

Brain function decline in healthy retired athletes who sustained their last sports concussion in early adulthood

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Recent studies have shown that the detrimental effects of sports concussions on cognitive and motor function may persist up to a few years post-injury. The present study sought to investigate the effects of having sustained a sports concussion more than 30 years prior to testing on cognitive and motor functions. Nineteen healthy former athletes, in late adulthood (mean age = 60.79; SD = 5.16), who sustained their last sport-related concussion in early adulthood (mean age = 26.05; SD = 9.21) were compared with 21 healthy former athletes with no history of concussion (mean age = 58.89; SD = 9.07). Neuropsychological tests sensitive to age-related changes in cognition were administered. An auditory oddball paradigm was used to evoke P3a and P3b brain responses. Four TMS paradigms were employed to assess motor cortex excitability: (i) resting motor threshold; (ii) paired-pulse intracortical inhibition and intracortical facilitation; (iii) input/output curve and (iv) cortical silent period (CSP). A rapid alternating movement task was also used to characterize motor system dysfunctions. Relative to controls, former athletes with a history of concussion had: (i) lower performance on neuropsychological tests of episodic memory and response inhibition; (ii) significantly delayed and attenuated P3a/P3b components; (iii) significantly prolonged CSP and (iv) significantly reduced movement velocity (bradykinesia). The finding that the P3, the CSP as well as neuropsychological and motor indices were altered more than three decades post-concussion provides evidence for the chronicity of cognitive and motor system changes consecutive to sports concussion.

Keywords: sports concussion; aging; cognitive dysfunctions; motor cortex inhibition alterations; motor execution slowness; neuropsychology; transcranial magnetic stimulation; rapid alternation movements

Abbreviations: ADHD = attention-deficit hyperactivity disorder; CSP = cortical silent period; ERP = event-related potentials; EEG = electroencephalogram; FDI = first dorsal interosseus; ISI = interstimulus intervals; LED = light-emitting diodes; LOC = loss of consciousness; MCI = mild cognitive impairment; MT = motor threshold; NFT = neurofibrillary tangles; RAM = rapid alternating movement task; RCFT = Rey-Osterrieth Complex Figure Test; TBI = traumatic brain injury; TMS = transcranial magnetic stimulation

Background

The growing scientific interest for sports concussion [Although the term concussion has been included in the Mild Traumatic Brain Injury category (mTBI) (WHO, 2005), it continues to be widely used in sports medicine] over the last 15 years is partly due to the rapid increase in its reported incidence (Kelly, 1999). In fact, the Centers for Disease Control and Prevention (1997) estimate that in the United States only, 50 000–300 000 contact sports athletes sustain a concussion during the course of a single year. The Prague Summary and Agreement Statement on concussion in sports (McCrary *et al.*, 2005) recently defined sports concussion as a complex pathophysiological process affecting the brain, induced by a near instant transfer of kinetic energy. With the vast majority of the literature on sports concussion dedicated to improving return-to-play decisions in the immediate post-concussion phase, the potential long-term sequelae of sports concussion have mostly been overlooked. The relatively transient nature of post-concussive symptoms reported by athletes coupled with the rapid recovery of gross cognitive and motor functions might explain the scarcity of studies detailing the long-term repercussions of sports concussions.

The seemingly benign effects of sports concussion on long-term brain functions have, however, recently been questioned. There is a growing body of evidence suggesting that there are cumulative effects of concussions that manifest as increased susceptibility to subsequent concussions as well as an increase in their severity (Gerberich *et al.*, 1983; Collins *et al.*, 2002; Guskiewicz *et al.*, 2003). More recent findings suggest that the effects of a concussion far outlast the acute phase. Guskiewicz and colleagues (2005) found that former athletes who suffered multiple concussions had a 5-fold prevalence of mild cognitive impairment (MCI) (a condition that converts at a rate of ~10–20% annually into dementia) compared with retirees without a history of concussion. Moreover, they observed an earlier onset of Alzheimer's disease in the concussed retirees than in the general American male population. In fact, traumatic brain injury (TBI) has been described as the most robust environmental Alzheimer's disease risk factor in the general population (Heyman *et al.*, 1984; Mortimer *et al.*, 1985; Guo *et al.*, 2000; Plassman *et al.*, 2000).

Up to now, these reports were mostly derived from epidemiological studies. While most studies that relied on classic neuropsychological tests to detect residual cognitive anomalies beyond the acute post-concussion phase were inconclusive (Barth *et al.*, 1989; Guskiewicz, 2002), event-related potentials (ERP), on the other hand, revealed to be fruitful. To date, most of the literature on ERPs and MTBI has looked at the modulation of the classic P3 response as a result of concussion. Classic oddball paradigms typically yielded P300 amplitude reductions and latency delays after MTBI (Werner and Vanderzant, 1991; Solbakk *et al.*, 1999; Dupuis *et al.*, 2000; Reinvang *et al.*, 2000; Potter *et al.*, 2001; Lavoie *et al.*, 2004; Gosselin *et al.*, 2006). Recent studies specifically conducted with asymptomatic concussed athletes showed persistent P300 latency delays (Gaetz and Weinberg, 2000) and amplitude attenuation (Gosselin *et al.*, 2006; De Beaumont *et al.*, 2007a). Reductions in the amplitude of the P300 component are thought to index memory updating (Donchin and Coles, 1988; Picton, 1992), subjective significance (Duncan-Johnson and

Donchin, 1977) and stimulus probability (Johnson and Donchin, 1978; Donchin and Coles, 1988), whereas P300 latency delays are associated with reduced performance on neuropsychological tests that assess how rapidly attentional resources can be allocated for memory processing (Polich *et al.*, 1983; Emmerson *et al.*, 1989; Reinvang, 1999). De Beaumont and collaborators (2007a) also demonstrated that the amplitude of the P300 component was unrelated to the time elapsed since the last sports concussion in a group of asymptomatic concussed athletes for whom 9 months up to 81 months had passed since the accident. This finding provided preliminary evidence suggesting that P300 amplitude reductions consecutive to sports concussions could be long-lasting.

A recent study using a three-tone oddball paradigm showed that moderate to severe TBI victims exhibited significant P3a/P3b amplitude attenuation as well as P3b latency delays relative to a group of healthy controls (Solbakk *et al.*, 2002). While the P3b component is analogous to the classic P300 described earlier, the P3a component, or novelty P300, is thought to reflect frontal lobe function (Comerchero and Polich, 1999; Polich, 2004) such that reduced P3a amplitude and latency delays have been associated with less efficient shifting of attentional resources to novel stimuli (Nordby *et al.*, 1999; Kopp *et al.*, 2006).

Interestingly, these two P300 subcomponents (i.e. P3a and P3b) also revealed to be useful clinical tools to detect early cognitive dysfunctions in both MCI and early onset Alzheimer's disease (Fjell and Walhovd, 2004; Polich, 2004; Golob *et al.*, 2007), for which recurrent sports concussions have been shown to be more susceptible than the general population (Guskiewicz *et al.*, 2005). A study by Golob and colleagues (2007) recently showed that the latency of the P300 component was further increased in MCI relative to age-matched controls. The recent dissociation of the P300 into its subcomponents also revealed greater age-related changes on both the latency and the amplitude of the P3a component relative to its P3b counterpart (Fjell and Walhovd, 2004; Polich, 2004). The sensitivity of these two subcomponents of the P300 to both MCI and sports concussions therefore makes them a good candidate to explore any possible association between sports concussions and the development of MCI in late adulthood.

Neuropsychological tests have also proven to be useful to characterize changes in cognitive functions associated with MCI (Kasai *et al.*, 2006; Wylie *et al.*, 2007). Among others, the Rey-Osterrieth Complex Figure Test (RCFT) was found to be particularly sensitive to episodic memory decline in MCI and early-stage Alzheimer's disease (Kasai *et al.*, 2006). Another study that used a traditional arrow flanker task (Eriksen and Eriksen, 1974) as a measure of selective attention/executive functions showed that MCI patients performed significantly worse than controls when flankers signaled an incongruent response (Wylie *et al.*, 2007).

In parallel, the recent emergence of studies on the potential sequelae of sports concussion on the motor system was partly fuelled by previous findings suggesting that nearly 17% of retired professional boxers developed early symptoms of mild confusion and ataxia quickly progressing to a 'Parkinsonian' cognitive decline. Considering that motor symptoms are typically the earliest clinical manifestation of chronic TBI (Rabadi and Jordan, 2001), it seemed plausible that the motor system could have been affected by concussive blows to the head. Based on its capacity to provide

a direct measure of central inhibitory/excitatory mechanisms of the motor system and knowing that these mechanisms are central elements to the production of movements (Reynolds and Pearson, 1993; Abbruzzese and Trompetto, 2002; Cantello, 2002; Cantello *et al.*, 2002), a transcranial magnetic stimulation (TMS) study showed reduced corticospinal excitability in the acute phase after a minor head injury (Chistyakov *et al.*, 2001). TMS also revealed that asymptomatic concussed athletes who sustained their last concussion on average 3 years prior to testing still exhibited a significantly prolonged cortical silent period (CSP) when compared with controls (De Beaumont *et al.*, 2007b). Furthermore, De Beaumont and colleagues (2007b) showed that the time elapsed since the last sports concussion did not influence the duration of the CSP, thus suggesting that abnormalities in intracortical inhibitory mechanisms of the primary motor cortex were relatively stable over time. Although the neurophysiological underpinnings modulating the duration of the CSP remain debated, research has typically attributed it to changes in intracortical inhibitory systems of the motor cortex mediated by GABA-b interneurons receptors (Siebner *et al.*, 1998; Werhahn *et al.*, 1999; Pierantozzi *et al.*, 2004; McDonnell *et al.*, 2006; Moller *et al.*, 2007). Although there is no direct evidence for the involvement of GABA receptors in post-concussive brain alterations, abnormal GABA transmission has been reported in rat models of brain injury (Kobori and Dash, 2006; Pascual *et al.*, 2007).

In addition to long-term intracortical inhibitory mechanisms abnormalities, two distinct types of dynamic motor function alterations have recently come to surface as a consequence of having sustained a mild TBI. Deficits in gait stability was found to persist at least 30 days post-injury in sports concussion victims (Slobounov *et al.*, 2007). Subsequent studies showed that gait stability was further reduced when concussion victims were asked to concurrently perform simple or complex cognitive tasks at 28 days post-injury (Parker *et al.*, 2006; Catena *et al.*, 2007). The second dynamic motor function alteration found in TBI victims is motor speed. TBI patients who performed normally on neuropsychological tests showed persistent motor slowness (or bradykinesia) when compared to matched controls on simple and complex reaction time tasks (Gray *et al.*, 1998). Knowing that sports concussions represent a mild form of TBI, it is plausible that sports concussions also result in motor execution slowness or bradykinesia.

This study purports three main objectives. The first objective was to verify whether the persistent electrophysiological and motor system abnormalities found in concussed athletes at 3 years post-injury would also be observed in a group of former athletes who sustained their last sports concussion more than 30 years ago. Knowing that the severity of both motor and electrophysiological alterations consecutive to sports concussion was unrelated to the time elapsed since the injury (De Beaumont *et al.*, 2007a, b), we hypothesized that former athletes who sustained their last concussion more than 30 years ago would exhibit significantly prolonged TMS-induced CSP as well as significant P300 amplitude reductions and latency delays relative to former athletes with no prior history of sports concussion. Moreover, because greater age-related changes are seen on both the latency and the amplitude of the P3a component relative to its P3b

counterpart (Fjell and Walhovd, 2004; Polich, 2004), we hypothesized that former athletes with concussion would show greater between-group differences on the P3a parameters.

The second objective of this study was to investigate whether former athletes who sustained their last sports concussion more than 30 years ago would show significant reductions on cognitive measures known for their acute sensitivity to MCI when compared to former athletes without concussion. In light of epidemiological evidence suggesting that sports concussions act as a risk factor for MCI (Guskiewicz *et al.*, 2005), we hypothesized that former athletes with concussion would perform significantly worse than former athletes without concussion on neuropsychological measures of memory (RCFT) and attention/executive functions (arrow flanker task) that were found to be highly sensitive to MCI and early onset Alzheimer's disease. Knowing that successful inhibitions on incongruent trials of a modified Flanker arrow test were associated with greater P3a amplitude in the general population (Liotti *et al.*, 2005), a corollary hypothesis would be that former concussed athletes who would perform worse on the arrow flanker task would be those who would show greater P3a attenuations. Likewise, based on previous studies that linked P3b amplitude with performance scores on memory tests (Wickens *et al.*, 1983; Kramer and Strayer, 1988), we hypothesized that former concussed athletes who would perform more poorly at the RCFT would be those who would show greater amplitude reductions on the P3b component.

The final objective of this study was to investigate whether former athletes who sustained their last concussion more than 30 years ago would be slower than former athletes without concussion on a rapid alternating movement task specifically selected for its proven sensitivity to detect bradykinesia symptoms (Beuter *et al.*, 1999). In light of a previous study that showed persistent motor execution slowness (or bradykinesia) in TBI victims who performed normally on neuropsychological tests (Gray *et al.*, 1998), we hypothesized that former athletes with concussion would be significantly slower than former athletes without concussion to complete pronation–supination cycles on a diadochokinesia task. Based on the established relationship between the duration of the CSP and several movement disorders for which bradykinesia is a cardinal symptom (Reynolds and Pearson, 1993; Cantello, 2002; Cantello *et al.*, 2002), we further hypothesized that former concussed athletes with a more prolonged CSP would be slower on a rapid alternating movement task (RAM or diadochokinesia task).

Methods

Participants

All 56 participants in this study were former university level athletes between the ages of 50 and 65 recruited with the help of University Athletics organizations. Fifty out of the 56 former athletes recruited for the purpose of this study had played for a Canadian University hockey team while the remaining six former athletes had played for the football team of the same Canadian University. Participants were included if they met all of the following: no history of alcohol and/or substance

abuse; no medical condition requiring daily medications or radiotherapy (malignant cancers, diabetes, hypertension and/or other cardiovascular diseases); no previous history of psychiatric illness, learning disability, neurological history (seizure, central nervous system neoplasm or brain tumour) or TBI unrelated to contact sports. Likewise, participants included in the present study had no history of sports concussion after their years spent playing for the university football/hockey team. In order to control for data contamination due to the protective properties of regular physical activity on the development of Alzheimer's disease (Lindsay *et al.*, 2002), participants had to report engaging in physical activity at least three times a week at the time of testing. Fifteen participants from the concussed group and 18 controls were still reuniting once a week to play recreational, contact-free ice hockey while they also enjoyed physical activities such as training at the gymnasium, playing golf, tennis, hiking, cross-country skiing and taking walks. The nature of physical activities that participants engaged in was comparable in both experimental groups. A total of 10 former athletes did not meet at least one of the aforementioned criteria and were consequently excluded from this study. Six more participants were excluded because they could not recollect sufficient information about their concussion history to enable group classification. The data from two other participants were excluded because of electrophysiological artefacts (see *Event-Related Potentials* section). The study was approved by the local ethics committee and all participants provided written informed consent prior to testing. Subjects received a financial compensation of \$60 CAD for their participation.

The study included two experimental groups. The first group consisted of 19 healthy former university level athletes between the ages of 50 and 65, with a mean age of 61 years ($SD=5.16$) and a mean level of education of 18 years ($SD=2.82$), who sustained their last sports concussion in early adulthood (between the ages of 20 and 30). The number of concussions sustained ranged from 1 to 5 and the time elapsed since their last concussion went from 27 to 41 years (mean = 34.74; $SD=9.21$). The severity of concussions sustained in former athletes ranged from Grade 2 (concussion symptoms or mental status abnormalities on examination that lasted more than 15 min, no loss of consciousness (LOC) to Grade 3 LOC, either brief (seconds) or prolonged (minutes) according to the American Academy of Neurology practice parameters (American Academy of Neurology Practice, 1997); they all classified as MTBI on the Glasgow Coma Scale (scoring between 13 and 15). The control group consisted of 21 former university level athletes between the ages of 50 and 65, with a mean age of 59 years ($SD=9.07$) and a mean level of education of 18 years ($SD=1.92$), who reported no prior history of concussion or neurological insult. The two groups were equivalent according to age [$F(1,39)=1.348$; $P>0.05$] and level of education [$F(1,39)=0.019$; $P>0.05$].

Procedure

The experiment consisted of two 3-h testing sessions that took place 1–5 weeks apart. The first session included the administration of a concussion history questionnaire, the Mini-Mental Status Examination (MMSE), a general health questionnaire, the ERP recordings and the TMS protocol. The second session consisted of the neuropsychological assessment and the diadochokinesia task (see below).

Concussion history questionnaire

A standardized concussion history form was administered to obtain detailed information about the number of previous concussions (if any), their approximate date, the description of the accident, and the nature and duration of on-field post-concussion severity markers

(confusion and/or disorientation, retrograde and/or anterograde amnesia and LOC). Sports concussion was defined as an injury resulting from a blow to the head that caused an alteration in mental status in which the severity was rated according to the criteria proposed by the practice parameters of the American Academy of Neurology (1997). All reported concussions were classified by a sports physician using the practice parameters of the American Academy of Neurology (1997).

General health questionnaire

A semi-structured health questionnaire was administered to screen for pre-determined inclusion criteria about lifestyle characteristics, life events and medical conditions that are known to exert an influence on general brain function. More specifically, the assessment of lifestyle and life habits included open and more structured questions about physical and cognitive activities engaged in as well as a history of substance abuse. This general health questionnaire also inquired about cardiovascular, neurological and psychiatric illnesses experienced during and after the university years as well as daily medications or treatment therapies that are known to exert an impact on brain function. Lastly, former athletes were asked to report recent subjective changes with their memory and other issues related to changes in cognition.

Cognitive mental status and neuropsychological assessment

The cognitive mental status and neuropsychological assessment segment of the present study was conducted in a quiet room. The MMSE was administered as a screening tool for cognitive impairment. The MMSE is an 11-question measure that tests orientation, attention, immediate and short-term recall, language and the ability to follow simple verbal and written commands (Folstein *et al.*, 1975). The maximum score is 30 and the total completion time ranged from 5 to 10 min. Folstein and colleagues (1975) originally proposed that a score of 23 or lower was indicative of cognitive impairment, while more recent studies have shown that greater sensitivity could be achieved with a cutoff score set at 24 or 25 (Braekhus *et al.*, 1995), especially with highly educated participants (Crum *et al.*, 1993).

The MMSE was followed by the administration of neuropsychological tests selected for their respective sensitivity to detect episodic memory and attention/executive functions alterations in MCI patients. In particular, the RCFT was administered to assess incidental learning and visual memory (Lezak, 1995). Participants were asked to draw from memory a complex figure at 3 min (immediate memory) and 30 min (delayed memory) after its initial copy. Scores were based on the 36-point scoring system developed by Osterrieth and Taylor (Lezak, 1995). The recognition condition immediately followed the 30-min delayed recall condition of the RCFT. Participants were provided with stimulus sheets and were instructed to circle the figures that were part of the complex figure design that had been copied and subsequently drawn. Twelve out of the 24 stimuli were part of the complex figure while the remaining 12 were not part of it. A correct response on the recognition condition was credited if the participant correctly circled a figure as having been part of the complex figure as well as when a figure that was not part of the complex figure had not been circled. The maximum correct score was 24. This test was shown to be particularly sensitive to episodic memory decline in MCI and early-stage Alzheimer's disease (Kasai *et al.*, 2006).

Participants were then asked to perform a modified arrow version of the computerized Eriksen flanker task (Eriksen and Eriksen, 1974). In this task, participants had to respond to the direction of a left or right

pointing target arrow while having to ignore flanking arrows that pointed either in the same or the opposite direction as the target arrow. The target arrow was located under a fixation point at the centre of the computer screen. The flanking arrow that had to be ignored was either presented to the left or to the right of the target arrow. This modified Eriksen flanker task included three experimental conditions. The congruent condition consisted of stimuli in which both the target arrow and the flanking arrow were pointing in the same direction (either left or right). The no-flanker condition corresponded to stimuli only consisting of a left–right oriented target arrow with no flanking arrow. The incongruent condition of the modified Eriksen flanker task consisted of a flanking arrow that pointed in the opposite left–right direction to that of the target arrow. The 180 stimuli presented in this task were distributed equally among the three experimental conditions and were presented in a random order at a fixed rate of 0.5 Hz. Participants had 5 s to provide their response to the target arrow. The 60 stimuli found in each experimental condition were counterbalanced according to target arrow direction, flanking arrow direction and the position of the flanking arrow (located either to the left or to the right of the target arrow). Reaction time scores and percent accuracy scores were independently computed for each of the three experimental conditions. The flanker interference effect, defined as the performance decrement caused by the insertion of an incongruent flanking arrow in contrast with the performance scores obtained when presented a congruent flanking arrow, were computed for both accuracy and reaction time scores. Previous studies have consistently found elevated response times as well as reduced percent accuracy scores in the incongruent condition relative to either congruent or no-flanker conditions (Eriksen and Eriksen, 1974; Eriksen and Schultz, 1979). A recent study using an arrow flanker task showed that MCI patients performed significantly worse than controls when flankers signalled an incongruent response (Wylie *et al.*, 2007). The administration and test procedures were standardized and uniform across participants.

Event-related potentials

The three-tone auditory oddball paradigm used in this study replicated the easy discrimination condition taken from Comerchero and Polich (1999) as it was demonstrated to be optimal for clinical purposes (Polich and Corey-Bloom, 2005). This auditory oddball paradigm consisted of three different stimuli presented in a random order: (i) a standard 1000 Hz tone presented in 80% of trials; (ii) a deviant 2000 Hz target tone presented in 10% of trials and (iii) a deviant 500 Hz non-target tone presented in 10% of trials. Participants were instructed to press a button of a response box as quickly as possible when they heard the target stimulus, while withholding their response to both standard and deviant non-target tones. Each participant performed one practice block of 20 trials followed by five experimental blocks of 200 trials. Stimuli were generated by the STIM (version 1.0.0.0.1) program from Neuroscan (Neurosoft, Inc. Sterling, USA) on a DELL computer located in an adjacent room [see Comerchero and Polich (1999) for a more detailed description].

The electroencephalogram (EEG) was recorded from 40 active Ag/AgCl electrodes (Neurosoft, Inc. Sterling, USA) mounted on an elastic cap and referenced to the average of the left and right mastoids. Electrodes were placed according to the extended International 10/20 system (Cooper *et al.*, 1980). A ground electrode was included in the montage and its impedance was kept below 5 k Ω . The EEG and EOG were digitized at 1000 Hz, high-pass filtered at 0.1 Hz, low-pass filtered at 100 Hz and averaged offline. Trials with artifacts at electrode sites of interest (Cz, Pz and Fz), eye blinks (Vertical eye movements > 100 μ V) were excluded from the analyses. ERP averages

(both for the P3a and the P3b components) were based on a minimum of 40 trials as this amount was found to be sufficient for the P300 components to be stable (Cohen and Polich, 1997). One participant from each experimental group did not fulfill this minimal requirement after artefact rejection and both were consequently excluded from further between-group comparisons. BrainVision Analyser software (Brain products, Inc., Germany) was used for data analysis. ERP waveforms were obtained after having followed the same steps as those described in a previous paper (Comerchero and Polich, 1999).

TMS recordings and data analysis

TMS was performed using a figure-of-eight coil positioned over the optimal position of M1 to elicit motor evoked potentials in the right first dorsal interosseus (FDI) muscle. This study consisted of four distinct TMS paradigms. The motor threshold (MT) at rest was calculated as the minimal stimulation intensity evoking a MEP of at least 50 μ V in five out of 10 consecutive trials when TMS was applied to the contralateral M1. The input output curve was computed using single TMS pulses of increasing intensities (90, 100, 110, 120, 130 and 140% of resting MT). Ten consecutive trials were collected for each condition. The order of presentation of the different TMS intensities varied randomly across participants. Interpulse interval was 6–8 s. According to the method of Kujirai and colleagues (1993), short interstimulus intervals (ISIs) of 2 and 3 ms were used to test intracortical inhibition while intracortical facilitation was obtained with long ISIs of 9, 12 and 15 ms. A subthreshold conditioning stimulus set at 80% of the resting MT preceded a supra-threshold test stimulus. This test stimulus was adjusted to produce an average MEP of 1 mV peak-to-peak amplitude (Kujirai *et al.*, 1993). We also included a test stimulus-alone condition set at \sim 120% of the resting MT to obtain baseline measurements. Ten consecutive trials were collected for each ISI and for the test stimulus alone condition. Interpulse interval was 6–8 s. Finally, the duration of the CSP was calculated at three TMS intensities. Five single-pulse stimulations for each of the three TMS intensities (110, 120 and 130 of MT intensity) were applied to the left M1 while participants maintained a voluntary isometric muscle contraction of the right FDI at \sim 10% of their maximum strength. Maximum right FDI strength, from which we derived the 10% voluntary isometric muscle contraction value, was recorded as participants were asked to push as hard as they could against a digital force gauge in a horizontal right-to-left motion for \sim 15 s. The intensity of the muscle contraction was digitized so that participants could regulate their exerted strength to a relatively constant level.

Diadochokinesia (RAM) task recordings and data analysis

Participants were seated on a straight back chair and kept elbows close to the trunk and flexed at an angle of 90°. Participants were instructed to rotate two hand-held spheres (diameter, 10 cm) as fast as possible with maximal movement amplitude (complete pronation–supination at the wrist). Two periods of 15 s were recorded (separated by a pause of 2 min) for each of the three conditions: both hands, left hand with the right hand immobile and right hand with the left hand immobile. To track the participant's hand position and orientation in 3D space, four infrared light-emitting diodes (LEDs) were placed at strategic positions on the spheres. The coordinates of the LEDs were recorded at a frequency of 200 Hz using a 3D motion analysis system (Optotrak Certus, Northern Digital inc.).

To assess overall performance at the RAM task, four main performance measures were computed using the algorithms developed by Okada and Okada (1983): duration, range, velocity and sharpness.

Duration represents the time taken to complete a full pronation–supination cycle (maximal amplitude wrist rotation), while the range is an averaged measure of angular displacement for each pronation–supination cycle. Velocity is a composite measure of Range/Duration (i.e. average angular displacement for a pronation–supination cycle/the time taken to complete this cycle). Velocity represents the main measure of interest in this study as it reflects slowness of movement or bradykinesia. It is also a more accurate performance measure as it corrects for the bias introduced by pronation–supination cycle with smaller angular displacement (smaller amplitude of wrist rotation) on the time taken to complete the cycle (i.e. less time should logically be taken to perform a pronation–supination cycle smaller in range). Finally, the measure of sharpness is used to calculate the delays associated with changes in direction when performing alternated movements (more delays reflect less sharp pronation–supination turns). Three participants from the concussed group and three controls had to be excluded from further analyses due to technical difficulties during 3D motion recordings (files containing 3D motion recordings for these six participants were corrupted and could no longer be opened for subsequent analyses).

Statistical analyses

All values are expressed as means \pm SD. EEG and behavioural data from the auditory oddball task, neuropsychological test scores, demographic information and EMG data obtained from consecutive recordings in all four TMS paradigms were subjected to standard descriptive statistics and ANOVAs for which Tukey's corrections for multiple comparisons were applied. In the paired-pulse paradigm, we computed for each participant a ratio between the mean MEP amplitude elicited by each ISI condition with that elicited by the mean MEP amplitude elicited by the test stimulus alone. Contrast analyses were computed to assess between-group differences in the duration of the CSP elicited by three different TMS intensities. Two-tailed Pearson correlations were computed to look at the relationship between electrophysiological measures of cognition (i.e. P3a and P3b) and neuropsychological test scores (i.e. memory and attention measures), as well as between the measure of motor cortex inhibition (i.e. duration of the CSP, see Results section) and that of dynamic motor function (i.e. motor execution speed on the RAM task). Finally, two-tailed Pearson correlations were drawn between the persistent concussion sequelae (both motor and cognitive) and the number of concussions, the time elapsed since the last concussion and concussion severity.

Results

Cognitive mental status and neuropsychological results

Results of the cognitive mental status examination and neuropsychological tests are summarized in Table 1. Former athletes with concussion obtained an equivalent total score at the MMSE to that of former athletes with no prior history of concussion [$F(1,38)=0.51$, $P>0.05$]. Every participant from both groups scored within the normal range at the MMSE.

Former athletes with a prior history of concussion performed significantly worse than controls on the recognition condition of the RCFT [$F(1,38)=5.76$, $P<0.05$] after Greenhouse–Geisser corrections were applied. While the two groups produced equivalent initial copy performances [$F(1,38)=0.47$, $P>0.05$],

Table 1 Between-group difference on neuropsychological measures of memory and attention after Greenhouse–Geisser corrections for multiple comparisons were applied

Measures	Controls Mean (SD)	Concussed Mean (SD)	F	P
MMSE				
Global score	29.0 (1.0)	29.3 (0.9)	0.51	>0.05
Key complex figure				
Copy	34.66 (2.5)	34.08 (2.87)	0.47	>0.05
Immediate recall	23.0 (6.6)	19.4 (6.7)	2.85	<0.1
Delayed recall	22.4 (6.4)	18.9 (6.5)	2.76	<0.1
Recognition	21.3 (1.9)	19.7 (2.0)	5.76	<0.05
Flanker				
No flanker RT	507.2 (77.9)	515.7 (81.7)	0.11	>0.05
No flanker accuracy	98.8 (1.96)	99.12 (1.50)	0.27	>0.05
Congruent RT	549.7 (104.6)	546.8 (82.0)	0.01	>0.05
Congruent accuracy	96.5 (3.5)	95.6 (8.6)	0.18	>0.05
Incongruent RT	603.0 (117.2)	610.1 (127.3)	0.03	>0.05
Incongruent accuracy	95.1 (3.1)	87.9 (13.7)	6.80	<0.05

both immediate recall [$F(1,38)=2.90$, $P<0.10$] and delayed recall [$F(1,38)=2.85$, $P<0.10$] conditions of the RCFT tended to be altered in concussed athletes. In addition, former athletes made significantly more errors when compared to controls on the incongruent condition of the arrow Flanker task [$F(1,39)=6.80$, $P<0.05$] after Greenhouse–Geisser correction while reaction time scores on the incongruent flanker condition did not differ between the two groups [$F(1,39)=0.03$, $P>0.05$]. The flanker interference effect calculated for accuracy scores was also found to be significantly greater in former concussed athletes relative to controls [$F(1,39)=5.66$, $P<0.03$], while that computed for reaction time scores did not differ across groups [$F(1,39)=0.61$, $P>0.05$]. As expected, accuracy as well as reaction time scores were found to be equivalent across groups on both congruent—(i) accuracy: [$F(1,39)=0.18$, $P>0.05$]; (ii) reaction time: [$F(1,39)=0.01$, $P>0.05$] and no flanker—(i) accuracy [$F(1,39)=0.27$, $P>0.05$]; (ii) reaction time [$F(1,39)=0.11$, $P>0.05$] conditions.

Electrophysiological results

Figure 1 depicts averaged P3a component waveform at Fz and averaged P3b waveforms at both Cz and Pz. ERP analyses were computed from predetermined electrodes known to record maximal P3b (Cz, Pz) and P3a (Fz) brain responses in this three-tone auditory oddball paradigm (Comerchero and Polich, 1999). Table 2 provides mean amplitude and latency values obtained for both P3a and P3b components from the auditory oddball task. While groups were equivalent on mean reaction time [$F(1,37)=0.00$, $P>0.05$] and response accuracy to the target stimulus [$F(1,37)=2.12$, $P>0.05$] of the auditory oddball task, former athletes with a history of concussion showed significant P3a latency delays [$F(1,37)=4.43$, $P<0.05$] along with significant amplitude reductions [$F(1,37)=5.66$, $P<0.05$] when contrasted with those of controls after Greenhouse–Geisser corrections were applied. Similar between-group effects on the latency of the P3b

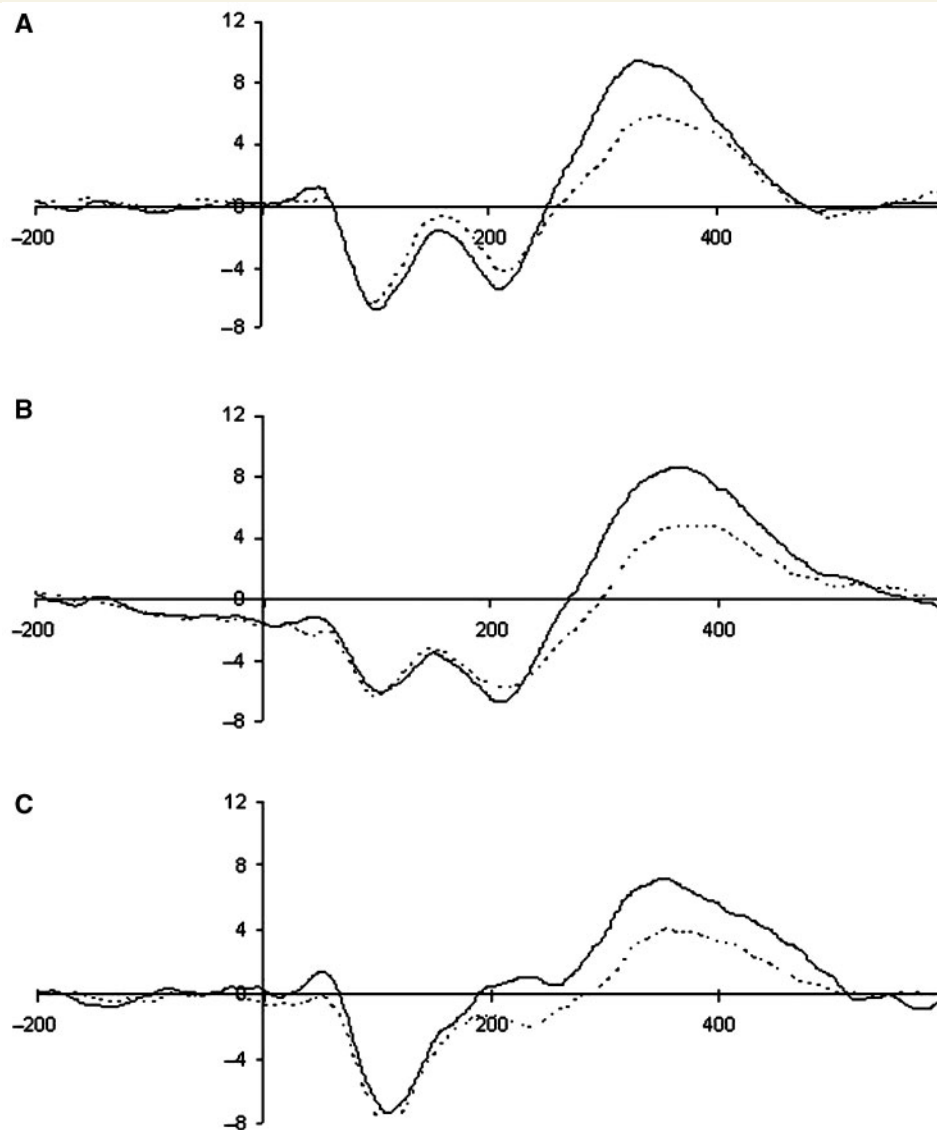


Figure 1 (A) Grand average P3b component evoked by target stimuli and recorded at Pz; (B) grand average P3b component evoked by target stimuli and recorded at Cz; (C) grand average P3a component evoked by deviant non-target stimuli and recorded at Fz. Group of former athletes with no prior concussion history: continuous black trace; group of former athletes with a history of sports concussion in early adulthood: dotted black trace.

Table 2 Between-group difference on the mean P3a/P3b components amplitude (μV) and latency (ms) recorded at Fz and Pz, respectively

Measures	Controls Mean (SD)	Concussed Mean (SD)	F	P
P3a				
Amplitude	4.50 (2.32)	2.94 (1.67)	5.67	<0.05
Latency	359.6 (35.5)	387.2 (44.9)	4.43	<0.05
P3b				
Amplitude	5.25 (2.11)	4.18 (1.99)	2.57	>0.05
Latency	362.9 (28.9)	397.6 (57.0)	5.58	<0.05

component were found at both Cz [$F(1,37)=6.47$, $P<0.05$] and Pz [$F(1,37)=5.58$; $P<0.05$] after Greenhouse–Geisser correction while the amplitude of the latter component also tended to be attenuated at Pz in former athletes with concussion [$F(1,37)=2.57$, $P<0.12$].

While none of the two-tailed Pearson correlations computed between P3a amplitude/latency and the RCFT conditions revealed to be significant, the amplitude of the P3a component and accuracy scores of former athletes with concussions at the incongruent condition of the Flanker task was highly significant ($r=0.606$, $P<0.006$) after Tukey's correction for multiple comparisons was applied. The P3a amplitude of former athletes with a prior history of sports concussion was also strongly correlated with the flanker interference effect computed for accuracy scores ($r=-0.710$,

$P < 0.001$) after Tukey's correction for multiple comparisons. When two-tailed Pearson correlations were drawn between the amplitude/latency of the P3b with performance measures on the two neuropsychological tests used in the present study, only the amplitude of the P3b component was found to be significantly correlated with accuracy scores of former concussed athletes at the recognition condition of the RCFT ($r = 0.51$, $P < 0.02$) after Tukey's correction for multiple comparisons.

TMS results

As previously found in younger athletes with concussion, only the duration of the CSP was found to be altered in former athletes with a prior history of concussion relative to controls [$F(1,37) = 8.18$; $P < 0.01$]. Further contrast analyses revealed that former athletes with concussions had significantly longer CSP than controls in each TMS intensity condition [at 110%: $F(1,37) = 8.32$, $P < 0.01$; at 120%: $F(1,37) = 7.54$, $P < 0.01$; at 130%: $F(1,37) = 6.17$, $P < 0.02$] (Fig. 2B). There was no group difference in MT [$F(1,38) = 0.16$; $P > 0.05$] (Fig. 2A), intracortical

inhibition [$F(1,38) = 0.02$; $P > 0.05$] (see Fig. 2D—ISIs of 2 and 3 ms), intracortical facilitation [$F(1,38) = 0.78$; $P > 0.05$] (see Fig. 2D—ISIs of 9 and 12 ms) and input–output curves [$F(1,38) = 2.21$; $P > 0.05$] (Fig. 2C) after Greenhouse–Geisser corrections were applied.

Diadochokinesia (RAM) task results

All four performance measures on a diadochokinesia test appeared to be diminished in former athletes with concussion relative to controls. Only velocity, as a composite measure of Range/Duration, however, was found to be significantly slower in former athletes with concussion relative to former athletes with no prior history of concussion [$F(1,32) = 8.08$, $P < 0.01$]. This significant group difference is not surprising considering that former athletes with concussion took more time on average to complete a pronation–supination cycle that exhibited reduced angular displacement (Range). Sharpness also tended to be diminished in former athletes with concussion relative to controls although

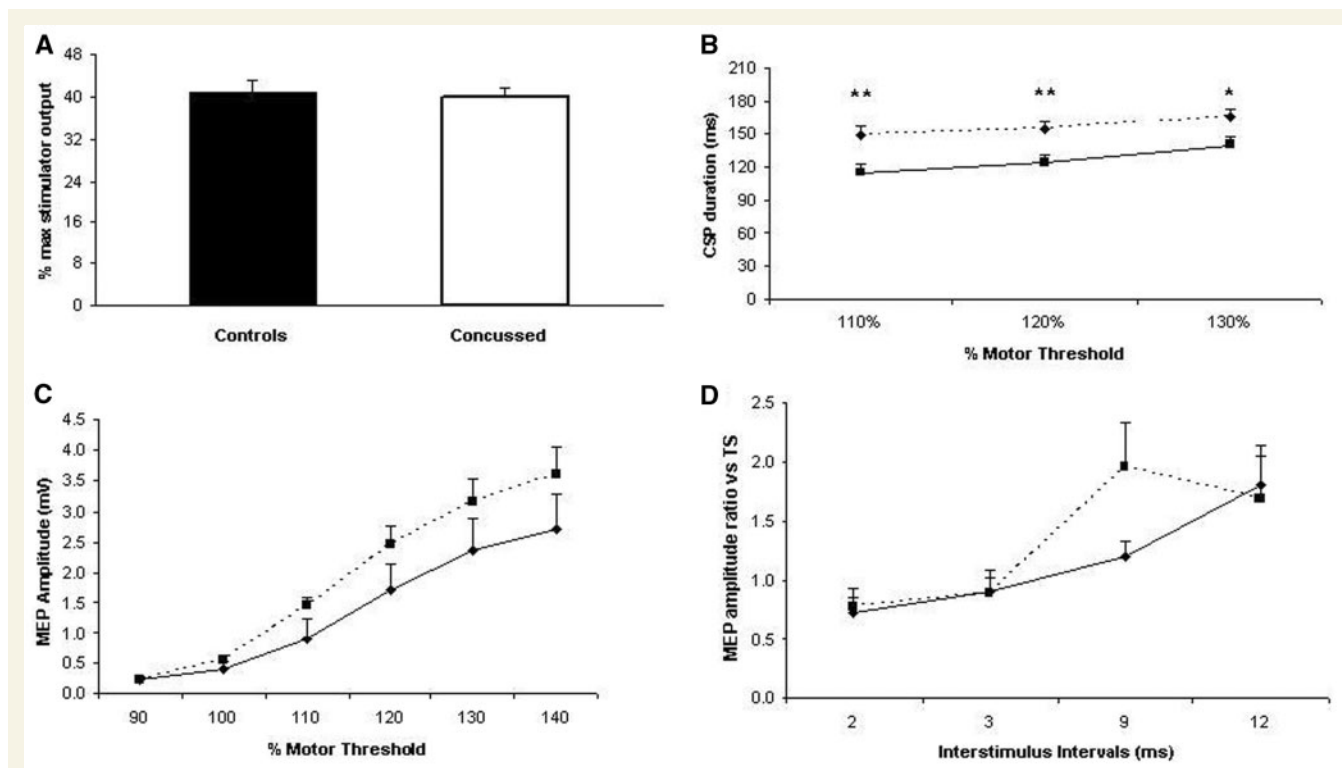


Figure 2 (A) Resting MT values expressed as a percentage of the maximum stimulator output for each experimental group [Former athletes with a prior history concussion (Concussed); Former athletes with no prior history of concussion (Controls)]; (B) CSP duration (in ms) when TMS of three different intensities (110, 120 and 130%), expressed as a percentage of the resting MT, are applied to the vertex while participants in each experimental group exert a voluntary isometric muscle contraction of the FDI muscle of the right hand at ~10% of maximum strength; (C) input/output curves for each experimental group showing the average MEP amplitude (in mV) when increasing TMS intensities (90, 100, 110, 120, 130 and 140%), expressed as a percentage of the resting MT, are applied to the vertex; (D) paired-pulse paradigm showing the ratio between MEP amplitude elicited when increasing ISI duration (2, 3, 9 and 12 ms) separate the conditioning stimulus from the test stimulus relative to the mean amplitude elicited by the test stimulus alone (TS). Group of former athletes with no prior concussion history: continuous black trace; group of former athletes with a history of sports concussion in early adulthood: dotted black trace. Error bars illustrated in Fig. 2A–D represent SE values. * $P < 0.05$; ** $P < 0.01$.

this between-group difference did not reach significance [$F(1,32)=2.190$, $P<0.12$] (Fig. 3).

The duration of the CSP elicited by TMS delivered at 120 and 130% of the resting MT was highly correlated with motor execution velocity when the dominant hand was rotating with the non-dominant hand immobile (at 120%: $r=-0.669$, $P<0.01$; at 130%: $r=-0.564$, $P<0.02$) as well as when both hands were simultaneously performing pronation–supination cycles (at 120%: $r=-0.567$, $P<0.03$; at 130%: $r=-0.501$, $P<0.02$) after Tukey's correction for multiple comparisons was applied.

None of the motor or cognitive measures that were found to be significantly altered in former athletes with concussions correlated either with the number of concussions sustained, the time elapsed since the last concussion or the severity of concussions sustained.

Discussion

The current study unveils that relative to a group of former athletes with no prior history of sports concussion, former athletes who sustained their last sports concussion more than 30 years ago: (i) exhibit cognitive and motor system alterations that closely resemble those found in previous electrophysiological and TMS studies conducted with asymptomatic concussed athletes tested at three years post-concussion (De Beaumont *et al.*, 2007a, b); (ii) show significant reductions on neuropsychological as well as electrophysiological measures of episodic memory and frontal lobe functions selected for their known sensitivity to MCI and early-onset Alzheimer's disease; and (iii) display significant motor execution slowness on a diadochokinesia task that significantly correlated with the duration of the TMS-induced CSP.

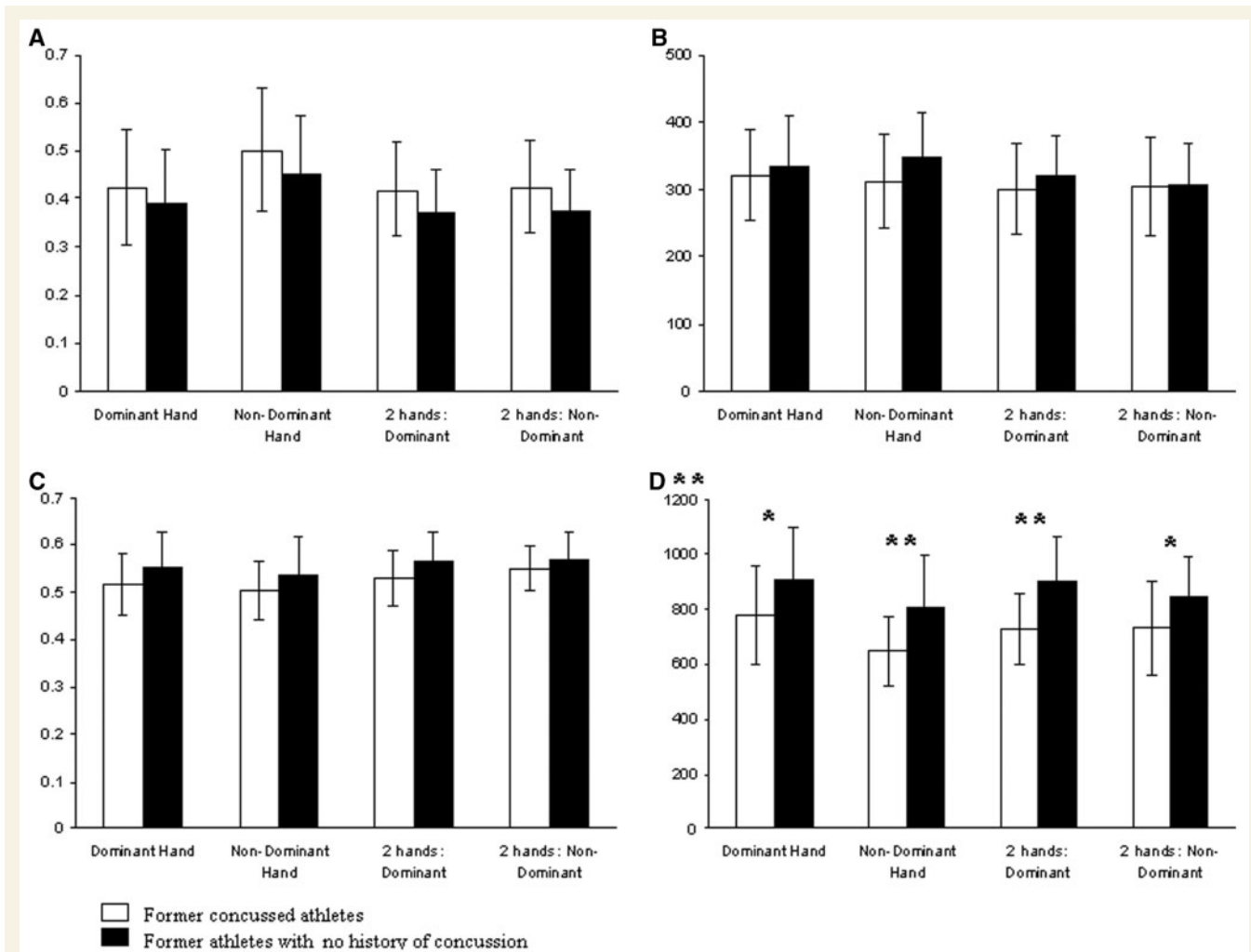


Figure 3 (A) Duration: Mean duration of a cycle of pronation and supination (in seconds); (B) range: mean angular displacement per cycle averaged over all cycles for all subjects (in degrees); (C) sharpness: mean of pronation and supination normalized velocities (Okada and Okada, 1983) averaged over all cycles for all subjects (the larger the number the less delay there is at the turn); (D) velocity: mean velocity for each cycle averaged over all cycles for all subjects (in degrees per second). Group of former athletes with no prior concussion history: black bar of the histogram; Group of former athletes with a history of sports concussion in early adulthood: white bar of the histogram. Error bars illustrated in Fig. 3A–D represent SD values. * $P<0.05$; ** $P<0.01$.

The findings of P300 component abnormalities in former athletes tested at 30 years post-concussion closely resemble those reported previously in athletes tested at three years post-concussion (De Beaumont *et al.*, 2007a). This suggests that P300 abnormalities may be an early and long-lasting manifestation among former athletes who sustained sports concussions in early adulthood. The three-tone auditory oddball paradigm used in this study in order to elicit both P3a and P3b subcomponents of the P300 further refined our current understanding of the persistent cognitive sequelae associated with sports concussions. While experimental groups were nearly as accurate and took an equivalent amount of time to respond to the target stimulus of the three-tone auditory oddball paradigm, P3b waveforms elicited by the target stimulus were significantly delayed in former athletes with a prior history of sports concussion relative to the control group. This finding is not surprising considering that P3 latency was shown to be unrelated to response selection processes (McCarthy and Donchin, 1981; Pfefferbaum *et al.*, 1986) and independent of behavioral response time (Duncan-Johnson and Donchin, 1980; Ilan and Polich, 1999). P3 latency is rather considered as a measure of stimulus classification speed (Kutas *et al.*, 1977; Polich, 1986) such that longer latencies are associated with worse performance on neuropsychological tests that assess how rapidly attentional resources can be allocated for memory processing (Polich *et al.*, 1983; Emmerson *et al.*, 1989; Reinvang, 1999). Interestingly, a similar increase in latency of the P3b component has recently been described in MCI relative to age-matched controls (Golob *et al.*, 2007). The amplitude of the P3b component also tended to be suppressed in former athletes with concussions when compared with controls. Previous studies demonstrated that the latter P300 component reflects memory updating (Johnson and Donchin, 1978) such that greater P3b amplitude is associated with better performance on memory tasks (Wickens *et al.*, 1983; Kramer and Strayer, 1988). In keeping with these findings, the current study disclosed a significant correlation between the amplitude of the P3b and performance scores on an episodic memory task, such that former athletes with a prior history of sports concussion whose P3b amplitude was more suppressed obtained lower scores at the recognition condition of the RCFT.

In the same vein, the P3a brain response elicited by the infrequent distractor stimulus of the three-tone oddball paradigm, for which participants were instructed to withhold their response, was significantly suppressed and delayed in the group of former athletes with concussion relative to the control group. P3a latency delays and amplitude reductions were shown to reflect reduced frontal lobe function efficiency particularly affecting one's ability to shift attentional resources to novel stimuli (Comerchero and Polich, 1999; Nordby *et al.*, 1999; Polich, 2004; Kopp *et al.*, 2006). In particular, a recent study demonstrated that unsuccessful inhibitions on incongruent trials of a modified Flanker arrow test were associated with lower P3a amplitude in both attention-deficit hyperactivity disorder (ADHD) patients and normal controls (Liotti *et al.*, 2005). The results from the present study are consistent with those findings as former athletes with concussion who made more errors on the incongruent flanker condition of the arrow Flanker task exhibited greater P3a amplitude reductions. It therefore seems that former concussed athletes with reduced P3a

amplitude who also perform more poorly on the incongruent condition of the flanker task have reduced inhibitory capacities relative to former athletes with greater P3a amplitude.

Besides P300 subcomponents alterations similar to those found in MCI patients (Golob *et al.*, 2007), former athletes with a prior history of sports concussion displayed significant episodic memory and attention/executive functions decrements on neuropsychological tests selected for their proven sensitivity to MCI and early onset AD. Episodic memory decline in former athletes with concussion relative to controls was found at the recognition condition of the RCFT, while immediate and delayed recall scores of the RCFT also tended to be lower. Interestingly, visual recognition memory impairments were recently found early in the course of patients with MCI (Barbeau *et al.*, 2004). The acute sensitivity of visual recognition memory tests to MCI was related to the distribution of neurofibrillary tangles (NFT), which is known as a core neuropathological hallmark of Alzheimer's disease (Selkoe, 1991). Clinical symptoms of Alzheimer's disease have been shown to correlate with the distribution of NFT (Arriagada *et al.*, 1992; Delacourte *et al.*, 1999). NFT initially develop in a subregion of the perirhinal cortex corresponding to Brodmann area 35 (Braak and Braak, 1991; Van Hoesen *et al.*, 1991). Animal studies have shown severe visual recognition memory impairments consecutive to perirhinal cortex lesion (Meunier *et al.*, 1993; Squire and Zola, 1996), while hippocampal damage did not impair performance (Murray and Mishkin, 1998). Similar visual recognition memory sparing was found in a patient with damage limited to the hippocampus (Mayes *et al.*, 2002). Although speculative, the greater visual recognition memory decline found in a group of former athletes with concussion relative to free recall conditions of the RCFT might be indicative of early stage NFT distribution within perirhinal cortex.

In parallel, response inhibition decline in former athletes with concussion relative to controls was revealed on a classic arrow Flanker task. While the two experimental groups obtained equivalent performance scores on both congruent and no flanker conditions of the arrow Flanker task, former athletes with concussion made significantly more errors than controls at the incongruent condition of the arrow Flanker task. The same pattern of results—namely increased response inhibition difficulties along with unaltered performance scores at the congruent condition of an arrow flanker task—was recently obtained in a group of MCI patients relative to controls (Wylie *et al.*, 2007). This significant flanker interference effect suggests that both MCI patients and former athletes who sustained their last sports concussion in early adulthood experience significantly more difficulties than controls to inhibit responses evoked by a competing source of interference. These deficits on neuropsychological tests of episodic memory and response inhibition are fairly robust bearing in mind that they were found in a group of highly educated former concussed athletes who maintained an active lifestyle and presented with no medical condition requiring daily medication. This is in sharp contrast with most neuropsychological studies of sports concussion conducted with young athletes that typically show return-to-baseline performance levels within a few weeks post-injury (McCrary *et al.*, 2005). This study therefore demonstrates that having sustained sports concussion more than 30 years ago

induces significant response inhibition and episodic memory decline measurable on both ERP and classic neuropsychological tests particularly sensitive to MCI and early-onset Alzheimer's disease.

Along with the higher prevalence of MCI found in former athletes with concussion (Guskiewicz *et al.*, 2005), research on age-associated compensatory mechanisms could help explain why neuropsychological tests performance alterations that most often resolve within 10 days post-injury resurface more than 30 years later. Knowing that P300 amplitude is positively correlated with the amount of attentional resources allocated to a particular task (Polich, 1988), a recent electrophysiological study used the P300 waveform component to assess how high versus average performing old, middle-age and young adults allocated processing resources on an attentional task (Riis *et al.*, 2008). Results from their study showed that P300 amplitude was significantly greater in high performing old adults relative to average performing old adults, whereas the amplitude of the P300 component did not differ between high versus average performing younger subjects. These findings suggest that high performing older adults managed the task by a compensatory neural mechanism associated with the allocation of more resources, as indexed by greater P300 component amplitude. Sports concussions may induce reductions in the ability to allocate attentional resources to a particular task for which former athletes with concussion who reached late adulthood can no longer compensate as efficiently as young concussed athletes. Follow-up studies would thus be required if we were to verify the potential relationship between the effects of remote sports concussion on cognition found in this study (i.e. pervasive P3a/P3b changes coupled with the lower performance on episodic memory and executive functions measures) and the likelihood of developing more severe cognitive symptoms associated with MCI. In addition, longitudinal studies are needed to determine whether sports concussions induce latent changes in cognitive function that come to surface with increasing age rather than simply acting as an accelerating agent to the aging process. Premature aging purports serious clinical implications considering that increasing age is the most potent risk factor of Alzheimer's disease (Lindsay *et al.*, 2002; Borenstein *et al.*, 2006).

The TMS assessment of motor cortex excitability performed in this study showed that the CSP was significantly prolonged in former athletes who sustained their last sports concussion more than three decades prior to testing. This is consistent with previous findings from our group that demonstrated CSP prolongation in concussed university level football players tested on average three years post-injury (De Beaumont *et al.*, 2007b). Along with their prolonged CSP relative to controls, former athletes with a prior history of sports concussion exhibited a significant slowness of movement, or bradykinesia, on a RAM task. Further correlational analyses established a strong relationship between the duration of the CSP and the movement velocity at the RAM task, such that former concussed athletes with more prolonged CSP tended to be slower at executing pronation–supination cycles. This finding suggests that the altered neurophysiological mechanisms that lengthen the CSP in concussed athletes could well be implicated among biological bases of the slowness of movement seen in former athletes with concussion when performing a RAM task.

This significant slowness to execute RAM task cycles was found in former athletes with concussion who do not otherwise report experiencing motor difficulties in their daily activities. This is consistent with a recent study that showed motor slowness on a RAM task in Parkinson's disease patients in the very early stage who had yet to experience the more debilitating symptoms of the degenerative disease (Koop *et al.*, 2008). It remains to be verified in further longitudinal studies whether former concussed athletes who were experiencing early signs of movement slowness at the time of testing will go on to develop incapacitating motor symptoms.

It is interesting to note that alterations in motor cortex excitability were limited to CSP duration whereas MT and intracortical inhibition/facilitation values were normal in formerly concussed athletes. Intracortical facilitation appears to involve glutamatergic neurons and NMDA receptors while short-interval intracortical inhibition is related to GABA_A receptors (Reis *et al.*, 2008). MT, for its part, is believed to reflect membrane excitability (Ziemann, 2004). The selective impairment in motor cortex excitability reported here suggests that the long-term effects of concussions are restricted to specific mechanisms within the motor cortex that may preferentially involve certain receptor subtypes. Although the neurophysiological underpinnings of the CSP remain debated, several studies have suggested that the duration of the CSP reflects GABA transmission, GABA_B receptor activity in particular (Siebner *et al.*, 1998; Werhahn *et al.*, 1999; Pierantozzi *et al.*, 2004; McDonnell *et al.*, 2006; Moller *et al.*, 2007). The CSP has proven to be sensitive to various neurological conditions such as sports concussions (De Beaumont *et al.*, 2007b), cerebellar ataxia (Restivo *et al.*, 2004), stroke (Catano *et al.*, 1997), Parkinson's disease (Cantello *et al.*, 2002), epilepsy (Macdonell *et al.*, 2001; Tataroglu *et al.*, 2004) and others (Tinazzi *et al.*, 2005; Lefaucheur *et al.*, 2006). Among those brain pathologies, sports concussions and cerebellar ataxia have both been associated with slowness of movement (Oechsner and Zangemeister, 1999; Restivo *et al.*, 2004). The sensitivity of the CSP to various neurological disorders coupled with its potential contribution to understanding motor symptoms such as bradykinesia stress the need to further investigate the likely involvement of GABA_B receptor activity in the modulation of the CSP.

Interestingly, a recent diffusion tensor imaging study (Kraus *et al.*, 2007) has shown reduced white matter integrity in the cortico-spinal tract, sagittal stratum and superior longitudinal fasciculus in mild TBI patients. Moreover, an index of global white matter neuropathology was related to cognitive function (attention/executive functions and memory domains) such that greater white matter pathology predicted more severe cognitive deficits. Thus, both the motor and cognitive phenomena observed in the present study could be accounted for by specific changes in white matter density. Although the significant motor slowness found in former athletes with concussion relative to controls was not associated with functional losses at the time of testing (all participants were still engaging in physical activity three times a week), it would be pertinent to follow those athletes to assess whether they develop more severe debilitating motor symptoms in relation with potential cognitive impairments as they get older.

The fact that only two former athletes from this study presented with three or more sports concussions prevented further comparisons with previous epidemiological findings suggesting increased MCI prevalence in former athletes who reported three or more sports concussions (Guskiewicz *et al.*, 2005). Alternatively, the present study provides preliminary evidence that having sustained only one or two concussions has the potential for cognitive and motor functions alterations observable in late adulthood. Further studies specifically looking at the magnitude of cognitive and motor alterations as a function of the number of previous sports concussion sustained is required if we are to clarify this issue.

One of the main limitations to the present study concerns the retrospective self-reports used to describe the history of sports concussion. Although we appreciate the clear advantages offered by prospective data over self-reports, sports concussions that occurred more than 30 years ago were for the most part overlooked by sports therapists unless LOC or post-traumatic amnesia were involved (Ward, 1964). To alleviate the risks of group misclassifications associated with self-reports of rather remote incidents, participants who reported being uncertain about their answers to the concussion history form were excluded from further analyses. Consequently, all former athletes in the concussion group reported having sustained at least one episode of either Grades 2 or 3 concussions while none reported having exclusively sustained Grade 1 concussions. The stringent set of exclusion criteria used to restrict participation only to healthy former athletes together with the absence of concussion victims who exclusively reported Grade 1 concussions limit the generalization of our findings to a subset of the population of former athletes with a prior history of concussion. Nevertheless, our findings provide compelling evidence that a history of sports concussions sustained early in life, in which the most severe injury was either a Grades 2 or 3 concussion, exert detrimental effects on cognition and motor system function. Further replications of the present study with a broader sample of former athletes that present with more diverse sports concussions history characteristics obviously need to be undertaken in order to assess whether sports concussions may be considered a risk factor in the early deterioration of brain functions.

Funding

Natural Sciences and Engineering Research Council of Canada (to M.L., H.T.); Canada Research Chairs programme (to M.L.); Canadian Institutes of Health Research postgraduate scholarships (to L.D.B.).

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