EVENT-RELATED POTENTIALS IN CONCUSSION DETECTION AND RECOVERY

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By: KYLE I. RUITER, BASc. HON.

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AUTHOR: Kyle I. Ruiter, BASc. Hon. (University of Guelph-Humber)

SUPERVISOR: Dr. John F. Connolly

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Abstract

Concussion, defined as a functional injury with complex symptomatology, affects millions annually and has been classified as a serious public health concern. Clinical tools currently available for concussion assessment fail to objectively measure cognitive function and thus, are inadequate for proper evaluation of the cognitive dysfunctions associated with the injury. As a result, investigation into the neurological consequences associated with concussion has become a prominent focus in neuroscience research. Traditionally, neuroimaging methods have been used primarily on concussion detection, while behavioural and neuropsychological assessments have been used for both concussion detection and cognitive-performance tracking. However, to date, minimal work has explored the use of neuroimaging to track the consequences of concussion at the neurophysiological level. Accordingly, the present thesis sought to investigate the clinical applicability of electroencephalography (EEG) as an effective neuroimaging tool capable of concussion detection, as well as its ability to objectively track neurophysiological changes over time. Event-related potentials (ERPs) were used to assess specific functions, or more accurately, dysfunctions of select cognitive processes as reflected by electrophysiological changes in the brain. Specifically, the Mismatch Negativity (MMN), N2b, and P300 were investigated to evaluate memory, attention, and executive control in concussed populations. The results of this thesis demonstrated alterations in each of the aforementioned ERPs, signifying cognitive dysfunctions linked to neurophysiological abnormalities in concussed populations. Of particular importance, Chapter 2 revealed the first instance of MMN abnormalities in a concussed population, Chapter 3 was the first to assess concussed adolescents at the acute stage of their injury, and Chapter 4 demonstrates the potential of ERPs to track neurophysiological changes from the acute to post-acute stages of the injury. Ultimately, the findings presented in this dissertation support the clinical viability of using ERPs to not only detect cognitive dysfunctions associated with concussion, but also to objectively track neurophysiological changes on the path to recovery.

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LIST OF ABBREVIATIONS AND SYMBOLS

Ag/AgCl: Silver/silver chloride

ANOVA: Analysis of variance

BDI: Beck Depression Inventory

BDI II: Beck Depression Inventory II

BOLD: Blood oxygen level dependent

BVA: BrainVision Analyzer

CEI: Cognitive Efficiency Index

CFL: Canadian Football League

CT: Computerized tomography

CTE: Chronic Traumatic Encephalopathy

dB: Decibels

DOC: Disorder(s) of consciousness

df: Degrees of Freedom

DRL: Driven-right leg

DT: Duration Tone

EEG: Electroencephalography

EOG: Electrooculogram

ERP: Event-related potential

fMRI: Functional magnetic resonance imaging

FT: Frequency Tone

GCS: Glasgow Coma Scale

HC: Healthy control

Hz: Hertz

ICA: Independent components analysis

IMP: Impulse Control

IT: Intensity Tone

ImPACT: Immediate Post-Concussion Assessment and Cognitive Testing

MCS: Minimally conscious state

MDD: Major Depressive Disorder

MMN: Mismatch negativity

MRI: Magnetic resonance imaging

MS: Motor Speed

ms: milliseconds

μV: Microvolts

PCSS: Post-Concussion Symptom Scale

PET: Positron emission tomography

rCFL: Canadian Football League group

ROI: Region of interest

SD: Standard deviation

SPL: Sound Pressure Level

ST: Standard Tone

SVM: Support vector machine

RT: Reaction Time

SF-36: Short-Form Health Survey 36

VBM: Verbal Memory

VIM: Visual Memory

VS: Vegetative state

US: United States

DECLARATION OF ACADEMIC ACHIEVEMENT

The present dissertation constitutes a ``sandwich'' thesis as defined by the School of Graduate Studies, McMaster University. I am the primary author of the three articles included in this dissertation, I conducted the literature reviews and wrote the manuscripts, designed the studies, and collected and analyzed all data. These studies comprised my doctoral research and are therefore included in the thesis. The roles of the co-authors for each paper are outlined below.

Chapter 2 is a reprint of an article published in *Clinical Neurophysiology.*
Ruiter, K. I., Boshra, R., Doughty, M., Noseworthy, M., & Connolly, J. F. (2019). Disruption of function: Neurophysiological markers of cognitive deficits in retired football players. Clinical Neurophysiology, 130(1), 111–121. https://doi.org/10.1016/j.clinph.2018.10.013

- Ruiter, K.I.
    - Literature review; study design; data collection; analysis; manuscript writing, preparation, and revision
- Boshra, R.
    - Data collection; analysis; manuscript revisions
- Doughty, M.
    - Manuscript revisions
- Noseworthy, M.
    - Manuscript revisions
- Connolly, J.F.
    - Study design; manuscript revisions

Chapter 3 is an article under review in *Brain Research.*
Ruiter, K. I., Boshra, R., Doughty, M., Noseworthy, M., & Connolly, J. F. (Under Review). Neurophysiological markers of cognitive deficits and recovery in concussed adolescents. Brain Research

- Ruiter, K.I.

    - Literature review; study design; data collection; analysis; manuscript writing, preparation, and revision
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Chapter 4 is an article prepared for submission to *Clinical Neurophysiology.*
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Additional Achievements

In addition to what is presented in within the chapters of this thesis, the author was a primary contributor on 4 other studies.

Blain-Moraes, S., Boshra, R., Ma, H. K., Mah, R., Ruiter, K., Avidan, M., Connolly, JF., & Mashour, G. A. (2016). Normal brain response to propofol in advance of recovery from unresponsive wakefulness syndrome. *Frontiers in human neuroscience*, 10, 248.

Boshra, R., Dhindsa K. Boursallie, O., Ruiter, K. I., Sonnadara, R., Doyle, T., Samavi, R., Reilly, J. P., & Connolly, J. F. From Group-Level Statistics to Single-Subject Prediction: Machine Learning Detection of Concussion in Retired Athletes. *IEEE* (Under Revision).

Boshra, R., Ruiter, K. I., DeMatteo, C., Reilly, J. P., & Connolly, J. F. Post-acute Neurophysiological Correlates of Concussion: Deep Learning for Clinical Assessment. Prepared for submission to *Scientific Reports*

Boshra, R., Ruiter, K. I., Dhindsa K., Reilly, J. P., \& Connolly, J. F. Beyond the Overly Simplified: Progression of Brain Connectivity Post-Concussion. Prepared for submission to *Annals of Neuroscie*

Chapter 1

1. Introduction

1.1 Thesis Objective & Overview

Concussion is a functional brain injury affecting core cognitive processes such as attention and memory. Currently, clinical tools available for assessing concussion fail to objectively measure cognitive function as manifested in behavioural alterations presumed to be caused by brain injury. Accordingly, a new application is needed not only for concussion diagnosis, but also one that will aid in treatment and rehabilitation. The intent of this thesis is to demonstrate how analyzing electrophysiological signals from the brain via electroencephalography (EEG) – and more accurately, event-related potentials (ERPs) – can be used as an effective neuroimaging tool capable of identifying and tracking cognitive changes in concussed populations. The hypothesis of this thesis is that ERP analysis is the most appropriate tool in identifying and tracking the neurocognitive dysfunctions associated with concussion.

This thesis is comprised of five main sections; including three original scholarly works. The pages have been renumbered for continuity within this thesis, however, the notation and reference style of the journals has remained unchanged. Chapter 1 provides an introduction to concussion including its definition, clinical history, epidemiology, as well as the current research and clinical tools used in concussion assessment today. Further, Chapter 1 outlines the shortcomings of current concussion assessments, while also providing evidence detailing the suitability of ERPs in assessing the neurocognitive alterations associated with concussion. Chapter 2 provides an empirical study published in *Clinical Neurophysiology* (Ruiter et al., 2019) demonstrating the capability of ERPs to measure cognitive changes in retired professional athletes with a history of multiple concussions; where their last concussion occurred on average nearly three decades earlier. Additionally, Chapter two provides compelling evidence of the suitability of ERPs to assess the long-term neurocognitive dysfunctions associated with

concussion. Chapter 3 provides another empirical study that is currently under review in *Brain Research*. Specifically, using the same experimental design as conducted in the first study, Chapter 3 assessed the neurocognitive consequences of concussion in adolescents in the acute stage of their injury, demonstrating for the first time the effectiveness of ERPs in measuring cognitive deficiencies in acutely-concussed adolescents. Furthermore, Chapter 3 demonstrates the suitability of ERPs to assess the neurocognitive consequences of concussion in the acute stage of the injury. Lastly, Chapter 4 describes the third and final empirical study of this thesis, presenting for the first time the viability of using ERPs to track concussion neurocognitive function and their changes over time at the neurophysiological level. This was accomplished by assessing concussed adolescents during the acute and post-acute stages of the injury. Collectively, Chapters 2, 3, and 4 provide compelling evidence showcasing the ability of ERPs to accurately detect and track neurocognitive dysfunctions in concussed populations relative to healthy controls regardless of age or time since injury and thus, demonstrate the suitability of ERPs to be integrated into the clinical environment. Finally, Chapter 5 gives a general discussion of the contributions, limitations, and future directions of the research presented herein.

1.2 Concussion defined

Concussion, often referred to as a mild traumatic brain injury (mTBI), is a functional injury characterized by a disturbance in neural function (Mendez et al., 2005; McCrory et al., 2009; McCrory et al., 2016). A concussion may result in a brief loss of consciousness, and is typically caused by a direct impact to the head, face, neck, or elsewhere on the body where a substantial external force is transferred to the head (McCrory et al., 2016). Specifically, it has been described as a consequence of traumatic biomechanical forces resulting in a complex pathophysiological process of biochemical changes in the brain (McCrory et al., 2009; Zhang et al., 2016).

Similar to traumatic brain injuries (TBI), concussion can result in a multitude of symptoms and prolonged health conditions. Symptoms, often complex in nature, can be a combination of emotional, cognitive, and physical detriment. In many cases, those suffering from a concussion report symptoms of memory loss, difficulties in concentration and attention, headache, fatigue, dizziness, depression, anxiety, and fluctuations in emotional well-being (Ryan & Warden, 2003;

Guskiewicz et al., 2007; Chrisman & Richardson, 2014). As time from impact increases, often initial symptoms will decline (Yeates et al., 2009). In fact, in 90% of concussion cases, symptoms resolve without any intervention within 21 days of the injury (McKeon et al., 2013). Unfortunately, however, swift symptom resolution is not always the case. Occasionally, early symptoms will continue as long as months, or even years after initial impact and clinical diagnosis (Gosselin et al., 2006; De Beaumont et al., 2009). In these cases, patients may be classified as having Post-Concussion Syndrome (PCS); a complex disorder where the outcome of symptom resolution is unknown (Willer & Leddy, 2006).

1.3 Epidemiology of concussion

Today, an estimated 52 million concussions occur every year world-wide (CDC, 2003), with over 4 million occurring in Canada and the US alone (Langlois et al., 2006; Daneshvar et al., 2011; Kraus et al., 2016). Although demographic information has been available for decades demonstrating that concussions are a serious public health issue (Ommaya & Gennarelli., 1974; Gronwall, 1977), it is only more recently that significant research efforts have begun on what has been described as an epidemic (Goldstein, 1990; see also Kelly, 1999). Fortunately, of late, the attitude towards concussions has changed drastically. Researchers, clinicians, and media personnel alike have begun taking concussions very seriously – and subsequently – so has the public. With lawsuits looming over multiple professional sports leagues, the pressure to determine the effects of, and solutions for, concussions has drastically increased.

1.4 History of concussion

In early concussion research, medical professionals used the expression “punch drunk” to describe the symptomatology associated with individuals who had suffered repeated mild head traumas (Martland, 1928). Specifically, the term originated from medical doctors who were describing the neurological and emotional abnormalities found in professional boxers (Martland, 1928). The term was later defined by medical professionals as dementia pugilistica (Millspaugh, 1937); or what we refer to today as: chronic traumatic encephalopathy (CTE) (Corsellis et al., 1973; Omalu et al., 2005, Mckee et al., 2009; Armstrong et al., 2016; Stern et al., 2019).

CTE is a neurodegenerative disease associated with atrophy of the brain, and subsequently, brain weight reduction. The effects found are similar to those of other neurodegenerative diseases such as Alzheimer's and other dementia-related neurological disorders (Stern et al., 2013). Research has demonstrated that CTE often manifests 8 to 10 years post regular repeated head traumas (McKee et al., 2009). Coincidentally, the symptoms found in individuals who were later shown to have suffered from CTE are similar to the effects found in those who have just suffered a concussion including emotional disparity, difficulty focussing, dizziness, and headaches (Ryan & Warden, 2003; McKee et al., 2009).

Recently, neuroscience research has found ample evidence to support the conclusion that repeated mild head trauma and concussions are strongly predictive of CTE (Omalu et al., 2005; McKee et al., 2009; Baugh et al., 2012). To illustrate the prevalence of CTE in those with a history of concussions, McKee et al. (2009) conducted a literature review of the 48 cases of neuropathologically verified CTE. McKee's review confirmed that an individual with an established history of concussions is more likely to develop neurodegeneration (atrophy) of the brain than individuals without such a history. Brain deterioration will cause memory disturbances and other cognitive dysfunctions, as well as behavioral and personality changes (McKee et al., 2009; Stern et al., 2013). Currently, however, science is only able to diagnose CTE in patients post-mortem. Thus, a clinical method of concussion assessment, in both acute and chronic situations, is needed in the clinical setting today in order to: 1) detect and evaluate neurophysiological alterations as a result of concussion upon initial diagnosis; 2) measure alterations or track recovery (if any) overtime; and 3) provide an early indicator or predictor of neurodegeneration diseases.

1.5 Behavioural methods of concussion assessment

Traditionally, concussions are assessed using neuropsychological testing. In addition to standard pencil-and-paper tests, computerized adaptations of neuropsychological tests, such as the Immediate Post Concussion Assessment and Cognitive Testing Tool (ImPACT), have become increasingly popular in concussion assessment (Iverson et al., 2003; Mendez et al., 2005; Randolph et al., 2005). However, despite increased use, the clinical validity and utility of these tests remain unclear. A comprehensive review by Randolph et al (2005) revealed that

neuropsychological testing of concussion lacked adequate test-retest reliability, and the differences between concussed and healthy populations frequently failed to reach statistical significance. They concluded that neuropsychological tests have not yet met the necessary criteria to be used in a routine standard of clinical care. Furthermore, research has demonstrated repeatedly that neuropsychological measures generally return to baseline in 5 to 7 days post-injury (e.g., Johnston et al., 2001; McCrea et al., 2003; Bleiberg et al., 2004; Belanger & Vanderploeg, 2005; Parker et al., 2007), demonstrating the unreliability of the assessments beyond the first week of diagnosis. Another shortcoming of neuropsychological assessments is the dependency of pre-injury baseline testing for optimal effectiveness. The goal behind baseline testing is to establish an athlete's so-called "normal" health and test performance. However, athletes are known to purposely perform poorly on their baseline tests so that their results during a suspected concussion would not look too poor relative to their baseline score (Erdal, 2012). This results in inaccurate concussion evaluations. In sum, although neuropsychological assessments are able to quantify the results of a patient's assessment, and permit inferences regarding their cognitive function, they fail to do it reliably. But more importantly, they fail to directly measure cognitive processing at the neurophysiological level.

In addition to neuropsychological testing, self-reported inventories of concussion symptomatology such as the Post-Concussion Symptom Scale (PCSS), are commonly administered to collect patient-specific symptoms and assess the severity of those symptoms. Specifically, the PCSS provides a list of common concussion-related symptoms where the patient is asked to evaluate the severity of each symptom on a scale ranging from 0 (no symptoms) to 6 (high symptom severity). The PCSS is utilized frequently in concussion research and has been proven effective in evaluating concussion symptomatology (Chen et al., 2007). Although many symptoms occur after a concussion, one of the most frequently reported symptoms is elevated levels of depression (Kontos et al., 2012). Accordingly, depression batteries such as the Beck Depression Inventory II (BDI II) are also commonly administered (e.g., Chen at al., 2008; Covassin et al., 2012; Kontos et al., 2012; Chrisman & Richardson, 2014). Unfortunately, other external factors may influence the assessment's derived score, such as: inability to work, loss of income, and strain on relationships (Fourtassi et al., 2011). Accordingly, depression batteries are unable to objectively determine if depression levels are

solely a result of the neurophysiological alterations caused by a concussion, or if they are a result of other external factors related to the injury. Ultimately, however, symptom inventories, whether inclusive of multiple symptoms or exclusive to one, fall victim to the subjectivity and reliability of patient responses.

1.6 Concussion assessment using structural neuroimaging and fMRI

In order to objectively measure the brain, neuroimaging methods must be employed. There are a variety of neuroimaging tools available for concussion assessment; however, many are inappropriate for diagnosis and treatment. Concussion, as defined in Section 1.1, is a functional injury – not a structural injury. Therefore, many neuroimaging techniques lack what is needed to accurately assess a concussion. For instance, tools such as MRI and CT, although used frequently in concussion evaluation in clinical environments, are not suitable measures of concussion assessment or diagnosis, as they are unable to measure functional consequences in the brain. Both MRI and CT are capable of measuring structural deficits such as hemorrhaging and atrophy and thus, while not suitable for concussion, are appropriate for diagnosing acquired and traumatic brain injuries (ABI/TBI). Accordingly, in an effort to gain insight into the neuro-functional consequences of concussion, research has investigated the suitability of assessing the pathophysiological and functional sequelae of concussion by using functional MRI (fMRI) (e.g., McAllister et al., 2001; Ptito et al., 2007; McCrea et al., 2009; Zhang et al., 2010).

By utilizing blood-oxygen-level-dependent (BOLD) imaging to measure and detect changes in cerebral blood flow, fMRI can assess neural activation, and subsequently, neurocognitive function non-invasively (Cabeza & Nyberg, 2000). Specifically, fMRI detects the consequence of neuronal changes in cortical matter by measuring alterations in blood perfusion or paramagnetic deoxyhemoglobin levels (Ptito et al., 2007). Of late, fMRI has become a prominent tool in concussion research (e.g., McAllister et al., 2001; Chen et al., 2004; Ptito et al., 2007; Terry et al., 2012; Zhu et al., 2012). However, despite its mainstream attention, fMRI has a substantial limitation: poor temporal resolution. In particular, although fMRI is exceptional at locating *where* in the brain neuro-functional alterations occur, it fails to accurately pinpoint precisely *when* these alterations transpire relative to external or internal events. Thus, when assessing concussion, where delays of neurocognitive processing are often the very nature of the

injury, it begs the question of whether fMRI is really the most suitable method of assessment, as it is unable to accurately evaluate the temporal deficits related to concussion. Finally, fMRI also fails to be an economically viable and accessible option, as it costs millions to purchase, install, and operate, and requires housing in a specific building infrastructure to work properly. Cost-effective, objective neuroimaging techniques capable of assessing the temporal deficiencies associated with concussion, such as EEG, appear to be the most suitable tool for concussion assessment.

1.7 Concussion assessment using EEG

There are two prominent types of EEG imaging techniques for concussion assessment: 1) resting-state recordings and 2) event-related potentials (ERPs) – a technique sometimes referred to as active-state. Although both imaging methods measure electrophysiological changes in the brain, the way in which data are collected differs. Resting-state EEG data collection, as the name suggests, is conducted by having a participant sit or lie down for an extended period of time without being presented stimuli or actively performing a task. Alternatively, the active-state approach of ERP analyses has stimuli either passively presented to a patient while distracted (e.g., watching a silent movie while auditory tones play in the headphones), or has a patient actively attend to stimuli being presented (clicking a button to a target auditory tone or visual image). Research has demonstrated that resting-state EEG may provide a reliable technique to identify persistent functional changes after a concussion (for a review see Conley et al., 2018); however, it is unable to objectively measure specific neurophysiological indices reflective of cognitive dysfunction. Accordingly, although potentially valuable in concussion identification, and perhaps even diagnosis, resting state EEG's inability to assess specific cognitive processes makes it unsuitable for guiding concussion rehabilitation efforts. Therefore, a neuroimaging method capable of pinpointing specific cognitive dysfunctions in acute and post-acute concussed patients, such as ERPs, may be the most suitable method of concussion identification and recovery-tracking.

ERPs, averaged electrophysiological brain responses during continuous EEG data recordings time-locked to stimulus presentation (Polich., 2007; Polich., 2012; Amin et al., 2015), are indices representative of core cognitive functions capable of documenting the presence, absence, and

characteristics of specific cognitive processes. Specifically, ERPs reflect the mass action of postsynaptic potentials generated during stimulus presentation (Brush et al., 2018). Notably, the capability of ERPs to provide insight into temporal mechanisms related to neural processes before, during, and after behavioral responses consequently provides insight into cognitive processes unattainable in traditional behavioural or neuropsychological assessments (Luck & Kappenman 2012; Brush et al., 2018). Specifically, EEG/ERP data is captured across multiple scalp locations via non-invasive (i.e., surface) electrodes placed directly on the scalp or embedded within a flexible cap in accordance with the International 10/20 System (Klem et al., 1999). The ability of ERPs to measure a plethora of cognitive processes at the neurophysiological level has subsequently resulted in decades of research validating the ability of ERPs to assess the neurocognitive dysfunctions associated with concussion (e.g., Gaetz et al., 2000; Lavoie et al., 2004; De Beaumont et al., 2009; Broglio et al., 2011; Baillargeon et al., 2012; Gosselin, et al., 2012; Moore et al., 2014; Moore et al., 2015; Ledwidge & Molfese, 2016; Fickling et al., 2019; Ruiter et al., 2019). Also, ERPs are able to capture these cognitive processes across multiple age groups and injury time-points (e.g., De Beaumont et al., 2009). The ability of ERPs to detect neurophysiological differences at multiple time-points since injury gives rise to the hypothesis that not only are ERPs likely suitable for concussion identification, but more importantly, they may be the most appropriate tool to track neurophysiological changes over the course of concussion recovery.

1.8 ERPs sensitive to concussion

Most commonly, ERP research investigating the effects of concussion employ an active "oddball" (Squires et al., 1975) paradigm (e.g; Polich & Margala, 1997; Lavoie et al., 2004; Gosselin et al., 2006; De Beaumont et al., 2009; Baillargeon et al., 2012; Ruiter et al., 2019). In particular, the oddball paradigm is a discrimination task that usually requires active processing of a stimulus in a sequence comprised primarily (e.g., 90%) of identical stimuli (standard) with one or more non-standard (deviant) stimuli interspersed (e.g., 10%) throughout the sequence (Polich, 2007). It is a task that requires participants to either actively differentiate between stimuli via corresponding mouse clicks or button presses. Although relatively simple, the oddball paradigm has been the hallmark task that has provided the most information pertaining to the neuro-functional consequences resulting from concussion. Specifically, it elicits the N200 and P300;

two ERPs well-established in cognitive neuroscience literature to be particularly sensitive to the neurocognitive dysfunctions associated with concussion (e.g., Gaetz et al., 2000; Broglio et al., 2009; De Beaumont et al., 2009; Broglio et al., 2011; Baillargeon et al., 2012; Ruiter et al., 2019).

The N200, generated in the anterior cingulate cortex (ACC) (Huster et al., 2010) known to support executive function-related cognitive processes (Carter et al., 1999; MacDonald et al., 2000), is a negative-going electrophysiological response peaking ~200 ms post stimulus onset. It is characterized by a fronto-central scalp distribution (Folstein & Van Petton., 2008; Broglio et al., 2009). The N200 has been linked to response inhibition, conflict monitoring, and executive control (Heil et al., 2000; Boksem et al., 2006; Folstein & Van Petton., 2008; Broglio et al., 2009). Interestingly, there is not one, but two negative components within the N200 time range which contribute to the total deflection of the N200 component (Näätänen, 1983). Specifically, the first (earlier) component is the MMN which (as detailed below) does not require attention to be evoked. However, the second negative component, "N2b", emerges temporally prior to the positive P300 response, and is evoked when the stimulus input is actively attended to and becomes superimposed on the MMN (Näätänen, 1983). Notably, within cognitive neuroscience literature, the terms N200 and N2b are often used interchangeably. When cognitive neuroscientists are using either of the terms, they are typically referring to the component that requires attention to stimulus input and is elicited prior to the P300 (i.e., the N2b).

The N2b has been used extensively in concussion research, with changes in the component reflecting cognitive dysfunction in executive control processes (Broglio et al., 2009; Ledwidge & Molfese, 2016; Brush et al., 2018). The N2b, although reliably shown to be affected by concussion (Broglio et al., 2009; Moore et al., 2015; Ledwidge & Molfese, 2016; Ruiter et al., 2019), differs markedly in *how* it is affected. This has resulted in considerable inconsistency in the literature. For instance, research has found the N2b to be attenuated (Broglio et al., 2009; Ruiter et al., 2019a), enlarged (Moore et al., 2014; Moore et al., 2015; Ledwidge et al., 2016), delayed (Moore et al., 2015; Moore et al., 2016; Ruiter et al., 2019), and unchanged (Gaetz et al., 2000; Gosselin et al., 2012) in concussed patients relative to controls. These inconsistencies are likely a result of differing factors relating to experimental design, as each of the studies

investigating N2b effects in concussed populations differed in at least one of the following aspects: 1) modality (visual vs. auditory), 2) tasks employed, 3) task complexity, 4) time since injury, 5) age-range, and 6) electrode sites/regions of interest (ROI) explored (see Brush et al., 2018 for a full review). Despite the considerable disparity in the literature demonstrating a panoply of abnormalities relative to healthy controls, the research is abundantly clear that the N2b is affected by concussion. Therefore, the inconsistency is not a reflection of whether or not the N2b – and the executive control processes it reflects – is affected by concussion, but rather, the way in which the N2b is affected as a result of differing experimental designs.

The P300 is a large positive-deflecting waveform characterized by a centro-parietal distribution peaking approximately 275 to 800 ms post-stimulus onset (Polich, 2007). Traditionally, as alluded to above, the P300 is elicited during an active oddball paradigm, where the component's amplitude and latency are reflective of the improbability of a target stimulus and the level of difficulty discriminating the target stimulus from other (standard) stimuli, respectively (Picton, 1992). More accurately, the P300 amplitude has been found to be proportional to the amount of attentional resources required for a given task, while its latency serves as a temporal measure of neural activity underlying attention allocation and immediate memory operations (Polich & Margala, 1997). In sum, the P300 is sensitive to cognitive workload (Allison & Polich, 2008) and reflects attentional and memory related processes (Fabiani et al., 1986; Polich et al., 2007). Also, the P300 can be further subdivided into two separate components – the P3a and the P3b (Polich et al. 2007).

The P3a, a more centrally-distributed response relative to the P3b, peaks 275-350ms post stimulus onset and is associated with the selection of stimulus information directed by attentional orienting (Rushby et al., 2005; Pontifex et al. 2009). Specifically, it reflects the release of previous attentional focus on a frequent stimulus to re-orienting attentional processes towards an infrequent stimulus (Squires et al., 1975; Polich et al. 2007), demonstrating its association to greater focal attention. Alternatively, the P3b, a centro-parietal response peaking 300-800ms post stimulus onset (Polich, 2007; Baillargeon et al., 2012), has been shown to reflect neuronal activity associated with revision of the mental representation of the previous event within a stimulus environment (Polich et al. 2007). Thus, the amplitude of the P3b is understood to reflect

the distribution of attentional resources when working memory is updated (Donchin & Coles, 1988; Polich et al. 2007). In other words, it is sensitive to both working memory and the amount of attentional resources involved in processing a stimulus. Of note, the cognitive processes the P300 reflects relate to concussion symptomatology, inasmuch as concussed patients often exhibit dysfunctions of memory and attention. Accordingly, the P300 has garnered considerable attention in concussion literature.

Traditionally, concussion literature focuses on modulation of the P3b, where research has shown repeatedly attenuated and/or delayed responses regardless of age, time since injury, or task complexity. In particular, relative to a healthy control sample, 18 studies have found reduced P3b amplitudes in concussed populations (Dupuis et al., 2000; Gaetz et al., 2000; Lavoie et al., 2004; De Beaumont et al., 2007; Broglio et al., 2009; De Beaumont et al., 2009; Thériault et al., 2009; Baillargeon et al., 2012; Ozen et al., 2013; Gosselin et al., 2012; Moore et al., 2014; 2015; 2016; 2017; Parks et al., 2015; Ruiter et al., 2019) and 5 have revealed delayed latencies (Gaetz et al., 2000; Gosselin et al., 2006; De Beaumont et al., 2009; Ledwidge & Molfese, 2016; Ruiter et al., 2019). Thus, research has clearly demonstrated the ability of the P3b to measure the neurophysiological effects of concussion, and their incontrovertible link to cognitive dysfunctions.

The P3b has been found to be affected in concussion populations regardless of whether the group assessed is symptomatic or asymptomatic, young or old, or received their last concussion years earlier (Gosselin et al., 2006; De Beaumont et al., 2009; Moore et al., 2015; Ruiter et al., 2019). For example, Gosselin et al (2006) examined the P300 using an auditory oddball task in symptomatic (n=10) and asymptomatic (n=10) concussed individuals relative to healthy controls (n=10). Their results revealed no significant differences between the two concussed groups; however, relative to controls, both the symptomatic and asymptomatic concussed groups revealed delayed and attenuated P3b responses. Further, a study conducted by Moore et al (2016) using an oddball task revealed attenuated P3b amplitudes in recently concussed children (ages 8-10) relative to age-matched healthy controls. Finally, De Beaumont et al (2009) and Ruiter et al (2019) revealed, relative to age-matched healthy controls, delayed and attenuated P3b responses in concussed individuals who had sustained their last concussion on average 30 years prior.

These studies provide evidence to suggest that neurophysiological manifestations of cognitive dysfunction are capable of lasting years beyond injury; a finding consistent with other fields of neuroscience such as CTE research (e.g., Stern et al., 2019). Ultimately, neuroscience research utilizing the P300 to measure cognitive dysfunction in concussed populations has proved effective across multiple modalities, tasks, age ranges, and times since injury; thus, future concussion-related research should focus on clinical applicability to aid in diagnosis, treatment, and rehabilitation.

Another component studied extensively in brain injury research is the MMN (e.g., Daltrozzo et al., 2007; Fischer et al., 2010; Morlet and Fischer, 2014; Blain-Moraes et al., 2016). The MMN is a negative-going waveform with a fronto-central scalp distribution peaking 150-250ms after a discriminant change within the auditory modality. Specifically, the MMN is elicited to a passive auditory oddball task where a deviant auditory stimulus occurs within an ongoing stimulus sequence consisting of primarily repetitions of the same stimulus (Näätänen et al., 1978; Näätänen et al., 2007). Research posits that the MMN is reflective of an automatic attention function linked to a predictive coding process (Garrido et al., 2008). Although the MMN - like the P300 - is elicited to an oddball task, a noteworthy distinction between the two is the fact that the MMN does not require active attention to be elicited. That is, the MMN requires a conscious state but not awareness to be elicited (Atienza et al., 2005; Fischer et al., 2010; Dykstra and Gutschalk, 2015). This is a key difference distinguishing the MMN from both the N2b and P300 that also emphasize the low level, automaticity of the MMN and the attention (or pre-attention) processing it reflects.

Historically, the MMN has been used exclusively in the assessment of what can be characterized as “catastrophic” brain injury such as coma, vegetative state, and minimally conscious state (e.g., Morlet & Fischer, 2014; Blain-Moraes et al., 2016). It has been shown to be a strong predictor of coma recovery (Kane et al., 2000) and has been used to evaluate cognitive abnormalities in mental disorders such as schizophrenia (Todd et al., 2003; 2008). Surprisingly, despite the wealth of literature validating the efficacy of the MMN in traumatic brain injury and other clinical domains, it was not until recently that the MMN was investigated in a concussed population. Specifically, to date, only one published study (see Chapter 4) has demonstrated

alterations in MMN in a concussed population (Ruiter et al., 2019). Briefly, the study revealed significantly attenuated MMN responses in retired professional North-American football players who had sustained their most recent concussion on average nearly three decades prior. The study was the first to document an entirely new level of cognitive dysfunction in a concussed population. However, although a never-before-seen effect was discovered, further investigation is needed to validate the effectiveness of the MMN in measuring cognitive dysfunction in concussed populations; an exploration that should commence with assessing concussed individuals in different age ranges and at various time-points since date of injury.

1.9 Current clinical tools in concussion

Unfortunately, due to the variety of health outcomes, a unified treatment and diagnosis of concussion has not been established. Today, despite significant advances in concussion research, diagnosis and treatment decisions continue to be made by clinicians who evaluate the physical signs and symptoms of the patient; a feat accomplished by administering assessments of physical, neurological, and cognitive symptoms in conjunction with their own clinical judgment. In particular, a clinician will typically evaluate a patient by collecting information from a combination of neuropsychological assessments, patient self-reporting of symptoms, and concussion-targeted questionnaires (Rees, 2003; McCrory et al., 2009; Cancelliere et al., 2014; McCrory et al., 2016). Clinicians will also take into account whether there was a loss of consciousness (LOC) and its duration and any signs of post-traumatic amnesia (PTA) after initial head trauma. (Borg et al., 2004). Consequently, it is abundantly clear that a clinician's diagnosis and treatment decisions are heavily dependent on their own clinical expertise, patient-response reliability, and the predictive strength of the estimates produced by the administered subjective tests.

In addition to subjective measurements, clinician's also use neuroimaging; however, the typical protocol involves nothing more than a structural MRI (or CT). Specifically, clinicians will typically order a CT scan when a patient is admitted with a suspected concussion (Collins et al., 2014). However, a CT scan is constrained to structural integrity observations and thus, is only suitable for determining whether or not there are any further complications beyond the concussion diagnosis (e.g., hemorrhaging). If concussion symptoms persist longer than the acute

stage of the injury, clinicians will often order an MRI for the patient (Collins et al., 2014). Again, however, the problems associated with MRI are similar to those of CT – measuring structural integrity of the brain and thus, also fails to take into account the neurocognitive dysfunctions associated with concussion. Thus, as it is clear that a new clinical neuroimaging technique capable of measuring the functional consequences of concussion is needed. For that reason, the next three chapters will investigate the ability of ERPs to measure the acute, post-acute, and long-term effects of concussion on cognitive functioning, as well as their ability to track neurophysiological changes during concussion recovery.

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Chapter 2

Abstract

Objective

Recent studies demonstrate that sports-related concussions can have negative consequences on long-term brain health. The goal of the present study was to determine whether retired Canadian Football League (CFL) athletes with a history of concussions exhibit alterations in neurocognitive functioning, along with changes in physical, social, and psychological health.

Methods

Our study compared nineteen retired CFL athletes' concussion histories to eighteen healthy age-matched controls with no history of concussion. Self-report inventories were used to assess depression, memory, attention, and general health. Neurophysiological markers of cognitive function were evaluated with event-related brain potentials (ERPs) as measured in two protocols: (1) A Mismatch Negativity (MMN) protocol for assessing the automatic early attentional brain mechanism; and, (2) a P300 auditory oddball task for assessing consciously controlled attention.

Results

Relative to controls, CFL players exhibited: response delays and reduced amplitudes in neurophysiological responses; overall decreases in cognitive function; and poorer scores on self-reports of physical, social, and psychological health; reflecting problems in all three categories.

Conclusion

Our findings demonstrate that multiple concussions sustained over several years can lead to altered cognitive and psychosocial function.

Significance

Neurophysiological markers of conscious and pre-conscious attention provide an objective assessment for evaluating long-term cognitive consequences of concussion.

Highlights

- For the first time, a deficit in a pre-attentive brain response has been linked to concussion.
- Former professional football players show significant deficits in Pain and Social Function.
- Former professional football players show elevated levels of depression and concussive symptoms.

Keywords

Concussion, mTBI, Event-related potentials, EEG, Behavioral assessment, Football

1. Introduction

An estimated 1.6–3.8 million sports-related traumatic brain injuries (TBIs) occur every year in the United States alone (Langlois et al., 2006a, Langlois et al., 2006b). An uncomplicated mild-traumatic brain injury (MTBI), more commonly referred to as concussion (Maroon et al., 2000, McCrory et al., 2009; Guskiewicz and Mihalik, 2011, Iverson et al., 2012, Zetterberg and Blennow, 2016), has been described as a serious public health concern (Ommaya and Gennarelli, 1974, Gronwall, 1977, McCrory et al., 2009). Concussion, a "complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces" (McCrory et al., 2009), has been shown to negatively affect cognition, social functioning, emotional wellbeing, and neurologic function years after initial diagnosis (Collins et al., 1991, DeKosky et al., 2010, Kraus et al., 2016). However, despite scientific evidence and knowledge of the post mortem neuropathology observed in former professional football players (Omalu et al., 2005, Mez et al., 2017), only the National Football League (in the U.S.) has acknowledged the connection between repeated football-related concussions and neuropathology. While the current emphasis on chronic traumatic encephalopathy (CTE) and other concussion-related neuropathologies is appropriate, it should not detract from the fact that neurophysiological signs of concussions are obtainable from living individuals and hold the promise of providing healthcare providers with evidence necessary for making clinical decisions.

Research has demonstrated repeatedly that in the evaluation of the long-term effects of concussion, electroencephalography (EEG) has become a viable assessment tool with diagnostic potential. In particular, event-related potentials (ERPs) have demonstrated their utility in assessing the cognitive function of concussed athletes (e.g., Gaetz et al., 2000, De Beaumont et al., 2009, Broglio et al., 2011, Baillargeon et al., 2012, Gosselin et al., 2012). A history of concussions is negatively correlated with electrophysiological indices of normal cognitive function and general brain health. This effect, often seen immediately after a concussion, may continue – or even worsen – over an extended period of time after the initial concussion diagnosis. For example, a study of attention and information processing capabilities using the P300 (P3a and P3b) recorded in an auditory oddball paradigm demonstrated delayed and attenuated P3a and P3b responses in former university athletes who had sustained their last concussion more than 30 years earlier (De Beaumont et al., 2009). These findings demonstrate

the long-lasting alterations of brain electrophysiology and the cognitive processes they reflect. The same report showed that the concussed group performed more poorly on neuropsychological tests of episodic memory and response inhibition; however, effects such as these are not reliably detected using neuropsychological assessment (see Broglio et al., 2011). There is a point where the ability of neuropsychological tests fail to reflect effects of brain injury. Specifically, neuropsychological tests, by their very nature, are indirect (and subjective) reflections of cognitive function (Lezak, 1995). Accordingly, in an effort to objectively assess cognitive function, other methods – such as EEG – have been shown to be more effective. For instance, several studies have demonstrated the correlation between multiple concussions and electrophysiological abnormalities (e.g., Dupuis et al., 2000, De Beaumont et al., 2007, Thériault et al., 2009).

Traditionally, ERP research investigating the cognitive effects of concussion examines changes in the P300 ERP response within the traditional active "oddball" paradigm. The P300, a component peaking anywhere between 300 and 800 ms after stimulus onset, depending on several cognitive parameters including perceptual and/or cognitive complexity (Duncan et al., 2009), can be subdivided into two separate components: P3a and P3b. The P3a has a fronto-central distribution that peaks at ~300 ms and has been linked to focal attention (Polich, 2007). The P3b, on the other hand, has a centro-parietal distribution that peaks at ~450 ms and is sensitive to the amount of attentional resources involved in processing a stimulus (Polich, 1987, Duncan et al., 2009). The oddball task requires the active processing of a stimulus sequence comprised primarily (e.g., 90%) of identical stimuli (the "standards") with "deviant" stimuli interspersed (e.g., 10%) throughout the sequence (Polich, 2007). Typically, subjects are required to respond (e.g., via a mouse click) indicating they have detected the deviant stimulus. Studies have shown that recently concussed individuals show reduced amplitudes and/or extended latencies in P3a or P3b responses (Dupuis et al., 2000, Gaetz et al., 2000). Additionally, research has revealed that the N2b, an ERP component related to features of intentionally directed attention, can also be used in the assessment of the neurocognitive effects of concussion (Broglio et al., 2009).

In addition to the P300, the MMN, an ERP component recorded in a passive oddball auditory stimulus sequence, has been used extensively in studies of catastrophic traumatic brain injury (Kaipio et al., 2001, Fischer et al., 2010, Morlet and Fischer, 2014, Blain-Moraes et al., 2016). The MMN is a negative-going waveform occurring ~150–250 ms in response to an auditory stimulus that is deviant from the ongoing sequence comprised mostly of the same stimulus (Näätänen et al., 1978). The MMN is emitted to the deviant stimulus despite there being no instructions to respond or even attend to the stimulus sequence (Näätänen et al., 2007) – an important distinction that emphasizes the low level, automaticity of the response and the type of attention (or pre-attention process) it reflects. Like the N2b, the MMN is elicited 150–250 ms post-stimulus onset. However, unlike the MMN, the N2b is only emitted during intentional attention-related processing. The N2b emerges prior to the P3a and reflects executive functioning (Patel and Azzam, 2005, Broglio et al., 2009). The N2b has been shown to be reliably smaller in those who have sustained a concussion (Broglio et al., 2009); a finding indicative of deficits in executive cognitive control. Despite extensive research using electrophysiological measures of the short-term effects of concussion, only the P300 has been used as a means of identifying the long-term negative effects (De Beaumont et al., 2009).

The present study sought to provide an extensive neurophysiological investigation conducted on individuals who had sustained a number of concussions and blows to the head during a professional football career. The research protocols enabled the investigation of a number of ERPs associated with different types of attention including those that serve as the neural infrastructure for memory formation. The present study examines a full range of neurophysiological responses associated with attention and its enabling of working memory and memory consolidation by examining the MMN, N2b, P3a, and P3b to investigate the neurocognitive long-term consequences of concussion. This study's contributions to the literature are two-fold: (1) the inclusion of a full range of ERP components in the same sample population; and, (2) the examination of the MMN for the first time in a group of individuals with multi-concussion histories with the most recent occurrence being on average close to three decades earlier. Specifically, this second point is of considerable importance because if the retired CFL players were to reflect a disruption in MMN processing, this would be the first time

a disruption of attentional mechanisms at levels that precede conscious processing were to be observed as a result of multiple concussions.1

It was hypothesized that retired CFL players would demonstrate greater deficits in automatic and intentional attention-related processing and working memory function as reflected by amplitude and/or latency differences in the MMN, N2b, P3a, and P3b components compared to age-matched controls. Research has demonstrated that concussions can affect physical, social, and psychological health (e.g., Kopjar, 1996, Emanuelson et al., 2003, Guskiewicz et al., 2007a, Guskiewicz et al., 2007b, Kerr et al., 2012). Accordingly, in an effort to capture these effects, the present study also collected self-report inventories of physical, social, and psychological health. Additionally, a computerized neurocognitive assessment tool measuring criteria such as reaction time and working memory was administered. The hypothesis regarding these data was that a generally lower quality of physical and psychological health, as well as poorer neurocognitive performance, would be found in the CFL group.

2. Materials and methods

2.1. Participants

Our study, approved by the Hamilton Integrated Research Ethics Board (HI-REB), Hamilton, Ontario, Canada, recruited nineteen retired Canadian Football League (CFL) athletes (rCFL) with histories of concussions (mean age = 57.6, range = 45–66 years) and twenty healthy age-matched control subjects (mean age = 53.7, range 45–61). Control subjects had no history of concussion or any other type of neurological disorder, and were recruited through the local newspaper, personal contacts, and McMaster University. Two of the control subjects were not included in the analyses for technical EEG recording reasons. All participants (all of whom were native English speakers and self-reported as having no hearing issues) provided informed consent, in accordance with the ethical standards of the Declaration of Helsinki, prior to participation in the experiment. Participants were assessed using the Immediate Post-Concussion Assessment and Cognitive Test (ImPACT), Beck Depression Inventory II (BDI II), Short Form Health Survey (SF-36), and the Post-Concussion Symptom Scale (PCSS).

2.2. Demographic data

Acquired through player self-reporting, the demographic data consists of the rCFL group's average age, years of education, number of concussions, number of years played, and number of years since last concussion (Table 1).

2.3. Behavioral tasks

The ImPACT assessment consists of 6 smaller sub-tests and provides 5 different composite scores, 1 symptomatology score, and 1 Cognitive Efficiency Index (CEI) score. The 5 composite scores include: (1) Verbal Memory (VBM), (2) Visual Memory (VIM), (3) Motor Speed (MS), (4) Reaction Time (RT), and (5) Impulse Control (IMP). Higher scores in the VBM, VIM, and MS composite scores are indicative of elevated levels of attentional processing, verbal and visual recognition memory, and processing speed; whereas, lower scores for RT and IMP demonstrate faster response times and better impulse control. The CEI score, a measure denoting a positive correlation between high scores and cognitive function level, is derived from the interaction between accuracy and speed on the Symbol Matching Test. Lastly, we used the symptomatology score to represent the subject's state at the time of testing.

2.4. Self-report batteries

The BDI II, SF-36, and PCSS self-report inventories were used to evaluate the general health and well-being on a day-to-day basis while the BDI II was used to evaluate the level of depression, and the SF-36 was used to evaluate general "everyday" health. The SF-36 evaluates health criteria such as: vitality, physical functioning, emotionality, mental state, pain, and the group's general health perceptions. Each category of the SF-36 is scored out of 100, with 100 being the best score health wise. For example, with regards to the Physical Function category, a score of 90/100 reflects better physical function than a score of 80/100. Also, a score of 90/100 in the Pain category reflects lower levels of pain than a score of 80/100. Lastly, the PCSS was used to evaluate how they felt on a regular basis in terms of symptoms such as: irritability, fatigue, emotionality, sadness, numbness, and sensitivity to light and noise. Specifically, each listed symptom on the PCSS is measured using a 0–6 likert-type scale. After administering the PCSS to a participant, each of the symptoms' scores are summed to equal the total PCSS score.

2.5. EEG stimuli and experimental conditions

Two separate protocols were used to examine two distinct cognitive processes. The first protocol, adapted from Todd et al (2008), was a P300 auditory oddball task that consisted of one Standard tone (ST, 1000 Hz, 80 dB SPL [sound pressure level], 50 ms duration) and three deviant tones differing from ST in Frequency (FT, 1200 Hz, 80 dB SPL, 50 ms), Intensity (IT, 1000 Hz, 90 dB SPL, 50 ms), and Duration (DT, 1000 Hz, 80 dB SPL, 100 ms). The protocol employed an inter-stimulus interval (ISI) of 1000 ms. Each deviant tone was presented 36 times representing 6% of the stimulus set while the ST was presented 492 times representing 82% of the stimulus set. To ensure participants were attending to the stimuli, they were asked to left-click to every ST and right-click to all deviant tones; this procedure was counterbalanced within subjects halfway through the protocol. The response requirement in this task was designed to engage active attentional processes and invoke the P3b.

The second protocol, developed by Todd et al (2008), was a longer version of the same auditory oddball task used in the first protocol, but with different procedures to enable the examination of pre-attentive processes as manifested by the MMN. A total of 2400 tones, with a 500 ms ISI, were used in this experiment with each deviant tone being presented 144 times representing 6% of the stimulus set, while the ST was presented 1968 times representing 82% of the stimulus set. Instead of attending to the stimuli, participants were informed that the tones were of no relevance to the study and instructed that they need to only watch a nature film. The film was an edited version of a nature program with the auditory track removed and only visually neutral scenes shown.

Lastly, protocols 1 and 2 were presented in that order but were separated by an additional experiment requiring participants to judge the grammaticality of spoken sentences and make a "correct/incorrect" manual response to each sentence. This task created a distraction break of 10–15 minutes between the two oddball tasks.

2.6. Procedure

Following informed consent and prior to the EEG testing, participants completed several self-report inventories: the PCSS, SF-36, and BDI II as well as the Edinburgh Handedness Inventory (Oldfield, 1971) and a general pre-screen that included criteria such as age, sex, general medical history, and current medications. After being briefed on the types of tests to be expected on the ImPACT, participants completed the ImPACT independently.

Following the ImPACT, participants were taken to a second lab space where they sat in a comfortable chair 90 cm from a computer monitor in a sound-attenuated room and partook in the EEG experiment. In Protocol 1, they were instructed to look at the white fixation cross located in the center of a black screen while they listened to tones through noise-cancelling headphones. They were instructed to attend to the stimuli and respond differentially to standard and deviant tones; a practice run was provided. In Protocol 2, participants watched the nature film while the tone sequence was presented without any instructions aside from watching the film. The experiment duration lasted approximately 50 minutes.

2.7. Electroencephalography recordings

EEG was recorded from 64 Ag/AgCl electrodes (International 10–20 system) using a BioSemi ActiveTwo system and a 0.01–100 Hz bandpass (with a 60 Hz notch filter employed) that was digitally sampled at 512 Hz. Five Ag/AgCl external electrodes were placed on the subject's nose, left and right mastoids, and above and over the outer canthus of the left eye. The EOG (electrooculogram) was recorded (using the same bandpass and sampling rate) from the external electrodes placed above and over the outer canthus of the left eye. EEG acquisition was referenced to the driven right-leg (DRL) and re-referenced offline to the average of the mastoids.

2.8. EEG data analysis

Using Brain Vision Analyzer (v2.01), EEG data were digitally filtered offline with a bandpass of 0.1–30 Hz (24 dB/oct) and downsampled to 500 Hz. Data were visually inspected and trials containing artifacts (e.g., due to movement) greater than 100 μV were removed. Additionally, ocular Independent Component Analysis (ICA), with a maximum voltage criterion of ±100 uV, was performed to remove vertical and horizontal eye-movement artifacts. Data were then

segmented into −200 ms pre- to 1000 ms post-stimulus intervals for the P300 protocol, and −200 ms to 600 ms for the MMN task and then averaged per condition. Only correct response trials were used for the P300 protocol. Difference waveforms were produced by subtracting ERPs to the Standard condition from those recorded to each of the deviant conditions (i.e., Intensity, Frequency, and Duration) in both protocols. Finally, a process of automated peak detection (Barr et al., 1978) was performed on the difference waveforms to obtain the maximal electrophysiological response of each ERP within their respective time windows. Within the P300 protocol, peak analyses were performed on the N1 (75–125 ms), N2b (170–270 ms), P3a (275–375 ms), and P3b (400–700 ms) components for each condition. Peak analyses within the MMN protocol were conducted for the N1 (75–125 ms), and MMN (150–250 ms). For N100 analyses, peak detection and all extracted values were calculated on the original waveforms (not on difference waves) as the N100 is also elicited to the ST.

2.9. Behavioral statistical analysis

Statistical analysis of the ImPACT, PCSS, SF-36, and BDI II were conducted using R Software (RStudio, Version 3.3.3). Group differences of the PCSS and BDI II were assessed using descriptive statistics and two-tailed t-tests with an alpha level of 0.05 (Table 2), while the ImPACT and SF-36 were assessed using descriptive statistics and two-tailed t-tests with Bonferroni-corrected significance thresholds of $P < 0.00833$ (0.05/6) and $P < 0.00625$ (0.05/8), respectively (Table 2).

2.10. EEG statistical analysis

The 64 electrode scalp positions on the head were divided into 20 segregated Regions of Interest (ROIs) (Frishkoff et al., 2011), with 3 to 6 electrodes per region. Regions were created by clustering electrodes from left (L), midline (M), and right (R) positions with frontal (F), central (C), and parietal (P) positions. Of those 20 ROIs, 9 were selected and subsequently grouped into 3 independent scalp sectors: Frontal (R–F, M–F, L–F), Central (R–C, M–C, L–C), and Parietal (R–P, M–P, L–P). Statistical analyses were performed for both amplitude and latency using univariate mixed-effects analysis of variance (ANOVAs) with an alpha level of $P < 0.05$ (Table 3). Degrees of freedom were corrected using the more conservative Greenhouse-Geisser estimates of epsilon (Greenhouse and Geisser, 1959, Girden, 1992, Maxwell and Delaney, 2004)

to ensure avoidance of Type 1 errors. EEG analyses were conducted on the peak amplitude (defined as the average amplitude within a time-window of −50 ms to +50 ms around the detected peak) and latency (defined from stimulus onset to the detected peak) of ERP components for each condition.

3. Results

3.1. Demographic

The demographic data shows that former CFL athletes had an average age of 57.6, averaged 16.68 years of education, reported on average 4.05 concussions over an average career length of 7.84 years, with an average of 28.11 years since their last concussion (Table 1). When comparing number of years of education to the control population, our statistical analyses revealed no significant difference ($t(35) = 0.17$, $P < 0.01$).

3.2. Behavioral

3.2.1. Computerized neurocognitive testing results

Contrary to our hypotheses, no significant differences in ImPACT scores were observed between the two groups (Table 2). However, the rCFL group exhibited scores reflective of marginally poorer performance in each of the categories. Specifically, former players scored lower in Verbal Memory (VBM), Visual Memory (VIM), Motor Speed (MS), and Cognitive Efficiency (CEI). Also, the rCFL group showed marginally slower response times which translated to a higher averaged score in Reaction Time (RT). Lastly, the rCFL group demonstrated higher levels of impulsivity as indicated by their higher average scores in Impulse Control (IMP).

3.2.2. PCSS, SF-36, and BDI II results

As hypothesized, when compared to controls, players demonstrated a decrease in general health and an increase in depression and concussive symptomatology (see Table 2). When comparing total PCSS symptomatology scores, the results revealed a significant difference between the two groups ($t(35) = 3.45$, $P < 0.01$). In particular, the rCFL group reported concussion-like symptomatology at more than four times the rate of healthy age-matched controls – with the most commonly reported symptoms being: sensitivity to light, irritability, sadness, emotionality, numbness or tingling, difficulty sleeping, and difficulty remembering. Also, a main effect of

group was found for total BDI II score ($t(35) = 3.37$, $P < 0.01$) – demonstrating elevated levels of depression in the rCFL group. Lastly, Bonferroni corrected t-tests on 8 different SF-36 categories revealed significant group differences in Social Function ($t(35) = 3.24$, $P < 0.005$) and Pain ($t(35) = 3.42$, $P < 0.005$).

3.3. Electrophysiological results

3.3.1. Attention, Voluntary: P300 protocol

A number of components were investigated within the attended oddball protocol. Examining the waveforms for the Controls, a clear N1 response is seen to stimulus onset with a typical fronto-central distribution (Fig. 1A, B, C); similar characteristics are observed in the rCFL group. The following N2b component exhibits a characteristic central distribution with minor representation at frontal sites (Fig. 1A, B, C). These waveform morphological features are also seen in the rCFL group although the N2b has increased frontal representation in the rCFL group that is seen in response to Duration (Fig. 1B) and Intensity (Fig. 1C) deviants, in particular. However, the comparative topographical maps for the P300 exhibit clear differences in the development and distribution of the P300 in response to each deviant stimulus type. In controls, the P3a element of the P300 exhibits a frontal distribution that extends in an anterior-posterior manner as far back as the occipito-parietal sites for Frequency and Intensity deviants (Fig. 1A, C) but shows only a frontocentral distribution for Duration deviants (Fig. 1B). These distributional effects suggest a combinatorial P3a and b in this waveform. The topographical maps for the rCFL group show a similar anterior-posterior distribution; however, a fairly striking left-sided absence of a response resulting in an unusual right asymmetry of the response is apparent across all types of deviants (Fig. 1A, B, C). The P3b occurring quite late for both Controls and rCFL groups exhibits a classic parietal distribution that is apparent and similar in both groups. The most striking feature of these waveforms is the near 50% reduction in P300 amplitude (both P3a and P3b) in the rCFl group across all conditions (Fig. 1) compared to Controls and the smaller but still notably reduced N2b amplitude again in the rCFL group.

Statistical analysis provided confirmatory support for observations (Table 3). Group differences were not observed for either the latency or amplitude of the N1. However, N2b amplitudes proved to be significantly smaller in the rCFL group compared to the control sample (F(1,

35) = 5.08, P < 0.05). Additionally, there was an interaction of Group X Condition for the N2b amplitudes (F(2, 70) = 4.91, P < 0.05) that post hoc analysis revealed was attributable to the much smaller amplitudes to Duration deviants in the rCFL group compared to Controls (F(1, 35) = 14.38, P < 0.01). There was a main effect of Group such that the P3a amplitudes in the rCFL group were significantly smaller than those exhibited in the Control sample (F(1, 35) = 6.34, P < 0.05). In addition, delayed response latencies were found for the P3b in the rCFL group compared to Controls (F(1, 35) = 15.32, P < 0.01). Lastly, we found a main effect of group on P3b amplitude (F(1, 35) = 8.08, P < 0.01) where the rCFL group exhibited a reduction in P3b amplitude compared to healthy control participants.

3.3.2. Attention, Pre-attentive automatic: MMN protocol

Two ERP components were investigated in the MMN Protocol: The N1 and the MMN. Observing the waveforms of the Control group, a clear N1 response can be seen to stimulus onset, followed closely by the MMN response. Both the N1, and MMN show a typical fronto-central scalp distribution (Fig. 2). Like the Control group, the rCFL group exhibit typical scalp distributions for both the N1 and MMN ERP components. However, unlike the Control group, the rCFL group shows an obvious reduction in both the N1 and MMN amplitude across all conditions (Fig. 2).

Our analyses on the N1 component showed a main effect of group (F(1, 35) = 5.74, P < 0.05) with the rCFL group exhibiting significant amplitude reductions. However, no main effect of group was found for latency. Similarly, the MMN showed no main effect of group for latency. However, a main effect of group reflecting the significantly smaller MMN amplitude found in rCFL participants was observed (F(1, 35) = 10.01, P < 0.01). Additionally, results showed a Group X Condition interaction (F(2, 70) = 5.98, P < 0.01). Post hoc multiple comparison tests revealed that the rCFL group had significantly reduced amplitudes in the Duration (F(1, 35) = 17.47, P < 0.01) and Frequency (F(1, 35) = 5.12, P < 0.05) conditions.

3.3.3. Correlation of EEG results to behavioral results and demographic data

Uncorrected tests of Spearman's Correlation between electrophysiological responses, behavioral assessments (i.e., PCSS, SF-36, and BDI II) and demographic data (i.e., age, years of education, number of concussions, and number of years played) failed to show significance.

4. Discussion

This study demonstrates that in comparison to healthy age-matched controls, former professional football players with a history of concussions have clear signs of cognitive and neurophysiological deficits. Further, this study shows they also self-report as having more problems with social, emotional, physical, and psychological health.

The current results demonstrate a general neurocognitive deficit as reflected by electrophysiological responses in individuals with a history of concussions (see De Beaumont et al., 2009). Previous research demonstrated that individuals who suffered their last concussion more than 30 years earlier showed similar results to those who had sustained their last concussion only 3 years earlier (De Beaumont et al., 2007, De Beaumont et al., 2009). These studies, and ours, provide evidence demonstrating that those with a history of concussions are more likely to continue exhibiting cognitive deficits years after initial concussion diagnosis. Our findings are consistent with work demonstrating that retired professional football players, on average, show neurocognitive problems later in life (Guskiewicz et al., 2005, Lehman et al., 2012, Small et al., 2013).

The abnormalities found in two different levels of attention as manifested by the P300 and MMN in this study further refine our understandings of the effects of concussions in professional football. Previous research has shown that the P300 latency is a valid measure of stimulus classification speed (Kutas et al., 1977, Polich, 1987) thus, it is reasonable to interpret increased latencies of the P300 as being a reflection of greater difficulties in allocating attentional resources for memory processing (Polich et al., 1983, Reinvang, 1999, Kok, 2001). In a similar vein, latency delays of the P3b component can be interpreted as indicative of slower cognitive processing speeds in the rCFL group.

Examination of the N2b component emitted within the P300 protocol demonstrated its central distribution (Näätänen and Gaillard, 1983, Lim et al., 1999). Evidence has shown that the N2b is generated in the cingulate cortex and tends to occur together with a frontal P3a (Folstein and Van Petten, 2008, Broglio et al., 2009). Further, the N2b is sensitive to stimulus deviance from an on-going sequence only when stimuli are being attended to; a characteristic demonstrating that the N2b requires and reflects conscious attention (Heil et al., 2000, Donkers and Van Boxtel, 2004, Folstein and Van Petten, 2008). Although the N2b scalp distribution was similar for rCFL and healthy controls, the response was found to be significantly smaller in retired professional football players with a history of sports-related concussions compared to age-matched controls (see Broglio et al., 2009). Based upon present theories (e.g., Näätänen and Gaillard, 1983, Folstein and Van Petten, 2008, Broglio et al., 2009), the decrease in N2b amplitude may reflect a deficit in the processing capacity of information contained in a stimulus.

With the addition of the MMN protocol, the current study adds a level of understanding to the cognitive consequences of concussions. As noted above, the MMN is associated with a level of "pre-attentive" processing (Näätänen et al., 1978, Light et al., 2007, Näätänen et al., 2007) that is elicited independently of conscious attention (Näätänen et al., 1978, Näätänen et al., 2007) while still requiring the individual to be in a conscious state (Blain-Moraes et al., 2016, Tavakoli et al., 2018). In addition, exclusively within the MMN protocol, our study found that professional football players demonstrated a significant reduction in N1 amplitude. The N1 is a pre-attentive ERP linked to the auditory cortex (Näätänen and Picton, 1987) that has been found to be sensitive to loudness (Keidel and Spreng, 1965), frequency (Butler, 1968), and sound onset (Spreng, 1980). The significant decrease in N1 amplitude may suggest difficulties in auditory processing.

Our results revealed that the rCFL players, on average, scored lower in every category of the SF-36. This finding indicates that the retired CFL players self-report overall poorer general health as compared to age-matched controls. Specifically, the current study found that rCFL players were significantly different from healthy controls in the Social Function and Pain categories. A recent study examining the long-term consequences of mTBIs on social function revealed that those who had previously suffered a concussion were 31% more likely to have moderately or severely

altered relationships with family members (Fourtassi et al., 2011). Although examination of social dysfunction at this level of detail was beyond the current study, it is not unreasonable to suggest that the noted problems in social function reported by the rCFL players in this study may, in part, be due to negatively altered family relationships. In addition to social function, the rCFL group reported significantly higher levels of pain. This finding is supported by the literature where there has been substantial evidence demonstrating that chronic pain can impair cognition and consequently alter ERPs (Kewman et al., 1991, Dick et al., 2003, Seminowicz and Davis, 2007). Thus, the poorer cognitive performance of the players may be, in part, due to elevated levels of pain.

In addition to general, social, and physical health, the current study also examined the long-term effects of concussion on emotional and psychological health by administering the BDI II. The results from the BDI II suggest that, on average, players have higher levels of depression-related symptoms. Depression symptoms can vary from emotional, to psychological, to physical in nature (Beck et al., 1996). Research has shown that head trauma, such as concussions, often result in higher levels of depressive symptomatology (Guskiewicz et al., 2007a, Guskiewicz et al., 2007b, Kontos et al., 2012). Also, depression has been shown to affect the P300 component (e.g., Kayser et al., 2000, Pelosi et al., 2000, Yang et al., 2011); however, there is no research pertaining to the effects of depression on the MMN. In the current study, BDI II results revealed that players scored almost 4 times higher than age-matched controls; a finding that supports the burgeoning literature that concussions result in a higher likelihood of depression or at the least, an increased susceptibility to depressive symptomatology (e.g., Guskiewicz et al., 2007a, Guskiewicz et al., 2007b, Chen et al., 2008, Kontos et al., 2012, Chrisman and Richardson, 2014). It is important to note, however, that despite the BDI scores being significant between the two groups, the CFL group BDI scores did not exceed in the clinical-cut off for depression.

Lastly, failing to see group differences in the ImPACT results may be attributable to the fact that the concussions were incurred years before the assessment; a finding similar to those revealed in other studies that involved even shorter time periods (e.g., Iverson et al., 2012). Additionally, our results revealed below-average CEI scores for both groups; a result that may be attributable to many of the participants being outside the ImPACT normative data age range of 59 years old

(Iverson et al., 2003). Furthermore, our results revealed very strong Impulse Control responses for both groups compared to what is considered "normal" according to the ImPACT normative database (Iverson et al., 2003). This result may be attributable to our participants being more concerned with accuracy rather than reaction time. Despite the lack of statistical significance between the two groups, the general trend of slightly poorer performance in the rCFL group in each of the categories agrees with previous literature that individuals with a history of concussions exhibit problems in memory, reaction time, motor speed, and overall cognitive capability (Collins et al., 1991, De Beaumont et al., 2009, Kontos et al., 2012).

5. Limitations

5.1. General

Players sustained approximately 4 concussions over an average career length of nearly 8 years (Table 1). However, the vast majority of concussions reported in this study were not clinically diagnosed; rather, they were identified by the athletes themselves. The lack of clinical diagnoses may be attributable to the limited awareness of and knowledge about concussions decades ago when many of these players were active in football. As a result, it is difficult to know definitively when the concussions occurred, the exact number of concussions, and their severity. Furthermore, behavioral and EEG results may have been partially affected by career length; however, our analysis failed to show any significant correlations between the rCFL demographic data (Table 1) and their behavioral (Table 2) or EEG results (Fig. 1 and Fig. 2). Also, a group study design, by its very nature, restricts the comparison among players of long-term cognitive function variability. Also, this study was unable to control for lifestyle of either the rCFL or healthy age-matched control groups. Lastly, an ideal control group for our study would have been comprised of another group of professional football players who had never sustained a concussion. A possible comparison group would be professional athletes from a different, less aggressive, lower impact sport (e.g., baseball or basketball), in an effort to speak to the potential physical health issues of professional sports not associated with concussion. While the appropriateness of such a control group is open to debate, it is undeniable that obtaining a group of football players who had never been concussed would be virtually impossible as North American-style football is widely regarded as a collision sport and the most violent team sport played in the world. For instance, the g-forces absorbed by these athletes from collisions with

other players and within the field of play itself has been discussed in terms of Newtonian physics and biomechanics (e.g., Barth et al., 2001, Guskiewicz et al., 2007a, Guskiewicz et al., 2007b). For example, prefacing with the fact that a motor vehicle accident resulting in "irreparable brain injury" is associated with acceleration forces as low as 30 g (Barth et al., 2001), the fact that the average g-force resulting in a concussion is 102.8 g (Guskiewicz et al., 2007a, Guskiewicz et al., 2007b) provides compelling evidence to suggest that concussive head impacts are capable of producing significant effects on neurophysiological processes and cognitive function. Also, Barth et al (2001) raised the critical question of whether exposure to repeated high-impact forces can lead to permanent brain damage. The current study contributes to the growing literature by demonstrating that repeated exposure to such forces does lead to permanent neurocognitive dysfunction in many individuals.

5.2. EEG assessment

Two players from the rCFL group reported comorbid health concerns that may have affected the results. Specifically, one CFL veteran had been diagnosed with rheumatoid arthritis and chronic pain, while another with chronic pain and depression. Both chronic pain and depression have been shown in previous studies to alter EEG results (e.g., Kewman et al., 1991, Dick et al., 2003, Sumich et al., 2006). The player who reported being diagnosed with rheumatoid arthritis and chronic pain had been prescribed Amitriptyline; a drug shown to have no effect on ERP outcomes (Veldhuijzen et al., 2006). In contrast, the player diagnosed with depression was prescribed Duloxetine; a drug used to treat major depressive disorder (MDD) and chronic pain (Brannan et al., 2005) that one study has shown to reduce ERP amplitudes (Xu et al., 2012). All other medications prescribed to various members of the rCFL group are not known to significantly affect ERP data. Lastly, there were three participants in the rCFL group who sustained their last concussion after retiring from professional football. Accordingly, we re-ran our analyses excluding these three participants; however, our ERP and behavioural outcomes remained unchanged. Even with these caveats that this study shares to varying degrees with the entire literature, the findings in this study demonstrate clearly the enduring effects of concussions on brain function years – and in some cases – decades later.

5.3. ImPACT and Self-Reported inventories

As noted above, our use of the ImPACT assessment procedure was not able to use the normative database provided with the ImPACT due to the norms not including information for participants as old as some of our former CFL players. To overcome this predicament, we compared ImPACT results between the rCFL and healthy age-matched control groups in order to provide a within-study database against which we could compare our ImPACT results for the rCFL players. Finally, each of our behavioural assessments (PCSS, BDI II, and SF-36) were self-reported in nature and, as a result, fall victim to personal bias, subjectivity and even deceit. However, that acknowledgment serves to emphasize the drawback associated with all behaviorally-based methods and demonstrates the importance and need for objective data that stands above behaviorally-based assessment tests.

6. Conclusion

The current study provides a comprehensive neurofunctional examination of former professional North American football players using event-related potential technology and a wide range of behavioral assessments. One of the most compelling take-away messages from this investigation is that the well-documented symptoms involving problems of attention and memory are clearly demonstrated in the P300 component both in terms of its amplitude (reduced) and its latency (delayed). However, the most revealing finding from this study is that an even earlier manifestation of attention-related activity that also reflects an early form of memory formation, the mismatch negativity (MMN), was also found to be reduced in amplitude. In contrast to the P300, the MMN occurs in the absence of conscious awareness of the deviant stimuli in the auditory stimulus sequence. In other words, the MMN represents an automatic pre-conscious-awareness response reflecting early attention and memory-related template formation (Näätänen et al., 2007). The discovery of abnormalities in the professional football veterans represents an entirely new level of documented dysfunction in those who have experienced multiple concussions and blows to the head. It remains to be determined if similar effects are observed after single or reduced numbers of concussions and whether the concept of a safe return to play is tenable.

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Authors Disclosure Statement

None of the authors have potential conflicts of interest to be disclosed.

Tables

Table 1
Individual and mean values of rCFL group's age, years of education, number of sustained concussions, number of years since last concussion, and number of years played professionally.

rCFL Demographics					
Player	Age	#Yrs of Educ. (Excl. Kindergarten)	# Concussions	# Yrs Since Last Concussion	# Yrs Played
1	62	14	7	14	12
2	45	17	1	13	13
3	60	17	2	32	13
4	59	16	2	36	11
5	54	16	4	7	1
6	48	18	2	27	3
7	63	15	11	31	10
8	63	19	3	36	14
9	57	19	2	33	5
10	48	18	8	2	5
11	64	16	6	38	4
12	61	17	2	37	3
13	47	18	3	16	9
14	64	16	3	36	11
15	66	18	4	39	6
16	53	15	2	31	5
17	57	17	3	34	1
18	66	16	1	45	11
19	58	15	11	27	12
Average	**57.63**	**16.68**	**4.05**	**28.11**	**7.84**

Table 2
Computerized neurocognitive ImPACT assessment tool means, standard deviations, degrees of freedom (df), t-values (*T*), and p-values (*P*) of composite scores for each category, as well as means, standard deviations, t-values, and p-values of the PCSS, BDI II, and SF-36 category scores for both the retired CFL (rCFL) and Control groups.

Symptomatology Scores					
Assessment	Control Mean (SD)	rCFL Mean (SD)	*df*	*T*	*P*
Post-Concussion Symptom Scale**	3.11 (5.78)	14.05 (11.88)	35	3.45	<0.01**
Beck's Depression Inventory II**	2.39 (2.83)	8.53 (7.21)	35	3.37	<0.01**
SF_36 Health Scores					
Category	Control Mean (SD)	rCFL Mean (SD)	*df*	*T*	*Bonf. Corrected P*
Physical Function	81.94 (28.56)	78.15 (19.21)	35	0.47	>0.00625
Limit. due to Physical Health	98.61 (5.89)	88.15 (23.46)	35	1.79	>0.00625
Limit. due to Emotional Health	98.15 (7.86)	80.70 (36.38)	35	1.94	>0.00625
Energy/Fatigue	70.83 (11.79)	62.63 (20.22)	35	1.47	>0.00625
Emotional Well-being	86.89 (6.83)	77.68 (18.28)	35	1.96	>0.00625
Social Function*	97.22 (5.35)	78.29 (23.59)	35	3.24	<0.00625*
Pain*	83.89 (18.49)	61.45 (20.67)	35	3.42	<0.00625*
General Health	79.72 (12.77)	72.11 (16.08)	35	1.56	>0.00625
ImPACT Scores					
Category	Control Mean (SD)	rCFL Mean (SD)	*df*	*T*	*Bonf. Corrected P*
Verbal Memory	82 (10.80)	77.42 (10.43)	35	1.31	>0.00833
Visual Memory	63.83 (14.46)	63.32 (12.38)	35	0.12	>0.00833
Motor Speed	34.19 (6.95)	30.74 (4.66)	35	1.77	>0.00833
Reaction Time	0.75 (0.15)	0.79 (0.16)	35	0.69	>0.00833
Impulse Control	1.44 (1.38)	1.89 (1.48)	35	0.94	>0.00833
Cognitive Efficiency Index	0.13 (1.17)	0.03 (0.23)	35	1.48	>0.00833

Notes:
a) SF_36 and ImPACT Scores are Bonferoni Corrected.
b) Bonferonni Alpha Calculation: 0.05/Number of Categories.
* Indicates Significance Between Groups <0.05.
** Indicates Significance Between Groups <0.01.

Table 3
Between-group differences of amplitude and latency for the N1 and MMN within the MMN Protocol, as well as the N1, N2b, P3a, and P3b within the P300 Protocol after Greenhouse–Geisser corrections for multiple comparisons were applied.

MMN Protocol				P300 Protocol							
N1 Amplitude				**N1 Amplitude**				**P3a Amplitude**			
Effect	*df*	*F*	*P*	*Effect*	*df*	*F*	*P*	*Effect*	*df*	*F*	*P*
Group	35	5.74	<0.05*	Group	35	1.88	>0.05	Group	35	6.34	<0.05*
Group:Condition	105	2.19	>0.05	Group:Condition	105	105	>0.05	Group:Condition	70	0.16	>0.05
Group:Region	280	2.96	>0.05	Group:Region	280	280	>0.05	Group:Region	280	1.15	>0.05
N1 Latency				**N1 Latency**				**P3a Latency**			
Effect	*df*	*F*	*P*	*Effect*	*df*	*F*	*P*	*Effect*	*df*	*F*	*P*
Group	35	0.8	>0.05	Group	35	0.12	>0.05	Group	35	1.24	>0.05
Group:Condition	105	0.79	>0.05	Group:Condition	105	0.25	>0.05	Group:Condition	70	1.01	>0.05
Group:Region	280	0.26	>0.05	Group:Region	280	0.83	>0.05	Group:Region	280	0.92	>0.05
MMN Amplitude				**N2b Amplitude**				**P3b Amplitude**			
Effect	*df*	*F*	*P*	*Effect*	*df*	*F*	*P*	*Effect*	*df*	*F*	*P*
Group	35	10.01	<0.01**	Group	35	5.08	<0.05*	Group	35	8.08	<0.01**
Group:Condition	70	5.98	<0.01**	Group:Condition	70	4.91	<0.05*	Group:Condition	70	1.06	>0.05
Group:Region	280	1.59	>0.05	Group:Region	280	0.42	>0.05	Group:Region	280	1.43	>0.05
MMN Latency				**N2b Latency**				**P3b Latency**			
Effect	*df*	*F*	*P*	*Effect*	*df*	*F*	*P*	*Effect*	*df*	*F*	*P*
Group	35	0.85	>0.05	Group	35	0.75	>0.05	Group	35	15.32	<0.01**
Group:Condition	70	1.24	>0.05	Group:Condition	70	0.1	>0.05	Group:Condition	70	3.28	>0.05
Group:Region	280	0.42	>0.05	Group:Region	280	0.85	>0.05	Group:Region	280	0.22	>0.05

Note: ":" denotes an Interaction.
* Indicates Significance Between Groups < 0.05.
** Indicates Significance Between Groups < 0.01.

Figures

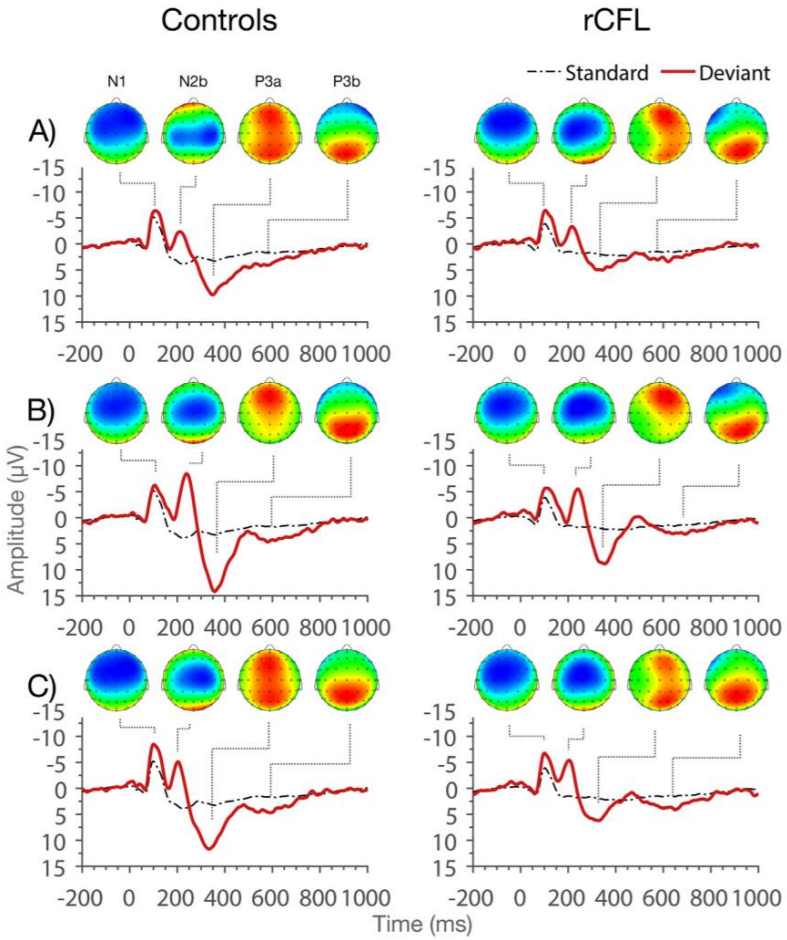

Fig. 1. Grand-averaged P300 protocol waveforms and their respective scalp distributions recorded at Cz, evoked by target stimuli, for each group (Controls Left, rCFL Right). (A): N1, N2b, P3a, and P3b components evoked in the Frequency condition. (B): N1, N2b, P3a, and P3b components evoked in the Duration condition. (C): N1, N2b, P3a, and P3b components evoked in the Intensity condition.

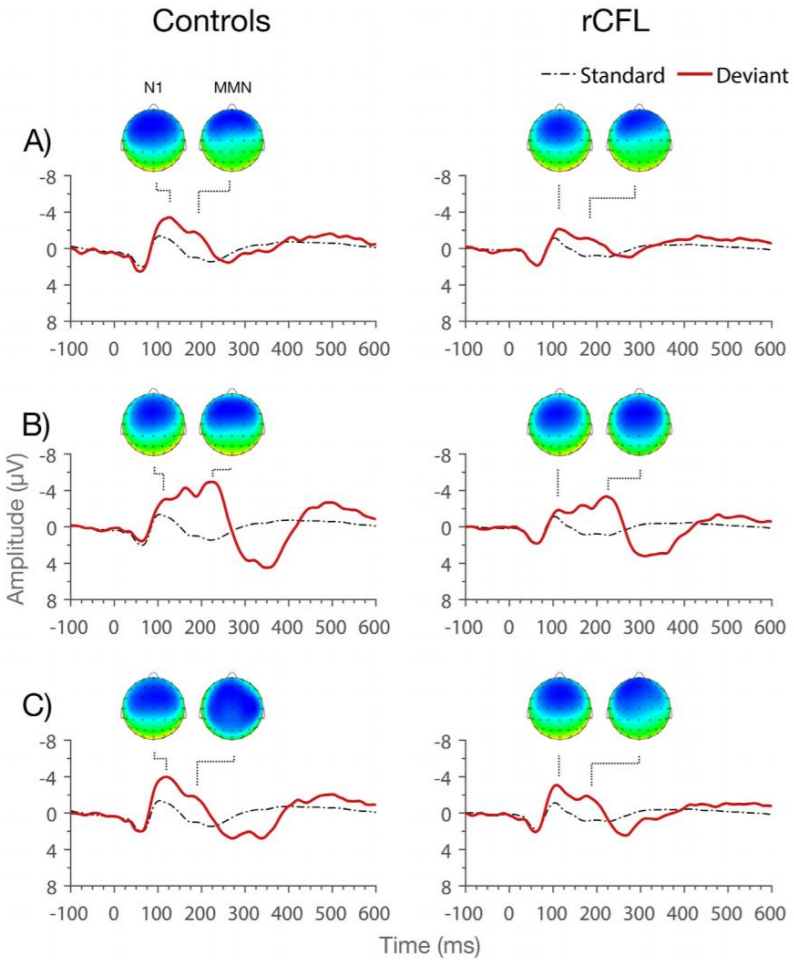

Fig. 2. Grand-averaged MMN protocol waveforms and their respective scalp distributions recorded at Cz, evoked by target stimuli, for each group (Controls Left, rCFL Right). (A): N1 and MMN components evoked in the Frequency condition. (B): N1 and MMN components evoked in the Duration condition. (C): N1 and MMN components evoked in the Intensity condition.

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Chapter 3

Abstract

Objective: The present study sought to determine: 1) whether concussed adolescents exhibited deficits in neurocognitive functioning as reflected by neurophysiological alterations; 2) if neurophysiological alterations could be linked to supplementary data such as the number of previous concussions and days since injury; and 3) if deficits in psychological health and behavioural tests increased during diagnosis duration.

Methods: Twenty-six concussed adolescents were compared to twenty-eight healthy controls with no prior concussions. Self-report inventories evaluated depressive and concussive symptomatology, while behavioral tests evaluated cognitive ability qualitatively. To assess neurophysiological markers of cognitive function, two separate auditory oddball tasks were employed: 1) an active oddball task measuring executive control and attention as reflected by the N2b and P300, respectively; and 2) a passive oddball task assessing the early, automatic pre-conscious awareness processes as reflected by the MMN.

Results: Concussed adolescents displayed delayed N2b and attenuated P300 responses relative to controls; showed elevated levels of depressive and concussive symptomatology; scored average-to- low-average in behavioral tests; and exhibited N2b response latencies that correlated with number of days since injury.

Conclusion: These findings demonstrate that concussed adolescents exhibit clear deficiencies in neurocognitive function, and that N2b response latency may be a marker of concussion recovery.

Keywords: concussion, mTBI, event-related potentials, EEG, adolescence, recovery

Highlights:

- A neurophysiological response reflective of executive processing has been linked to concussion recovery

- Concussed adolescents demonstrate increased deficits in attention and executive control
- Presents the first report of event-related potential deficits in acute cases of concussion in the adolescent population

1. Introduction

Concussion has been defined as a consequence of traumatic biomechanical forces resulting in a complex pathophysiological process of biochemical changes in the brain (McCrory et al., 2009; Zhang et al., 2016). Affecting over 3 million people annually in the United States alone (Langlois et al., 2006; Broglio et al., 2009; Daneshvar et al., 2011; Kraus et al., 2016), concussions have been shown to affect behavior, cognition, and neurophysiological function negatively (Collins, et al., 1999; Ellemberg et al., 2009; DeKosky et al., 2010; Kraus et al., 2016).

Recently, the effects of concussion within the adolescent population have garnered increased attention (Reddy et al., 2008; Grady, 2010; Master et al., 2012; Zhang et al., 2016) with a recent meta-analysis revealing that the largest increase of concussion incidence occurs in the adolescent population (Zhang et al., 2016). Adolescence, a period in human growth where significant changes in cognition, behaviour, and brain development occur (Blakemore & Choudhury, 2006), may be a time where both concussion incidence (Zhang et al., 2016) and neurological harm (Baillargeon et al., 2012) are maximal. Clearly, a better understanding of the neurophysiological effects of concussion on this population is in order.

In an effort to investigate the effects of concussion in adolescence, early research has focused primarily on behavioural measures such as self-report symptom inventories, behavioral tests, and neuropsychological assessments (e.g., Lovell et al., 2003; Hinton-Bayre, 2012; Echemendia et al., 2013). For instance, a study investigating memory dysfunction using the Immediate Post Assessment Concussion Tool (ImPACT) revealed that recently concussed high school athletes demonstrated significant deficits in memory function up to 7 days post injury (Lovell et al., 2003). Furthermore, a study evaluating the age-related differences associated with concussion between adolescent and young-adult populations revealed that adolescent athletes are more susceptible to prolonged concussion effects (Field et al., 2003). These findings identify the detrimental behavioral effects of concussion; however, they fail to objectively identify any associated neurophysiological damage. Accordingly, in addition to behavioural measures, there is a need for objective measurement of the effects of concussion using, for example,

neurophysiological recordings when assessing the effects of concussion in adolescent populations.

Event-related potentials (ERPs), averaged neurophysiological brain responses in electroencephalographic (EEG) recordings time-locked to stimulus presentation (Polich., 2007; Polich., 2012; Amin et al., 2015), have proven their value in assessing the neurophysiological effects associated with concussion in adult populations (e.g., Gaetz et al., 2000; De Beaumont et al., 2009; Broglio et al., 2011; Baillargeon et al., 2012; Gosselin, et al., 2012; Ruiter et al., 2019). Traditionally, ERP literature has focused on previously concussed populations, whether symptomatic (i.e., chronic) or asymptomatic. Participants' date of injury to date of testing ranges on average from 1.7 months (Lavoie et al., 2004) to approximately 30 years (De Beaumont et al., 2009; Ruiter et al., 2019). However, in almost 90% of cases, concussion symptoms resolve within 21 days (McKeon et al., 2013); thus, it is interesting to note that, to date, there has not been a group-wise ERP study investigating the acute effects (≤ 21 days) of concussion in symptomatic adolescent participants.

Generally, ERP research on concussion employs an active "oddball" (Donchin et al., 1978) protocol (e.g., Rugg et al., 1988; Gosselin et al., 2006; Ruiter et al., 2019). This protocol has been utilized to examine the effects of concussion on two ERP components in particular: the P300 and the N2b (e.g., Gaetz et al., 2000; Broglio et al., 2009; De Beaumont et al., 2009; Broglio et al., 2011; Baillargeon et al., 2012; Ruiter et al., 2019). The N2b is generated from the anterior cingulate cortex (ACC) (Huster et al., 2010) - an area associated with executive function and other executive-related cognitive processes (Carter et al., 1999; MacDonald et al., 2000). The N2b is a negative-deflecting neurophysiological response peaking ~200 ms post stimulus onset and characterized by a fronto-central scalp distribution linked to response inhibition, response conflict monitoring, and executive control (Boksem et al., 2005; Folstein & Van Petton., 2008; Broglio et al., 2009). Research has demonstrated attenuated N2b responses in adult concussed populations relative to healthy controls (Broglio et al., 2009), reflecting cognitive dysfunction in both response inhibition and executive control.

The P300 is a positive-deflecting neurophysiological response peaking ~275ms to 700ms post stimulus onset (Polich, 2007). Depending on the cognitive tasks performed, the P300 has been shown to be sensitive to attention (Gray et al., 2004), memory (Polich., 2007), and cognitive workload (Allison et al., 2008). Concussion literature has predominantly investigated the modulation of the P3b component. The P3b has a centro-parietal scalp distribution that appears ~300 to 700 ms post stimulus onset (Baillargeon et al., 2012), and reflects attentional and working memory processes (Polich., 2007). The P3b has been shown repeatedly to be reduced and/or delayed in the adult concussion literature, thus, demonstrating its utility in assessing the pathological neurophysiological effects associated with concussion (e.g., Dupuis et al., 2000; Lavoie et al., 2004, De Beaumont et al., 2009; De Beaumont et al., 2012).

To date, only one study has used ERPs to identify the neurophysiological deficits resulting from concussion in an adolescent population. Baillargeon et al (2012) found significantly attenuated P3b responses in asymptomatic concussed adolescents (ages 13-16) approximately 6 months post-injury compared to healthy age-matched controls. In addition, only the adolescent group, relative to the child (ages 9-12) and adult (ages 18+) concussed groups, scored worse in the behavioural working memory task. Their study concluded that the adolescent group was most susceptible to working memory deficiencies following a concussion as reflected by both neurophysiological and neuropsychological evidence. This research supports the notion that concussion is likely to disrupt frontal lobe function; the brain region commonly associated with working memory (Thompson-Schill et al., 2002).

The Mismatch Negativity (MMN) is another component studied extensively in traumatic brain injury research (e.g., Doltrozzo et al., 2007; Fischer et al., 2010; Morlet and Fischer, 2014; Blain-Moraes et al., 2016). The MMN, a negative-deflecting ERP occurring ~150-200ms post stimulus onset (Näätänen et al., 1978) that reflects an automatic attention function linked to a predictive coding process (Garrido et al., 2008) requiring a conscious state but not awareness (Atienza et al., 2005; Fischer et al., 2010; Dykstra and Gutschalk, 2015). Like the P300, the MMN is elicited in an oddball paradigm; however, unlike the P300, the MMN does not require active attention to be evoked. Historically, the MMN has been used solely in what can be characterized as “catastrophic” brain injury populations (e.g., coma, vegetative state, minimally

conscious state). It was not until recently that the MMN was investigated in a concussed population and found to be significantly reduced in retired professional football players who had sustained their last concussion almost 30 years earlier (Ruiter et al., 2019); demonstrating the efficacy of the MMN in evaluating the long-lasting neurophysiological deficits of mild traumatic brain injuries (mTBI) such as concussion. However, the MMN has not been investigated in recently-concussed populations.

This study builds on research demonstrating neurophysiological abnormalities reflective of the cognitive consequences of concussion. In particular, it contributes to the small literature on adolescent concussion by extending the breadth of cognitive functions - and their neurophysiological manifestations - being assessed. It was hypothesized that amplitude reductions and/or latency delays would be seen in each of the assessed ERP components for the concussed participants compared to controls. Specifically, the present study investigated a full range of neurophysiological responses associated with memory, executive control, and attention by examining the MMN, N2b, and P300 components. To align with previous literature, the ImPACT, Child Depression Inventory (CDI), and Post-Concussion Symptom Scale (PCSS) were administered to gain a better understanding of symptom levels and behavioral functions associated with the concussed participants. The present study extends previous literature by being the first study to utilize ERPs to investigate the neurophysiological effects associated with symptomatic, acutely concussed adolescent participants, in addition to being the first to examine the MMN in an acutely concussed population.

2. Results

2.1 Demographic, Behavioral, and Symptomatology results

Results from the demographic data revealed that the concussed group's average age was 15.04, that they had sustained on average 1.88 previous concussions, and had participated in EEG testing on average 20.15 days after sustaining their most recent concussion (Table 1). According to ImPACT normative data, the results revealed that female concussed participants scored "Low-Average" in Verbal Memory, Visual Memory, and Motor Speed, as well as "Borderline" (almost "Impaired") in Reaction time (Table 2). Male concussed participants, on the other hand, scored "Average" in Verbal Memory and Visual Memory, "Low-Average" in Motor Speed, and

"Borderline" in Reaction Time (Table 2). Normative values for Impulse Control and CEI scores were unavailable. Furthermore, on average, the concussed group scored 55.08 in concussive symptomatology and 56.07 in depressive symptomatology; demonstrating elevated levels of concussion symptoms and "Slightly above average" levels of depression according to the CDI.

2.2 Neurophysiological results

2.2.1 MMN Protocol (automatic attention)

When examining the waveforms and topographies in the MMN protocol (Fig. 1), N1 waveforms can be seen across groups and conditions with clear topographical differences between the groups and across conditions. Response amplitudes, in particular, differed between groups as reflected by the fact that when data were scaled based on the N1 exhibited by the control group, the N1 representation in the concussed group was not observable – an effect seen most clearly in the topographies of the response (thus, note scaling differences for the two groups in Figure 1). MMN responses to stimulus onset revealed no discernible differences between groups. However, a drastic size difference between the two conditions was seen where the FT condition had significantly smaller amplitudes compared to the DT condition. Between the two groups, MMN scalp distributions in the FT condition showed a typical fronto-central distribution in the control group, whereas a more frontal-exclusive representation can be seen in the concussed group.

A Group main effect ($P < 0.01$) and a Group X Region interaction reflected the significantly reduced N1 amplitudes observed in the concussion group ($P < 0.01$). Post-hoc analyses of the interaction emphasized the pervasiveness of the amplitude effect in the concussion sample with significant differences observed across all 9 ROIs for each condition: L-F ($F(1, 52) = 14.68$, $P < 0.01$); M-F ($F(1, 52) = 16.21$, $P < 0.01$); R-F ($F(1, 52) = 10.65$, $P < 0.01$; L-C ($F(1, 52) = 14.11$, $P < 0.01$); M-C ($F(1, 52) = 15.52$, $P < 0.01$); R-C ($F(1, 52) = 7.64$, $P < 0.01$); L-P ($F(1, 52) = 5.55$, $P < 0.05$); M-P ($F(1, 52) = 11.01$, $P < 0.01$); and R-P ($F(1, 52) = 7.10$, $P < 0.01$). Further, a Group X Region interaction ($P < 0.01$) in N1 latency was observed where specific ROIs M-P ($F(1, 52) = 4.93$, $P < 0.05$) and R-P ($F(1, 52) = 6.37$, $P < 0.05$) were found to be significantly delayed in the concussed group. No significant amplitude or latency effects were observed for the MMN.

2.2.2 P300 Protocol/N2b (voluntary attention, memory, response inhibition/conflict monitoring)
The P300 oddball protocol evoked multiple ERP components differentially associated with sensory/perceptual and cognitive processes (Fig. 2). An observational summary of the findings shows a clear N1 sensory/perceptual response with a typical fronto-central distribution for both groups in each condition (Fig. 2A, B). In contrast to the similarity between groups for the N1 – a fundamentally sensory response – the cognitive responses exhibited a range of contrasts between adolescents who had been concussed and the healthy control population. The N2b differed markedly across groups and conditions in two different ways. In the FT condition, while typical N2b amplitudes can be seen in both groups, the response occurred significantly later (~ 25 ms) in the concussed group. Furthermore, N2b responses in the DT condition were larger than those in the FT condition, with no visually-discernible differences between the two groups in either amplitude or latency. While the two groups exhibited very similar fronto-central distributions for the N2b in the DT condition, a more prominent frontal distribution was observed in the FT condition for the concussed group.

In terms of the late positivities, clear P3b responses were observed in both groups and in both conditions. However, while the distribution of the response in the control population was widespread in both conditions, the distribution exhibited in the concussed group showed a more centro-parietal distribution. Lastly, a late positive component (LPC) was found in the 500-700 ms in the control group for each condition, with the response being larger in the DT condition. The concussed group also exhibited a LPC in both the DT and FT conditions; however, the response had a more concentrated parietal distribution compared to the control group's more centro-parietal distribution. In addition, notable differences between the two groups can be seen in the topographies (Figure 2A, B).

Within the P300 protocol, statistical analyses (See Table 4) revealed no main effect for either amplitude or latency for the N1; however, a significant Group X Region interaction in latency ($P < 0.01$) was observed. Post-hoc analysis revealed a delayed response latency in the M-F region ($F(1, 52) = 4.30$, $P < 0.05$). A main effect of Group was found for the N2b where response latencies within the concussed group were significantly delayed ($P < 0.05$). Additionally, there

was a Group X Condition interaction ($P < 0.05$) where post-hoc analysis determined that response latencies within the FT condition were attributable to slower response latencies in the concussed group compared to the controls ($F(1, 52) = 11.68$, $P < 0.01$). Moreover, a Group X Region interaction ($P < 0.01$) was revealed where the response latencies in the L-C ($F(1, 52) = 9.22$, $P < 0.01$), L-F ($F(1, 52) = 11.61$, $P < 0.01$), L-P ($F(1, 52) = 5.03$, $P < 0.05$), M-C ($F(1, 52) = 7.99$, $P < 0.05$), M-F ($F(1, 52) = 10.82$, $P < 0.01$), and R-F ($F(1, 52) = 8.56$, $P < 0.01$) ROIs were found to be significantly slower in the concussed group relative to the control group. Although no main effect was found for N2b amplitude a Group X Region interaction was observed ($P < 0.01$). Post-hoc analysis revealed significantly smaller amplitudes in L-F ($F(1, 52) = 4.71$, $P < 0.05$) and R-F ($F(1, 52) = 5.69$, $P < 0.05$) regions in the concussed group.

A main effect of group ($P < 0.01$) was found for P3b amplitudes reflecting the concussed group's significantly attenuated response amplitudes compared to the control group. Additionally, a Group X Region interaction ($P < 0.01$) was found with post-hoc analyses showing significantly reduced amplitudes in the L-C ($F(1, 52) = 5.65$, $P < 0.05$), L-F ($F(1, 52) = 10.91$, $P < 0.01$), M-F ($F(1, 52) = 11.22$, $P < 0.01$), R-C ($F(1, 52) = 10.79$, $P < 0.01$), and R-F ($F(1, 52) = 18.17$, $P < 0.01$) ROIs. No effects of P3b latency differences were observed. Finally, a Group X Region interaction ($P < 0.01$) for the LPC was found in the 500 to 700 ms time window; an effect reflecting the significantly decreased amplitudes for the concussed group at frontal ROIs [L-F ($F(1, 52) = 5.92$, $P < 0.05$), M-F ($F(1, 52) = 7.37$, $P < 0.01$), and R-F ($F(1, 52) = 10.8$, $P < 0.01$)].

2.3 Post-hoc correlational analyses

A series of simple linear regression analyses applied to the demographic data demonstrated that N2b latencies in the FT condition within the aggregated frontal regions (L-F, M-F, R-F) were trending towards significance to the number of days since last concussion ($F(1, 24) = 3.73$, $P = 0.06$, $R2 = 0.13$). However, when applying the analysis to aggregated M-F and R-F ROIs exclusively, results revealed that number of days since last concussion was predictive of N2b latency ($F(1, 24) = 5.08$, $P < 0.05$, $R2 = 0.17$). This finding reveals that as the number of days since concussion increased, N2b response latencies decreased, ($B = -0.57$, $P < 0.05$). Furthermore, age was predictive of N2b latency ($F(1, 24) = 4.47$, $P < 0.05$, $R2 = 0.16$). Thus,

N2b response latencies decreased as a function of age ($B = -4.49$, $P < 0.05$). Accordingly, both age and days since injury were predictive of N2b latency in the concussed population. Finally, behavioral and symptom scores in the concussion group did not correlate significantly with the neurophysiological data.

2.4 Subset Neurophysiological Results

Separate analyses were conducted on the 17 concussed participants who sustained their concussion less than 21 days (average 12) before date of testing. The delayed N2b response latencies for the concussed group compared to controls remained significant ($F(1, 43) = 4.84$, $P < 0.05$). Also a Group X Condition interaction ($F(1, 43) = 6.51$, $P < 0.05$) revealed slower response latencies in the FT ($F(1, 43) = 10.44$, $P < 0.01$) condition for the concussed group. Statistical analyses of this subset yielded similar results to what is reported above for those over 21 days (except for the P3b amplitude main effect.

2.5 Subset post-hoc correlational analyses

A series of simple linear regression analyses were also calculated on the subset of 17 concussed participants who sustained their last concussion < 21 days prior to testing. The subset (17) group results revealed that number of previous concussions remained unrelated ($P > 0.05$) to N2b latency. Also, days since last concussion was significantly correlated to N2b latency ($F(1, 15) = 5.11.03$, $P < 0.05$, $R2 = 0.25$). Thus, like in the entire concussed group, as the number of days since concussion increased, the N2b response latencies decreased ($B = -1.88$, $P < 0.05$). Interestingly, age was no longer found to be significantly correlated to N2b response latency ($P > 0.05$). In summary, both age and days since concussion were predictive of N2b response latencies in the entire (26) concussed group, while only days since injury was found to be significant in the subset (17) group. Regressions were not calculated on the 9 participants who sustained their injury > 21 days at the time of testing as no main effect was found between the 9 subjects and the control group.

3. Discussion

3.1 Behavioural Findings

The concussed adolescent group self-reported numerous symptoms and high levels of symptom severity on the PCSS. Common symptoms included: headaches, sadness, difficulty concentrating, difficulty remembering, sensitivity to light and noise, and feelings of emotional instability. These results demonstrated the physical and emotional toll those who have recently sustained a concussion endure on a day-to-day basis until recovery, and are aligned with prior findings (e.g., Ryan & Warden., 2003; Lucas., 2011; Covassin et al., 2013). CDI results revealed that the concussed adolescents had higher average levels of depressive symptomatology than neurologically healthy controls; a finding that previous work has shown clearly in adolescence (Chrisman et al., 2014) and other age groups (Chen et al., 2008; Kontos et al., 2012; Strain et al., 2013).

Behavioral results as assessed by the ImPACT proved unconvincing. The adolescent group performed at low-average to average levels in all categories except Reaction Time (RT), where both male and female results revealed what is referred to as a Borderline score (Table 2). Poor RT performance has been shown repeatedly to be a common impairment in concussed populations (Warden et al., 2001; Eckner et al., 2010; Kontos et al., 2012); however, it is noteworthy that other behavioral scores associated with performance such as Verbal and Visual Memory, and Motor Speed were unaffected. This finding may be attributable to behaviourally manifested cognitive deficits returning to pre-concussion performance in as little as 5 to 10 days post injury despite other lingering symptoms (Johnston et al., 2001).

3.2 Neurophysiological Findings

The neurophysiological data demonstrated the neurocognitive consequences associated with concussion. The data obtained in the P300 protocol was particularly clear in demonstrating differences between the healthy control participants and those adolescents who had sustained a concussion with the latter showing significantly delayed N2b latencies and reduced P3b amplitudes.

The N2b, a response associated with inhibitory executive functions (Heil et al., 2000), such as response inhibition and conflict monitoring (Folstein & Van Petten, 2008), has been shown in previous literature to be affected by concussion (Broglio et al., 2009). In the present study, a significant delay of ~25 ms was found in the N2b response latency for the concussed adolescent group providing evidence of a disruption in executive control processes - a finding complementary to previous concussion research (Howell et al., 2013). This N2b response delay in the concussed group was also seen in the subset containing only those group members who sustained their concussion ≤ 21 days prior to testing. Results such as these add to the evidence that claims of symptom resolution in 90% of concussion cases within 21 days (McCrea et al., 2003; Guskiewicz et al., 2003; McKeon et al., 2013; inter alia) are dependent on how symptoms are assessed or measured. Some of the neurophysiological manifestations of cognitive dysfunction after concussion clearly are capable of lasting years (e.g., De Beaumont et al., 2009; Ruiter et al., 2019). However, the current data set suggests that some measures, such as the neurophysiological marker for executive function employed in this study, may reveal a recovery trend that begins within the 21-day window but also continues (meaning that symptoms had not yet resolved) when data from up to 58 days is included.

Post-hoc regression analyses on the N2b data sets provided an additional layer of insight on relating the neurophysiological responses of the concussed group to their demography, symptomatology, and behavioral data. Specifically, days since injury was found to be predictive of N2b response latencies as was, in a marginally nonsignificant effect, age. When the complete sample of concussed participants was considered, N2b latencies decreased as the number of days since concussion increased. Similarly, N2b latencies decreased as a function of age. No effects on the N2b were found as a function of number of concussions; although the total number of prior concussions was less than 2 per person and the range of prior concussions was 0 – 6 and clearly skewed.

When similar linear regression analyses were conducted on the subsample of 17 concussed participants who were tested within 21 days of their injury, results were comparable to the larger analysis with all of the concussed participants, with decreases in N2b latencies being significantly related to an increased number of days since the time when they sustained their

concussions. This relationship between decreased N2b latencies with increased number of days since being concussed in this subsample was not accompanied by a significant relationship with age.

Although there is evidence demonstrating that both amplitude and latency decrease with increasing age (e.g., Amenedo et al., 1998; Lamm et al., 2006; for a review; Lewis et al., 2006) there is a wealth of evidence that is either contradictory or more nuanced. For example, the literature provides evidence indicating that N2b latency continues to shorten in healthy population samples over time until maturity at ~25 years of age (Arain et al., 2013) at which point, response latencies become more delayed as age increases. Lamm et al. (2006) found latency decreases across a small age span (ages 7 – 16 yrs) – a finding that can then be integrated with Amenedo et al.'s (1998) evidence to provide a trajectory of N2b latency across an age span overlaps with some of the participants in the current study. In contrast, to these findings of shortening latencies until young adulthood, other work has provided compelling evidence that N2b latency remains unaffected between childhood and adolescence (e.g., Johnstone et al., 1996). The most important piece of information to remember is that the N2b latencies observed in the concussed group may have exhibited a decreasing latency related to time since injury but in all analyses, the latency of the concussed group remained significantly delayed even when compared to a slightly older control sample. If there was any type of age confound in the current study, we argue it was minimal as apparent by the age effect disappearing in the subset analysis.

Taken together the analyses of the neurophysiological response associated with the executive function(s) involved in the task used in this study revealed that while the concussed group exhibited significantly delayed latencies compared to the healthy controls, there remained a new discovery showing that as days since injury increased N2b response latency decreased. This result indicates that as recovery from concussion progresses, the N2b latency begins its return to time periods reflective of typical cognitive performance. It is particularly important to note that this effect remained significant in the subset of the concussed group tested within 21 days of their injury. This finding emphasizes the importance of this particular ERP component as a measure sensitive to the recovery of important cognitive functions; and also demonstrates its reliability in different sample sizes. These findings also emphasizes the utility of ERP

components as clinical state "trackers" of various cognitive functions after brain injury, as well as recovery of those functions. In the current investigation, the N2b latency stands out as being able to track neurophysiological markers of cognitive abnormalities associated with concussion and subsequent improvement over time.

The P3b reduction found in the present study is consistent with previous concussion literature (Lavoie et al., 2004; Theriault et al., 2009; Baillargeon et al., 2012) and provides further evidence that specific neurophysiological markers of attention and working memory function can track commonly reported cognitive symptoms of concussion (Gronwall., 1989; Broglio et al., 2009; Theriault et al., 2011; Ozen et al., 2013).

Our previous study observed both a P3a and P3b response (Ruiter et al., 2019). In contrast, the present study interpreted the current findings as being a different pairing of responses, a P3b and LPC complex – due primarily to differences in response topographies. In the DT condition of the earlier study, both the concussed and control participants exhibited typical fronto-central topographies characteristic of the P3a. However, in the present study, both the FT and DT conditions in each group revealed scalp topographies characteristic of P3b responses (Fig. 2A, B). In addition, the LPC reflected a type of recollected information process that appeared in a continuous memory-based processing task of button presses to more (the standard) or less (the deviants) frequently occurring stimuli. Within this context, the current findings can be seen as reflecting decisional factors including accuracy of response decisions and, in particular, confidence in response selection (Finnigan et al., 2002). The response did not differ between the two groups, but was not seen at all in the prior study and has not been reported in the primarily adult concussion literature. As a result, the role of the LPC in concussion remains to be determined.

The P3b amplitude reduction found in the present study is consistent with the extensive literature reporting smaller P300 amplitudes associated with concussion (Lavoie et al., 2004; Theriault et al., 2009; Baillargeon et al., 2012); and the current study provides further evidence that specific neurophysiological markers of attention and working memory function can track commonly reported symptoms of cognitive dysfunctions linked to concussion (Gronwall., 1989; Broglio et

al., 2009; Theriault et al., 2011; Ozen et al., 2013). P3b amplitudes were most notably smaller than those of controls at frontal and central topographical locations.

Amplitudes of the LPC at frontal sites were found to be significantly reduced when compared with controls (Fig. 2A, B). Uncovering a LPC in the current study was not anticipated but fits other aspects of the observed data in its reflection of executive function as well as its consequent abnormality in concussed individuals. Based on work examining late positivities and executive functions including work on the frontal selection positivity (FSP) (Kenemans et al., 1993) and the frontal P3 (P3f) (Makeig et al., 1999) (see Perri & Di Russo, 2017 for review), what we refer to as a LPC occurs in the context of memory functions and decision structures that are, like FSP and P3f, linked to executive functions. In the current context, the LPC reflected a type of recollected information process that appeared in a continuous memory-based processing task of button presses to more (the standard) or less (the deviants) frequently occurring stimuli. Within this context, the current findings can be seen as reflecting decisional factors including accuracy of response decisions and, in particular, confidence in response selection (Finnigan et al., 2002).

The hypothesis for the current study, based on Ruiter et al. (2019) that the MMN would differ between the two groups was not supported. This failure to replicate the first examination of the MMN in older individuals with a history of multiple concussions is important. Like the N2b and LPC effects found in the present study, the failure to identify differences in the MMN represents a new piece of information in the examination of concussion from a neurophysiological perspective. The current study is the first examination of the MMN in an acute concussion adolescent population just as our examination of the MMN in the earlier study was the first examination of the response in an adult concussion population. Putting together these two novel sets of data highlights that 1) the older population with a history of many concussions and repeated blows to the head (Ruiter et al., 2019) exhibited abnormalities in the MMN while, 2) the adolescent population with fewer than two previous concussions showed no MMN abnormalities at all. These two facts raise the question of whether concussion-related MMN abnormalities represent a biomarker for having reached the point of irreversible neurophysiological and cognitive dysfunction; or, might MMN abnormalities occur earlier at some mid-point between the two samples we have tested and thus serve as a warning of an impending point of

irreversibility. To answer this question an examination of the MMN in concussion is needed in different age groups and with different histories of concussion incidences.

4. Conclusion

In summary, the present study provides a detailed investigation of neurophysiological markers of cognitive dysfunction in concussion as manifested in acutely injured adolescents. The findings of this study highlight the range of cognitive dysfunctions consequent to concussion as reflected by the MMN, N2b, P300 (P3b) and the LPC. The results also support and extend previous literature in demonstrating the unreliability of subjective psychological health tests and evaluations.

The current study provides evidence for possible markers of recovery processes with the finding that N2b response latencies changed (decreased) toward more normal response times as days since injury increased; a finding indicating that decreasing N2b latencies and associated cognitive improvements in executive control, appear to be a marker of, or a prognostic for, concussion recovery. Also, the absence of automatic attention abnormalities (as manifested by the MMN) in this adolescent population contrasts sharply with earlier findings we observed in individuals with more significant and longer histories of concussion. This finding suggests that the MMN abnormalities seen in concussion could serve as a potential marker of irreversible cognitive dysfunction linked to concussion. This proposal could be more than hypothetical given recent positron emission tomography work demonstrating higher tau levels in brain regions affected by chronic traumatic encephalopathy (CTE) (Stern et al., 2019) including brain regions associated with neural populations known to generate the MMN (Alho, 1995; Jemel et al., 2002; Opitz et al., 2002).

5. Methods and Materials

5.1 Participants

Twenty-six (26) adolescent (19 Females [ages: 13-17; μ: 15.4]; 7 Males [ages: 13-16; μ: 14]) patients diagnosed at the McMaster Children's Hospital with a concussion, were compared to 28 healthy control (23 Females [ages: 17-21; μ: 19.2]; 5 Males [ages: 19-22; μ: 19.6]) participants with no prior history of concussion. The study was approved by the local ethics board and all participants provided informed consent in accordance with the ethical standards of the

Declaration of Helsinki prior to study participation. All participants were native English speakers and self-reported as having no hearing issues.

5.2 Demographic data

Collected through participant self-reporting, the demographic data consisted of each participant's sex and age for both the control and concussed groups, while concussed participants also reported number of previous concussions, and number of days since the most recent concussion to the date of the EEG testing (Table 1).

5.3 Behavioral Tests

The ImPACT was administered to the concussed population prior to EEG testing (Table 2). The ImPACT is a computerized neurocognitive test designed to measure sports-related concussions (Iverson et al., 2003). It is comprised of 6 independent tests providing 5 composite scores (Verbal Memory, Visual Memory, Motor Speed, Reaction Time, and Impulse Control) and a Cognitive Efficiency Index (CEI) score. Scores for the ImPACT were compared against age and gender matched normative data (percentiles) provided by the developers (Iverson et al., 2003).

5.4 Self-Reported Symptomatology Inventories

The PCSS and CDI (Kovacs, 1992) were used to evaluate concussion and depression symptomatology, respectively (Table 3). The PCSS was used to measure the severity of concussive symptoms such as: fatigue, headaches, and sensitivity to light and noise, whereas, the CDI was used to assess depressive symptoms exclusively.

5.5 EEG Task, Stimuli, & Experimental Conditions

5.5.1 P300 – Active

The first protocol employed a P300 active auditory oddball task consisting of 4 tones: 1) Standard Tone (ST, 1000 Hz, 80 dB SPL [sound pressure level], 50 ms duration), 2) Frequency Tone (FT, 1200 Hz, 80 dB SPL, 50 ms), 3) Duration Tone (DT, 1000 Hz, 80 dB SPL, 100 ms), and Intensity Tone (ID, 1000 Hz, 90 dB SPL, 50 ms). Due to technical issues, responses to IT (presented 6% of the time) were discarded from all analyses in this study. The ST was presented 492 times (82% of the stimulus set) while the deviant tones (FT and DT) were presented 36

times each (12% [6% each] of the stimulus set). Tones within the protocol had an inter-stimulus interval (ISI) of 1000 ms. Throughout the duration of the protocol, participants were asked to left-click to every ST and right-click to every deviant tone to ensure they were actively attending to the presented stimuli; response side was counterbalanced within participants.

5.5.2 MMN – Passive

The second protocol administered was a longer version of the same auditory oddball task used in the P300 protocol; however, participants were instructed to ignore the tones and to focus solely on the visually-neutral silent film presented on the screen in front of them. This protocol was designed to elicit automatic attention /predictive coding processes manifested by the MMN. The ST was presented 1968 times (82% of the stimulus set) while the deviant tones were presented 144 times each (12% [6% each] of the stimulus set). Tones within the protocol had an ISI of 500 ms.

To create a distraction between the two oddball tasks, the protocols were separated by a 10-minute language comprehension task where participants judged the semantic congruity of spoken sentences.

5.6 Procedure

Prior to EEG testing, all participants completed the Edinburgh Handedness Inventory (Oldfield, 1971) and a general pre-screen form regarding characteristics such as age, sex, and general medical history, while the concussed group also completed the ImPACT, PCSS, and CDI.

Participants wore noise-cancelling headphones while seated in a comfortable chair facing a computer screen in a sound-attenuated room. In the first protocol, participants were instructed to look at a fixation cross located in the center of the computer screen while they actively listened - and differentially responded - to a series of standard and deviant tones. In the second protocol, participants were instructed to focus solely on a visually-neutral silent film, and that the auditory tone sequence being presented during the film was of no importance to the study. The experiment took approximately 50 minutes.

5.7 Neurophysiological Recordings

EEG data were recorded online from 64 Ag/AgCl active electrodes (BioSemi ActiveTwo system) inserted into a flexible cap in accordance with the International 10-20 System. Analog data were recorded at 0.01–100 Hz bandpass and digitized at a sampling rate of 512 Hz with a 60 Hz notch filter. Five Ag/AgCl external electrodes were placed on the nose, each mastoid, as well as above and beside the outer canthus of the left eye. Using the same bandpass and sampling rate, eye movements (electrooculography) were recorded from the two external electrodes placed near the left eye. During EEG acquisition, data were referenced to the DRL (driven right-leg) and were subsequently re-referenced offline to the linked (averaged) mastoids.

5.8 EEG Data Analysis

EEG data were analyzed offline using Brain Vision analyzer (v2.01) software. Data were filtered with a bandpass of 0.1-30 Hz (24 dB/oct). After filtering and removal of segments containing artifacts not related to eye movements, ocular Independent Component Analysis (ICA) was applied to correct for vertical and horizontal eye movements. Data from the P300 protocol were segmented into -200 ms pre-stimulus and 1000 ms post-stimulus onset intervals for all experimental conditions. Similarly, data from the MMN protocol were segmented, changing the interval to -200-600 ms. Following segmentation, data were averaged per condition for each protocol. Only correct responses from the P300 protocol were used for analysis.

Difference waves were calculated only for the MMN by subtracting standard condition ERPs from each of the deviant condition ERPs. For both protocols, automatic peak detection (Barr et al., 1978) was performed within the respective time windows of each ERP component: N1 (75 – 125 ms), N2b (170 – 270 ms), and the P300 (275 – 700 ms) for each condition (ST, FT, and DT) in the P300 protocol, and on the N1 (75 – 125 ms) and the MMN (150 – 250 ms) in the MMN protocol.

5.9 Statistical Analysis

5.9.1 Demographic, Behavioral, and Symptomatology Data

Average age, number of previous concussions, and the average number of days since concussion at the

time of EEG testing were tabulated (Table 1) as were average behavioral test scores (Table 2), and levels of concussive and depressive symptomatology (Table 3).

5.9.2 EEG Data

Nine Regions of Interest (ROIs) were created by clustering electrodes from left (L), midline (M), and right (R) locations with frontal (F), central (C), and parietal (P) positions from the available 64 electrodes creating Frontal (R–F, M–F, L–F), Central (R–C, M–C, L–C), and Parietal (R–P, M–P, L–P) areas (Ruiter et al., 2019). Mixed-effects analyses of variance (ANOVAs) were performed for each ERP and condition for both amplitude and latency with an alpha level of $P < 0.05$. To minimize Type 1 errors, all ANOVAs used Greenhouse-Geisser adjusted degrees of freedom (Greenhouse & Geisser, 1959). Peak amplitude was acquired by taking the average value in a -50 ms to +50 ms time-window around the detected peak; latency was defined as the time from stimulus onset to the maximal point (positive or negative depending on the ERP component) within the defined component windows. Statistical analyses were conducted using R statistical software (R, Version 3.3.3)

5.9.3 Correlational analyses

When ANOVAs revealed a main effect of concussion between the two groups, subsequent linear regressions were calculated to assess the relationship between the concussed populations' ERP components' amplitudes and/or latencies and their behavioral, symptom, and demographic data (Baillargeon et al., 2012). All statistical analyses were conducted using R statistical software (R, Version 3.3.3).

5.9.4 Investigating acutely concussed subset

Despite the average days since concussion being less than 21, there were 9 concussed adolescent participants who were tested after 21 days post-injury (6 Females [ages: 13-17; μ: 15.83]; 3 Males [ages: 13-16; μ: 13.67]). Accordingly, an additional analysis with the same steps as described above were conducted on the 17 remaining participants who had sustained their concussion an average of 12 days prior to testing (13 Females [ages: 13-17; μ: 15.23]; 4 Males [ages: 13-16; μ: 14.25]).

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Authors Disclosure Statement

None of the authors have potential conflicts of interest to be disclosed.

Tables

Table 1

Concussed Participant Demographic Data					Control Participant Demographic Data		
Participant	Sex	Age	# of Previous Concussions	# Days Since Last Concussion	Participant	Sex	Age
1	F	17	6	36	1	F	19
2	F	16	0	20	2	F	20
3	F	13	1	5	3	F	19
4	M	14	2	23	4	F	19
5	M	13	2	30	5	F	21
6	M	16	2	7	6	F	21
7	F	17	2	14	7	F	20
8	F	16	6	8	8	F	19
9	F	15	1	17	9	M	19
10	F	15	1	9	10	F	19
11	F	17	1	17	11	F	19
12	M	13	5	14	12	F	21
13	F	15	1	13	13	F	21
14	F	17	4	15	14	M	22
15	F	17	3	30	15	F	20
16	F	13	0	7	16	F	20
17	F	13	1	8	17	F	19
18	M	15	2	19	18	M	19
19	F	17	1	12	19	M	19
20	M	14	1	58	20	F	17
21	F	14	0	30	21	M	19
22	F	17	2	39	22	F	19
23	F	16	2	26	23	F	18
24	F	14	1	6	24	F	17
25	M	13	1	13	25	F	17
26	F	14	1	48	26	F	19
AVERAGE	[redacted]	**15**	**1.88**	**20.15**	27	F	18
[redacted]					28	F	20
					AVERAGE	[redacted]	**19.29**

Table 1: Individual and mean values of age and sex for both the control group and concussed adolescent group, as well as the number of previous concussions and days since last concussion for the concussed adolescent group.

Table2

Concussed Participant ImPACT Mean Scores (Female)							
Participant	**Age**	**Verbal Memory**	**Visual Memory**	**Motor Speed**	**Reaction Time**	**Impulse Control**	**CEI**
1	17	81	64	32.33	0.91	5	0.3
2	16	66	60	28.55	0.7	9	0.12
3	13	83	49	28.73	0.74	11	0.24
7	17	67	59	28.33	0.68	6	0.17
8	16	72	89	35.95	0.65	10	0.17
9	15	91	79	29.67	0.7	4	0.53
10	15	96	88	35.98	0.54	1	0.5
11	17	98	65	30.17	0.76	2	0.34
13	15	69	57	23.95	0.73	14	0.29
14	17	98	77	42.93	0.61	3	0.53
15	17	74	61	41.28	0.61	16	0.48
16	13	79	68	32.9	0.59	22	0.26
17	13	99	63	31.33	0.71	2	0.42
19	17	72	56	39.08	0.69	3	0.2
21	14	67	63	26.55	0.77	7	0.19
22	17	91	50	36.7	0.71	2	0.32
23	16	47	31	18.23	0.99	1	0.19
24	14	67	58	33.17	0.76	9	0.2
26	14	84	81	36.55	0.6	9	0.27
AVERAGE	**15.42**	**79**	**64.11**	**32.23**	**0.71**	**7.16**	**0.3**
Concussed Participant ImPACT Mean Scores (Male)							
4	14	91	82	26.85	0.66	12	0.3
5	13	51	55	20.9	0.91	0	0.14
6	16	84	84	28.38	0.67	5	0.26
12	13	89	88	24.8	0.72	4	0.39
18	15	99	95	42	0.66	2	0.42
20	14	70	55	22.13	0.82	7	0.12
25	13	83	88	38.33	0.84	10	-0.1
AVERAGE	**14**	**81**	**78.14**	**29.06**	**0.75**	**5.71**	**0.22**

Table 2: Concussed adolescent group mean ImPACT assessment composite scores for each category (Female upper; Male lower).

Table 3

Table 3

Concussed Group Concussive and Depressive Symptom Scores		
Participant	**PCSS Total Score**	**CDI Total Score**
1	109	71
2	55	68
3	54	68
4	20	76
5	64	49
6	33	57
7	35	46
8	94	52
9	92	67
10	67	51
11	50	46
12	101	63
13	41	43
14	24	58
15	58	46
16	17	43
17	12	47
18	46	44
19	53	62
20	55	49
21	59	68
22	60	71
23	80	67
24	55	63
25	32	46
26	66	55
AVERAGE	**55.08**	**56.07**

Table 3: Individual and mean values of PCSS and CDI scores for the concussed adolescent group.

Table 4

Table 4

MMN Protocol				P300 Protocol							
N100 Amplitude				N100 Amplitude				P3b Amplitude			
Effect	df	F	P	Effect	df	F	P	Effect	df	F	P
Group	52	13.13	< 0.01*	Group	52	0.24	> 0.05	Group	52	7.17	< 0.01*
Group:Condition	52	0.01	> 0.05	Group:Condition	52	0.1	> 0.05	Group:Condition	52	0.09	> 0.05
Group:Region	416	8.49	< 0.01*	Group:Region	416	1.89	> 0.05	Group:Region	416	8.03	< 0.01*
N100 Latency				N100 Latency				P3b Latency			
Effect	df	F	P	Effect	df	F	P	Effect	df	F	P
Group	52	0.39	> 0.05	Group	52	0.04	> 0.05	Group	52	0.01	> 0.05
Group:Condition	52	2.19	> 0.05	Group:Condition	52	0.29	> 0.05	Group:Condition	52	3.95	> 0.05
Group:Region	416	7.05	< 0.01*	Group:Region	416	3.64	< 0.01*	Group:Region	416	2.06	> 0.05
MMN Amplitude				N2b Amplitude				LPC Amplitude			
Effect	df	F	P	Effect	df	F	P	Effect	df	F	P
Group	52	0.16	> 0.05	Group	52	1.85	> 0.05	Group	52	2.2	>0.05
Group:Condition	52	0.04	> 0.05	Group:Condition	52	0.01	> 0.05	Group:Condition	52	0.5	> 0.05
Group:Region	416	1.1	> 0.05	Group:Region	416	7.15	< 0.01*	Group:Region	416	6.06	< 0.01*
MMN Latency				N2b Latency				LPC Latency			
Effect	df	F	P	Effect	df	F	P	Effect	df	F	P
Group	52	0.05	> 0.05	Group	52	6.6	< 0.05*	Group	52	0.02	> 0.05
Group:Condition	52	0.14	> 0.05	Group:Condition	52	5.11	< 0.05*	Group:Condition	52	3.25	> 0.05
Group:Region	416	0.68	> 0.05	Group:Region	416	6.7	< 0.01*	Group:Region	416	0.79	> 0.05

Note: ":" denotes an Interaction

* Indicates Significance Between Groups < 0.05

Table 4: Between-group differences of amplitude and latency (Greenhouse–Geisser corrections applied). Left: N1 and MMN within the MMN Protocol. Right: N1, N2b, P3b, and LPC within the P300 Protocol.

Figures

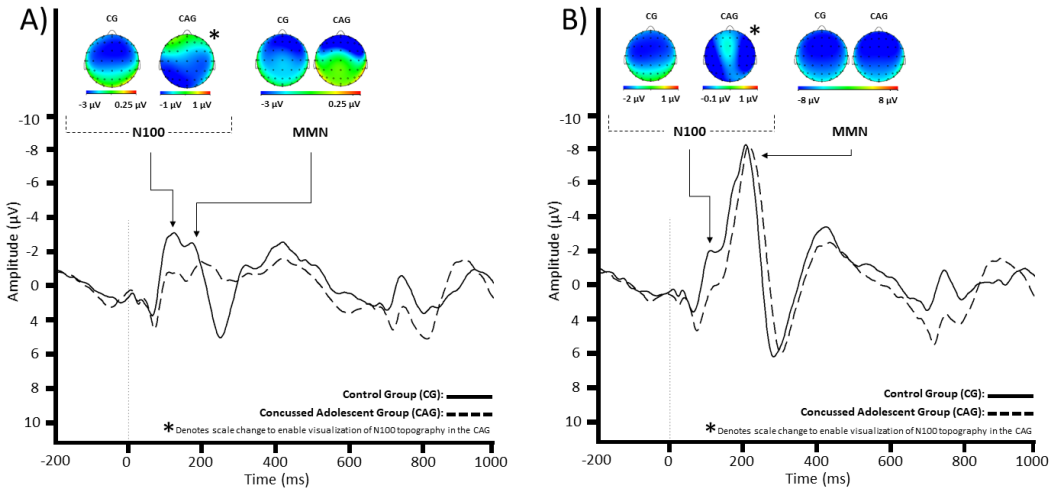

Figure 1: Grand-averaged MMN protocol waveforms and their respective scalp distributions recorded at Cz, in response to target stimuli, for each group (Control group: solid line; Concussed adolescent group: dotted line). (A): N1 and MMN components evoked in the Frequency condition (FT). (B): N1 and MMN components evoked in the Duration condition (DT).

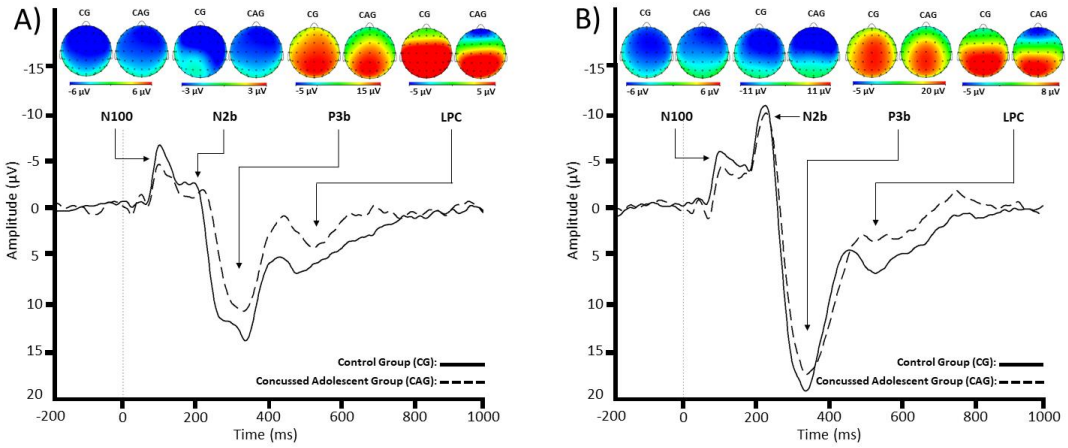

Figure 1: Grand-averaged P300 protocol waveforms and their respective scalp distributions recorded at Cz, in response to target stimuli, for each group (Control group: solid line; Concussed adolescent group: dotted line). (A): N1, N2b, P3a, and P3b components in response to the Frequency condition (FT). (B): N1, N2b, P3b, and LPC components in response to the Duration condition (DT).

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Chapter 4

Abstract

Objective: Numerous studies have demonstrated negative consequences of concussion on brain health. The present study sought to measure the cognitive functioning of concussed adolescents by evaluating: 1) whether neuropsychological health and behavioral function would improve as days since injury increased; 2) whether neurophysiological alterations reflective of neurocognitive dysfunction would occur; 3) whether observed neurophysiological alterations would improve as days since injury increased; and 4) whether those neurophysiological improvements prove effective in tracking concussion recovery.

Methods: Twenty-eight healthy controls were compared to nineteen concussed adolescents. Concussed adolescents were tested twice, where the test results were compared between Test 1 and Test 2, as well as each test being independently compared to the control group. Concussive and depressive symptoms were assessed using self-report inventories and the King Devick measured cognitive function. An active auditory oddball task was employed to assess neurophysiological markers pertaining to cognitive functions specific to executive control and attention as reflected by the N2b and P3b, respectively.

Results: In Test 1, concussed adolescents demonstrated delayed and attenuated N2b responses, as well as attenuated P3b responses relative to controls. In Test 2, N2b responses returned to normative values, while P3b alterations remained. From Test 1 to Test 2, concussed adolescents showed improvements in behavioral function, as well as concussive and depressive symptomatology.

Conclusion: These findings demonstrate compelling evidence of: 1) the effectiveness of the N2b response in both concussion detection and tracking recovery; and 2) the likelihood of the P3b being reflective of non-transient neurophysiological damage.

Keywords: concussion, mTBI, event-related potentials, EEG, adolescence, recovery

Introduction

The largest increase of concussion incidence occurs in adolescence (Zhang et al., 2016), a period in human growth where research has shown concussions may be the most harmful (Baillargeon et al., 2012). Concussion, a consequence of biomechanical forces resulting in biochemical changes in the brain (McCrory et al., 2016), has been demonstrated repeatedly to alter cognitive function (Guskiewicz et al., 2005; Baillargeon et al., 2012; Kraus et al., 2016; Ruiter et al., 2019a). However, despite recent progress in identifying neurophysiological deficits associated with concussion (e.g., Broglio et al., 2009; De Beaumont et a., 2009; Baillargeon et al., 2012; Kraus et al., 2016; Ruiter et al., 2019), little has been done to track recovery at the neurophysiological level.

Recently, clinical applications have begun to move beyond traditional symptomatology reports and pencil-and-paper tests to more advanced methods of physical and neurophysiological measures such as eye-movement and resting-state electroencephalography (EEG) diagnosis aids (Heitger et al., 2009; Prichep et al., 2013). However, despite both methods showing promise in the diagnostic and identification aspect of concussion, to date, neither has been revealed capable of tracking recovery. Accordingly, an objective, neurophysiological measure of concussion-recovery tracking remains unavailable in today's clinical environments.

Event-related potentials (ERPs) are one such promising method of quantifying cognitive function at the neurophysiological level. ERPs are averaged electrophysiological responses time-locked to stimulus presentation in EEG recordings (Polich., 2007; Polich., 2012), reflective of core cognitive domains. Research has proven ERPs to be effective in measuring concussion effects in both acute and chronic (Post-concussion syndrome (PCS)) patients (e.g., De Beaumont et al., 2012; Fickling et al., 2019). In addition, ERPs are uniquely capable of identifying the persistent neurocognitive consequences of concussion long after symptom resolution (Broglio et al., 2009; De Beaumont et al., 2009; Baillargeon et al., 2012; Ruiter et al., 2019a). This ability to measure concussion effects at multiple time points gives rise to the preliminary hypothesis that ERPs are an effective tool in tracking concussion recovery.

The N2b and P3b are two ERPs used extensively in measuring the neurocognitive effects of concussion. The P3b, a positive deflecting response that appears ~300 to 700 ms post stimulus onset, is reflective of attentional and working memory processes (Polich., 2007). The N2b is a negative-deflecting neurophysiological response peaking ~200 ms post stimulus onset linked to response inhibition and executive control (Broglio et al., 2009). Both the P3b and N2b have been shown repeatedly to be affected by concussion — consequently reflecting cognitive dysfunction in memory, attention, and executive control (e.g., Dupuis et al., 2000; Lavoie et al., 2004, Broglio et al., 2009; De Beaumont et al., 2009; De Beaumont et al., 2012; Ruiter et al., 2019a).

This is the first longitudinal study designed to track concussion at the neurophysiological level from diagnosis (acute) to post-acute in an adolescent population. It was hypothesized that amplitude alterations and/or latency delays would be observed in the assessed ERP components for the concussed patients relative to controls for the first EEG session, and that those differences would improve by the second EEG session — subsequently demonstrating within-subject ERP response improvement between the two sessions. The present study investigated executive control, attention, and memory as reflected by the N2b and P3b. The Child Depression Inventory (CDI), King-Devick (KD), and Post-Concussion Symptom Scale (PCSS) were also administered at each EEG session to track symptom levels and behavioral functions over time.

Materials & Methods

Participants

Nineteen (19) adolescent (15 Females [14.93 years old]; 4 Males [13.5 years old]) patients diagnosed at the McMaster Children's Hospital with a concussion were tested initially in the acute stage of the injury (<21 days), then subsequently 4.85 months (148 days) later (Table 1). The 19 concussed adolescents were a subset of a previous study we conducted (Ruiter et al., 2019) containing 26 participants. Twenty-eight (28) healthy control (23 Females [19.2 years old]; 5 Males [19.6 years old]) participants with no prior history of concussion were the comparison group for both testing sessions. The study was approved by the local ethics board and all participants provided informed consent in accordance with the ethical standards of the

Declaration of Helsinki prior to study participation. All participants in the present study self-reported as having no hearing issues.

Demographic, Behavioral, and Symptom data

Demographic data (Table 1) consisted of participants' sex and age for both the control and concussed groups. Concussed participants also reported number of previous concussions and date of injury. The KD, a concussion-specific behavioral task based on rapid number naming speed (see Galletta et al., 2011), was administered to the concussed population prior to each EEG testing session. The PCSS and CDI were also administered prior to each EEG testing session to evaluate concussion and depression symptomatology, respectively (Table 1).

EEG Task, Stimuli, & Experimental Conditions

A P300 active auditory oddball task consisting of 3 tones (Frequency [FT], Duration [DT], Intensity [IT]) as described in Ruiter et al. (2019a) was employed. To ensure participants were actively attending to the presented stimuli, they were asked to right-click to each deviant tone and left-click to every standard tone (ST); button presses were counterbalanced within participants. Due to technical issues, only two deviant tones (FT and DT) were used in the analyses.

Procedure

All participants completed a general pre-screen form (age, sex, general medical history, etc.), while the concussed group also filled the self-reported inventories detailed above. Noise-cancelling headphones were used to present the auditory stimuli during EEG recording. Participants were instructed to actively listen - and differentially respond to the presented stimuli. Experiment duration was ~10 minutes.

Electrophysiological Recordings

EEG data were recorded at 0.01–100 Hz bandpass (and a 60 Hz notch filter) and digitized at a sampling rate of 512 Hz. In accordance with the International 10-20 System, data were recorded online from 64 Ag/AgCl active electrodes (BioSemi ActiveTwo system). Using the same bandpass and sampling rate, data were recorded from 5 Ag/AgCl external electrodes placed

above and beside the left eye, on the nose, and on each mastoid. Electrooculography (EOG) data were recorded from the two external electrodes placed near the left eye. Data were referenced online to the DRL (driven right-leg).

EEG Data Analysis

Offline, EEG data were re-referenced to the linked mastoids and filtered with a bandpass of 0.1-30 Hz (24 dB/oct). All artifactual segments were marked for removal using visual-inspection. Ocular Independent Component Analysis (ICA) was applied to correct for artifacts resulting from eye movements. Data were segmented into -200 ms pre-stimulus and 1000 ms post-stimulus onset intervals for each experimental condition. Data were baseline corrected, then averaged per condition for each protocol. Only correct responses were used for analysis. Automatic peak detection (Barr et al., 1978) was performed within the respective time windows of each ERP. Peak analyses were performed on the N2b (170 – 270 ms), and the P300 (275 – 700 ms) for each condition. EEG data were analyzed using Brain Vision Analyzer (v2.01).

Statistical Analysis

Demographic, Behavioral, and Symptomatology Data

We calculated the average age, number of previous concussions, number of days since concussion, behavioral test scores, and levels of concussive and depressive symptomatology (Table 1). Bonferroni corrected paired two-tailed t-tests were calculated on the KD, PCSS, and CDI results to measure changes, if any, between testing sessions.

EEG Data

Nine (9) independent Regions of Interest (ROIs) were created by clustering electrodes from left (L), midline (M), and right (R) positions with frontal (F), central (C), and parietal (P) positions from the available 64 electrodes creating Frontal (R–F, M–F, L–F), Central (R–C, M–C, L–C), and Parietal (R–P, M–P, L–P) independent scalp areas (Ruiter et al., 2019a). Peak amplitude values were obtained by taking the average value in a -50 ms to +50 ms time-window around the detected peak, while latency values were defined as the time from stimulus onset to maximal response. Analyses were performed using univariate mixed-effects analysis of variance

(ANOVAs) and adjusted using Greenhouse-Geisser (Greenhouse & Geisser, 1959) when the sphericity assumption was violated.

Results

Demographic, Behavioral, and Symptom results

The concussed group's average age was 14.63, they sustained on average 1.53 previous concussions, and after sustaining their most recent concussion they participated in their first EEG testing on average 17.53 days later, and their second 147.95 days (Table 1). PCSS and CDI scores decreased over time, revealing reduced symptomatology between the two test dates ($P < 0.05$). KD Time scores improved ($P < 0.01$) while KD Error scores did not ($P > 0.05$).

Electrophysiological results

Both the control and concussed groups exhibited clear electrophysiological responses to deviant (FT and DT) stimuli of the auditory oddball task (Figure 1). As observed in the control group, the concussed group had morphologically-typical N2b and P3b responses in both tests for each deviant; however, for Test 1, clear N2b attenuation and latency delays can be observed for the concussed group in both conditions. P3b responses also demonstrated a clear reduction relative to controls across conditions. In addition to the N2b and P3b, a Late Positive Component (LPC) can be seen for each group, with an attenuated response in the concussed group relative to the controls. In Test 2, N2b responses showed clear improvement in each condition, with the response returning to almost identical amplitude and latency in the DT condition. P3b responses, however, remained relatively unaffected between the two tests in each condition. Finally, the LPC had a clear improvement in the DT condition, however, it remained seemingly unaffected in the FT condition.

Test 1 vs. Controls

Statistical analyses (Table 2) revealed a main effect of Group for N2b latency, where responses were delayed in the concussed group relative to the controls ($P < 0.05$). Additionally, there was a Group X Condition interaction ($P < 0.05$), where post-hoc analysis showed slower response latencies in the concussed group within the FT condition ($P < 0.01$). A Group X Region

interaction ($P < 0.01$) was revealed where the response latencies in the L-C , L-F , M-C , M-F , and R-F ROIs were found to be slower in the the concussed group ($P < 0.05$). A main effect of Group was also observed for amplitude, where post-hoc analysis revealed a Group X Region interaction ($P < 0.01$) where L-C , L-F , M-F , R-F , and R-C were found to be increased in the control group ($P < 0.05$).

A main effect of group ($P < 0.01$) was found for P3b amplitudes reflecting attenuated response amplitudes in the concussed group. A Group X Region interaction ($P < 0.01$) was found with post-hoc analyses showing reduced amplitudes in the L-C , L-F , M-C , M-F , R-C , and R-F ROIs ($P < 0.05$). No effects of P3b latency differences were observed. Finally, no main effect for LPC was found in the 500 to 700 ms time window; however, a Group X Region interaction ($P < 0.01$) was found where ROIs L-F , M-F , R-F, and R-C demonstrated increased amplitudes for the concussed group ($P < 0.05$).

Test 2 vs. Controls

No main effects were observed for the N2b between the second EEG testing and the control group. However, a Group X Region ($P < 0.01$) interaction was found for both N2b amplitude and latency, as well as a Group X Condition ($P < 0.05$) for amplitude. Post-hoc analyses failed to reveal any significant differences.

A main effect of P3b amplitude ($P < 0.01$) was observed between Test 2 and the control group. Additionally, a Group X Region interaction was revealed ($P < 0.01$) where ROIs L-F, M-F, R-F, L-C, and R-C were found to be reduced in the concussed group ($P < 0.05$). Finally, a Group X Region ($P < 0.01$) interaction for amplitude was found for the LPC where ROIs L-F, M-F, R-F, and R-C were found to be significantly attenuated in the concussed group.

Test 1 vs. Test 2

No differences were found between the two groups between the two testing sessions. However, a main effect of N2b latency was trending towards significance ($P < 0.1$).

Discussion

Behavioral Findings

PCSS scores (Table 1) dropped dramatically from Test 1 to Test 2, demonstrating a significant reduction in subjectively assessed symptom severity. In particular, 8 participants showed symptom resolution, 2 showed near symptom resolution (Score =< 6), 6 showed symptom improvement, and 3 failed to show improvement. These results are consistent with the notion that concussion recovery varies considerably on a per-patient basis (McCrea et al., 2003). Depression levels, as recorded from the CDI (Table 1), showed improvement from Test 1 to Test 2; a finding consistent with previous research demonstrating elevated levels of depression during injury in adolescence (Chrisman et al., 2014). Finally, KD-Time scores improved from Test 1 to Test 2, while KD-Error scores did not (Table 1). These findings are compatible with prior concussion research in adolescents (Tjarks et al., 2013).

Neurophysiological Findings

The neurocognitive consequences associated with concussion were observed in the N2b, P3b, and LPC revealing clear signs of cognitive dysfunction. Although not typically explored in concussion research, the aforementioned LPC can be seen clearly in the 500-700 range in the control group (Figure 1). Similar waveform morphology can also be observed in Tests 1 and 2 of the concussed group (Figure 1); however, the responses are noticeably more negative-going. Statistical anlyses support Figure 1 observations where frontal regions exhibited reduced amplitudes in Tests 1 and 2 of the concussed group relative to the controls. Previous literature has hypothesized the LPC may be reflective of decisional factors such as response accuracy and confidence in response selection (Finnigan et al., 2002; Ruiter et al., 2019b). However, the LPC has not been thoroughly explored in concussed populations and thus, requires further investigation.

P3b responses (Figure 1) were attenuated in the concussed group relative to the control group, reflecting difficulties in attention and working memory, consistent with previous research (e.g., Theriault et al., 2009; Baillargeon et al., 2012). Of particular interest, unlike the N2b, the P3b remained significantly reduced relative to the control group in both Test 1 and Test 2. This

finding is consistent with previous concussion literature where P3b responses were attenuated in those who sustained their last concussion as early as 1.7 months prior (Lavoie et al., 2004), to as late as 30 years earlier (De Beaumont et al, 2009; Ruiter et al., 2019a). The findings of the present study, and those of previous work, provide evidence that alterations in P3b amplitude are reflective of non-transient neurophysiological damage resulting from concussion; a conclusion drawn in numerous fields of neuroscience research. For example, Chronic Traumatic Encephalopathy (CTE) research supports the notion of permanent effects of concussion, where increased tau levels and substantial neurodegeneration are observed in those with concussion histories (McKee et al., 2009; Stern et al., 2019). Ultimately, the present study, among many others, provides compelling evidence that concussions permanently affect neurophysiology.

Relative to controls, the N2b showed significantly delayed and enlarged responses in Test 1 for the concussed group (Figure 1), findings that are consistent with previous research suggesting deficiencies in response inhibition and executive control (Moore et al., 2015). In addition, N2b responses demonstrated a clear improvement by Test 2 (Figure 1), as the responses were neither delayed, nor enlarged. Our statistical results support what Figure 1 illustrates, as the main effect of Group subsided from Test 1 to Test 2 for both amplitude and latency (Table 2). These results are consistent with prior research in both the adolescent (Moore et al., 2015) and adult (Ledwidge et al., 2016) concussed populations, and also suggest a degree of neurocognitive recovery, reflecting improvement of response inhibition and executive control.

Test 2 analyses provided an additional layer of insight on the neurophysiological responses of the concussed group. As was hypothesized, N2b response amplitudes and latencies were no longer found to be significantly different relative to the control group, demonstrating clear neurophysiological improvement. Additionally, the concussed group's N2b response latencies were trending towards significance ($P < 0.1$) from Test 1 to Test 2, suggesting improvements of executive control. These findings not only support the present study's hypothesis, but are also consistent with prior work (Ruiter et al., 2019b). Accordingly, as also demonstrated in previous work, N2b latency continues to standout as a potential biomarker to detect concussion and track recovery (Ruiter et al., 2019b).

The N2b appears to be particularly sensitive to concussion, where numerous studies have showcased its alteration at different timepoints since date of injury (Broglio et al., 2009; Moore et al., 2015; Ledwidge et al., 2016; Ruiter et al., 2019a; Ruiter et al., 2019b). However, to date, the relationship between the N2b and concussion remains inconsistent. There are, however, several probable reasons for this inconsistency: 1) differing modalities (visual vs. auditory), 2) task complexity (oddball vs. flanker/switch), 3) time since injury, and 4) age-range. To examine the interaction of these factors across different studies in the literature, 7 studies were considered, relaying varying amplitude and latency effects of the N200 or the N2b (Brush et al., 2018; Ruiter et al., 2019b). For example, two studies found reduced amplitude (Broglio et al., 2009; Ruiter et al., 2019a), three found increased amplitude (Moore et al., 2014; Moore et al., 2015; Ledwidge et al., 2016), three found increased latencies (Moore et al., 2015; Moore et al., 2016; Ruiter et al., 2019b), and two failed to find any alterations at all (Gaetz et al., 2000; Gosselin et al., 2012). Importantly, of the two studies that failed to find N2b alterations, one failed to explore frontal regions where the N2b is known to be maximal (Gaetz et al., 2000), and the other employed a working memory task more suitable for modulating the P3b (Gosselin et al., 2012), a component reflective of working memory processes. For a full review of the studies referenced, see Brush et al (2018).

Despite the considerable inconsistency in the literature, the point remains abundantly clear that the N2b is altered in concussed populations. Thus, it can be argued that what is actually lacking in concussion literature today is not the inconsistency of neurocognitive consequences as reflected by the N2b, but rather, the inconsistencies in experimental design, tasks employed, demography, and time since injury. However, the hypothesis of the current study, based on Ruiter et al., (2019b), that the concussed group would reveal delayed N2b response latencies, has held true; adding another layer of evidence linking the N2b to neurocognitive deficits associated with concussion.

ERP research investigating concussions tend to be in the frame of mind that all responses are reduced as a result of concussion. However, as mentioned above, recent research has revealed increased N2b amplitudes in concussed populations (Moore et al., 2014; Moore et al., 2015; Ledwidge and Molfese, 2016). In the present study, we hypothesize that the enlarged responses

observed are a combination of: 1) the acuteness of the injury; and 2) the age of the concussed demographic. To date, research has not investigated the effect of the N2b in acute populations and thus, we speculate the recency of the injury may result in the requirement of additional processing resources (cognitive reserve); an effect observed in fMRI concussion research where cognitively effortful tasks result in more neurological connections in concussed populations relative to controls (McAllister et al., 2001). Alternatively, previous research investigating the effects of the N2b in adult populations with concussion histories has found reduced N2b amplitudes (e.g., Broglio et al., 2009; Ruiter et al., 2019), while research exploring concussion effects in adolescent populations has found the opposite (Moore et al., 2015). Our results are therefore consistent with previous research, and we hypothesize that this effect may be a result of the considerable growth and development of the brain during adolescence; a time where the effects of concussion have been argued to be maximal (Baillargeon et al., 2012).

Limitations

The present study does have some limitations; in particular, the concussed and control groups differ in age. Although some research has suggested that N2b amplitude and latency decrease as a function of increasing age (Amenedo et al., 1998; Lamm et al., 2006), these findings are not reliably observed in the literature. For example, some research has indicated that N2b latency continues to shorten until maturity (~25 years old) (Arain et al., 2013), while other work found no alterations in the N2b from childhood to adolescence (Johnstone et al., 1996). Importantly, compared to controls, increased N2b latencies were observed in Test 1 of the concussed group of the present study. This increase in latency normalized in Test 2 and was trending towards significance in the Test 1 vs. Test 2 comparison. Therefore, the current interpretation of the data from this study remains that N2b responses are altered in acutely-concussed adolescents, but that responses improve over time and return closer to what can be considered “normal.” While there is a possibility of age impacting that result, we argue that to be improbable given the literature referenced.

Conclusion

The present study provides a comprehensive investigation into the neurocognitive dysfunctions attributable to concussion as reflected by the N2b, P3b, and LPC. Further, this is the first longitudinal study to provide compelling evidence for possible neurophysiological markers of cognitive recovery after the acute stage of concussion, while also corroborating with previous work suggesting concussions cause non-transient neurophysiological damage. Specifically, N2b responses improved as days since injury increased in both amplitude and latency; a finding reflective of improvements in executive control processes. These findings provide strong evidence to suggest that N2b responses are capable of both concussion identification and recovery-tracking in adolescent populations. Finally, P3b responses failed to improve over time, demonstrating not only prolonged issues of working memory and attention, but also the likelihood of irreversible neurophysiological damage, a conclusion formulated across many fields of neuroscience.

Figures

Figure 1 (Fz)

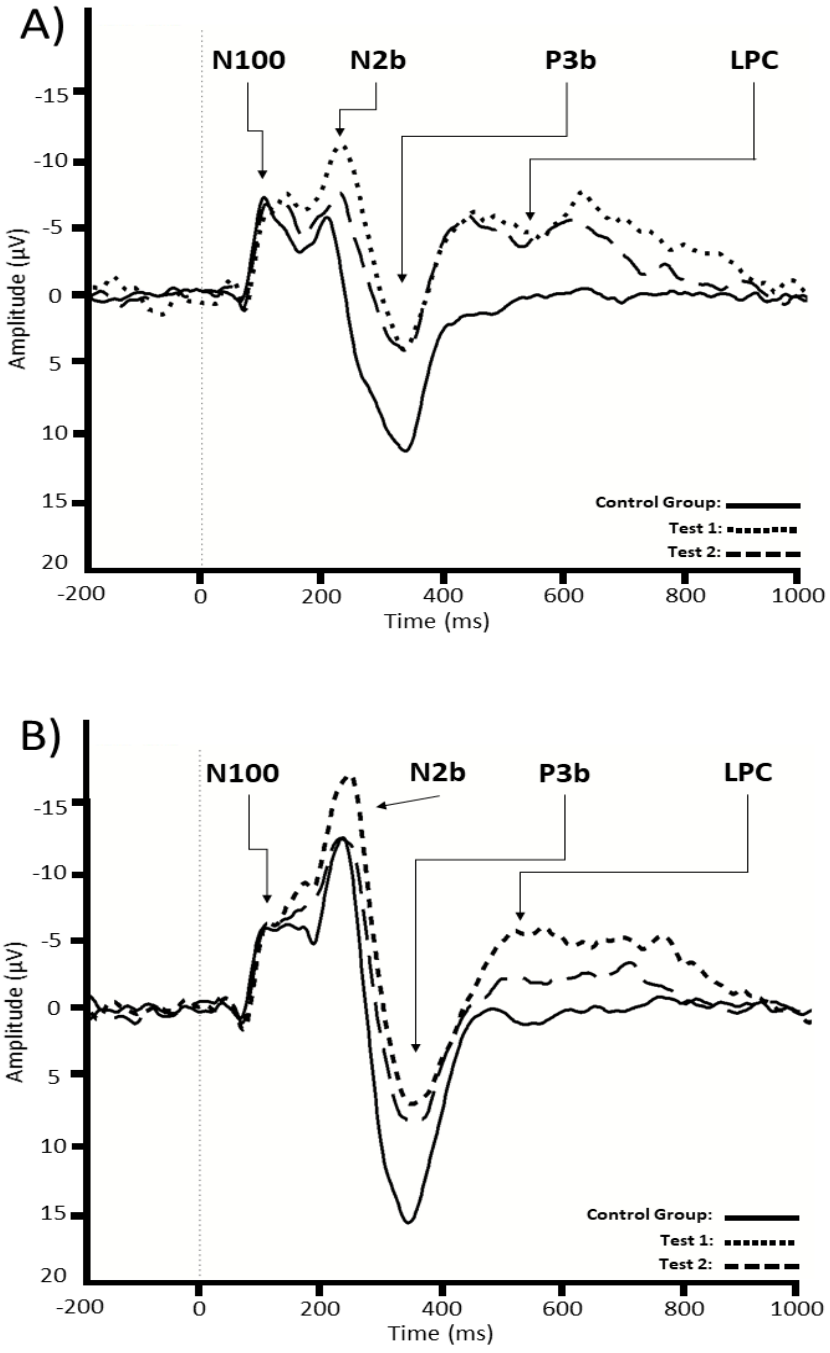

Figure 1: Grand-averaged waveforms recorded at Fz in response to target stimuli for each group (Control group: solid line; Test 1: dotted line; Test 2: dashed line) for Frequency (A) and Duration (B) conditions.

Tables

Table 1

Demography, Symptomatology, and Behavioral Results														
ID	**Sex**	**Symptom Resolution (Y/N)**	**Age**	**# of Previous Concussions**	**Test 1 Days Since Injury**	**Test 2 Days Since Injury**	**Test 1 PCSS**	**Test 2 PCSS**	**Test 1 CDI**	**Test 2 CDI**	**Test 1 KD-Time**	**Test 2 KD-Time**	**Test 1 KD-Error**	**Test 2 KD-Error**
1	F	N	16	0	20	225	55	54	68	59	47	33	0	0
2	F	N	13	1	5	121	54	17	68	68	60	56	22	0
3	M	Y	13	2	23	86	20	0	76	40	54	54	0	0
4	F	Y	17	2	14	139	35	0	46	40	73	57	0	0
5	F	Y	15	1	17	79	92	6	67	43	102	53	0	0
6	F	Y	15	1	9	211	67	0	51	41	60	49	0	0
7	F	Y	14	1	17	163	50	0	46	42	96	41	1	0
8	M	N	13	5	14	104	101	54	63	54	58	53	0	0
9	F	N	17	4	15	240	24	24	58	63	37	32	0	0
10	F	N	17	3	30	135	58	11	46	47	56	43	0	0
11	F	Y	13	0	7	98	17	0	43	40	48	40	0	1
12	F	Y	13	1	8	85	12	0	47	40	61	57	0	5
13	M	N	15	2	19	187	46	31	44	49	60	53	0	0
14	F	N	17	1	12	180	53	20	62	66	59	49	0	1
15	F	N	14	0	30	172	59	82	68	76	48	56	1	1
16	F	N	16	2	26	174	80	46	67	55	132	69	0	2
17	F	Y	14	1	6	181	55	0	63	42	45	37	0	0
18	M	Y	13	1	13	113	32	0	46	49	39	36	0	0
19	F	Y	13	1	48	118	66	3	55	52	45	40	0	1
Average			14.63	1.53	17.53	147.95	51.37	18.32	57.05	50.84	62.11	47.79	1.26	0.58
Cross-test differences							(t(36) = -5.47, P < 0.01)		(t(36) = -2.42, P < 0.05)		(t(36) = -3.23, P < 0.01)		(P > 0.05)	

Table 1: Individual and mean values of the concussed group for age, sex, symptom resolution, and number of previous concussions; in addition to days since injury, PCSS, CDI, and KD scores for Tests 1 and 2. Also, cross-test differences of symptomatology and behavioural scores.

Table 2

Electrophysiological Results											
Test 1 vs. Controls				Test 2 vs. Controls				Test 1 vs. Test 2			
N2b Amplitude				**N2b Amplitude**				**N2b Amplitude**			
Effect	*df*	*F*	*P*	*Effect*	*df*	*F*	*P*	*Effect*	*df*	*F*	*P*
Group	45	5.4	< 0.05*	Group	45	0.4	> 0.05	Group	36	2.2	> 0.05
Group:Condition	45	0.38	> 0.05	Group:Condition	45	0	> 0.05	Group:Condition	36	0.4	> 0.05
Group:Region	45	16.6	< 0.01*	Group:Region	45	9.6	< 0.01	Group:Region	36	1.5	> 0.05
N2b Latency				**N2b Latency**				**N2b Latency**			
Effect	*df*	*F*	*P*	*Effect*	*df*	*F*	*P*	*Effect*	*df*	*F*	*P*
Group	45	4.15	< 0.05*	Group	45	0	> 0.05	Group	36	2.9	> 0.05
Group:Condition	45	5.72	< 0.05*	Group:Condition	45	6.2	< 0.01*	Group:Condition	36	0	> 0.05
Group:Region	45	7.51	< 0.01*	Group:Region	45	2.8	< 0.01*	Group:Region	36	1.7	> 0.05
P3b Amplitude				**P3b Amplitude**				**P3b Amplitude**			
Effect	*df*	*F*	*P*	*Effect*	*df*	*F*	*P*	*Effect*	*df*	*F*	*P*
Group	45	9.77	< 0.01*	Group	45	7.8	< 0.01*	Group	36	5.7	> 0.05
Group:Condition	45	0.06	> 0.05	Group:Condition	45	0	> 0.05	Group:Condition	36	8.5	> 0.05
Group:Region	45	11.2	< 0.01*	Group:Region	45	6.7	< 0.01*	Group:Region	36	4	> 0.05
P3b Latency				**P3b Latency**				**P3b Latency**			
Effect	*df*	*F*	*P*	*Effect*	*df*	*F*	*P*	*Effect*	*df*	*F*	*P*
Group	45	0.12	> 0.05	Group	45	0	> 0.05	Group	36	0	> 0.05
Group:Condition	45	1.67	> 0.05	Group:Condition	45	0.8	> 0.05	Group:Condition	36	0.2	> 0.05
Group:Region	45	1.52	> 0.05	Group:Region	45	0.9	> 0.05	Group:Region	36	0.4	> 0.05
LPC Amplitude				**LPC Amplitude**				**LPC Amplitude**			
Effect	*df*	*F*	*P*	*Effect*	*df*	*F*	*P*	*Effect*	*df*	*F*	*P*
Group	45	2.98	> 0.05	Group	45	3.4	> 0.05	Group	36	0	> 0.05
Group:Condition	45	3.79	> 0.05	Group:Condition	45	2.9	> 0.05	Group:Condition	36	0.2	> 0.05
Group:Region	45	7.77	< 0.01*	Group:Region	45	3.8	< 0.01*	Group:Region	36	1.1	> 0.05
LPC Latency				**LPC Latency**				**LPC Latency**			
Effect	*df*	*F*	*P*	*Effect*	*df*	*F*	*P*	*Effect*	*df*	*F*	*P*
Group	45	0.01	> 0.05	Group	45	0.6	> 0.05	Group	36	0.6	> 0.05
Group:Condition	45	3.48	> 0.05	Group:Condition	45	4.3	< 0.05*	Group:Condition	36	0	> 0.05
Group:Region	45	0.56	> 0.05	Group:Region	45	1.1	> 0.05	Group:Region	36	1.2	> 0.05
Note: ":" denotes an Interaction								* Indicates Significance			

Table 2: Amplitude and latency effects (Greenhouse–Geisser corrections applied) for N2, P3b, and LPC for Test 1 vs. Controls (Left); Test 2 vs. Controls (Middle); and Test 1 vs. Test 2 (Right).

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Chapter 5

5.0 General

This thesis has examined the application of ERPs in concussed populations across different age groups and injury time-points. Chapter 1 outlined the history and epidemiology of concussion, the current tools available for concussion assessment and their limitations, as well as a comprehensive review of ERPs and their suitability to assess cognitive dysfunction in concussed populations. I concluded that while many assessment tools are capable of evaluating specific aspects of the injury, whether they describe symptomatology, evaluate psychological and/or behavioural processes, or demonstrate where in the brain a lack of activation occurs, they all pose limitations in concussion assessment that ERPs either solve or minimize. Chapter 2 was an empirical study that compared former North-American professional football players each with a history of concussion to healthy age-matched controls. The study demonstrated clear signs of cognitive and neuropsychological deficits in the concussed population, while also demonstrating that the former athletes self-reported as having increased issues of social, emotional, physical, and psychological health. Chapter 3 presented a detailed investigation of neurophysiological markers of cognitive dysfunction as manifested in acutely concussed adolescents, where cognitive dysfunction was found to decrease as days since injury increased. Finally, Chapter 4 was a longitudinal study tracking the improvement of cognitive processing in adolescents from the acute to post-acute stage of the injury, where neurophysiological improvements were observed between the first test and the second test, reflecting cognitive recovery as time since injury increased. This final chapter (5) will discuss the contributions, significance, and implications of the findings presented and their limitations, as well as proposed future research directions.

5.1 Contributions and Significance

The empirical study presented in Chapter 2, *Disruption of function: Neurophysiological markers of cognitive deficits in retired football players*, published in *Clinical Neurophysiology (2019),* was the first study to evaluate the effects of multiple concussions in retired Canadian Football League (CFL) athletes using ERPs. Consistent with previous literature, this study demonstrated attenuated P300 responses in a concussed population (e.g., De Beaumont et al., 2009). However,

of particular significance, this study was the first to demonstrate attenuated MMN responses in those with a history of concussion. As a result, this is the first study to observe neurocognitive deficits in an automatic pre-conscious-awareness response reflecting early attention and memory-related template formation (Näätänen et al., 2007) within a concussed population. Accordingly, this finding represented an entirely new, previously undocumented dysfunction in retired professional football players with concussion histories.

Chapter 3, *Neurophysiological markers of cognitive deficits and recovery in concussed adolescents*, currently under review in *Brain Research*, was the first study to use ERPs to investigate the effects of concussion in an acutely-concussed adolescent population. Consistent with previous research, this study revealed the concussed population has neurocognitive consequences in memory, attention, and executive control as reflected by the N2b and P300 (e.g., Broglio et al., 2009; De Beaumont et al., 2009; Moore et al., 2015). However, of particular importance, it was the first study to provide evidence to suggest that the N2b may be capable of tracking improvements of executive control processing; a conclusion drawn from the fact that the response latency of the N2b was found to be correlated with days since injury. The final significant contribution this study demonstrated was the unobserved differences in the MMN between the two groups; a finding that was unexpected and contrary to the study's hypothesis as MMN alterations were observed in the previous study. However, as a result, it provided first evidence to suggest that MMN abnormalities in those with a history of concussion may be representative of a biomarker for permanent, irreversible cognitive dysfunction.

Finally, Chapter 4, *Tracking concussion recovery in adolescents using neurophysiological markers: An ERP Study*, prepared for submission to *Clinical Neurophysiology*, was the first study to investigate the neurocognitive dysfunctions attributable to concussion from the acute to post-acute stage of injury in an adolescent population. In line with Chapters 2 and 3, this study also supported prior research suggesting concussions cause irreversible neurological damage (e.g., De Beaumont et al., 2009; McKee et al., 2009; Stern et al., 2019). This was reflected by P300 responses failing to improve from the acute stage of the injury to the post-acute stage; a finding indicative of long-lasting consequences of memory and attention-related processes. Importantly, however, this is the first longitudinal study to provide strong evidence to suggest

ERPs are an appropriate measure for tracking concussion recovery at the neurophysiological level. Aligned with the findings unveiled in Chapter 3, this study revealed that N2b responses improved as days since injury increased; a result reflective of improvements in executive control processes over the course of injury recovery. Ultimately, this study provided an additional layer of evidence to support the viability of the N2b to be used as a marker for both concussion identification and injury recovery-tracking in adolescent populations.

5.2 Limitations

The three studies presented in this dissertation pose several limitations that must be considered when evaluating their scientific contributions. A limitation common across the three studies was the relatively small sample sizes employed. Although sample sizes were appropriate by literature standards, they were not suitable for clinical studies where validation of clinical applicability is derived. For instance, to determine the clinical effectiveness of a new Medical Device or method of analysis, a minimum clinical trial sample size of 100 participants (per group) within a specific age-range is required (Kaplan et al., 2004). Accordingly, as the sample sizes were 19 concussed and 18 healthy, 26 concussed and 28 healthy, and 19 concussed and 28 healthy in Chapters 2, 3 and 4, respectively, and differed in age, they did not meet the minimum participants required for clinical application validation. Another limitation across each of the studies is the fact that they were each conducted in a group-wise comparison manner. The very nature of group study design restricts the ability to account for variability between subjects. In each of the studies, when exploring individual variations amongst the participants, considerable variability could be observed within the concussed groups. Accordingly, the future direction of ERP research, as will be discussed in section 5.3, is to conduct single-trial and single-subject analyses. In addition to these common limitations, each Chapter posed limitations exclusive to their study design.

A limitation of Chapter 2 was that most of the concussions reported were not clinically diagnosed; rather, they were identified by the athletes themselves. This demonstrates a possibility of inaccuracy as the athletes were asked to remember concussions they sustained as far back as 30 years. The reason the vast majority of reported concussions went undiagnosed is twofold: 1) many of these athletes sustained their injury when concussions were not well understood; and 2) many occurred during the era of the “walk it off” mentality. However, that

being said, the point remains that the accuracy of whether or not a concussion occurred, and the exact year in which it occurred, remains subjective and dependent on patient-response reliability. Another factor that was unable to be controlled for was the type of control group. Although sex- and age-matched, a perfect control group for comparison would be one consisting of other professional football players who had never sustained a concussion in their careers. However, the likelihood of collecting such a sample can be considered virtually impossible, considering North-American style football is well regarded as the most violent team sport in the world where contact to the head occurs at every play for many of the positions.

The main limitation in Chapters 3 and 4 was the fact that the control group differed in age relative to the concussed group – a difference of approximately 5 years. Research investigating the age-related differences in adulthood have reliably demonstrated that ERP response amplitudes and latencies reduce and lengthen as age increases (Pfefferbaum et al., 1984; Polich, 1996). For example, Pfefferbaum et al (1984) showed that from ages 18 to 90 ERP responses decrease at a rate of 1-1.5 ms per year. Unfortunately, however, when examining adolescent populations, the literature is far more inconsistent on the matter. For example, Lamm et al (2006) found latency decreases from childhood to adolescence, while Johnstone et al (1996) demonstrated no alterations at all. Also, a study conducted by Arain et al (2013) showed that responses reduce until approximately the age of 25 when the brain is thought to reach its full maturity. Accordingly, age may have had an impact on our findings, however, given the work referenced, the difference may be marginal at best. Further research is needed to truly understand the effect age will have on ERP response amplitudes and latencies. In my view, to determine definitively if age differences were contributing factor to the results found in these two studies, future work must explore the age-related effects from adolescence to early adulthood (e.g., ages 14-24).

Much of the research exploring the neurophysiological consequences of concussion also examines their relationship with symptomatology (e.g., Gaetz et al., 2000; Baillargeon et al., 2012). The idea behind this investigation is that a concussed patient's symptoms – and symptom recovery – should be able to be linked to neurophysiological or neurocognitive consequences. In other words, as symptoms recover so too should neurological consequences. Unfortunately,

analyses in Chapters 3 and 4 failed to support this hypothesis. This result may be due to within-sample variance of ERP responses and the lack of statistical power available from small sample sizes. Also, there has also been research to suggest that neurophysiological changes occur prior to behavioural changes (e.g., Armandfard et al., 2018); thus, symptom resolution may not occur until later on in the recovery process for some of the patients tested. Chapters 3 and 4 were, however, able to correlate N2b response latency and amplitude to days since injury. This finding does pose a caveat as this was accomplished post-hoc; a type of analyses criticized for statistical bias as it can fit a hypothesis to an observed result (Curran-Everett & Milgrom, 2013). However, for Chapter 3 in particular, the relationship remained in the subset group analyses, consequently demonstrating the reliability of the N2b to track cognitive alterations. Lastly, in Chapter 4 exclusively, the control group was used as a comparative group twice: for both Tests 1 and 2. Accordingly, for the purpose of consistency, it would have been ideal if the control group could have also been tested twice at similar time points as the concussed group. However, test-retest data on many ERP components (including those used in this research) indicate reasonable test-retest reliability (Ravden & Polich 1999; Polich & Herbst, 2000; Walhvod et al., 2002) by circumstantial evidence of excellent data for the P300 as a clinical assay (e.g., Polich & Herbst, 2000; Mah & Connolly, 2018)

Future Directions

The findings presented in this dissertation open several avenues for future research. The most immediate of these would be single-trial and single-subject analyses. Conventionally, ERP analyses employ multi-trial averaging to a post-stimulus or pre-response signal to capture electrophysiological data linked to cognitive processing (Delorme et al., 2015). However, research has shown reliably that cognitive processing varies from trial-to-trial in many experiments (Blankertz et al., 2011). For example, intra-subject variability (ISV) of the P300 has been shown reliably to be linked to single-trial reaction-times (Ritter et al., 1972; Kutas et al., 1977; for a review see Verleger, 1997). Therefore, while trial-averaging is valuable in capturing the average cognitive processing of an individual or group, it fails to identify the variability within a single-subject and assumes that the event-related responses produced are more or less similar across single trials (Ouyang et al., 2017). Although knowledge of ISV can be traced back over 40 years, it was not until recently that neuroscience research began to explore the issue

further; a delay that was likely due to a lack of readily-available computational power (Delorme et al., 2015). Consequences of concussion vary significantly across individuals and thus, the employment of single-trial analyses would aid in identifying the ability of a specific patient's cognitive processing. This analysis is critical as higher within-subject variability may reflect more significant deficits of cognitive processing. However, even when investigating the ISV differences in a concussed individual, a method of identifying how different the individual is relative to a neurologically healthy population is still at large; therefore, in addition to single-trial analyses, single-subject analyses also need to be explored further in concussed populations.

Machine Learning (ML) is one such technique being increasingly used in concussion research in an effort to algorithmically evaluate the cognitive processing of concussed individuals (e.g., Cao et al., 2008; Prichep et al., 2012). In particular, supervised learning models of binary classification known as Support Vector Machines (SVMs) (Cortes et al., 1995) have become a promising tool in identifying differences in ERP responses in brain injured populations (e.g. Armanfard et al., 2018; Fickling et al., 2019; Boshra et al., 2019). Accordingly, hypothesizing that such a methodology could be used to classify concussed patients from healthy control participants proves tenable. In fact, recent work conducted by Boshra et al (2019) supports this theory by demonstrating the reliability of SVMs in differentiating healthy controls from concussed patients (>80% accuracy). The benefit of such a method is its ability to remove human error and the naturally occurring biases of clinical judgement. Accordingly, such a method should continue to be explored as a potential assessment and diagnostic of concussion.

Lastly, as alluded to throughout this dissertation, the next major step is to utilize ERPs in a clinical setting specific to concussion assessment. As more data is collected, further insights can begin to be extracted from the data, whether through traditional ERP analyses or through new analysis methods such as ML. In an effort to keep adoption of ERPs into the clinical environment simple, traditional analyses seems tenable as a starting point. Specifically, this would entail collecting a large normative data bank of ERP data, akin to that of MRI data available today, and compare each newly concussed patient to that of the average healthy control population ERP data for that particular individual's demography. Once established in a clinical setting, new methods of analyses such as SVMs should be used to evaluate and assess the intra-

subject cognitive processing variability, as well as the general difference of one patient to that of the average healthy brain. Finally, once adoption has taken place, clinical trials to demonstrate the efficacy of ERPs to be a diagnostic (rather than only an assessment) for concussion would be the next foreseeable step; a step that would consequently minimize the role of clinical judgement in concussion diagnosis.

Conclusion

This thesis has investigated the ability of ERPs to accurately detect cognitive dysfunctions in concussed populations relative to healthy controls regardless of age or time since injury. In particular, this dissertation was the first to: 1) show a new area of cognitive dysfunction in a concussed population as revealed by the MMN; 2) test acutely-concussed adolescents; and 3) demonstrate that the N2b may be a potential biomarker to assess neurophysiological recovery from the acute to post-acute stages of concussion recovery. Furthermore, it provides strong evidence to suggest that ERPs are a suitable method of concussion assessment in the clinical environment, while simultaneously arguing for the next step to be the integration of conventional ERP methodology into the clinical setting, with more advanced analysis techniques to follow soon after. Taken together, the arguments presented in this thesis, and the results supporting them, provide substantial evidence demonstrating the utility of ERPs to be adopted into the clinical setting of concussion assessment, and more specifically, neurophysiological recovery and rehabilitation.

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