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Disruption of function: Neurophysiological markers of cognitive deficits in retired football players

Kyle I. Ruiter [a,b,*], Rober Boshra [b,c,d], Mitchell Doughty [c], Michael Noseworthy [b,c], John F. Connolly [a,b,c,d,e,*]

[a] Department of Linguistics and Languages, McMaster University, Togo Salmon Hall 513, 1280 Main Street, West Hamilton, ON L8S 4M2, Canada
[b] ARiEAL Research Centre, McMaster University, L.R. Wilson Hall, 1280 Main Street, West Hamilton, ON L8S 4M2, Canada
[c] School of Biomedical Engineering, McMaster University, ETB-406, 1280 Main St., West Hamilton, ON L8S 4K1, Canada
[d] MaRS Centre, Vector Institute, Canada
[e] McMaster University, Department of Psychology, Neuroscience and Behaviour, Canada

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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.

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.

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, 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

* Corresponding authors at: Department of Linguistics and Languages, McMaster University, Togo Salmon Hall 513, 1280 Main Street, West Hamilton, ON L8S 4M2, Canada.
E-mail addresses: ruiterki@mcmaster.ca (K.I. Ruiter), boshrar@mcmaster.ca (R. Boshra), doughtmw@mcmaster.ca (M. Doughty), nosewor@mcmaster.ca (M. Noseworthy), jconnol@mcmaster.ca (J.F. Connolly).

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function years after initial diagnosis (Collins et al., 1999; 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., 2007; 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

[1] A thesis (Kaipio ML. Mismatch Negativity (MMN) and P3a Abnormalities in Traumatic Brain Injury. Studies in Psychology 2016:116) indicated that mild to severe traumatic brain injuries were examined using ERPs including the MMN. However, the thesis reported on "moderate-to-severe traumatic brain injury" only and explicitly noted that "ERP studies on patients with mild TBI are not recounted here" (Page 40).

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.

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**

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

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.

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

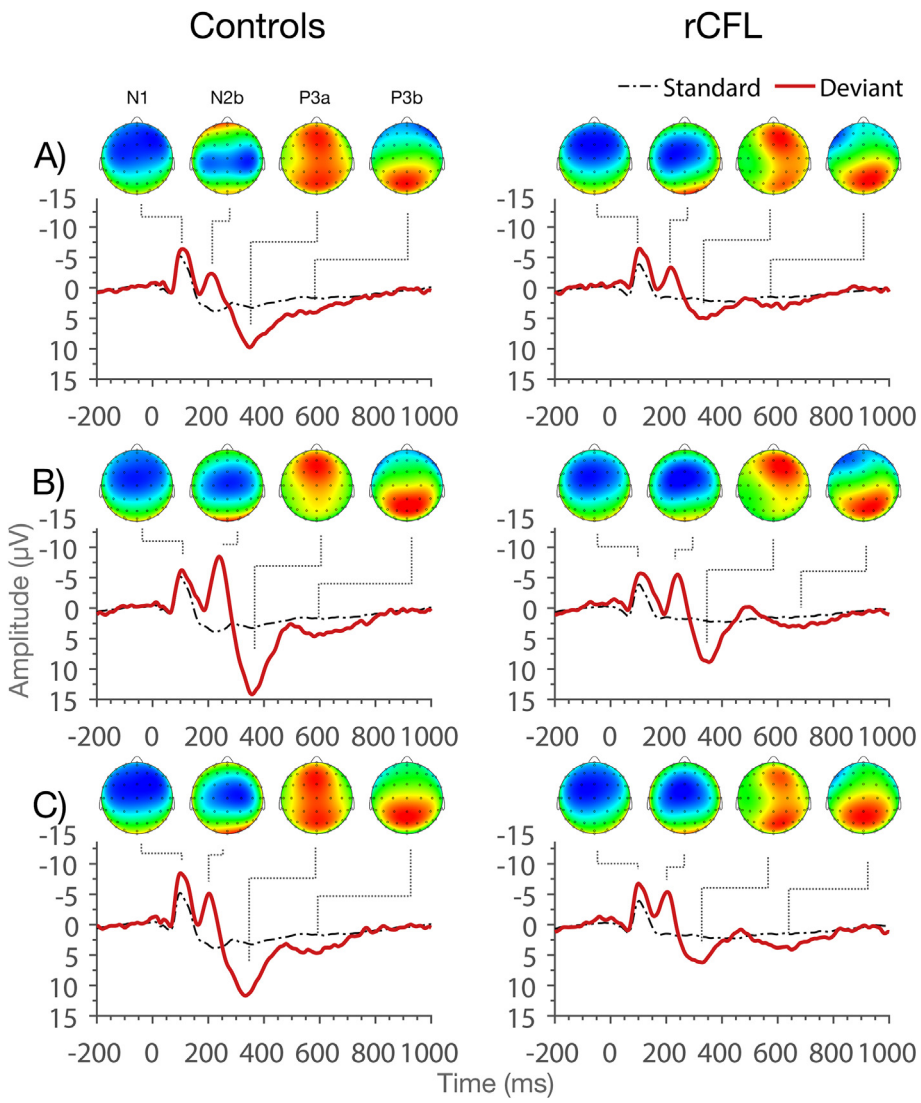

Fig. 1. Grand-averaged P300 protocol waveforms and their respective scalp distributions recorded at Cz, evoked by target stimuli, for each group (Controls Left, rCFL Right). (A): N1, N2b, P3a, and P3b components evoked in the Frequency condition. (B): N1, N2b, P3a, and P3b components evoked in the Duration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

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.

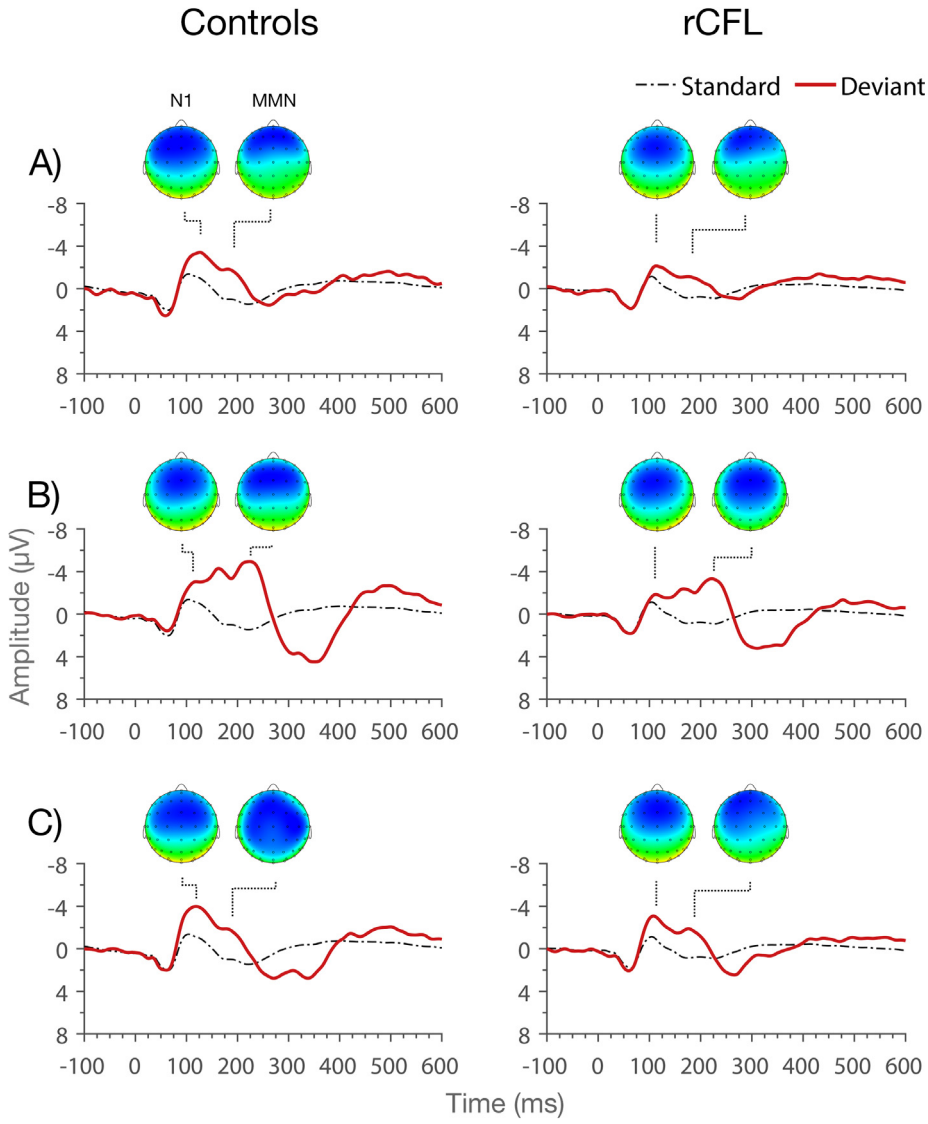

Fig. 2. Grand-averaged MMN protocol waveforms and their respective scalp distributions recorded at Cz, evoked by target stimuli, for each group (Controls Left, rCFL Right). (A): N1 and MMN components evoked in the Frequency condition. (B): N1 and MMN components evoked in the Duration condition. (C):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

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., 2007; 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., 2007; 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., 1999; 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., 2007). 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., 2007) 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.

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