of cTBS, N70 amplitudes were larger when tactile stimuli were presented alone than with a visual distractor; after cTBS, N70 amplitudes were smaller when the evoking stimuli were presented alone. This attenuation of N70 amplitude in the lone tactile stimulus condition is consistent with data examining other EEG components in patients with lesions of the prefrontal cortex which shows decreased excitation in response to relevant stimuli, and decreased inhibition of responses to irrelevant stimuli.[6]

It is acknowledged that there is considerable interplay between attention and multisensory integration [1,40,80]. It stands to reason that attention also has an important and complex relationship with multisensory selection processes, including sensory gating, the focus of the present research. The present study represents a step toward a greater understanding of this relationship. There is evidence that top-down and bottom-up attentional effects are subserved by different cortical networks, which may explain why cTBS to the PFC affected top-down but not bottom-up attentional processing. Corbetta and Shulman [3] review evidence that attributes top-down attentional processing to a network consisting of the intraparietal cortex and the superior frontal cortex, and bottom-up attention to areas of the temporoparietal cortex and inferior frontal cortex, mostly

lateralized to the right hemisphere. As the PFC is considered part of the superior frontal cortex, it would be expected that disrupting function of the PFC would disrupt top-down but not bottom-up attention, which is consistent with the results of the experiment presented here. Other studies disagree about the specific cortical areas involved in each of these processes, depending on the imaging techniques and experimental designs: Bledowski *et al.* [40] used fMRI to identify a slightly different network involved in processing targets and distractors in an oddball paradigm, while Talsma *et al.* [1] review research and suggest that the network subserving bottom-up processing is a subset of the top-down attentional network. It is clear, despite these discrepancies, that areas of cortical activity do in fact differ in response to top-down and bottom-up attentional demands, supporting the findings of the present study that cTBS to the PFC could interrupt top-down attention while leaving bottom-up processes unaffected.

Downregulating PFC function may have increased the cost of a distractor on tactile but not visual grading accuracy, with a trend toward a statistically significant increase in distractor cost after cTBS in the tactile grading condition. This may be explained by the effect of cTBS on the tactile-evoked N70, which was less enhanced in response to relevant stimuli after cTBS. The increased cost score may be reflective of the disruption in target stimulus processing rather than impaired distractor gating.

It is also possible that bottom-up rather than top-down attentional mechanisms are responsible for the impaired task accuracy in the presence of the distractor. In the previous research upon which the present study was based [75], participants were significantly less accurate in grading tactile stimuli in the presence of a visual distractor than when tactile stimuli were presented alone, and there was no accuracy difference in grading visual

stimuli with or without a tactile distractor. Top-down attentional mechanisms were hypothesized to be responsible for the previous results, and the different post-stimulus latencies at which top-down attention led to gating in each sensory modality were thought to underlie the loss of grading accuracy in the presence of distractor stimuli. This theory was tested in the present experiment, with the hypothesis that disrupting PFC activity would disrupt top-down attentional mechanisms and cause a loss of visual grading accuracy in the presence of a tactile distractor. However, the results do not support this hypothesis, since disrupting PFC function did not affect the cost of distractor presentation during visual grading, even though the electrophysiological data indicated that the cTBS protocol disrupted top-down attentional control of tactile stimulus processing. Instead, it is more likely that the presence of a distracting stimulus induces a behavioural cost via bottom-up, or stimulus-driven, attentional mechanisms, as these mechanisms were shown from the electrophysiological data to be unaffected by cTBS to the PFC.

If the loss of accuracy in this experimental task is due to stimuli capturing attention, the fact that visual but not tactile distractors decreased accuracy of grading in the opposite sensory modality suggests a substantial difference between these two sensory modalities in the properties that form the basis for attentional allocation. Modality-specific variations in stimulus processing have been previously shown in studies examining integration of stimuli in two different sensory modalities, and while the present study examined sensory gating, some parallels may be drawn between crossmodal attentional processes. Top-down visuospatial attention has a considerable effect on the processing of concurrent auditory stimuli, but spatial attention to auditory stimuli has a minimal effect on the integration of visual stimuli from disparate spatial locations [1]. In contrast, it is the temporal

characteristics of auditory stimuli that can affect visual stimulus processing [1]. It is possible that the characteristics of the visual and vibrotactile stimuli presented in the present study were not optimal to induce interactions in the processing of the distractor stimuli. The visual stimuli were presented as bars of varying heights in the same general location, within a box on a computer screen, while the tactile stimuli were vibrations of varying amplitudes. It is possible that varying other attributes of these stimuli would change the results of the experiment presented here. It is also possible that the visual and tactile stimuli used in the present study vary in their inherent salience. Kastner and Ungerleder [80] assert that stimulus salience is an important factor in bottom-up attention, because these attentional processes are driven by stimulus features, as well as the dissimilarity of a stimulus from adjacent distractors. Humans are surrounded by complex visual scenes in daily life, and may have adapted to assign greater salience to visual stimuli than to vibrotactile. It is also possible that every time a visual stimulus was presented in the present protocol, the presence of the box in which it appeared led to its height being automatically graded. The tactile stimuli, presented as discrete bursts of vibration separated in time, did not have such an inherent frame of reference for comparison. Previous work has shown that cortical processing of visual stimuli differs depending on task requirements, with greater ERP amplitudes generated when the requirement was to grade, rather than simply detect, stimuli [63]. While participants were not explicitly instructed to grade visual distractor stimuli in the present experiment, the presentation of these stimuli within a box may have made them implicitly graded, which could have made them more salient, and more demanding of cortical resources. Repeating the present experiment but varying the visual stimuli differently, perhaps varying the brightness rather

than their height within a predetermined frame, would be a useful comparison, making the variation in visual stimulus intensity more similar to the variations in tactile stimulus intensity, and perhaps rectify differences in stimulus salience.

The previous work upon which the present experiment was based reported that task-relevance modulated the amplitude of the visually-evoked P2 potential, without any changes in P1 or N1 amplitudes [75]. The present study used the same experimental paradigm, with the addition of a cTBS intervention, so it was expected that the pre-cTBS EEG results would replicate the results of the previous study. However, the present experiment found that shifting task demands did not modulate visual ERPs. While in contrast to Adams, Popovich and Staines [75], this result is consistent with some literature suggesting that early visual ERPs are modulated primarily in response to changes in spatial location [65–67]. Work by Eimer [68], however, has shown enhanced negativities to attended visual stimuli, as compared to unattended, between 200 and 280 ms post-stimulus; this consistent with results from Adams, Popovich and Staines [75] and in contrast to the present work. It is clear that, ultimately, the effect of changes in task-relevance on the visually-evoked P2 potential requires further investigation.

It is important to note that sham cTBS was not utilized in this experiment. There are two options for sham collections: not turning the stimulator on, or applying stimulation at a very low intensity. The former option not used in this study, as participants can easily tell whether or not cTBS was applied. The latter option was also ruled out based on data which show that even low stimulation intensities can affect the N70 potential. Opitz *et al.* [73] used a sham cTBS condition with a biologically inert "coil" and headphones to replicate the experience of the cTBS protocol. Although the sham cTBS protocol produced a magnetic

field approximately 20 times less than than the real cTBS condition, they found that both real and sham cTBS over the left DLPFC decreased the amplitude of specific SEPs including the P50-N70 potential [73], which was a main ERP of interest in the present study. Based on the finding that even low-strength electric fields from sham cTBS can influence N70 amplitude, the present study was designed with a pre- and post-cTBS comparison to avoid any possible confounding effects that sham cTBS may have on the N70 potential of interest.

3.5 Conclusion

This study demonstrated that both top-down and bottom-up attentional mechanisms are responsible for early modality-specific changes in cortical processing of stimuli with and without cross modal distractors. Top-down attentional processes, induced by changing task demands, were linked to PFC activity. Bottom-up or stimulus-driven processes operated independently of the PFC and may be linked to changes in accuracy on a sensory grading task. More research is required to fully clarify the modulation of early and late visual ERPs by task-relevance, and the attentional mechanisms underlying this modulation.
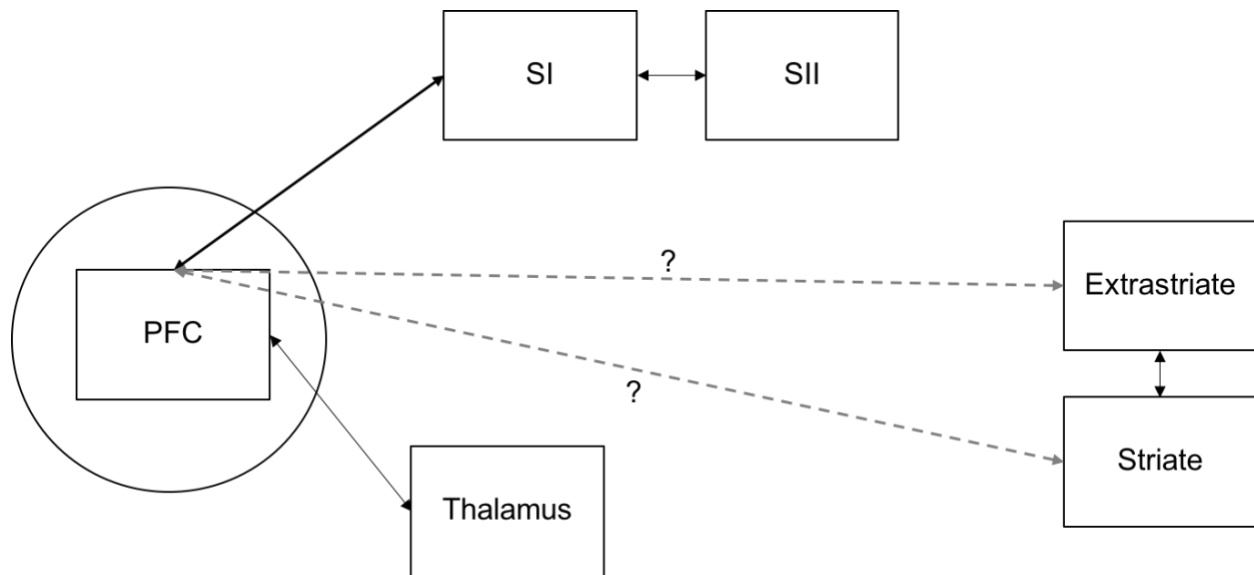
Figure 3.5: Conceptual model of study 2 findings

Study 2 tested the role of the PFC in the modulation of ERP amplitude by top-down and bottom-up variations in attentional orienting. By measuring ERP amplitudes both before and after PFC excitability was attenuated, study 2 reinforced that the PFC plays a key role in top-down orienting of attention in the somatosensory domain (solid line). However, since study 2 did not replicate the modulation by task-relevance in the visual modality which was seen in study 1, it was not possible to define the role of the PFC in the visual domain and the lines in the model remain dashed.

Chapter 4: Study 3- Changes in relevancy-based gating of visual and tactile stimuli after recovery from concussion
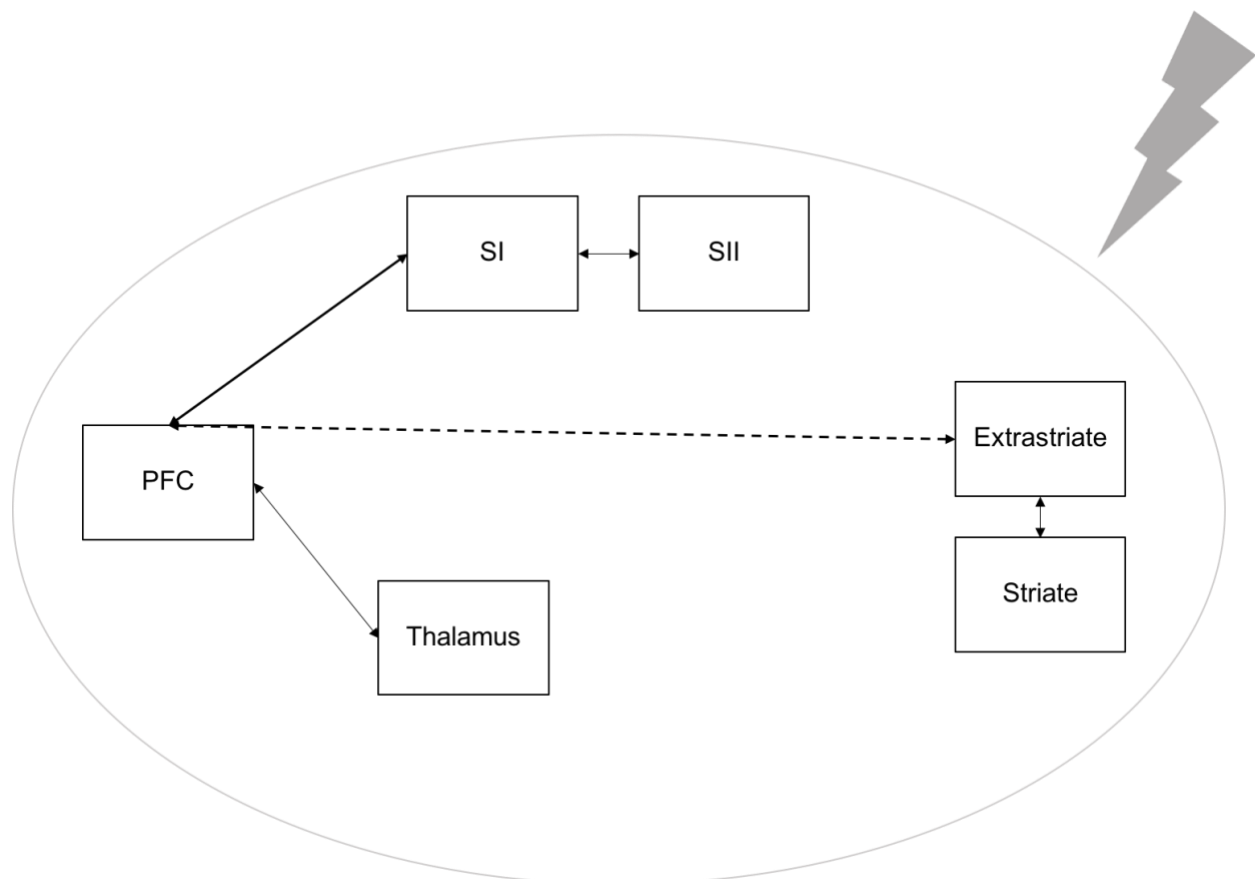
Figure 4.1: Conceptual model of study 3 design

Study 3 was designed to understand the influence of a history of concussion injury (represented by the gray lightning bolt) on the top-down modulation by task-relevance of sensory-specific cortical representations. Since concussion is not a focal injury, it is represented as having potential effects on all cortical areas. The combined results of the previous two studies of this thesis suggest that the PFC plays an influential role in early

tactile-specific cortical stimulus representation in SI, as well as perhaps in later visual-specific cortical stimulus representation, likely in extrastriate areas.

4.1 Introduction

At the present time, concussion is an injury diagnosed and defined by its symptoms. Research is ongoing to find objective tools or measures to define when a concussion has occurred or when recovery is complete, but for now, clinicians and scientists must rely on patients' symptom reports to direct clinical care and research. Clinical conversations with patients often include descriptions of symptoms which suggest increased distractibility or difficulty filtering irrelevant stimuli; for example, "I can't talk to a friend in a coffee shop - the ambient noise is too distracting." A possible explanation for this is that the concussions may affect attentional orienting in some patients, particularly the ability to filter out distracting stimuli. This filtering is referred to as sensory gating, which is the inhibition of sensory information transmission from the periphery to the cortex in order to protect higher cortical centers from being overcome with irrelevant incoming information [50–52]. The present study was designed to investigate whether a group of patients, after recovery from concussion, exhibited different cortical or behavioural responses when performing a sensory grading task under shifting conditions of task relevance and with or without distractions.

There is growing evidence that concussions leave lasting effects on patients, even after symptoms have resolved and patients appear recovered. Compared to controls with no history of concussion, patients who have recovered from concussion have been shown to have deficits in visuomotor control, decision-making, and dynamic stability [81]; longer reaction times on a complex visuomotor mapping task [82]; and decreased amplitudes of

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specific event-related potentials (ERPs) on electroencephalography (EEG) [7,26,27,29,30]. Concussions may cause neurological deficits which persist even after symptoms have resolved, indicating a need to better understand the mechanisms underlying concussion symptoms and more sensitive measures to assess whether full neurological recovery has occurred.

Therefore, the objective of the present research was to investigate changes in sensory gating, an important component of attentional orienting, after recovery from concussion. Previous work by our lab found that cortical responses to task-irrelevant tactile stimuli were attenuated at an early stage of processing, 70 ms post-stimulus presentation, during a sensory grading task, while task-irrelevant visual stimuli were attenuated much later, approximately 270 ms post-stimulus[75]. When the stimuli were presented as unattended distractors during the same task, visual distractors significantly decreased cortical responses to relevant tactile stimuli and impaired accuracy during tactile grading, while tactile distractors had no significant effect on ERPs to task-relevant visual stimuli or on accuracy during visual grading [75]. It was theorized that because task-irrelevant tactile stimuli were gated out of the processing stream at an early stage, they did not affect processing of concomitant visual stimuli; in contrast, task-irrelevant visual stimuli were subject to gating much later, which led these stimuli to have distracting effects both electrophysiologically and behaviourally. The aim of the present study was to investigate how a history of concussion affected these cortical correlates of task relevance and distractibility. The first hypothesis of the present experiment was that sensory gating based on task-relevance would be impaired in participants with a history of concussion, leading to impaired suppression of N70 and P2 cortical responses to task-irrelevant

stimuli. The second hypothesis was that the disruption in relevancy-based gating in the concussion history group would result in decreased visual-evoked ERPs when the evoking stimuli are presented with a concurrent tactile distractor. Finally, the third hypothesis of the present work was that the presentation of unattended distractor stimuli would negatively affect task accuracy in the visual grading task in the group with a history of concussion, due to the expected disruption in early relevancy-based gating of tactile stimuli.

4.2 Methods

Participants

Electroencephalographic (EEG) and behavioural data were collected from fourteen volunteers with a history of concussion (8 female, six male, aged 18-31), and thirteen with no history of concussion (8 female, 5 male, aged 19-28). All participants in the control group had no history of diagnosed or suspected concussion; all in the concussion history group had a history of diagnosed concussion, but were fully recovered, symptom-free, and medically cleared to return to full participation in school, activities of daily living, and sporting activities. No restrictions were placed on maximum number of concussions, time since most recent concussion, recovery time, or age at time of injury for those in the concussion group. Control participant data has been examined on its own and published previously [75]. (See Table 4.11 for participant characteristics). Participants had no history of substance abuse, psychoactive drug treatment, or neurological disease or impairment, other than concussion(s) for those in the concussion history group. All experimental

procedures were approved by the University of Waterloo's Office of Research Ethics, and all participants provided written informed consent to participate.

Table 4.1: Demographic information for control and concussion history participants. *Number of concussions refers to self-report of medically diagnosed concussions. Values are expressed as means +/- standard deviation.*

Group	Number of particpants	Age (years) +/- SD	Number of concussions +/- SD	Time since most recent injury (months) +/- SD	Length of recovery from most recent injury (months) +/- SD
Control	13	21.9 +/-2.7	0	---	---
Concussion history	14	22.1 +/-3.9	2.3 +/-2.2	39.1 +/-30.2	4.0 +/- 4.8

Experimental Design

The experimental task required participants to approximate the amplitude of discrete visual and tactile stimuli by applying a graded motor response to a pressure-sensitive bulb. The stimuli were presented either in isolation, as unimodal tactile (T) or visual (V) stimuli, or simultaneously, as crossmodal visual and tactile stimuli (VT). A single trial consisted of tactile, visual, or dual stimulus presentation. Experimental blocks lasted for approximately three and a half minutes, and contained 54 stimuli each presented for 500 ms, with 2.5 s between trials. The experimental design consisted of ten to twelve blocks of trials divided among two attention manipulations, five to six blocks per manipulation, presented in random order. Participants were required to attend, and produce a force-graded response, to approximate the amplitude of tactile stimuli (presented as unimodal or crossmodal)

during the tactile grading blocks, and visual stimuli (presented as unimodal or crossmodal) during the visual grading blocks.

Experimental Paradigm

Each participant was seated comfortably for the duration of the experiment. They fixed their gaze on a computer screen for all blocks, and rested the palmar surface of the second digit of the left hand on a device which delivered vibrotactile stimuli. Participants judged the amplitude of the stimulus type they were instructed to respond to, or track, for that block: either tactile alone, visual alone, or crossmodal, and made a graded motor response by squeezing a pressure-sensitive rubber bulb with their right hand. When responding to tactile stimuli, participants were asked to apply enough force to the pressure-sensitive bulb to approximate the vibration amplitude of each tactile stimulus presented. They were asked to do this each time a tactile stimulus was presented, whether it was presented alone or in combination with a visual one. The visual condition was similar, with participants applying force to the bulb to correspond to the height of a bar appearing on the computer screen, regardless of whether or not a tactile stimulus accompanied it. A third condition was collected in the control group only, for comparison with previously collected data: when responding to both visual and tactile stimuli, these participants were asked to add the height of the visual stimulus and the amplitude of the tactile stimulus and apply a corresponding force to the pressure-sensitive bulb representing the summation. To ensure force output on these combined trials never exceeded an individual's maximum capacity, no single stimulus required a squeeze of more than 25% of the participant's maximum force output and combined responses never

exceeded 50%. However, this condition was not necessary to address the questions of the present research, so it was not collected in the concussion history group.

The experimental trials were preceded by a training session, which lasted approximately 5 min. In the training session, two bars were presented on the computer screen: a blue bar, controlled by the participant squeezing the pressure bulb, and a yellow one which varied randomly in height. The objective was for participants to raise the blue bar to the height of the yellow bar by applying a graded force to the pressure bulb. The blue bar provided visual feedback to teach participants how to use the bulb to grade the visual stimuli. At the same time, the amplitude of the vibrotactile stimulus applied to the subject's finger varied proportionally to match the force applied to the bulb. In this way, the training program connected the visual and vibrotactile stimuli through the means of the force applied to the pressure-sensitive bulb. During experimental trials, the blue response bar was absent, depriving participants of feedback about the accuracy of their grading performance, and the amplitude of the vibrotactile stimuli varied independently of the visual stimuli.

Stimuli

The target visual stimulus was a yellow bar (6 cm wide) which appeared in the center of a black box presented on a black computer screen. The bar was visible for 500 ms and appeared at randomized heights within the box. Tactile stimuli were presented to the second digit of the left hand using a custom-made vibrotactile device. These stimuli were created by the conversion of digitally-generated waveforms to analog signals (DAQCard 6024E, National Instruments, Austin, TX) and amplifying the signal (Bryston 2BLP, Peterborough, Ontario, Canada) using a custom program written in LabVIEW (version 8.5;

National Instruments). Variations in the amplitude of the voltage driving the vibrotactile device resulted in proportional changes in the tactile stimulus applied to the finger. The amplitude of each vibration was constant within a trial and varied randomly between trials. The average stimulus amplitude across all trials which included a tactile stimulus did not differ between the experimental conditions, and the frequency of the vibration was held constant at 25 Hz. In order to prevent auditory perception of the vibrotactile stimuli, participants wore earbud headphones during the experiment which delivered white noise throughout the training and experimental tasks (White Noise Ambience Lite, Logicworks version 2.70, Apple App Store).

Data acquisition and recording parameters

Behavioural data were recorded using a custom program written in LabVIEW (version 8.5, National Instruments, Austin, TX). Participants applied force to the pressure-sensitive bulb that caused air to move through a rubber tube in a closed system, leading to a pressure change that was measured by a pressure sensor and converted to a voltage. There was a linear relationship between the pressure measurement and the voltage produced. EEG data were recorded from 32 electrode sites (32 channel Quik-Cap, Neuroscan, Compumedics, NC, USA) in accordance with the international 10–20 system for electrode placement and referenced to the linked mastoids. Impedance was maintained less than 5 kΩ. EEG data were collected with a DC–100 Hz filter and digitized at 500 Hz (Neuroscan 4.5, SynAmps2, Compumedics, NC, USA). Data were then saved for subsequent analysis.

Data analysis

EEG analysis

Analysis of the EEG data began with epoching, followed by baseline correction to the pre-stimulus interval and the application of a 0-50 Hz band pass filter. Epochs were 600 ms in length, beginning 100 ms before stimulus onset, and epochs contaminated by blinks, muscle contractions, or eye movements were eliminated by visual inspection before averaging. Between 90 and 108 trials per participant were collected for each stimulus type, and after contaminated trials were eliminated, the final trace for each experimental condition consisted, on average, of 62 artifact-free epochs for the control group, and 83 artifact-free epochs for the concussion history group.

For all ERP analysis, potentials were calculated as peak-to-peak amplitudes between the peak of interest and the preceding potential of opposite polarity, except for the P50 amplitude which was calculated relative to the baseline. Separate three-way mixed-model ANOVA analyses were carried out on the amplitudes and latencies of each potential to make between-group comparisons, with attention instruction (T, V), stimulus presented (T, V, VT), as within-subject factors and group (control, concussion history) as the between-group factor. Data sets were tested for normality to validate the use of parametric tests, and transformed when necessary to uphold the assumptions of the ANOVA model. Since N70 and P2 ERP amplitudes have been shown to be modulated by attention in the control group [75], pre-planned contrasts were conducted on these potentials in the post-concussion group. Specifically, these contrasts tested the hypotheses that the modulation by task-relevance which was seen in the control group would not be replicated in the group with concussion history, and that the presentation of a task-irrelevant distractor in the

opposite stimulus modality would significantly decrease the visually-evoked P2 ERP amplitude in the concussion history group.

Behavioural data were analyzed by comparing the amplitude of the target stimulus to the amplitude of the response created by the participant squeezing the pressure-sensitive bulb. The response was compared to the amplitude of the target stimulus to calculate a percentage of the ideal response, but the difference between ideal and actual response was not the focus of the present experiment. Since the hypothesis was that presenting a distracting stimulus would impair accuracy when compared with the undistracted condition, a cost score was calculated by dividing the percent ideal response during the distracted condition by the percent ideal response from the undistracted condition and multiplying by 100. This was then subtracted from a potential maximal score of 100 to obtain the cost of presenting the distractor. This was done for both the control and concussion history groups, and T-tests were used to compare how a history of concussion affected the cost of a distractor on grading in each modality.

4.3 Results

Event-related potentials

Figure 4.2 shows grand average traces of tactile ERPs at electrode CP4. Of the fourteen participants in the concussion history group from whom data was collected, one lacked discernible N70 peaks; in the previously published control group, two of the thirteen participants lacked discernible P50 and N70 peaks. The grand average traces are constructed from the responses of the remaining participants to the presentation of tactile stimuli.
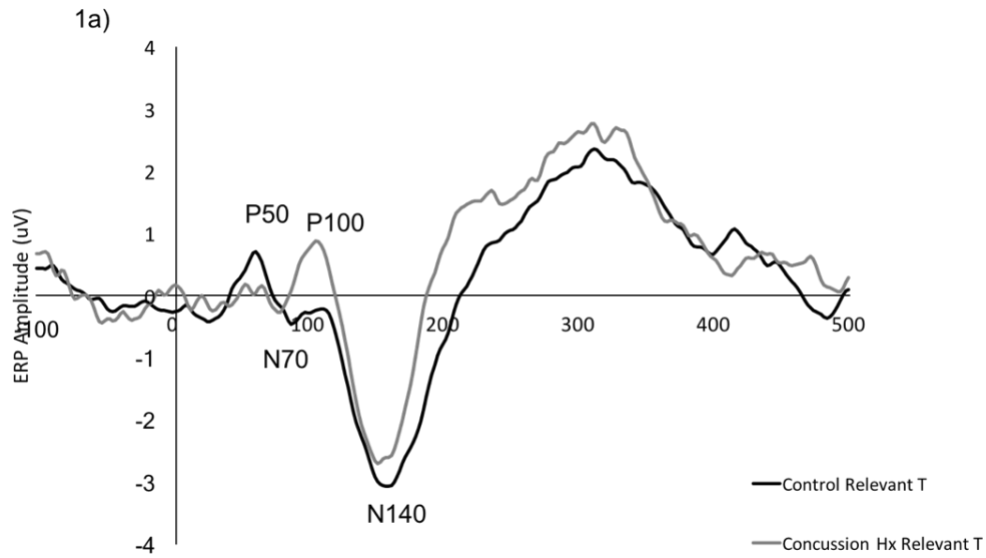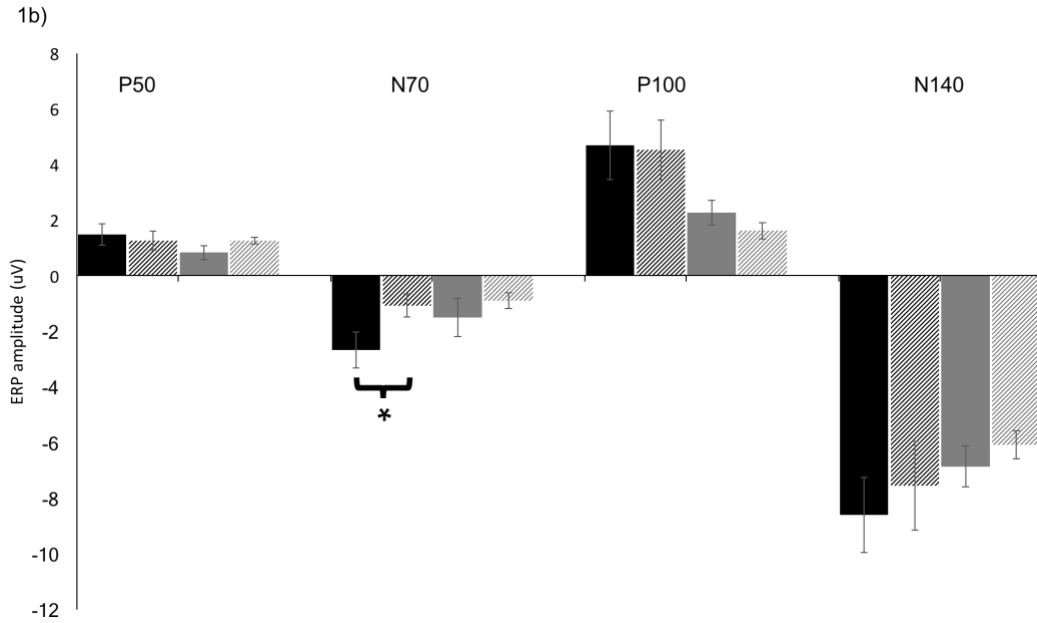
1a)

Figure 4.2: Tactile-evoked ERPs

a) Grand average waveform (n=14), generated in response to the presentation of task-relevant

tactile stimuli. ERP components of interest are labelled for electrode CP4. The black trace was

generated in the control group and the gray trace was generated from the group with a history

of concussion.

1b)

b) Peak-to-peak tactile-evoked amplitudes in response to task-relevant (solid bars) or task-irrelevant (striped bars) tactile stimuli. P50 and N70 amplitudes were measured at electrode CP4, P100 and amplitudes were measured at FCz. Data collected from the control group is shown in black, and from the concussion history group in gray. N70 amplitudes to tactile stimuli were significantly higher in the control group when tactile stimuli were task-relevant as compared to when they were not. There was no difference in N70 amplitude in the group with a history of concussion (* indicates significant to p < 0.05; error bars indicate standard error).
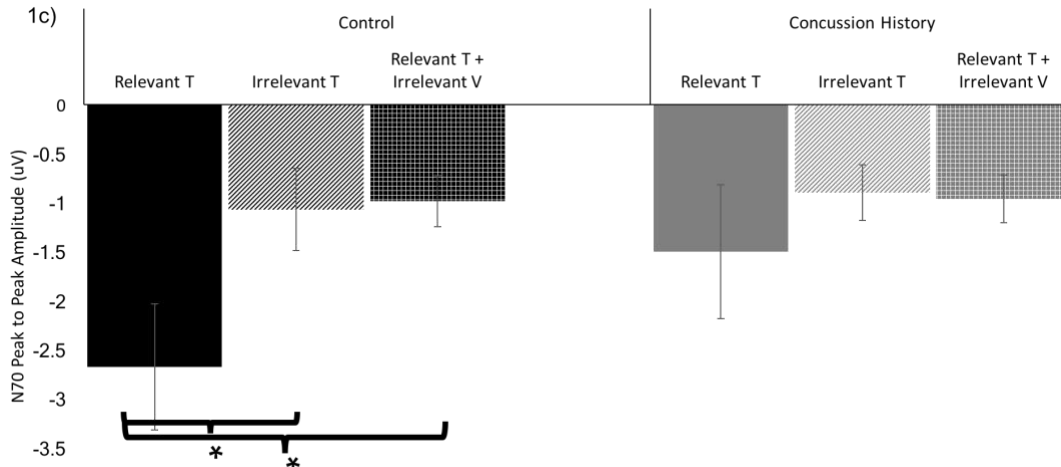
c) Peak-to-peak N70 amplitude to tactile stimuli when the stimuli were task-relevant (solid

bars), when they were irrelevant (striped bars), and when they were presented with a

simultaneous irrelevant distractor (hatched bars). Data collected from the control group is

shown in black, and from the concussion history in gray. In the control group, the N70 was

significantly attenuated when tactile stimuli were task-irrelevant as well as when they were

presented with simultaneous distractors (* indicates p < 0.05; error bars indicate standard

error). There were no differences between conditions in the concussion history group.

The amplitude and latency of the P50 potential was calculated from eleven control

and thirteen concussion history participants who demonstrated a clear P50 component.

The P50 was generated by tactile stimuli and not observed in response to unimodal visual

stimuli. It was maximal at electrode CP4 overlying contralateral somatosensory cortex, and

analysis was conducted using the potentials from this electrode. In the control group, the

mean P50 latency was 58.4 +/- SE 1.1 ms, and in the concussion history group, the P50

potential occurred with a mean latency of 53.2 +/- SE 0.4 ms. Three-way ANOVA analysis of

P50 latency revealed no significant main (group: $F_{1,25}=1.56$, p=0.22; attention: $F_{1,25}=0.67$,

p=0.42; stimulus: $F_{1,25}$=2.06, p=0.16) or interaction (group, stimulus, and attention: $F_{2,24}$=0.84, p=0.44; group and attention: $F_{1,25}$=0.28, p=0.60; group and stimulus: $F_{1,25}$=1.30, p=0.27) effects on P50 latency. The mixed-model ANOVA analysis of P50 amplitude showed a trend toward a significant main effect of group ($F_{1,25}$=3.58, p=0.07) but no significant main effects of stimulus type ($F_{1,25}$=2.22, p=0.15) or attention ($F_{1,25}$=0.48, p=0.49), as well as no significant interactions between any of the factors (group, stimulus and attention: $F_{2,25}$=0.15, p=0.87; group and attention: $F_{1,25}$=0.34, p=0.57; group and stimulus: $F_{1,25}$=2.53, p=0.12) (Figure 4.2b).

EEG tracings demonstrated a clear N70 component in response to vibrotactile stimuli in thirteen control participants and thirteen with a history of concussion. The N70 was maximal at CP4, overlying contralateral somatosensory cortex, and statistical analysis was conducted using the potentials from this electrode. The mean N70 latency was 78.7 +/- SE 1.1 ms in the control group, and 70.25 +/- SE 0.51 ms in the concussion history group. A three-way mixed model ANOVA conducted on N70 latency revealed a significant interaction between the factors group, attention and stimulus ($F_{2,24}$=3.83, p=0.04). This interaction was tested by conducting two separate two-way ANOVAs on the N70 latency values from each group. In the control group, there was a significant interaction between attention and stimulus type ($F_{1,11}$=7.06, p=0.02), while in the concussion history group the interaction between attention and stimulus type trended toward significance ($F_{1,13}$=3.57, p=0.08) but main effects were not significant (attention: $F_{1,13}$=0.00, p=0.99; stimulus type: $F_{1,13}$=0.00, p=0.99). (Figure 1b). The mixed model ANOVA with N70 amplitude as the dependent variable showed no significant main effects of group ($F_{1,25}$=0.81, p=0.38), stimulus type ($F_{1,25}$=3.20, p=0.09), or attention ($F_{1,25}$=0.79, p=0.38), and no significant

interaction effects (group, stimulus and attention: $F_{2,23}$=1.88, p=0.18; group and attention: $F_{1,25}$=0.28, p=0.60; group and stimulus: $F_{1,24}$=0.35, p=0.56). Pre-planned contrasts were conducted using the data from the concussion history group, in order to make direct comparisons with contrasts run and previously published in the control group [75]. In the group with a history of concussion, N70 amplitudes to tactile stimuli were not significantly different when subjects were responding to tactile stimuli than when they were responding to visual ($F_{1,37}$=1.63, p=0.20). However, data from the control group found that N70 amplitudes to tactile stimuli were significantly larger when subjects were attending and responding to tactile stimuli than when they attending and responding to visual ($F_{1,58}$=5.32, p=0.02). The second contrast tested the difference between ERP responses to lone tactile stimuli and to tactile stimuli presented with a simultaneous visual distractor, and found no significant difference in the concussion history group ($F_{1,37}$=2.78, p=0.10). This was in contrast to the control data, which showed that N70 amplitudes were significantly larger when participants with no history of concussion were presented with unimodal tactile stimuli than when the tactile stimulus was presented with a task-irrelevant visual distractor ($F_{1,58}$ = 7.31, p = 0.009) (Figures 4.2b and c).

EEG tracings collected from all subjects demonstrated a clear P100 component in response to vibrotactile stimuli. It was distributed bilaterally at parietal electrode sites and were maximal at electrode FCz, therefore analysis of P100 was conducted at this electrode The mean P100 latency was 101.2 +/- SE 1.4 ms in the control group, and 105.1 +/- SE 0.15 ms in the concussion history group. A three-way mixed model ANOVA with P100 latency as the dependent variable revealed no significant main effects (group: $F_{1,25}$=0.86, p=0.36; stimulus type: $F_{1,25}$=0.31, p=0.58; attention: $F_{1,25}$=1.35, p=0.26), and no interaction effects

between any of the factors on the latency of the P100 potential (group, attention and stimulus type: $F_{2,24}=2.37$, p=0.11; group and attention: $F_{1,25}=1.66$, p=0.21; group and stimulus type: $F_{1,25}=0.16$, p=0.69). Three-way mixed-model ANOVA analysis of P100 amplitude showed a significant main effect of group ($F_{1,25}=5.50$, p=0.03), but no significant main effects of stimulus type ($F_{1,25}=1.64$, p=0.21) or attention ($F_{1,25}=0.12$, p=0.73). There were also no significant interaction effects (group by attention by stimulus type: $F_{1,25}=1.31$, p=0.29, group by attention: $F_{1,25}=2.65$, p=0.12, group by stimulus type: $F_{1,25}=0.53$, p=0.47). The significant main effect of group was explored by completing a two-way repeated measures ANOVA on the data from the concussion history group and comparing this with the two-way ANOVA conducted previously using control group data. When each group was examined individually, there was no significant interaction between attention and stimulus type (controls: $F_{2,59}=1.64$, p=0.20; concussion history: $F_{1,39}=0.55$, p=0.46), and no significant main effect of attention (controls: P100: $F_{2,59}=1.77$, p=0.18; concussion history: $F_{1,39}=1.61$, p=0.21). The concussion history group had a trend toward a significant main effect of stimulus type ($F_{1,39}=3.56$, p=0.07) which was not present in the control participants ($F_{1,59}=0.41$, p=0.52), and which may explain why the mixed-model ANOVA showed a significant main effect of group. However, since this did not reach significance with additional testing, it will not be considered further (Figure 4.2b).

The N140 component was also demonstrated by all participants, distributed bilaterally and maximal at FCz. The mean N140 latency was 149.5 +/- SE 2.2 ms in the control group, and 156.1 +/- SE 0.41 ms in the concussion history group. Three-way mixed model ANOVA analysis of N140 latency revealed a significant main effect of stimulus type ($F_{1,25}=5.79$, p=0.02) and a trend toward a significant main effect of attention ($F_{1,25}=3.66$,

p=0.07). The main effect of group did not reach significance ($F_{1,25}$=1.50, p=0.23). Interactions between terms did not reach significance (group, attention and stimulus type: $F_{2,24}$=0.57, p=0.57; group and attention: $F_{1,25}$=2.39, p=0.13; group and stimulus type: $F_{1,25}$=2.95, p=0.10). The significant main effect of stimulus type was explored by conducting separate two-way ANOVA analyses of the N140 latency values from each group. In the control group, there was a significant main effect of stimulus type ($F_{1,12}$=4.80, p=0.05) and a trend toward a significant main effect of attention ($F_{1,12}$=4.21, p=0.06) but no interaction between these terms ($F_{1,11}$=0.71, p=0.42). In the concussion history group, there were no significant main or interaction effects (attention: $F_{1,13}$=0.11, p=0.75; stimulus type: $F_{1,13}$=0.67, p=0.43; attention and stimulus type: $F_{1,13}$=0.01, p=0.93). A three-way mixed-model ANOVA of N140 amplitude showed a significant main effect of stimulus type ($F_{1,25}$=11.37, p=0.002), but no significant main effects of group ($F_{1,25}$=1.34, p=0.26) or attention ($F_{1,25}$=0.83, p=0.37). There was a trend toward a significant interaction effect between group, attention, and stimulus type ($F_{1,25}$=2.97, p=0.07) but no other interaction effects reached significance (group by attention: $F_{1,25}$=0.84, p=0.37, group by stimulus type: $F_{1,25}$=0.70, p=0.41). The significant main effect of stimulus type was explored by conducting a two-way repeated measures ANOVA of the N140 amplitudes collected from the concussion history participants for comparison with the control group statistics published previously. When each group was examined individually, there was no significant interaction between attention and stimulus type (controls: $F_{2,60}$=0.46, p=0.63; concussion history: $F_{1,39}$=0.01, p=0.94), and a trend toward a significant main effect of attention in the control group ($F_{1,60}$=3.60, p=0.06) but not in the group with a history of concussion ($F_{1,39}$=2.96, p=0.09). Neither group showed a significant main effect of stimulus type

(controls: $F_{1,59}=0.41$, $p=0.52$; concussion history: $F_{1,39}=3.33$, $p=0.08$), so the significant main effect of stimulus type which was shown in the mixed-model ANOVA will not be considered further (Figure 4.2b).

Figure 4.3a shows a grand average trace of the ERPs generated in response to visual stimuli. The figure depicts the ERPs that occurred in response to visual stimuli when subjects directed attention toward and away from visual input.
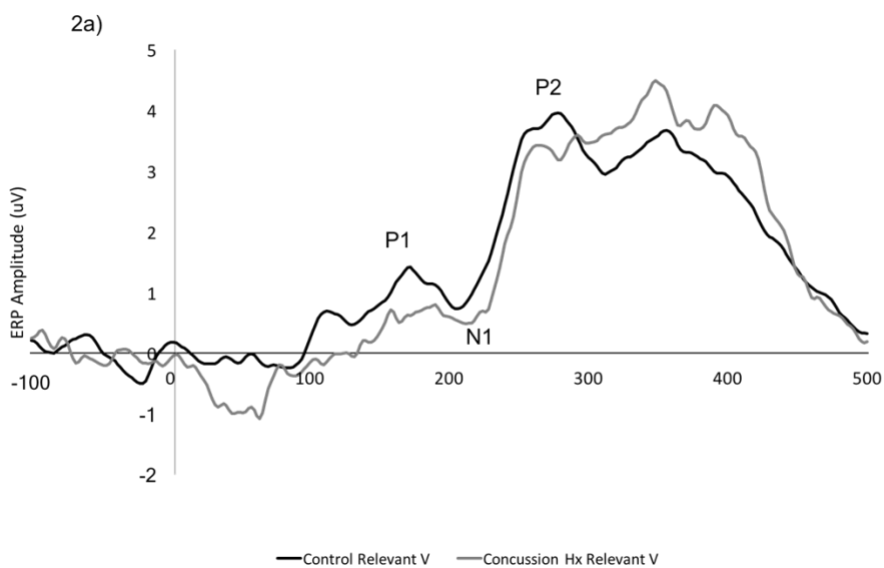

Figure 4.3: Visually-evoked ERPs

a) Grand average waveform (n=14), generated in response to the presentation of lone visual stimuli. ERP components of interest are labelled for electrode Pz. The black line denotes data generated from control group, and the gray line was generated from those with a history of concussion.

2b)
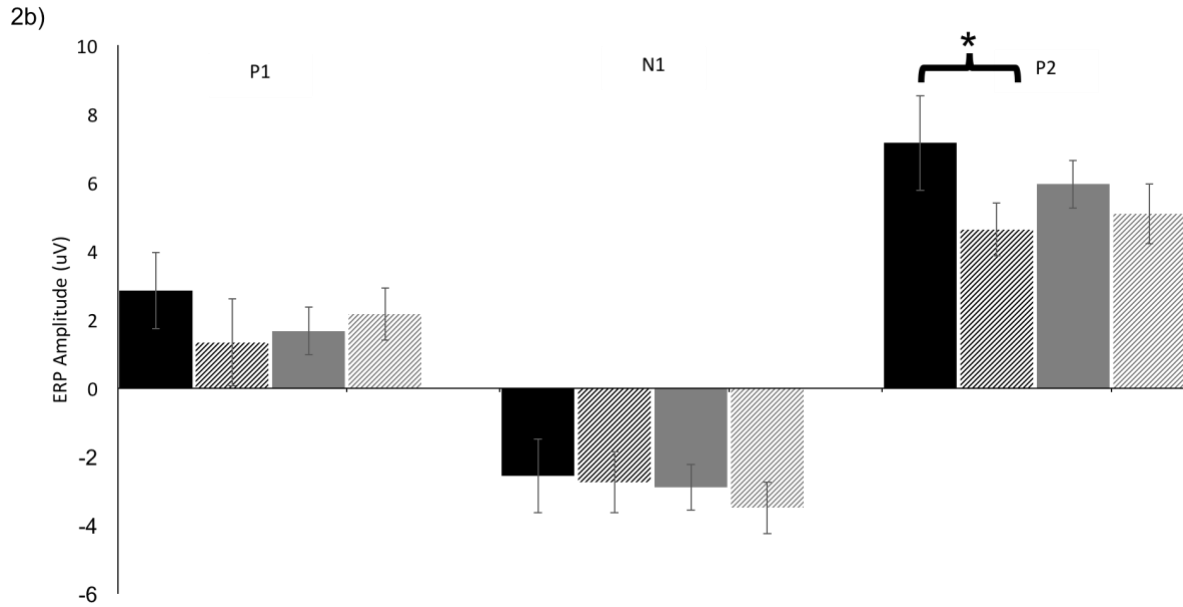
b) Peak-to-peak amplitudes of visually-evoked ERPs at electrode Pz, when visual stimuli were task-relevant (solid bars) and when they were irrelevant (striped bars). Data from control participants is shown in black, and data from those with a history of concussion is shown in gray. In the control group, P2 was significantly attenuated when the evoking visual stimuli were task irrelevant (* indicates p < 0.05; error bars indicate standard error). There were no differences between conditions in the concussion history group.

2c)
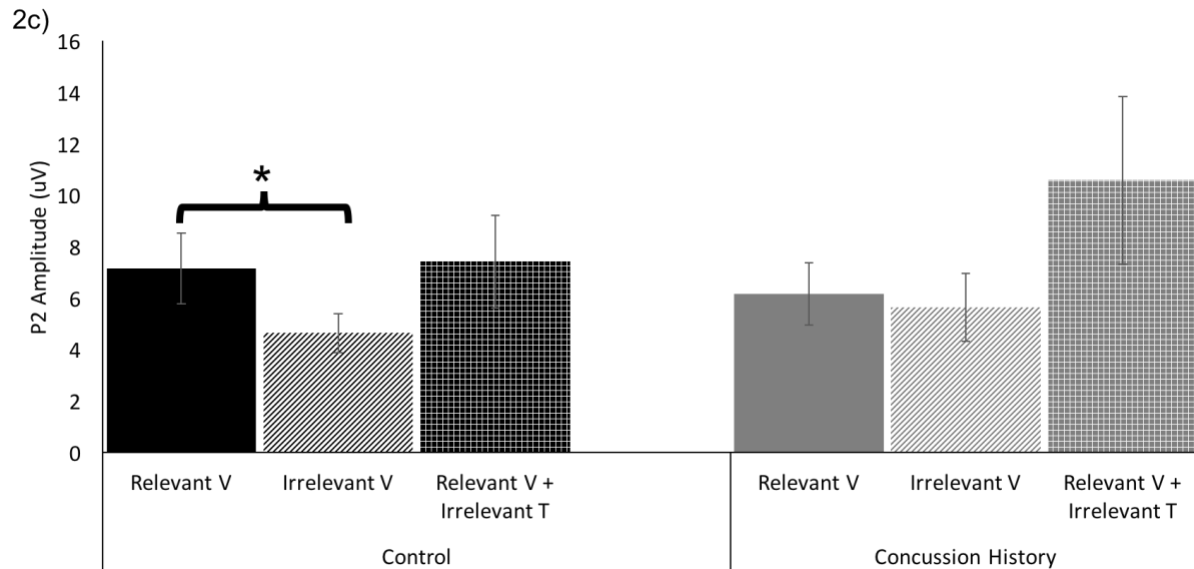
c) Peak-to-peak P2 amplitude to visual stimuli when the evoking visual stimuli were relevant (solid bars), when they were irrelevant (striped bars), and when they were presented with a simultaneous irrelevant tactile distractor (hatched bars). In the control group (black), P2 amplitudes to task-relevant stimuli were significantly higher than to task-irrelevant stimuli (* indicates significant to p < 0.05; error bars indicate standard error). There were no differences between conditions in the concussion history group (gray).

Eleven of thirteen subjects in the control group and all fourteen in the concussion history group demonstrated three clear ERP components in response to visual stimuli, labelled P1, N1, and P2. All were maximal at electrode Pz, distributed bilaterally, and not observed in response to tactile stimuli. Three-way mixed model ANOVA analysis of latency revealed no significant main effects of group (P1: $F_{1,25}$=2.02, p=0.17; N1: $F_{1,25}$=0.35, p=0.56; P2: $F_{1,25}$=1.78, p=0.19), attention (P1: $F_{1,25}$=1.61, p=0.22; N1: $F_{1,25}$=0.38, p=0.55; P2:

$F_{1,25}=0.41$, p=0.53), or stimulus type (P1: $F_{1,25}=0.53$, p=0.48; N1: $F_{1,25}=0.01$, p=0.92; P2:

$F_{1,25}=0.15$, p=0.70). There were also no interactions between the three terms (P1:

$F_{2,25}=0.31$, p=0.74; N1: $F_{2,25}=0.15$, p=0.86; P2: $F_{2,25}=1.31$, p=0.29) or between group and

attention (P1: $F_{1,25}=0.43$, p=0.52; N1: $F_{1,25}=0.81$, p=0.38; P2: $F_{1,25}=2.34$, p=0.14) or group

and stimulus type (P1: $F_{1,25}=0.40$, p=0.54; N1: $F_{1,25}=0.23$, p=0.63; P2: $F_{1,25}=2.11$, p=0.16).

Mixed model ANOVAs were performed to test differences in ERP amplitudes. Results

showed no significant effects of group (P1: $F_{1,25}=0.10$, p=0.75; N1: $F_{1,25}=0.02$, p=0.90),

stimulus type (P1: $F_{1,24}=0.11$, p=0.74; N1: $F_{1,24}=0.00$, p=0.95), or attention (P1: $F_{1,23}=0.04$,

p=0.84; N1: $F_{1,24}=0.06$, p=0.82), nor any significant interaction effects (group by attention

by stimulus type - P1: $F_{1,23}=0.25$, p=0.78; N1: $F_{1,23}=0.32$, p=0.73; group by attention - P1:

$F_{1,23}=0.11$, p=0.74; N1: $F_{1,24}=0.24$, p=0.63; group by stimulus type - P1: $F_{1,24}=0.23$, p=0.64;

N1: $F_{1,24}=2.50$, p=0.13) (Figure 4.3b). The mixed-model ANOVA, when used to examine the

amplitudes of the P2 potential showed a trend toward a significant main effect of stimulus

type ($F_{1,24}=4.05$, p=0.06), but no other significant main or interaction effects (group:

$F_{1,25}=0.05$, p=0.83; attention: $F_{1,24}=1.41$, p=0.25; group by attention: $F_{1,24}=1.16$, p=0.29;

group by stimulus type: $F_{1,24}=0.11$, p=0.74; group by attention by stimulus type: $F_{1,23}=0.03$,

p=0.97). As with the N70 amplitude data, pre-planned contrasts were conducted using the

P2 potentials from the concussion history group, in order to test the hypothesis that P2

modulation by task-relevance would be decreased in those with a history of concussion

(Figure 4.3c). In the group with a history of concussion, P2 amplitudes to tactile stimuli

were not significantly different when subjects were responding to visual stimuli than when

they were responding to tactile ($F_{1,35}=0.06$, p=0.82). When the control group's data was

tested, P2 modulation was not anticipated, so pre-planned comparisons were not made;

significance was therefore established using post-hoc testing. A post-hoc Tukey test conducted on data from the control group found that P2 amplitudes to visual stimuli were significantly larger when subjects were attending and responding to visual stimuli than when they attending and responding to tactile (p<0.05). The second contrast tested in the concussion history group compared P2 responses to relevant lone visual stimuli with P2 responses generated to visual stimuli presented with simultaneous distractors, and found no significant difference in P2 amplitude between these stimulus conditions ($F_{1,35}$=2.85, p=0.10); in the control group, a post-hoc Tukey test found no significant difference between these stimulus conditions in the control group (p < 0.05).

Behavioural performance

Independent T-tests were conducted within each sensory modality to test the change in accuracy caused by a distractor in the control group as compared to the group with a history of concussion (Figure 4.4). For tactile grading, there was a significantly greater cost of a visual distractor on task accuracy (t(19) = -5.01, p < 0.0001) in the concussion history group (M = 49.32, SD = 21.27) as compared to the control group (M = 17.37, SD = 10.42). Similarly for visual grading, there was a significantly greater cost of a tactile distractor on task accuracy (t(25) = -3.15, p = 0.02) in the concussion history group (M = 34.4, SD = 19.40) as compared to the control group (M = 11.81, SD = 17.29).

3)
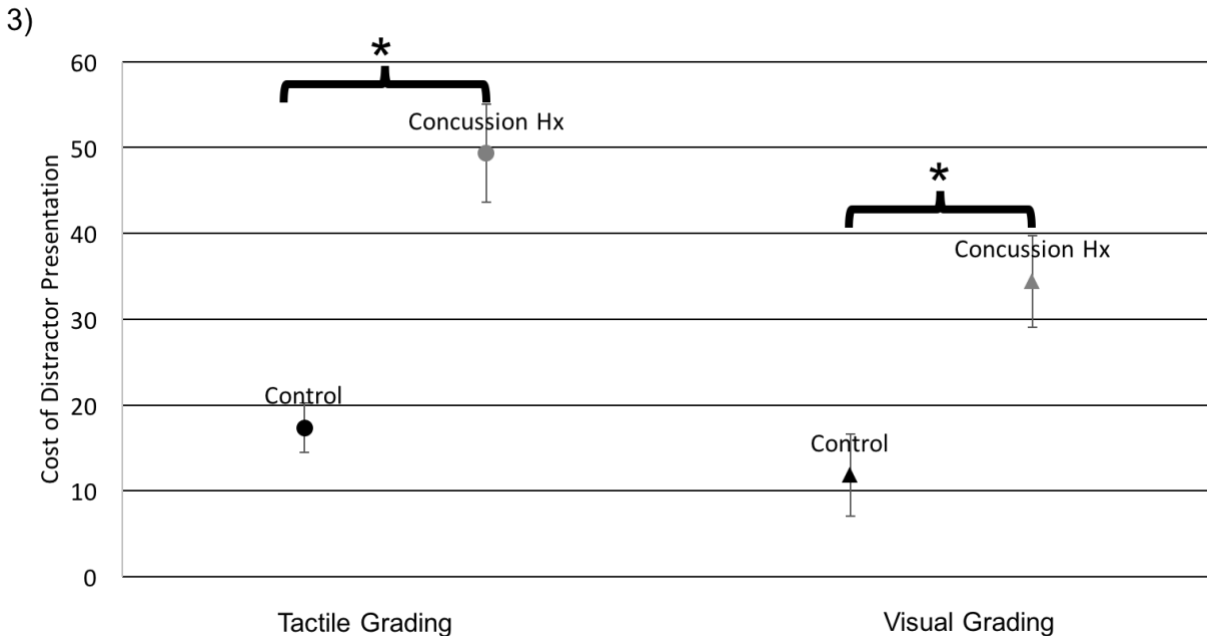
Figure 4.4: Cost of presenting a simultaneous distractor.

Accuracy cost when target stimuli are presented with simultaneous distractors, for both tactile (circles) and visual (triangles) grading conditions. Black markers represent the control group; gray markers represent the concussion history group. There was a significant increase in distractor cost during both grading conditions in the group with a history of concussion, as compared to controls. (Error bars denote standard deviation).

4.4 Discussion

Individuals who had recovered from concussion injuries showed diminished relevancy-based modulation of the specific ERPs as compared to individuals with no history of concussion. Previous work using the same task as the present experiment found that the tactile-evoked N70 and visually-evoked P2 were attenuated when the evoking stimuli were

task-irrelevant. In addition, the previous work found that presentation of a visual distractor led to attenuation of the N70 potential, and decreased tactile grading accuracy. These electrophysiological and behavioural differences were hypothesized to occur as a consequence of the differences in the timing of relevancy-based gating in the visual and tactile modalities. Because relevancy effects in the somatosensory domain were exerted 70 ms after stimulus presentation, irrelevant stimuli were gated out of the processing stream at this early stage. In the visual domain, relevancy effects were exerted much later, with stimuli gated out of the processing stream approximately 270 ms after presentation. This between-modality difference in the timing of relevancy-based gating was the hypothesized explanation for why a visual distractor stimulus altered cortical and behavioural correlates in the opposite sensory domain, while a tactile distractor did not.

The first hypothesis of the present study was supported by the results of the experiment: relevancy-based gating of sensory stimuli sensory was shown to be impaired in individuals who have recovered from concussion injuries. In the concussion history group, neither the tactile-evoked N70 nor the visually-evoked P2 were significantly different when the evoking stimulus modality varied in task relevance. This is in contrast to the results of the control group, which showed that both the N70 and P2 potentials were significantly larger when the respective evoking stimuli were relevant to the sensory grading task. The loss of N70 modulation by task relevance in the concussion history group appears to be due to less N70 enhancement in the task-relevant condition as well as less attenuation in the task-irrelevant condition. This pattern is similar to that seen in literature examining patients with prefrontal cortical damage. Patients with lesions to the PFC have demonstrated less attenuation of auditory ERPs to distractor stimuli, suggesting a failure in

inhibitory control over the processing of irrelevant stimuli, and implicating the PFC in the modulation of cortical responses to sensory stimuli based on their relevance to an experimental task [6]. Patients with PFC lesions have also shown decreased early (125 ms) and late (200-650 ms) cortical responses to visual stimuli [83], a finding consistent with the attenuation of the visually-evoked P2 response in the concussion history group during the present experiment.

There is a growing body of literature showing electrophysiological abnormalities in patients after concussion. Compared to a control group, participants with symptomatic concussion injuries showed decreased N350 and P300 amplitudes, as well as slower reaction times and decreased task accuracy, during a visual working memory task [28]. In contrast to the concussion history group in the present experiment, the participants who had sustained concussions in Gosselin *et al*. [28] were symptomatic, which may have contributed to their electrophysiological and behavioural findings. However, EEG changes have also been shown in groups who have recovered from concussion, similar to the population studied in the present experiment. Most literature examining electrophysiological consequences of concussion has focused on examining changes in the P3 potential (also known as the P300) [26,29], thought to index attention and cognitive efficiency [28,29]. The P3 ERP has been shown to be selectively suppressed in amplitude during a visual oddball task in a group of participants who had recovered from concussion, with the greatest degree of suppression in participants who had sustained more concussions [26]. The N2pc potential, thought to index visuospatial attention, was unaffected by concussion history, confirming that a history of concussion does not generally suppress cortical activity but exerts specific effects only on certain potentials

[26]. Although the present study focuses on modality-specific tactile and visual ERPs instead of general indices of cortical function, the suppression or loss of modulation after concussion appears consistent.

The second hypothesis of the present study was that visual-evoked ERPs would be smaller when the evoking stimulus was presented with a concurrent tactile distractor. This was based on the finding that tactile distractors were effectively gated out due to their task-irrelevance in the control group, and the expectation that concussion history would disrupt this gating and make the tactile stimuli act as the visual did during the tactile grading task. This hypothesis was not supported by the results of the present experiment, which showed that the visual P2 was significantly larger when the evoking visual stimulus was presented with a concurrent tactile distractor. In the opposite sensory modality, the control group data showed that the tactile N70 was significantly smaller when evoked by tactile stimuli presented with a distractor as compared to lone tactile stimuli; in contrast, there was no significant difference in N70 amplitude between the same two conditions in the group with a history of concussion. The data suggests that relevancy-based gating was not the mechanism underlying the ability of these simultaneous stimuli to act as distractors when irrelevant.

Task relevance is an example of a top-down, or cortically-driven, influence on sensory gating, which is itself a component of attentional orienting. Attention involves various mechanisms to allocate processing resources toward particular stimuli [1], including integrating multiple sensory inputs or gating others out of the processing stream. Top-down orienting refers to attention being voluntarily directed toward a general location, a sensory modality, or a specific stimulus, in accordance with goals or task demands [1–

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3,40]. Attention can also be captured by a stimulus, regardless of how the stimulus relates to the goal or task at hand; this bottom-up or stimulus-driven orienting occurs independently of voluntary control, depending on the salience of a stimulus, as well as its visual, spatial, or temporal properties [1,2]. The results of the present experiment suggest that bottom-up factors may be more responsible for the changes in ERP amplitude during the concurrent stimulus presentation conditions than the top-down influence of the task-relevant modality. It is also possible that the lack of difference between modality-specific cortical potentials when stimuli were presented with and without distractors is related to interactions between top-down and bottom-up factors. During a sensory integration task, P50 amplitudes have been shown to be more enhanced when a tactile stimulus was presented with a task-relevant visual stimulus than when two tactile stimuli were presented together [84]. If concussion history alleviated top-down, relevancy-based modulation of cortical responses, there may have been more opportunity for between-stimulus effects to affect the N70 or P2 ERPs when distractors were presented during the modality-specific sensory grading tasks. For example, tactile evoked N70 ERPs were smaller in the presence of a visual distractor in the control group, and there was no significant difference between the distracted and undistracted conditions in the concussion history group. The disruption of top-down gating of visual distractors could have resulted in stimulus-driven effects during the dual-stimulus condition, enhancing the N70 amplitudes in the concussion history group.

The final hypothesis of the current experiment was that the presentation of unattended distractor stimuli would negatively affect task accuracy in the visual grading task in the group with a history of concussion. This was based on the expectation that gating based on

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task-relevance would be disrupted after concussion, allowing stimuli into the processing stream which were previously gated out of it and negatively affecting behaviour. The results of the present study show that the behavioural cost of presenting a simultaneous distractor was significantly higher in the concussion history group than in the control group. In the present experiment, the increased cost to task accuracy may be explained by the impairment in relevancy-based modulation shown in the electrophysiological results. More generally, though, correlation of electrophysiological findings with the results of behavioural tests is inconsistent in populations after concussion, and two main theories exist to explain this discrepancy. One theory states that the brain uses its available resources to compensate for damage by differentially recruiting other brain networks or by utilizing alternative cognitive strategies to optimize performance, a concept known as cognitive reserve [29,30].   If participants are able to access cognitive resources held in "reserve" or change their cognitive strategy to maintain baseline functional performance [30], it may help to explain how significant ERP waveform changes post-concussion can coexist with baseline-level performance on neuropsychological tests. An alternative explanation for the discrepancy between ERP changes and task performance may be that recovery from concussion is a two-step process. The first step is thought to involve compensatory mechanisms which produce rapid initial recovery of function, followed by a second step consisting of prolonged neuronal recovery [7]. It is during this period of long-term recovery that deficits may be apparent on electrophysiological measures while task performance appears to have recovered. Further research is required to delineate when cognitive reserve is accessed and then no longer required, and to delineate the nature and time course of ERP changes following concussion.

People with symptomatic injuries have been shown to have both decreased performance on working memory tasks as well as decreases in ERPs associated with working memory and attention processes [28]. However, measures of both task performance and cortical function show much more variable results when examined in individuals who have recovered and are asymptomatic at the time of testing; some studies show normal performance [26] while others show deficits on a diverse range of behavioural and electrophysiological outcome measures [15,27,81,85]. Other studies have shown significant differences in either electrophysiology or task performance only when participants were stratified according to the number of concussions they had sustained [30,82].

It should also be noted that the type of task is a major factor in differences between task performance and electrophysiology: more complex activities, such as those requiring dual-tasking, may be more sensitive to performance decrements. Even without a dual-tasking component, the task used in the present experiment showed that grading accuracy suffered when a distractor stimulus was delivered to those with a history of concussion, even though these participants had been deemed medically recovered from their concussion injuries. This raises the question of how recovery from concussion should be defined, and suggests that relying on symptom resolution is an incomplete metric upon which to base decisions about concussion resolution.

4.5 Conclusion

This study provides evidence that concussion has effects on cortical processing and accuracy on a sensory grading task which persist even after symptoms have resolved and individuals have returned to normal activities of daily living. Cortical correlates of top-down attentional orienting appear to be disrupted after concussion, which may have contributed to differences in responding to task-relevant stimuli when faced with simultaneous distractors. As well, there was a significantly greater cost to task accuracy when distracting stimuli were presented to participants with a history of concussion than to controls. More research is required to characterize how concussion history affects the inter-related nature of top-down and bottom-up attentional orienting processes, and to understand how electrophysiological and behavioural outcomes can be correlated to provide a more objective measure of recovery in this population.
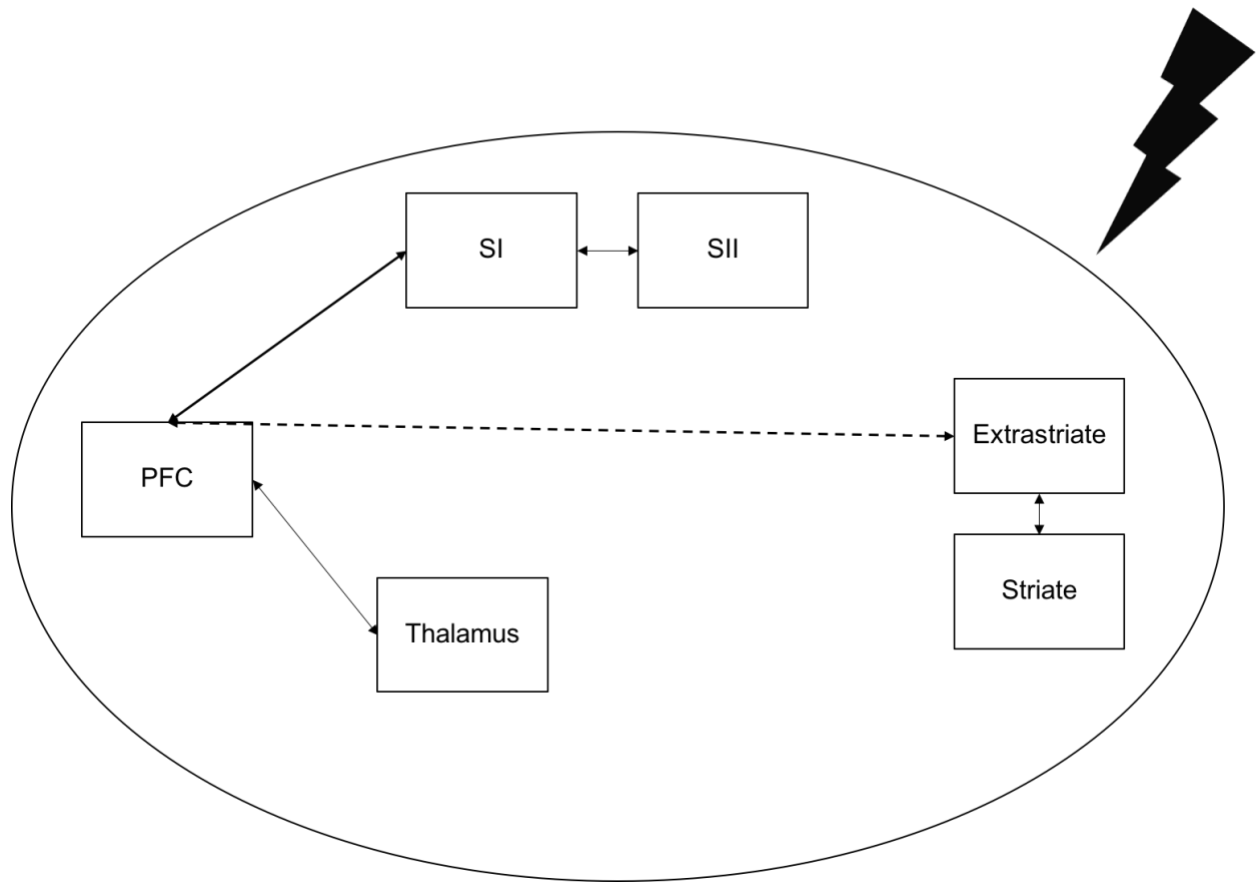
Figure 4.5: Conceptual model of study 3 findings

The results of study 3 confirm that a history of concussion has a significant disruptive effect (represented by the darkened lightning bolt) both on the modulation of modality-specific cortical representations of visual and tactile stimuli as well as on measures of sensory grading accuracy (not shown in model). The non-specific nature of a concussion means that the effects of the cannot be localize to a specific cortical area, so the lightning bolt is shown as affecting the entire network (large oval).

Chapter 5: General Thesis Discussion

This thesis had three aims underlying the study design and hypotheses: to characterize the electrophysiological and behavioural correlates of attentional orienting during a sensory selection task, to understand the cortical mechanisms involved in sensory selection under conditions of varying task-relevance and in the presence of distractor stimuli, and to probe whether a history of concussion injury is correlated with sensory gating dysfunction. The main findings of this thesis are summarized in the following set of diagrams, which highlight the contributions of each study.
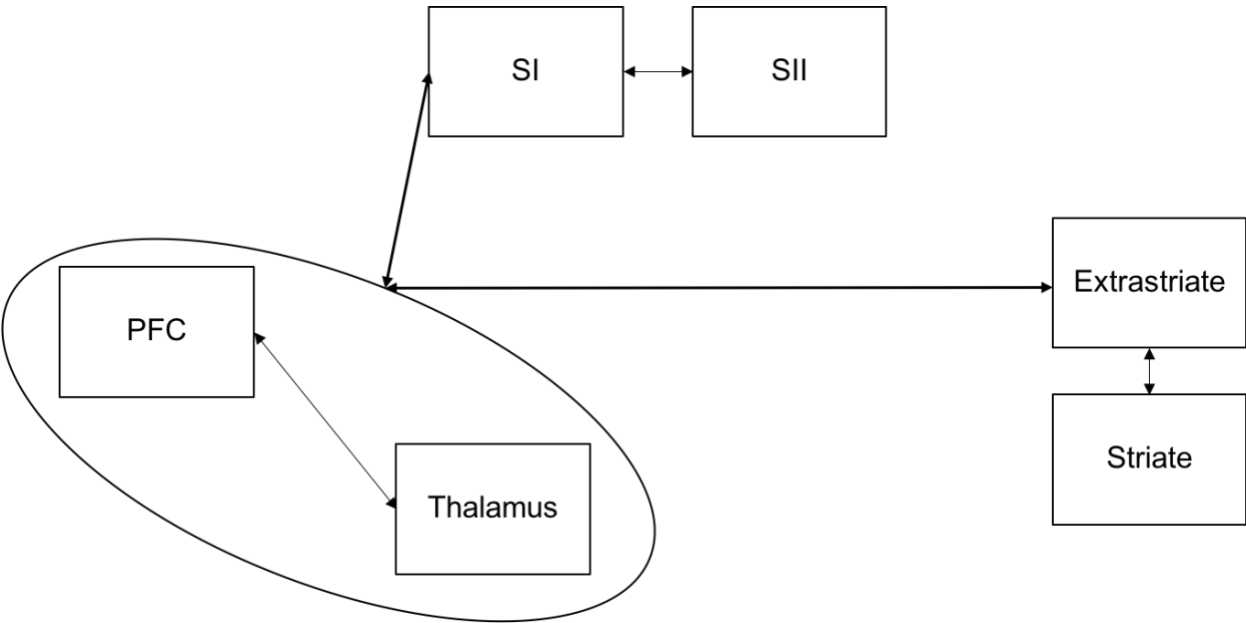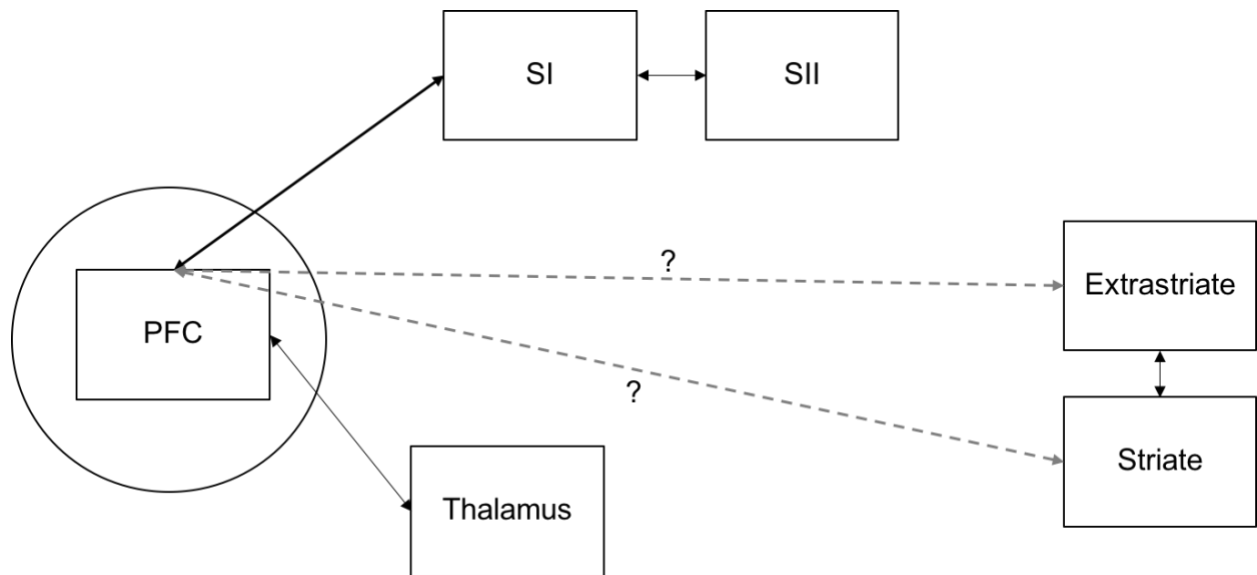

Figure 5.1: Study 1 summary of findings
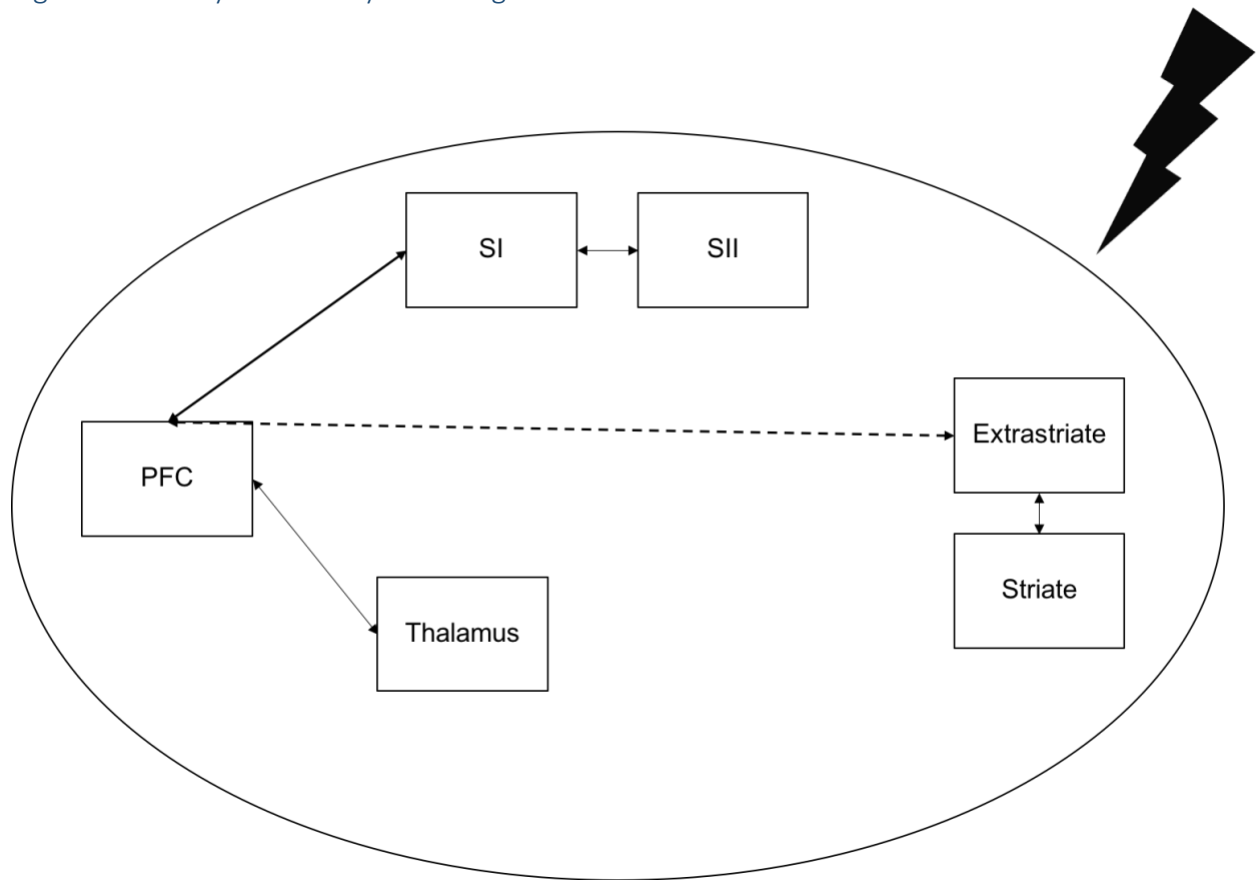
Figure 5.2: Study 2 summary of findings

Figure 3: Study 5.3 summary of findings

The three studies that comprise this thesis show that specific ERPs are sensitive to modulation based on task-relevance, that the prefrontal cortex is a key node in relevancy-based gating networks, and that those with a history of concussion show evidence of altered attentional orienting which persists even after symptoms have resolved.

The first study set out to determine how task-relevance affected early modality-specific cortical representations of visual and tactile stimuli, as well as the effects of presenting a distractor stimulus in a different sensory modality. The hypothesis that task-relevance would modulate cortical responses to both tactile and visual stimuli was supported by the findings of study 1, and suggested a relationship between relevancy-based gating and the cortical and behavioural responses to distractor stimuli. Somatosensory stimuli were subject to relevancy-based gating at an early stage, 70 ms post-stimulus, and as distractor were ineffective in influencing cortical or behavioural processing of visual stimuli. In contrast, visual stimuli showed evidence of gating based on task-relevance approximately 270 ms post-stimulus, and had a significant effect on both the cortical processing of tactile stimuli and task accuracy during tactile grading. The tactile-evoked N70 is generated in SI, and modulation of this potential indicates that attentional effects are exerted early in the somatosensory domain, in the primary receptive zones. The cortical site of P2 generation is less clear, but is likely within extrastriate cortical regions. The results of study 1 suggest that relevancy-based modulation at early post-stimulus latencies, and thus within primary sensory receptive zones, rendered irrelevant tactile stimuli ineffective as distractors. In contrast, relevancy effects in the visual domain occurred later and in sensory association areas, leading to visual stimuli exerting distracting effects.

Study 2 was designed to test the theory that top-down attentional orienting was responsible for the sensory gating effects seen in study 1. Top-down attentional orienting is controlled by a network of cortical and subcortical structures which includes the PFC, and patients with PFC lesions have impaired sensory gating and increased distractibility [4–6]. Study 2 disrupted PFC activity using cTBS, a TMS protocol which transiently decreases cortical excitability in targeted brain regions [86]. The results of study 2 partially supported the hypothesis that top-down gating based on task-relevance would be diminished by PFC inhibition. The data showed that transiently disrupting PFC activity impaired relevancy-based gating of somatosensory stimuli, indicating that top-down attentional orienting mechanisms were an important component of this modulation. However, the data from this group of participants did not show modulation of P2 by task-relevance before cTBS was applied, so this study was unable to make conclusions about the effects of top-down modulation on relevancy-based gating of P2. The hypothesis that attenuating PFC activity would disrupt early gating of tactile distractor stimuli and result in altered cortical and behavioural responses during a visual grading task was not supported by the results of the experiment: whether or not tactile-evoked ERPs were subjected to relevancy-based gating did not change how a tactile distractor affected either visual ERP amplitudes or visual grading accuracy.

The third overall aim of this thesis was to address the clinical suggestion that a history of concussion injury disrupts the gating of distracting or irrelevant sensory information. Studies 2 and 3 were collected concurrently, with study 3 finishing later due to challenges in recruiting a cohort of participants with a history of concussion. As such, the hypotheses tested in study 3 were generated before study 2 was completed, and therefore

not informed by the results of study 2. The results of study 3 supported the hypothesis that relevancy-based gating would be disrupted in participants with a history of concussion, as the amplitudes of both the tactile-evoked N70 and visually-evoked P2 were not significantly different when the evoking stimuli were task-relevant as compared to when they were task-irrelevant. The second hypothesis, however, was not supported by the data: although relevancy-based gating of tactile stimuli was disrupted in the post-concussion group, these stimuli led to no significant difference in visually-evoked ERP amplitudes when they were presented as distractors. Finally, task accuracy was significantly different between the control and post-concussion groups: sensory grading was significantly less accurate in the group with a history of concussion when a distractor was presented, regardless of the modality being graded.

5.2 Implications

1. N70 amplitude is modified by tasks demanding sensory selection

The N70 ERP component appears uniquely sensitive to the sensory selection task utilized in this thesis. Previous work has shown that the P50 potential is modulated by task-relevance during tasks requiring integration of temporally-coincident stimuli in different sensory modalities [48]. When the data set from Popovich and Staines (2014) was re-examined, there was no significant difference in N70 amplitude evoked by simultaneous visual and tactile stimuli. The requirement to select between conflicting stimuli modulated only the N70 component, while the P50 was only affected when task demands required integration of the same stimuli. The stimuli in both experimental designs were identical; the only difference between Popovich and Staines (2014) and study 1 of this thesis was the

instruction to participants. In contrast to the sensory selection task of study 1, Popovich and Staines' (2014) experiment required participants to combine stimuli. This indicates that it was not the presentation of the two stimuli that modulated N70 amplitudes in study 1, but specifically the requirement to select between them, reinforcing that task demands have a substantial impact on the timing of multisensory processing. This leads to interesting questions about the generators of these specific ERP components. While both the P50 and N70 are known to be generated in the primary somatosensory cortex (S1), the results of study 1 suggest that they may be localized to slightly different neuronal sub-populations within S1.

2. Bottom-up attentional orienting mechanisms may represent an important component of distractor stimulus processing

The experimental task employed in studies 1 through 3 utilized two different attentional orienting mechanisms to compare how grading was affected by attentional orienting. Shifting conditions of task relevance is an example of modulating top-down orienting of attention. Presenting a distractor stimulus incorporates both top-down and bottom-up orienting mechanisms. There is evidence that top-down and bottom-up attentional effects are subserved by different cortical networks, which may explain why, in study 2 of this thesis, cTBS to the PFC affected top-down but not bottom-up attentional processing. Task-relevance remains an important driver of top-down orienting, but the presentation of two simultaneous stimuli introduces opportunities for between-stimulus interactions. The fact that there was a trend toward significantly decreased accuracy of tactile but not visual grading when distractors were presented suggests a difference

between the visual and somatosensory modalities in the properties that form the basis for attentional allocation, such as the salience of the stimuli. The tactile stimuli varied in amplitude, while the visual stimuli varied in the height at which they were displayed. The amplitude of the tactile vibrations may have modulated salience more substantially than varying the height of the visual stimulus did. It is also possible that presenting the visual stimuli at varying heights within a box on a computer screen inadvertently changed the demands of the visual grading task. While participants were not instructed to grade visual distractor stimuli in the present experiment, the presentation of these stimuli within a box may have led to them being implicitly graded, and sensory grading tasks have been shown to generate ERPs of greater amplitude than sensory detection tasks [63]. Repeating the present experiment but varying the visual stimuli differently, perhaps varying the brightness rather than their height within a predetermined frame, may help disentangle the interactions between bottom-up and top-down attentional orienting that occur in the task used in studies 1 through 3. Top-down and bottom-up mechanisms may also have interacted with each other when a relevant stimulus was presented simultaneously with an irrelevant one. It is possible that increased cortical excitability resulting from the disruption in relevancy-based gating of the visual stimuli led to greater opportunity for bottom-up interactions between the visual and tactile stimuli and, in turn, increased the amplitude of the tactile-evoked N70.

3. Implications for understanding the neuroscience of concussion

There are striking similarities in the cortical responses and behavioural outcomes between participants with diminished PFC excitability and those who have recovered from

concussions. Both after cTBS to the PFC and in those with a history of concussion, N70 amplitudes were less enhanced in the condition when tactile stimuli were task-relevant as well as less attenuated in the task-irrelevant condition, and the combined effect in both cases led to the overall loss of modulation by task relevance. However, the cost of distractor presentation was significantly higher in those with a history of concussion, regardless of the modality being graded. The similarity in N70 modulation between those with a history of concussion and the group in which PFC excitability had been attenuated does not mean that the PFC is the site responsible for concussion deficits - such a conclusion is beyond the scope of this thesis, does not fit with the understanding of concussion as a non-focal brain injury, and is likely a gross oversimplification of the functional mechanisms and roles of the PFC. However, the accumulation of evidence showing that concussion disturbs functions such as sensory gating and working memory which are understood to be prefrontally-mediated, suggests a connection we currently do not understand. One theory is that the mechanism of concussion, an injury induced by shearing or torsional forces, affects long axons and myelinated tracts such as those connecting distant cortical and subcortical areas, more than it affects those travelling shorter distances. The substantial connectivity of the PFC with other areas of cortex, as well as with subcortical structures like the thalamus and TRN to subserve attentional orienting functions, may be particularly impacted by the shearing of long axons. Alternatively, PFC-related functions may appear more affected by concussion simply because the PFC is so interconnected that it is impacted by concussion-related damage to one or more of several brain regions. It is also possible that prefrontally-mediated functions are harder to compensate for - there is less cognitive reserve available to subserve these higher-order functions, or less available to perform the PFC's integrative

functions. Regardless, this thesis is not meant to hold the PFC solely responsible for concussion-related deficits, but it does contribute to some significant ongoing questions in the concussion neuroscience community.

5.3 Limitations and Rationale

In addition to the specific limitations detailed in each chapter, there are some additional general limitations to the three studies of this thesis. The first is the inherent difficulty in trying to correlate changes in electrophysiology with differences in behavioural outcomes. Changes in cortical excitability shown on EEG are contributors to changes in behaviour, but other downstream factors exist which influence behavioural responses without affecting EEG traces. There is simply not a one-to-one relationship between electrophysiology and behaviour, so correlating cortical and behavioural responses must be done with caution. In the concussion literature, ERPs are commonly analyzed along with neuropsychological tests designed to assess higher order cognitive functions such as working memory. Some studies have shown that changes in cortical excitability are correlated with suboptimal task performance, while others show task performance to be preserved, making the discrepancy between cortical and behavioural measures a topic of interest and debate. It has been posited that the brain can compensate for damage by differentially recruiting other brain networks or by utilizing alternative cognitive strategies to optimize performance, a concept known as cognitive reserve [30,87]. When study participants show significant ERP waveform changes post-concussion while still performing at baseline levels on neuropsychological tests, the theory of cognitive reserve suggests that they are accessing cognitive resources held in "reserve" or employing alternative cognitive strategies to

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maintain baseline functional performance [30]. An alternative explanation for the maintenance of behavioural performance in the face of electrophysiological change is that recovery from concussion may be a two-step process. The first step is thought to involve compensatory mechanisms which produce rapid initial recovery of function, followed by a second step consisting of prolonged neuronal recovery [7]. This theory suggests that if participants are tested during the period of long-term recovery, deficits in neural function may be apparent on EEG but not captured by gross behavioural measures. It is also possible that the ability to access cognitive reserve varies in the time after injury, and further research is required to understand the intricacies of the relationship between electrophysiology and behaviour in the context of concussion.

The difficulty in correlating EEG modulation with changes in behavioural outcomes is illustrated in Figure 4.
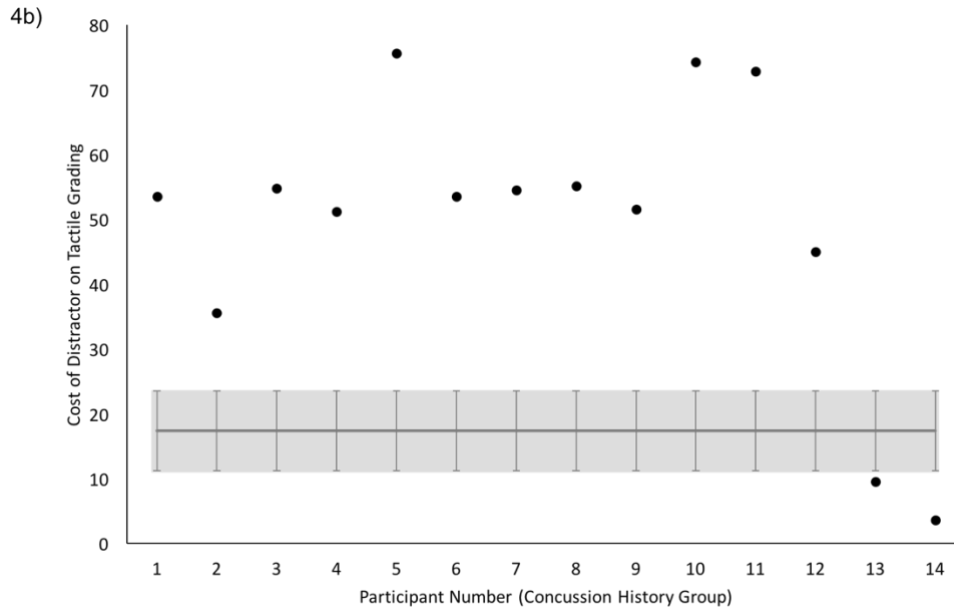

4a)
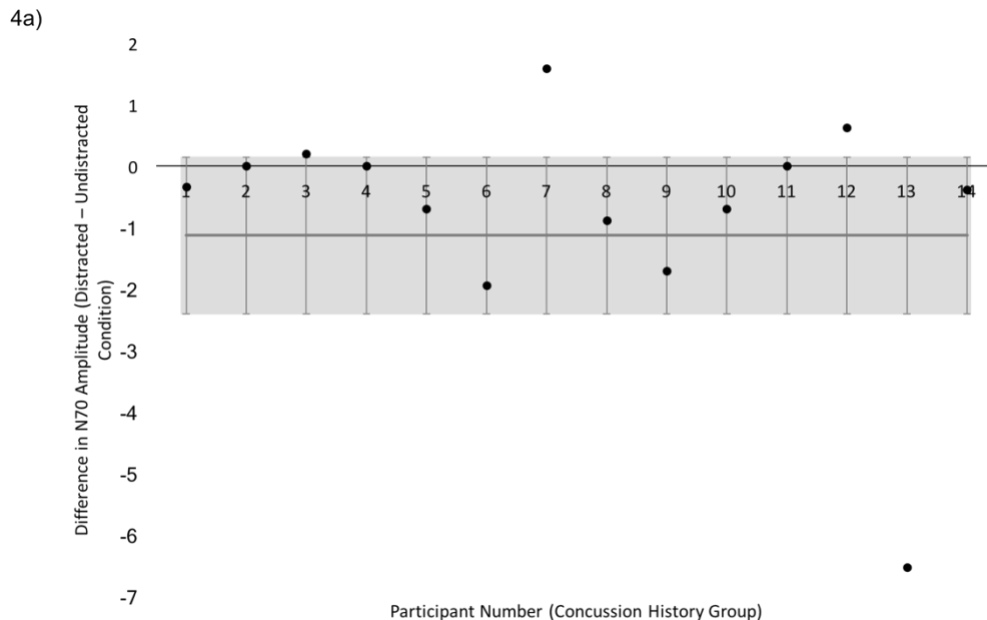
Figure 5.4: Confidence interval analysis. 95% confidence interval analysis of a) N70 amplitude modulation and b) cost of distractor presentation on tactile grading accuracy. In both cases, a 95% confidence interval band (shown in gray) was constructed from control group data, and data from each individual in the group with a history of concussion was plotted against that confidence interval (black dots).

A difference score was calculated by subtracting the N70 amplitudes generated during the undistracted condition from those generated during the distracted condition. In this way, a score of 0 would indicate that N70 was not modulated by the change in relevance, a positive score would indicate that the N70 was more negative during the distracted condition, and a positive score would indicate that the N70 was less negative, or smaller, during the distracted condition. A 95% confidence band was created from data collected from the control group and data from each individual participant in the concussion history group was plotted against this band (Figure 4a). A 95% confidence band was also created

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using the behavioural cost scores from the control group, and the cost scores from each

participant with a history of concussion was plotted against this band (Figure 4b). It was

expected that participants who fell outside of the confidence interval band on one measure

would also fall outside on the other, but this was not the case. Individuals numbered 1

through 12 scored higher than controls on the distractor cost measure, while participants

13 and 14 had lower distractor cost scores than control participants. In contrast, only

individuals 7, 12, and 13 fell outside of the confidence interval band for the N70

modulation score. Participants 7 and 12 fell above the band, indicating that N70 was less

modulated by the simultaneous presentation of distractors with the evoking stimuli.

Participant 13 fell below the band, indicating that N70 amplitude was larger in this

participant during the distracted condition. Task accuracy is affected by cortical responses

to the stimuli being graded in this task, but by other factors as well, which is reflected in the

lack of correlation between individuals in Figure 4a and 4b. However, Figure 4 illustrates

the wide variability between individuals in the concussion history group. Concussion is an

injury with variability in mechanism of injury, physical presentation, and recovery time. It

is not surprising that there was wide variability between individuals in this group, and

while grouping individuals according to the number of injuries they had sustained, length

of recovery, or age at time of injury may have shown some between-group differences, it is

important to examine variability between individuals when the injury being investigated is

as heterogeneous as concussion.

Despite the difficulty in correlating EEG amplitude modulation to behavioural

outcomes, EEG was used in this thesis as it is the best method currently available to answer

the questions of interest. This thesis was designed to test how early cortical

representations of visual and tactile stimuli are subject to top-down and bottom-up modulation in order to orient attention. EEG is able to characterize early cortical responses with a high degree of temporal specificity. The results of study 1 showed that the task of interest in these studies led to modulation at early post-stimulus latencies in the somatosensory domain, and later latencies in the visual domain. This was interpreted as evidence that relevancy-based modulation of tactile stimuli was occurring in primary receptive zones, and relevancy-based modulation of visual stimuli occurred in association or extrastriate areas. EEG lacks the spatial resolution to confirm this hypothesis, but confirming the anatomical locations where relevancy-based modulation occurred was not the focus of this thesis. Studies 2 and 3 built upon study 1 by asking questions related to how the PFC contributes to relevancy-based modulation and how this modulation is affected by a history of brain injury; therefore, maintaining temporal specificity was essential to finding and characterizing these differences. EEG remained the best imaging methodology to test these questions.

Although it is difficult to characterize the relationship between EEG and behavioural measures, task accuracy was an important independent outcome measure for the studies of this thesis. Previous work has shown that, for a task requiring sensory integration, early tactile-evoked ERPs were most modulated by task relevance when the task required grading the amplitude of stimuli [63]. Although the present series of experiments examined sensory selection rather than integration, a task demanding stimulus grading whas chosen in the design of study 1 to maximize relevancy-based modulation. When the results of study 1 confirmed that the grading task did lead to significant modulation of modality-specific cortical representations of stimuli, the task was carried through studies 2 and 3 in

order to answer the remaining specific research questions. A sample behavioural trace is shown below:
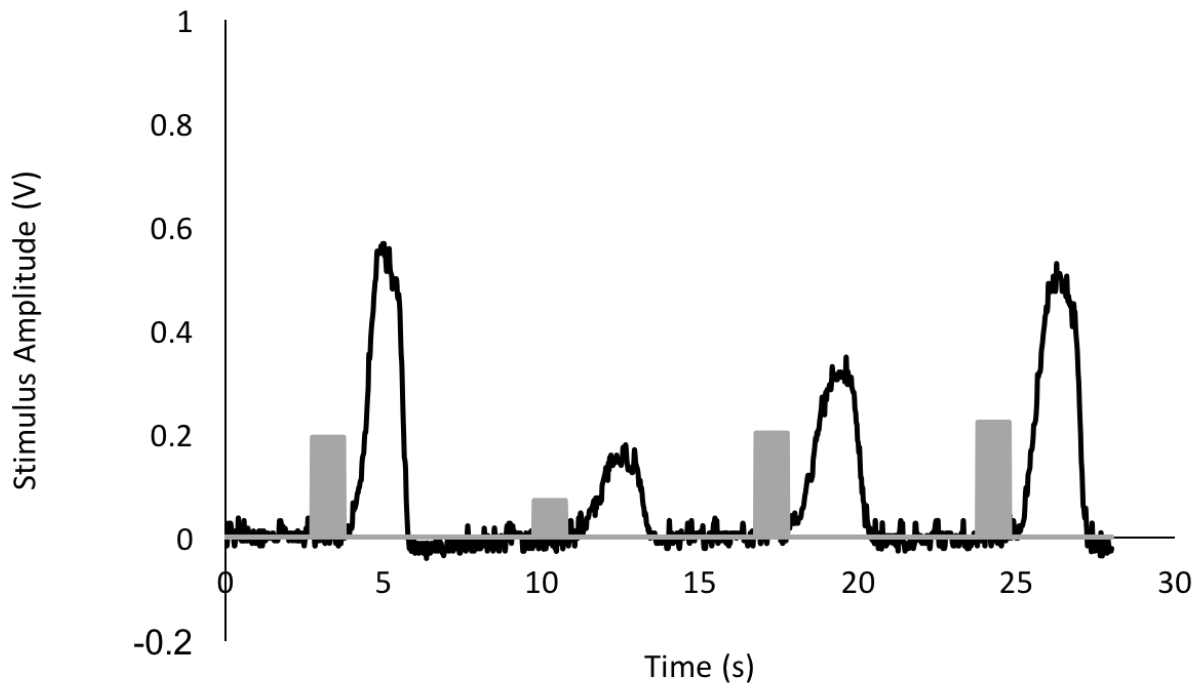
Figure 5.5: Sample behavioural data. This graph represents the target stimulus amplitude (shown in gray) and the amplitude of participant responses to each stimulus (shown in black). Amplitude is represented as a voltage, as specific voltage amplitudes were used to drive the vibrotactile stimulus delivery device (gray) or change the height of the visual stimulus on the computer screen. The pressure bulb that participants squeezed to produce their response was part of a closed, air-tight system, with the bulb connected to a pressure sensor via rubber tubing. The pressure sensor converted pressure changes to voltage changes, which are represented in the response trace (black).

It was important to account for the possibility that participants would over- or undershoot when making their responses, and then correct by squeezing more or less. To ensure that

participant responses were captured most accurately, the behavioural data was analyzed in two ways. In the first method, the peak amplitude of the participants' responses were quantified and compared. In the second method, a window of 100ms was created after the peak amplitude was recorded in order to capture any correction made if a participant perceived that they overshot the response they wanted to make. When data obtained from these two analysis methods was compared, there was no significant difference in peak amplitude measurements, so the behavioural responses shown in all three studies of this thesis were obtained using the first analysis method. It is likely that, since no feedback on response accuracy was provided after each trial, participants did not feel the need to make substantial corrections to the strength of their squeeze. Since they were making their grading decisions based on their internal representation of the stimuli, they had no reason to suspect that this representation was wrong. However, it was possible that participants'' internal representations shifted as the experiment went on, or that participants were less attentive during later trials, leading to a loss of grading accuracy. To assess this, response accuracy was compared between the first and last trials, for both visual and tactile grading, for a representative sample of participants. No significant accuracy differences were found between the first and last trials.

All of the studies that comprise this thesis examine changes in cortical activity using EEG, a technology with its own inherent limitations. EEG measures electrical activity at the scalp to reflect changes in electrical activity at the cortical surface. It has excellent temporal specificity, but because the signal is attenuated by the bone and tissue interface between the cortical surface and the measuring electrodes, and because signals can be volume conducted to more than one electrode at once, spatial sensitivity is compromised. In the

context of this thesis, the use of EEG limits the ability to make conclusions about the anatomical areas responsible for the changes observed in cortical activity. In particular, study 1 raises questions about the cortical or subcortical generators of N70, and whether N70 may be generated by a different neuronal subpopulation in S1 than P50. Once again, the poor spatial resolution of EEG leaves this as a hypothesis, as it was not the primary focus of the present research. A tool such as fMRI, which has excellent spatial resolution, would be a more appropriate choice to study this question in the future. Obtaining images while participants complete sensory selection and integration tasks may shed light on the cortical generators of these potentials within S1. Past work using fMRI has shown the largest percent BOLD signal change in S1 when task demands require integration of visual and tactile stimuli, as compared to lone visual or tactile stimuli [47]. When ERPs were measured in response to the same task demands, P50 amplitudes were largest during the integration task [48]. Since the studies of this thesis found that N70 amplitudes were smaller during a sensory selection task than when grading lone tactile stimuli, it is hypothesized that a sensory selection task would also produce a smaller percent BOLD signal change on fMRI than either integrating visual and tactile stimuli or responding to lone tactile stimuli.

Finally, the task used in the studies of this thesis is a contrived means to manipulate task relevance and stimulus presentation, and while these are important factors in sensory processing in daily life, the task used in the experiment in does not fully replicate the variety and fluidity of manipulations that occur in daily life. However, the studies of this thesis represent an important starting point in understanding how sensory processing is

affected by task relevance and sensory gating in more complex sensory environments, and form the foundation for future research.

5.4 Future Directions

There are several logical questions stemming from the results of the present work. The first and most pressing relates to the limitations of the sensory grading task used in the studies of this thesis. A fourth study was proposed as part of this thesis, and collection of the data is ongoing. The purpose of this linked study is to test how sensory gating is affected during postural control, a task which is more relevant to daily life than the one used in the studies of this thesis. Additionally, postural control is an outcome of interest in people with a history of concussion, as there are many unanswered questions about balance recovery after concussion. A review of the literature found some evidence supporting the return of postural stability to baseline levels within a few days of concussion injury; however, other studies showed that when more sophisticated measures of dynamic stability were assessed, deficits in center of pressure (COP) control were observed more than nine months after the athletes had been medically cleared to return to play [87]. The idea that postural control may be precarious or maintained by different mechanisms after concussion was the impetus for testing sensory gating during a postural control task: analysis of COP variation may be a more sensitive measure of behavioural performance when testing the gating of irrelevant stimuli. It is hypothesized that in a sample with no history of concussion, cortical responses will be largest when the evoking stimuli are relevant and the postural control task is not demanding of attentional

resources, and smallest when the evoking stimuli are irrelevant and the postural control task is the most challenging, and in those with a history of concussion, sensory gating based on task-relevance is hypothesized to be disrupted such that the difference between the conditions of relevance and postural control will be blunted. It is also hypothesized that the post-concussion participants will show greater COP variability across all standing conditions than those with no history of concussion.

The studies of this thesis were designed to test relevancy-based gating and processing of stimuli in the somatosensory and visual modalities because they are most relevant to my background in physiotherapy clinical practice, but another logical question is how auditory stimuli are affected by task-relevance and by the presentation of a distractor in another sensory modality. Additionally, relevancy-based gating appears to be affected by task-switching demands. Switching between sensory modalities, as was done in the present thesis, likely involves different attentional orienting mechanisms than switching between two stimuli presented in the same sensory modality [72]. Similarly, since the sensory selection task used in the present series of studies showed modulation of N70 while previous work by this lab group showed P50 modulation during tasks requiring sensory integration, changing the task demands may help disentangle the intricacies of how cortical areas interact to respond to complex sensory situations.

5.5 Conclusions

In this thesis, we have demonstrated that the tactile-evoked N70 ERP is modulated by task-relevance in tasks requiring top-down selection of relevant from irrelevant inputs,

that transiently disrupting PFC activity impairs this top-down gating based on task-relevance, and that those who have recovered from concussion exhibit persistent electrophysiological abnormalities that do not correlate with their accuracy on a sensory grading task. Taken together, these findings suggest that PFC is involved in the top-down gating of somatosensory stimuli based on task relevance but not bottom-up relevancy-based interactions between visual and tactile stimuli. The studies of this thesis also provide evidence that resolution of concussion symptoms does not indicate pre-injury cortical function has resumed, and raise questions about the involvement of the PFC in the functional disturbance of concussion.

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