Université de Montréal

The Long-Term Effects of Sports Concussion

par
Louis De Beaumont

Département de psychologie
Faculté des Arts et des Sciences

Thèse présentée à la Faculté des Études Supérieures et postdoctorales
en vue de l'obtention du grade de doctorat
en Psychologie – Recherche et Intervention
option Neuropsychologie clinique

Octobre 2009

Université de Montréal
Faculté des études supérieures et postdoctorales

Cette thèse intitulée :

The Long-Term Effects of Sports Concussion

Présentée par :
Louis De Beaumont

a été évaluée par un jury composé des personnes suivantes :

Michelle McKerral, président-rapporteur
Maryse Lassonde, directeur de recherche
Miriam Beauchamp, membre du jury
John Scott Delaney, examinateur externe
Robert Forget, représentant du doyen de la FES

List of abbreviations

3D: three dimensional
AAN: America Academy of Neurology
AD: Alzheimer's disease
AGA: Anterograde amnesia
AP: Anteroposterior
ApEn: Approximate entropy
ApoE4: Apolipoprotein epsilon 4
BTVM: Brief Test of Visual Memory
Ca+: Calcium ion
CIHR: Canadian Insitute of Health Research
CND: Canadian
COP: Centre-of-pressure
CS : Conditioning stimulus
CSF: Cerebrospinal fluid
CSP: Cortical silent period
CT: Computerised tomography
DTI: Diffusion Tensor Imaging
EEG: Electroencephalography
EMG: Electromyography
EOG: Electrooculogram
ERPs: Event-Related Potentials
FDI: First dorsal interrosseus
GABA: Gamma-Aminobutyric Acid
GCS : Glasgow Coma Scale
HEOG: Horizontal electrooculogram
Hz: Hertz
ICF: Intracortical facilitation
ICI: Intracortical inhibition
ISI : Interstimulus inhibition
K+: Potassium ion
LED: Light-emitting diode
LICI: Long-interval intracortical inhibition
LOC: Loss of consciousness
LTP: Long-term potentiation
M1: Primary motor cortex
MCI: Mild cognitive impairment
MEP: Motor evoked potential
ML: Mediolateral
MMSE: Mini-Mental Status Examination
MRI: Magnetic Resonance Imaging
Ms : milliseconds
MT: Motor threshold
mTBI: mild traumatic brain injury
NCAA: National Collegiate Athletic Association
NFT: Neurofibrillary tangles
NMDA: N-methyl-D-aspartate

NSERC: Natural Sciences and Engineering Research Council of Canada
PAS: Paired-associative stimulation
PCS: Post-Concussion Symptoms Scale
PSU: Pennsylvania State University
RAM Rapid Alternating Movement
RCFT: Rey-Osterrieth Complex Figure Test
RGA: Retrograde amnesia
RMS : Root mean square
rMT: resting motor threshold
S1: Primary somatosensory cortex
SAI: Short-afferent inhibition
SCAT: Sport Concussion Assessment Tool
SD: Standard deviation
SDMT: Symbol Digit Modalities Test
SE : Standard Error
TAI: Traumatic axonal injury
TBI : Traumatic brain injury
TMS: Transcranial Magnetic Stimulation
TS : Test stimulus
US: United States
VEOG: Vertical electrooculogram

Résumé

Questions : Cette thèse visait à répondre à deux questions fondamentales : 1) Est-ce que les athlètes qui présentent un historique de commotions cérébrales du sport en conservent des effets délétères à long terme? ; et 2) Est-ce que les effets néfastes des commotions cérébrales récurrentes sur le fonctionnement tant cognitif que moteur sont cumulatifs? **Devis expérimental :** À l'aide d'un plan d'investigation double-cohorte réalisé avec un groupe d'athlètes évoluant au niveau universitaire et un autre formé d'anciens athlètes universitaires testés plus de trois décennies plus tard, les quatre études qui composent cette thèse ont employé des méthodes raffinées d'investigation des fonctions cognitives et motrices pour en déceler des atteintes persistantes. **Méthodologie :** Les potentiels évoqués cognitifs ainsi que les tests neuropsychologiques ont permis de sonder le fonctionnement cognitif de ces athlètes alors que la stimulation magnétique transcrânienne, une plateforme de force permettant de mesurer la stabilité posturale ainsi qu'un système d'enregistrement tridimensionnel des mouvements rapides alternatifs ont servi à l'évaluation de l'intégrité du système moteur. **Résultats :** Cette thèse a permis de déceler des altérations persistentes et cumulatives des fonctions cognitives et motrices. De plus, ces subtiles atteintes observées chez les jeunes athlètes, affectant essentiellement des marqueurs neurophysiologiques sous-cliniques du fonctionnement cognitif et moteur, s'étaient accentuées chez les anciens athlètes universitaires qui montraient un déclin quantifiable tant des fonctions cognitives que motrices. **Discussion :** Ces résultats suggèrent d'une part que les commotions cérébrales du sport entraînent des altérations cognitives et motrices chroniques qui s'accentuent en fonction du nombre de commotions cérébrales subies. D'autre part, les effets délétères des commotions cérébrales du sport sur le fonctionnement cognitif et moteur combinés à ceux associés au processus de vieillissement entraînent un déclin cognitif et moteur quantifiable en comparaison aux anciens athlètes n'ayant jamais subi de commotions cérébrales.

Mots-clés : Commotions cérébrales du sport, effets à long terme, neuropsychologie, neurophysiologie, déclin cognitif, système moteur, excitabilité du cortex moteur, potentiels évoqués cognitifs, stimulation magnétique transcrânienne, stabilité posturale, mouvements rapides alternatifs.

Abstract

Question: This thesis aimed to address two fundamental issues: 1) Are there long-lasting effects of sports-related concussion on cognitive and motor functions? and 2) Are the adverse effects of recurrent concussions cumulative? **Experimental Design:** The cross-sectional thesis design included a group of active university-level athletes as well as a group of former athletes recruited more than three decades after their university years who were tested on neurophysiological measures of both cognitive and motor system functions. **Methods:** Event-Related potentials and neuropsychological tests were used to assess cognitive functions while transcranial magnetic paradigms were used to assess motor cortex excitability, a force platform was used to assess postural stability and a 3-dimensional recording device was used to track hand position when performing a rapid alternating movement task. **Results:** This thesis disclosed persistent and cumulative alterations of both cognitive and motor functions after sports concussions. Furthermore, subclinical, neurophysiological alterations found in young concussed athletes were exacerbated in former athletes with concussions who displayed quantifiable cognitive and motor functions decline more than three decades post-concussion. **Discussion:** These results suggest that sports concussions induce cognitive and motor functions abnormalities that worsen as a function of the number of concussions sustained. Moreover, findings from the present thesis indicate that the deleterious effects of sports concussion on cognitive and motor system functions combined to those associated with the aging process lead to quantifiable decline on both cognition and motor functions.

Keywords : Sports concussions, long-term effects, neuropsychology, neurophysiology, cognitive decline, motor system, motor cortex excitability, event-related potentials, transcranial magnetic stimulation, postural stability, rapid alternating movements.

Table des matières

Liste des tableaux

Liste des figures

This thesis is dedicated to those who suffer
from this silent epidemic….

Remerciements

Devant l'impossibilité de remercier tous ceux qui ont influencé ma formation depuis le tout jeune âge jusqu'à son achèvement, je m'en tiendrai à souligner l'apport tout spécial de personnes qui se sont avérées essentielles à la réussite de mon parcours doctoral.

À ma directrice de recherche Maryse Lassonde. Premièrement, je vous remercie infiniment de la liberté et de la confiance que vous m'avez accordée. Vous avez été à travers ces années un modèle inspirant tant par vos accomplissements exceptionnels que par vos qualités humaines.

À Hugo Théoret. Je te remercie de tout le temps que tu m'as consacré depuis ces dernières années. Toujours à l'écoute, tu as su par la justesse et la profondeur de tes interventions m'inspirer à me dépasser.

À Martin Thériault. Ton amitié, humanisme et support inconditionnel m'ont été absolument nécessaires. Merci mon vieux !

À Sébastien Tremblay. Merci infiniment pour ton amitié, ton intégrité, ta loyauté, ta confiance, et ton éthique de travail. Travailler en étroite collaboration avec toi depuis les quelques dernières années a été pour moi un immense privilège. Tu me manqueras.

À mes parents. Merci pour votre amour. La rigueur et l'éthique de travail que vous m'avez transmises m'ont donné l'essentiel.

À ma Maude. Merci pour tout le reste.

1. Introduction

1.1. WHAT A TRAUMATIC BRAIN INJURY IS…

1.1.1. Definition and Prevalence

A traumatic brain injury (TBI) is caused by a blow or jolt to the head or a penetrating head injury that disrupts the function of the brain. Not all blows or jolts to the head result in a TBI. The severity of a TBI may range from "mild," i.e., a brief change in mental status or consciousness to "severe," i.e., an extended period of unconsciousness or amnesia after the injury (Langlois, Rutland-Brown, & Wald, 2006).

TBI subtypes

i. **Open (penetrating) head injury:** An open head injury occurs when a high-velocity object (projectile) fractures the skull and lesions brain tissues or the surrounding membranes. The open wound created by such insertion of a projectile into brain structures renders open head injury victims at risk from infection and contamination. Accidents involving firearms account for nearly 40% of all TBI-related deaths in the United States (Control, 2003).

ii. **Closed head injury:** A closed head injury occurs when kinetic energy of varying magnitude is applied to the head without fracturing the skull. The ensuing consequences of a closed head injury are directly related to the force of the impact as the brain is damaged when colliding against the skull wall. Closed head injuries account for the vast majority of TBI cases (Control, 2003).

Recent data from the Centers for Disease Control and Prevention (2003) show that, on average, approximately 1.4 million people sustain a TBI each year in the United States. TBI represents the most prevalent cause of long-term or lifelong disability among adults and annual costs, whether direct medical costs or indirect costs such as lost productivity, amounted to 60 billion dollars in the United States in 2000 (Langlois et al., 2006). Males are about twice as likely as females to sustain a TBI (Langlois et al., 2006). About 75% of those accidents are concussions or other forms of mild TBI (Control, 2003) and leading causes of TBI are falls (28%), motor vehicle accidents (20%), collisions (20%), and assaults (11%). While similar Canadian statistics on TBI and its consequences are still lacking, recent evidence collected in the province of Ontario found roughly equivalent incidence rates of mild TBI admitted to Emergency Departments to those reported in the United States (Guerrero, Thurman, & Sniezek, 2000; Ryu, Feinstein, Colantonio, Streiner, & Dawson, 2009).

The conceptual definition of a mild traumatic brain injury proposed by the Centers for Disease Control and Prevention (2003) is an injury to the head as a result of blunt trauma or acceleration or deceleration forces that result in one or more of the following conditions:

- **Any period of observed or self-reported**:

  - Transient confusion, disorientation, or impaired consciousness;

  -Dysfunction of memory around the time of injury;

  - Loss of consciousness lasting less than 30 minutes.

- **Observed signs of neurological or neuropsychological dysfunction, such as:**

  - Seizures acutely following injury to the head;

  - Among infants and very young children: irritability, lethargy, or vomiting following head injury;

  - Symptoms among older children and adults such as headache, dizziness, irritability, fatigue or poor concentration, when identified soon after injury, can be used to support the diagnosis of mild TBI, but cannot be used to make the diagnosis in the absence of loss of consciousness or altered consciousness.

1.1.2. Severity of TBI

The severity of a TBI may range from "mild," i.e., a brief change in mental status or consciousness to "severe," i.e., an extended period of unconsciousness or amnesia after the injury (Langlois et al., 2006). The Glasgow Coma Scale (GCS) is the TBI severity scale now used in most hospitals and emergency departments throughout the world (1988). Introduced in 1974 as a means of assessing depth and duration of impaired consciousness and coma, the GCS was also created for use in gauging deterioration or improvement at the emergent and acute stages of brain damage or lesions, as well as in predicting the ultimate outcome (G. Teasdale & Jennett, 1974). By observing a patients' eye opening, verbal performance, and motor response, the GCS allowed to more accurately define gradations in the comatose state than by only measuring duration of unconsciousness. Patient' condition is assessed on three distinct aspects of consciousness (eye opening on a scale of 4 to 1, motor response on a scale of 6 to 1, and verbal response on a scale of 5 to 1) with the sum

total of scores of the three categories resulting in the total GCS score. When using the GCS as a classification measure of TBI severity, patients achieving total scores of 8 or less are classified as "in coma" or having a severe TBI, scores of 9 to 12 are classified as moderate TBI, and 13 to 15 as mild TBI or no head injury.

Figure 1: Glasgow Coma Scale

EYE OPENING	
Spontanous	4
To speech	3
To pain	2
No opening	1
VERBAL RESPONSE	
Conversation	5
Confused	4
Non Sense	3
To sounds	2
No Response	1
MOTOR RESPONSE	
To command	6
Localizing	5
Arm flexion	4
Arm extension	3
Generalizing	2
No response	1

1.2. SPORTS CONCUSSION AS A SUBTYPE OF MILD TBI

1.2.1. Prevalence and public awareness

Among causes of mild TBI which represent nearly 80% of all cases of TBI (Ruff, 2005), sports concussions are by far the most prevalent as recent epidemiological data estimated that nearly 50,000 to 300,000 contact sports athletes in the United States sustain a concussion every year (Control, 2003).

Epidemiological data gathered from 100 US high schools and 180 colleges were analyzed to calculate rates, describe patterns, and evaluate potential risk factors for sport-related concussion across different sports. This study showed that nearly 41% of all concussion cases resulted from participation in football (Gessel, Fields, Collins, Dick, & Comstock, 2007). However, a recent study showed that ice hockey, soccer and football had comparable yearly rates of concussions per 10 000 players who were admitted to the Emergency Departments in the United States (Delaney, 2004). It therefore seems that these three contact sports involve equivalent risk of concussions. The aforementioned epidemiological study also showed that the greatest incidence of concussion was found at the high school (5.6%) and collegiate division III (5.5%) levels, suggesting that there is an association between level of play and the proportion of players injured (Gessel et al., 2007). Moreover, another epidemiological study found that players who sustained one concussion in a season were three times more likely to sustain a second concussion in the same season compared with uninjured players (Guskiewicz, Weaver, Padua, & Garrett, 2000).

Most alarming, the number of concussions occurring is most likely underestimated. According to a study conducted by McCrea and colleagues (2004), 49% of athletes in high school who sustain a concussion did not report it. The main reason evoked is that the seemingly benign post-concussion symptoms are not severe enough to be reported. Likewise, a study conducted by Delaney and collaborators (Delaney, Lacroix, Leclerc, & Johnston, 2000) revealed that 44.8% of athletes in the Canadian Football League reported having experienced post-concussion symptoms in the years prior to the study. Among them, only 18.8% recognized having sustained a concussion.

In spite of these disconcerting findings, the reported incidence of sports concussions has grown at an accelerated pace over the last 15 years and is now considered a major public health concern (Kelly, 1999). New discoveries on the pervasive effects of sports concussions together with recurrent injuries occurring to high-profile professional athletes have contributed to raising unprecedented public awareness that the effects of concussions were not as benign as what was once thought.

1.2.2. Definition

According to the Prague Summary and Agreement Statement on concussion in sports (P. R. McCrory et al., 2005), sports concussion is defined as a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces. This definition was further broken down to include a range of clinical, pathological and biomechanical features intrinsic to sports concussions:

1. Concussion may be caused by a direct blow to the head, face, neck, or elsewhere on the body with an "impulsive" force transmitted to the head;

2. Concussion typically results in the rapid onset of a short lived impairment of neurological function that resolves itself spontaneously;

3. Concussion may result in neuropathological changes but the acute clinical symptoms largely reflect a functional disturbance rather than structural injury;

4. Concussion results in a graded set of clinical syndromes that may or may not involve loss of consciousness. Resolution of the clinical and cognitive symptoms typically follows a sequential course;

5. Concussions are typically associated with grossly normal structural anatomy as revealed by magnetic resonance imaging (MRI) and computerised tomography (CT) scan .

1.2.3. Classification of sports concussions

Based on recommendations from the Summary and Agreement Statement of the 2nd International Conference on Concussion in Sport (P. R. McCrory et al., 2005), concussion severity can be determined retrospectively and classified as either simple or complex concussion. Simple concussion, which accounts for most sports concussion cases, is defined as a concussion for which associated symptoms resolved within 7-10 days without complications. Complex concussions include cases where athletes suffer persistent

symptoms, specific sequelae (eg, concussive convulsions, prolonged loss of consciousness (>1 minute) or prolonged cognitive impairment following the injury. This group may also include athletes who suffer multiple concussions over time or where repeated concussions occur with progressively less impact force (Iverson, 2007; P. R. McCrory et al., 2005).

Very little is known about interindividual factors intervening to render an athlete more susceptible to fall into the category of complex concussion relative to those who sustain simple concussion. Future studies that systematically look at various concussion characteristics—clinical manifestations (confusion, memory problems, loss of consciousness), anatomical localization (such as cerebral vs. brainstem), biomechanical impact (rotational vs. linear force), genetic phenotype apolipoprotein epsilon 4 (ApoE4) positive vs. ApoE4 negative) and neuropathological changes (structural injury vs. no structural injury) (P. R. McCrory et al., 2005)— are likely to help shed some light on action mechanisms more common to each concussion subtype.

The following sections will discuss in further details the biomechanics and neuropathophysiology of concussive injuries.

1.3. HOW SPORTS CONCUSSIONS OCCUR

1.3.1. Biomechanics of concussive injuries

As most people agree that no two concussions are alike, they all share at least one feature in common. They all involve the near instant transfer of kinetic energy. The brain

floats within a protective shield filled with cerebrospinal fluid called subarachnoid space (Kandel, Schwartz, & Jessell, 2000). Its gelatinous and elastic properties guard the brain from colliding against the walls of the skull when the head is moved. However, when kinetic energy applied to the head exceeds the subarachnoid space cushioning properties, the brain will come into contact with the bones of the skull causing distortion, compression and deformation of neural tissue. The brain absorbs energy as a result of acceleration forces, while deceleration forces cause it to release kinetic energy when colliding with the skull (Shaw, 2002). To date, at least four distinct biomechanical processes have been identified in the induction of a concussive state: 1) Coup and contre-coup impact between the surface of the brain and the walls of the skull; 2) Traction of the brainstem neurons due to forceful movement of the hemispheres; 3) Compression of the skull bone responsible for compression of neural tissue and elevated intracranial pressure levels; and 4) Acceleration of the head about the axis of the brain (Shaw, 2002).

Coup and contre-coup were shown to occur as a result of such acceleration/deceleration forces applied to the brain (Ommaya, Goldsmith, & Thibault, 2002). Sequelae associated with coup injuries are those observed directly beneath the point of impact on the skull while those in contre-coup injuries occur elsewhere on the surface of the cortex, most predominantly opposite to the site of impact (Shaw, 2002). With sudden acceleration injury, movement of the brain lags behind that of the skull whereas deceleration injuries occur as the brain continues to move after the skull has abruptly halted. Football players will often escape being concussed from a direct impact to the head if they tense their neck muscles prior to collision so as to restrict the magnitude of head

motion thereby allowing kinetic energy to be dispersed throughout the whole body instead of being fully absorbed by the brain (R. C. Cantu, 1992). An accelerative/decelerative injury can be sustained either by impact or impulse. Impact involves a direct contact to the head, while impulse refers to an accelerative force that sets the head in motion without directly striking it (Shaw, 2002). Furthermore, acceleration/deceleration forces can either be transferred to the brain in a straight line passing through the head's centre of gravity or in a tangential line and arc around its centre of gravity (Greenwald, Gwin, Chu, & Crisco, 2008). In football, concussions occurring as a result of head-on, helmet-to-helmet collisions are often due to an imbalance between the inertial linear forces carried by each colliding opponent (Broglio et al., 2009; Greenwald et al., 2008). In contrast, rotation of the brain within the skull induced by inertial force transferred to it in a tangential line occurs typically when a player rushing up the field gets hit by an opponent coming from an angle (Broglio et al., 2009).

Abrupt movement of the head due to inertial forces is implicated in more than coup contre-coup types of injuries. Although scarcely documented in the sports concussions literature, cortical, subcortical and brainstem white matter tracts are susceptible to stresses and strains as the cerebrum rotates about its junction with the fixed brainstem (Gentry, 1994; Gentry, Godersky, & Thompson, 1988; Hashimoto, Nakamura, Richard, & Frowein, 1993; Parizel et al., 1998; Paterakis, Karantanas, Komnos, & Volikas, 2000; Shibata, Matsumura, Meguro, & Narushima, 2000). Shearing and stretching of interconnected pathways are common manifestations of inertial forces applied to the brain (Besenski, 2002; Besenski, Broz, Jadro-Santel, Pavic, & Mikulic, 1996; Ommaya et al., 2002;

Ommaya, Rockoff, & Baldwin, 1964). Consequently, the maintenance of alertness and responsiveness, which are activities principally mediated by structures located in the midbrain and upper brainstem, are vulnerable to mechanical disruption by these stresses and strains.

Another type of mechanical brain injury that might possibly be involved in concussive injury is compression of the skull. In this instance, a concussive injury is incurred when the skull temporarily indents or bends at the site of impact without fracturing (Bayly, Black, Pedersen, Leister, & Genin, 2006; Bayly et al., 2005). The newly occupied space triggers pressure waves and pulses as a result of brain tissue compression. These pressure waves and pulses are thought to be diffusely transmitted to the brainstem and to other cranio-cervical junctions (McIntosh et al., 1996). Increases in intracranial pressure are associated with tissue shift or deformation and shearing stresses.

At this time, there is no existing animal or other experimental model that precisely reflects a sporting concussive injury. Experimental models of more severe concussive injuries have proposed that a complex cascade of biochemical, metabolic and gene expression changes occur (Hovda et al., 1995). Whether similar metabolic changes occur in sports concussion remains largely unknown at this time (McIntosh et al., 1996). However, the close resemblance between sports concussion and more severe forms of TBI in terms of neurologic impairments observed immediately post-injury and of residual post-concussion symptoms suggest that the latter share similar underlying mechanisms. Although probably to a lesser extent, it is likely that the biomechanical forces applied to the brain in sports

concussion could be sufficient to induce a sudden, uncontrolled chain reaction similar to the neurometabolic cascade triggered by more severe TBI.

1.3.2. The neuropathophysiology of concussion

Research on the pathophysiology of concussive injuries was initially instigated in order to elucidate the neurometabolic cascade that preceded diffuse axonal injury, which was held responsible for the symptoms of the post-concussion syndrome. Early work conducted by Courville (1953) suggested that the nature of these post-concussion symptoms was intimately related to the susceptibility of certain brain areas to traumatic blows to the head. As Courville (1953) demonstrated decades ago, neuronal tissues located within close vicinity of the frontotemporal bones are most vulnerable to mechanical strains and stresses induced by concussive injury which, in turn, prevent affected neuronal assemblies to play their usual role on brain function. For instance, memory deficits that often occur following concussive injuries could readily be explained by temporarily disturbed connections within the medial temporal lobe, while deficits in learning, emotional decoding, inhibition, difficulty related to decision-making in unstructured situations, and an inability to regulate behaviour according to internal goals and constraints could just as well be explained by momentarily compromised communication within the ventromedial portion of the prefrontal cortex (Pandya & Yeterian, 1996).

Although diffuse axonal injury is common subsequent to moderate or severe TBI (Povlishock, Becker, Cheng, & Vaughan, 1983; Povlishock & Katz, 2005), compelling evidence from animal work showed that the pathophysiology of mild TBI leaves neurons

and neuronal systems vulnerable but not destroyed (Iverson, 2005). Recent high-spatial resolution neuroimaging studies confirmed previous animal work suggesting preserved neuronal integrity following mild TBI (Aubry et al., 2002) despite the enduring belief that post-TBI symptoms are due to diffuse axonal damage. What is rather observed in mild TBI patients is a gradual process in which a very small proportion of badly damaged axons swell and eventually separate, while the vast majority of surrounding axons that are initially affected recover over time (Iverson, 2005). Incidentally, the term diffuse axonal injury has progressively been replaced by traumatic axonal injury as it more accurately describes the few damaged axons embedded among mostly intact axons seen in mild TBI (Mac Donald et al., 2007; Pettus, Christman, Giebel, & Povlishock, 1994). In light of accumulating evidence suggesting that neuronal systems are mostly preserved in mild TBI, the latter brain pathology appears to be a deficit of function rather than one of structure.

Accordingly, investigators have turned to the study of the neurometabolic cascade and its mediating effects on brain function in their effort to uncover potential mechanisms of action underlying post-concussion symptoms. The impending description of the multi-faceted metabolic cascade that immediately follows mild TBI has strongly been inspired by the work of Giza and Hovda (2001). Research has shown that immediately after a concussive injury, neurotransmitters are indiscriminately released and uncontrolled ionic fluxes ensue. The binding of excitatory neurotransmitters, such as glutamate, to the N-methyl-D-aspartate (NMDA) receptor leads to further neuronal depolarization with efflux of potassium and influx of calcium (Giza & Hovda, 2001). Due to severe disruptions in ionic gradients, ion-specific pumps are activated by the cells so as to restore resting

membrane potential. Because these ion-specific pumps require much energy to operate, a dramatic increase in glucose consumption ensues. This hypermetabolism occurs in the context of diminished cerebral blood flow, and the disparity between glucose supply and demand triggers a cellular energy crisis. The rapid exhaustion of glucose supply causes the concussed brain to undergo a period of depressed metabolism. Persistent increases in calcium were also shown to impair mitochondrial oxidative metabolism, thereby exacerbating the energy crisis (Awasthi, Church, Torbati, Carey, & Pryor, 1997; Deng, Thompson, Gao, & Hall, 2007). This period of depressed neurometabolism that immediately follows hyperexcitation in mild concussion is thought to gradually return to baseline levels within 6 to 7 days post-injury (Giza & Hovda, 2001). Interestingly, the duration of transient post-concussion symptoms concords with the time taken for the concussed brain to recover baseline metabolism levels (McCrea et al., 2003). This highly similar time course has been interpreted as evidence that the neurometabolic cascade of concussive injury underlies the post-concussion symptoms reported by athletes in the acute post-concussion phase (Giza & Hovda, 2001). More research that systematically controls for the progression of the neurometabolic cascade while assessing its concomitant clinical manifestations is required to validate this widespread belief.

1.4. WHAT THE EFFECTS OF SPORTS CONCUSSIONS ARE…

1.4.1. In the first few minutes (on-field symptoms)

In the first few minutes that immediately follow a concussion, the athlete may experience a wide range of symptoms that vary both in terms of intensity and duration.

Among them, disorientation, loss of consciousness and post-traumatic amnesia have been identified to index concussion severity. While several other scales are available, the American Academy of Neurology (1997) has perhaps been the most cited concussion severity grading scales in the scientific literature. Concussion severity assessment has traditionally been performed on-field during the first few minutes that immediately follow the accident. Sports therapists using the AAN grading scale have typically assessed concussion severity according to the following system:

- Grade 1: Trauma-induced alteration in mental status causing transient confusion for less than 15 minutes, without loss of consciousness;

- Grade 2: Trauma-induced alteration in mental status that lasted for more than 15 minutes but without loss of consciousness.

- Grade 3: Trauma-induced alteration in mental status accompanied with either brief or prolonged loss of consciousness.

Important limitations have been raised concerning the poor predictive value of concussion severity grades on post-concussion recovery. The traditional approach to severe traumatic brain injury utilizing loss of consciousness (LOC) as the primary measure of injury severity has met limitations in assessing the severity of sporting concussive injury. Findings in this field showed LOC association with specific early deficits but failed to predict post-concussion outcome (Lovell, Iverson, Collins, McKeag, & Maroon, 1999; McCrea, Kelly, Randolph, Cisler, & Berger, 2002). In parallel, recent evidence showed

that the presence of amnesia, not loss of consciousness, was predictive of symptom and neurocognitive deficits following concussion (Collins et al., 2003). However, published evidence suggests that the nature, burden and duration of post-concussion symptoms appear more important than the presence or duration of amnesia alone (Lovell et al., 1999; P. R. McCrory, Ariens, & Berkovic, 2000). Converging evidence on the lack of association between the presence and duration of on-field concussion severity markers and the course of recovery has rendered the use of traditional concussion severity grading scales obsolete. The newest Summary and Agreement Statement on concussions in sports (P.R. McCrory et al., 2009) supported the notion that such concussion severity grading scales should be abandoned in favor of combined measures of recovery. In fact, the expert panel maintained its prior position presented at the Vienna conference on concussion in sport (Aubry et al., 2002) suggesting that concussion severity could only be determined in retrospect after all concussion symptoms have cleared and cognitive function has returned to baseline. From a clinical perspective, this significant theoretical shift away from the immediate, on-field symptoms to assess concussion severity forced clinicians to thoroughly monitor recovery of acute symptoms occurring from the sideline up to their resolution most often taking place within 14 days from the injury (P. R. McCrory et al., 2005).

1.4.2. On the sidelines (from a few minutes up to 48 hours)

Concussion diagnosis is based on the sideline assessment of neurologic symptoms. A few minutes after the accident concussed athletes may be experiencing clinical symptoms, physical signs, cognitive impairment, and/or loss of consciousness (P. R. McCrory et al., 2005). These symptoms include:

Cognitive features

- Unaware of period, opposition, score of game
- Confusion
- Amnesia
- Loss of consciousness

Typical self-reported post-concussion symptoms

- Headache or pressure in the head
- Balance problems or dizziness
- Nausea
- Feeling "dinged", "foggy", stunned, or "dazed"
- Visual problems—for example, seeing stars or flashing lights, double vision
- Hearing problems—for example, ringing in the ears
- Irritability or emotional changes

Physical signs

- Loss of consciousness/impaired conscious state
- Poor coordination or balance
- Concussive convulsion/impact seizure
- Gait unsteadiness/loss of balance
- Slow to answer questions or follow directions
- Easily distracted, poor concentration

- Displaying inappropriate emotions—for example, laughing, crying
- Vomiting
- Vacant stare/glassy eyed
- Slurred speech
- Personality changes
- Inappropriate playing behaviour—for example, running in the wrong direction
- Significantly decreased playing ability

The Sport Concussion Assessment Test (SCAT) is a 5-minute concussion diagnosis test battery specifically designed to detect anomalies in any of these spheres. In short, the SCAT (refer to Table 2) seeks for signs of concussions (LOC, unresponsiveness, balance problems, convulsive activity); symptoms commonly associated to sports concussions (Post-Concussion Symptom Scale is a 19-item Likert scale from 0 (none) to 6 (severe)); memory impairments (orientation questions and retrograde memory); cognitive impairments (episodic memory impairments on both an immediate and a 3-minute delayed recall of five words, attentional regulation, information processing speed); and neurologic impairments (speech, eye motion and pupil dilation, pronator drift and gait assessment). Sideline evaluation of cognitive function is an essential component in the assessment of this injury. Brief neuropsychological test batteries such as the Maddocks questions (Maddocks, Dicker, & Saling, 1995) and the Standardised Assessment of Concussion (McCrea et al., 1998) that assess attention and memory function have been shown to be practical and effective. Previous evidence has shown that standard orientation questions (i.e.; time of day, location, person) are unreliable in the sporting situation when compared with memory

assessment (Maddocks et al., 1995; McCrea, Kelly, Kluge, Ackley, & Randolph, 1997). If any one of the previous symptoms or problems is detected with the SCAT, a head injury should be suspected (P. R. McCrory et al., 2005) and the athlete should be taken out of competition. This recommendation from the expert panel of the recent Summary and Agreement Statement on concussion in sport is supported by compelling evidence documenting catastrophic consequences of recurrent concussions in athletes who returned to competition during the same game (R. C. Cantu, 1998; P. McCrory, 2001a; P. R. McCrory & Berkovic, 1998). While the term second impact syndrome was used to discuss the highly controversial cases of high school and college football players who died after having sustained recurrent concussions before symptoms from the first head injury had resolved (R. C. Cantu, 1998), others have documented diffuse cerebral swelling following repetitive concussions that was associated with severe complications (P. R. McCrory & Berkovic, 1998). Along those lines, recent animal work demonstrated the existence of a temporal window of metabolic brain vulnerability to second mTBI that had profound consequences on mitochondrial-related metabolism (Vagnozzi et al., 2007).

Once these transient, gross neurologic impairments observed on the sideline in the first few minutes/hours after the accident have subsided, the athlete enters a slow, progressive recovery period. Recent estimates suggested that nearly 70% of concussed athletes no longer report experiencing post-concussion symptoms and have regained baseline performance levels on neuropsychological testing within 10-14 days post-injury (Collins, Grindel et al., 1999; R. J. Echemendia, Putukian, Mackin, Julian, & Shoss, 2001; Hinton-Bayre & Geffen, 2002; P. R. McCrory et al., 2005).

1.4.3. From a few hours up to 14 days post-concussion

Getting some rest during time out of competition is the usual treatment prescribed to the slow, progressive recovery period in uncomplicated cases of sports concussion (Ruben J. Echemendia, 2006). In addition to post-concussion symptoms that might be present during sideline assessment (refer to SCAT), symptoms specific to the post-concussion recovery phase might emerge. These symptoms include:

- Sadness
- Nervousness
- Trouble falling asleep
- Sleeping more than usual
- Sensitivity to light
- Sensitivity to noise

Although symptomatology varies widely during the acute post-concussion phase, headache is the most commonly reported and perhaps the most debilitating symptom occurring during this period (Guskiewicz et al., 2003; P. R. McCrory et al., 2000). Knowing that headache is associated to vasoconstriction consecutive to oxygen deprivation (Wilson, Foresman, Gamber, & Wright, 1998), the energy crisis consecutive to the neurometabolic cascade following concussive injury was proposed to at least partially mediate post-concussion headache (P. McCrory, 2000, 2001b). This is supported by recent evidence showing that the chronological course of the neurometabolic cascade and post-concussion symptoms recovery was very much alike. In fact, a nationwide National Collegiate Athletic Association (NCAA) concussion study has prospectively measured

immediate effects and natural recovery course relating to symptoms, cognitive functioning, and postural stability following sport-related concussion (McCrea et al., 2003). Out of the 1631 collegial football players who had undergone baseline testing on the aforementioned measures, 94 of them sustained a concussion throughout the course of a 3-year period. They were compared to 56 uninjured athletes who also underwent assessment of symptoms, cognitive functioning, and postural stability immediately, 3 hours, and 1, 2, 3, 5, 7, and 90 days after injury. The latter study revealed that on average, symptoms resolved by day 7, cognitive functioning improved to baseline levels within 5 to 7 days, and balance deficits dissipated within 3 to 5 days after injury (McCrea et al., 2003). Similarly to the gradual recovery of neurometabolic balance (Giza & Hovda, 2001), post-concussion symptoms recovery also follows a progressive course. In a prospective study that included 2905 football players from 25 US Colleges tested at preseason, 194 athletes sustained a concussion over three successive seasons. Headache was the most commonly reported symptom at the time of injury, followed by dizziness/balance difficulties and feeling cognitively "slowed down". Among the 167 players experiencing a headache at the time of their concussion, 149 (89.2%) still reported having a headache 3 hours after injury, 110 (65.9%) 24 hours after injury, 41 (24.5%) at postinjury day 5, and 23 (13.8%) at postinjury day 7. On average, overall symptom duration was about 3.5 days, and 87.8% achieved full symptom resolution within one week after injury (Guskiewicz et al., 2003).

Considerable emphasis is given to post-concussion symptoms in the management of sports concussions as the number and duration of post-concussion symptoms were shown to be somewhat reliable markers of injury severity and a valuable guide for return to play

(P. R. McCrory et al., 2000). In addition to assisting in sideline concussion diagnosis, the SCAT also proposes an empirically validated, stepwise return-to-play protocol. This stepwise process involves six incremental stages (see listed below) during which athletes should remain symptom free at all times before returning to competition. The SCAT is the return-to-play protocol endorsed by the last Summary and Agreement Statement on concussion in sport (P. R. McCrory, 1999).

SCAT return-to-play protocol

1. No activity, complete rest. Once asymptomatic, proceed to level 2.
2. Light aerobic exercise such as walking or stationary cycling, no resistance training.
3. Sport specific exercise—for example, skating in hockey, running in soccer; progressive addition of resistance training at steps 3 or 4.
4. Non-contact training drills.
5. Full contact training after medical clearance.
6. Game play.

According to the SCAT return-to-play protocol (P. R. McCrory et al., 2005), the athlete should only proceed to the next level if asymptomatic at the current level for 24 hours. If any post-concussion symptoms occur, the patient should drop back to the previous asymptomatic level and try to progress again after being symptom free for at least 24 hours.

In parallel, recent data suggest that cognitive recovery may precede or follow clinical symptom resolution suggesting that the neuropsychological assessment of cognitive

function should be an important component in any return to play protocol (Bleiberg et al., 2004). Once considered as the gold standard to return-to-play decision making, current knowledge underlining neuropsychological test's substantial vulnerability to serial testing together with known practice effects (Lovell et al., 2007; Moser et al., 2007) emphasize that it should not be the sole basis of a return to play decision but rather be seen as a complementary tool to clinical decision making (P. R. McCrory et al., 2005). In particular, having to rely on normative data when baseline testing is absent introduces numerous potential biases due to the singular nature of concussive injuries.

Although receiving general acceptance from clinicians in the sports concussion community, recommendations for return-to-play protocols proposed by consensus statements of expert panels do not benefit from solid empirical support. While not undermining the value of clinical judgment earned through years of experience working with concussed athletes, there is a clear lack of knowledge about the validity, reliability and clinical significance of return-to-play criteria proposed by the SCAT or any other concussion assessment battery. The management of concussion occurring in athletes was recently characterized as an "anxiety disorder" typically occurring among sports medicine physicians and athletic trainers (Mayers, 2008). Diagnosis, although defined in consensus statements by expert committees, cannot be precisely confirmed by currently available imaging or laboratory procedures, and no specific therapy has been proven effective (Mayers, 2008). Lacking reliable and specific measures of brain damage and/or dysfunction, physicians and trainers have relied on the resolution of symptoms (at rest and with exertion) and, where available, neuropsychological tests to provide *estimates* of the

appropriate time for athletes to resume practice and play. In addition to its lack of empirical support, the reliability of the two core components used to estimate post-concussion recovery can be questioned. In light of evidence showing that concussed athletes are under-reporters (Delaney, Lacroix, Leclerc, & Johnston, 2002; McCrea et al., 2004) who tend not to report experiencing post-concussion symptoms due to their seemingly benign nature (McCrea et al., 2004) coupled with their willingness to return to play as quickly as possible (P. R. McCrory, 1999), athletes who minimize and/or deny symptoms to promote their quicker return to play further complicate the utility of these recommendations. In addition, although alternate versions of neuropsychological tests are used by clinicians at post-concussion retests, these do not control for potential biases due to habituation with the testing procedure (Lezak, 1995). In fact, empirical data warn clinicians about the validity of such alternate versions of neuropsychological tests administered within a 2-year period (Lezak, 1995).

Despite a relative shift toward a more holistic approach to the management of concussion cases and the general consensus over limitations restricting the repetitive utilization of neuropsychological tests to assess recovery (P. R. McCrory et al., 2005), the overwhelming domination of the neuropsychology of sports concussion over the last two decades has had a profound impact on the sports concussion literature. Perhaps most importantly, a handful of landmark neuropsychological studies of sports concussions published in distinctly reputable scientific journals (Collins, Grindel et al., 1999; Collins, Lovell, & McKeag, 1999; R. J. Echemendia et al., 2001; Guskiewicz, 2002; McCrea et al., 2003) have contributed to instill the debatable practice of no longer assessing cognitive

functions in asymptomatic athletes whose neuropsychological tests performance has returned to baseline levels. Surprisingly enough, this invigorated consensus was reiterated in the last Summary and Agreement Statement on Sports concussions despite accumulating evidence of persistent effects of sports concussions using different methods to assess cerebral functions for at least one month in most concussed athletes tested (Catena, van Donkelaar, & Chou, 2007a, 2007b; Cavanaugh et al., 2006; Dupuis, Johnston, Lavoie, Lepore, & Lassonde, 2000; Gaetz & Weinberg, 2000; Gosselin, Theriault, Leclerc, Montplaisir, & Lassonde, 2006; Lavoie, Dupuis, Johnston, Leclerc, & Lassonde, 2004; Parker, Osternig, Van Donkelaar, & Chou, 2006).

Because the techniques that reveal persistent cerebral dysfunctions are not easily amenable to routine study of many patients, as they require complex equipment, skilled procedure performance, and sophisticated interpretation of results in the light of their clinical significance, it is not suggested that they should systematically be included in current return-to-play protocols. Since return-to-play criteria are still based on expert opinion rather than on empirical evidence, we can no longer ignore persistent cognitive and motor alterations consecutive to sports concussions. To this end, lengthening the time out of competition to allow better recovery should be envisaged considering the increased likelihood of recurrent concussions found in the first few weeks after the accident (Guskiewicz et al., 2003).

In short, a considerable amount of work remains to be undertaken to move from return-to-play decision making based on level 4 evidence (supported solely on expert

opinion) to evidence-based medicine (level 1) that integrates individual clinical expertise with the best available external clinical evidence from systematic research (Sackett, Rosenberg, Gray, Haynes, & Richardson, 1996).

1.4.4. From 14 days up to late adulthood

With the vast majority of the literature on sports concussion dedicated to improving the diagnosis, treatment, and recovery of sports concussions in the acute post-concussion phase (Kelly, 1999), 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. However, four converging bodies of evidence have compellingly demonstrated that the effects of sports concussions on brain functions might not be as benign as we have long thought. Firstly, vast epidemiological studies have shown that athletes presenting with a prior history of sports concussions are more at risk of sustaining subsequent concussions (Guskiewicz et al., 2003; Zemper, 2003). Second of all, athletes with a prior history of concussions were found to suffer from more severe and longer-lasting post-concussion symptoms than those who suffered from their first concussion (Collins et al., 2002; Guskiewicz et al., 2003; Iverson, Gaetz, Lovell, & Collins, 2004). Thirdly, having sustained concussions in early adulthood has been associated with an increased prevalence of mild cognitive impairments (MCI) in retired professional contact sports athletes (Guskiewicz et al., 2005). Finally, the use of more sophisticated brain investigation techniques has revealed cognitive (Dupuis et al., 2000; Gaetz, Goodman, & Weinberg,

2000; Gaetz & Weinberg, 2000; Gosselin et al., 2006; Lavoie et al., 2004), balance control (Cavanaugh et al., 2006) and gait stability (Catena et al., 2007b; Parker et al., 2006) anomalies that outlast currently accepted return-to-play criteria (i.e.; the athlete no longer report experiencing post-concussion symptoms and perform normally on neuropsychological tests) (P. R. McCrory et al., 2005).

i. **Concussed athletes show an increased vulnerability to recurrent concussions**

Perhaps the most compelling study on the increased susceptibility to subsequent concussions included nearly 3000 football players from the NCAA (Guskiewicz et al., 2003). This study revealed that college athletes with a history of three concussions or more and to a lesser extent one or two concussions, are significantly more at risk to sustain another concussion (Guskiewicz et al., 2003). In the same vein, a recent two-year prospective study reported that the risk of sustaining a concussion in football was 5.8 times greater if the athlete had already sustained a concussion (Zemper, 2003).

ii. **Multiply concussed athletes suffer more severe post-concussion symptoms**

Athletes with a prior history of concussions were found to suffer from more severe and longer-lasting post-concussion symptoms than those who suffered from their first concussion. Along those lines, a study conducted with secondary school varsity football players found that athletes who had previously sustained a concussion that resulted in loss of consciousness were four times more likely to sustain another concussion involving LOC (Gerberich, Priest, Boen, Straub, & Maxwell, 1983). In a more recent study, Collins and collaborators (2002) found that athletes with a history of multiple concussions were

significantly more likely to experience an initial LOC combined with anterograde amnesia and confusion after a new concussive episode. They reported that only 5% of athletes with no prior history of concussion experience LOC, whereas 26% (5.2 odds ratio) of the repeated-concussion athletes experienced LOC after a subsequent injury. In parallel, the same study found that only 9.4% of players with no prior history of traumatic brain injury demonstrated prolonged post-injury mental status alterations, as opposed to 31.6% (3.36 odds ratio) of players with multiple concussions. When the four primary on-field severity markers were considered simultaneously (positive LOC, anterograde amnesia, retrograde amnesia, and confusion), only 3.7% of athletes with no history of concussion showed evidence of three to four markers, whereas 26.3% of the multiple concussion group suffered from three to four severity markers (9.3 odds ratio). In addition, recent data suggest that athletes with a history of more than three concussions recover significantly more slowly from the adverse effects of concussions than athletes who had sustained only one concussion at the time of testing (Guskiewicz et al., 2003). Furthermore, a recent neuropsychological study has looked at the additive deleterious impact of multiple concussions on cognitive measures immediately after a new concussion. This study showed that when tested two days post-injury, athletes with a history of multiple concussions scored significantly lower on memory tests than those who had sustained only one concussion (Iverson et al., 2004). In addition, multiply concussed athletes were 7.7 times more likely to show a drop in memory performance in the acute phase immediately following the injury than other concussed athletes with no prior history of concussion (Iverson et al., 2004).

iii. **Retired concussed athletes at a higher risk of mild cognitive impairments**

A recent epidemiological study by Guskiewicz and colleagues (2005) not only supported the notion that the seemingly benign impact of sports concussion on long term brain function has traditionally been undervalued, but it established a relationship between a history of recurrent sports concussions and late-life cognitive impairments in retired professional athletes. More specifically, this study showed that athletes who had sustained three or more concussions throughout their career were five times more likely to develop mild cognitive impairment (MCI), a condition characterized by early memory impairments that convert at a rate of about 10-20% annually into dementia (Guskiewicz et al., 2005). Moreover, they observed an earlier onset of Alzheimer's disease (AD) in the concussed retirees than in the general American male population (Guskiewicz et al., 2005). Although specification of whether and how TBI may trigger a long-term process of neurodegeneration remains frequently debated (Levin, 1995), results from the mild TBI literature have provided plentiful support for the association between concussive injuries and the later development of Alzheimer's disease. In fact, TBI was found to be among the most robust environmental AD risk factor in the general population (Guo et al., 2000; Heyman et al., 1984; Mortimer, French, Hutton, & Schuman, 1985; Plassman et al., 2000).

iv. **Persistent brain function alterations beyond the acute post-concussion phase**

Finally, the use of more sophisticated brain investigation techniques has revealed cognitive (Gaetz & Weinberg, 2000; Gosselin et al., 2006), balance control (Cavanaugh et al., 2006) and gait stability (Catena et al., 2007a; Parker et al., 2006) alterations that persisted beyond the acute post-concussion phase.

a. Persistent cognitive functions alterations

Turning to more fine-tuned brain investigation methods helped uncover residual cognitive function alterations that went unnoticed on classic neuropsychological tests. A review on the clinical usefulness of electrophysiological procedures for the assessment of MTBI suggested that event-related potentials (ERPs) provide perhaps the most promising alternative to detect subtle cognitive function changes following the injury (Gaetz & Bernstein, 2001). 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 (Dupuis et al., 2000; Gosselin et al., 2006; Lavoie et al., 2004; Potter, Bassett, Jory, & Barrett, 2001; Reinvang, Nordby, & Nielsen, 2000; Solbakk, Reinvang, Nielsen, & Sundet, 1999; Werner & Vanderzant, 1991). Recent studies specifically conducted with asymptomatic concussed athletes showed persistent P300 latency delays (Gaetz & Weinberg, 2000) and amplitude attenuation (Gosselin et al., 2006). Reductions in the amplitude of the P300 component are thought to index memory updating (Donchin & Coles, 1988; Picton, 1992), subjective significance (Duncan-Johnson & Donchin, 1977) and stimulus probability (Donchin & Coles, 1988; Johnson & Donchin, 1978), whereas P300 latency delays are associated with reduced performance on neuropsychological tests that assess how rapidly attentional resources can be allocated for memory processing (Emmerson, Dustman, Shearer, & Turner, 1989; Polich, Howard, & Starr, 1983; Reinvang, 1999).

b. Pervasive balance control anomalies

Besides investigating cognitive functions impairments after sports concussions, assessment of postural stability (balance control) was introduced to assist clinicians in determining when concussed athletes who experienced balance problems immediately after an injury could safely return to play (P. R. McCrory et al., 2005). Although sophisticated measures have been developed to assess balance control in varying environmental contexts (Cavanaugh, Guskiewicz, Giuliani et al., 2005; Cavanaugh, Guskiewicz, & Stergiou, 2005; Guskiewicz, Perrin, & Gansneder, 1996; Guskiewicz, Ross, & Marshall, 2001), typical testing procedure requires participants to stand as steadily as possible in an upright position on a force platform with their eyes open and their feet side-by-side, parallel at pelvis width. Postural stability represents movement amplitude (in both mediolateral (ML) and anteroposterior (AP) directions) computed from the centre-of-pressure (COP) displacement (Guskiewicz et al., 2001). Approximate entropy (ApEn) value changes, which reflect abnormal randomness of centre-of-pressure (COP) oscillations (Cavanaugh, Guskiewicz, & Stergiou, 2005) in both ML and AP directions, were reliably found immediately following a sports concussion (Cavanaugh et al., 2006; Cavanaugh, Guskiewicz, & Stergiou, 2005). Compared to preinjury levels, COP oscillations of concussed athletes were less random (Cavanaugh et al., 2006; Cavanaugh, Guskiewicz, & Stergiou, 2005), and concussed athletes who showed increased regularity tended to display lower equilibrium scores (i.e.; postural instability) (Cavanaugh et al., 2006; Cavanaugh, Guskiewicz, & Stergiou, 2005). Day-to-day assessment of postural stability recovery revealed significantly depressed ApEn values still present at 4 days post-injury even among athletes whose initial postural instability had resolved (Cavanaugh et al., 2006).

From altered balance control in an immobile, upright position emerged the investigation of balance control during gait. Relative to controls, concussed athletes still exhibited significantly reduced gait stability at 28 days post-injury (Parker et al., 2006). This study also showed that performing simple or complex cognitive tasks exacerbated gait stability differences between concussed athletes and controls while also significantly reducing concussed athletes' walking velocity when tested 28 days post-injury (Parker et al., 2006).

1.5. THESIS OBJECTIVES

The main objectives of the present thesis were twofold:

i. To cross-sectionally investigate lifelong changes in cognitive and motor systems functions using methods sensitive to the effects of mild TBI that outlast the acute post-injury phase;

ii. To systematically study the cumulative detrimental effects of recurrent sports concussions on cognitive and motor systems functions.

1.6.RESEARCH DESIGN

Four distinct experiments have been conducted in an attempt to meet these thesis objectives. The following sections will provide the rationale and justification for selecting the specific study methods/measures in each experiment.

1.6.1. Experiment 1

Long-term electrophysiological changes in athletes with a history of multiple concussions (published in *Brain Injury*, 2007).

In light of previous electrophysiological evidence suggesting that asymptomatic concussed athletes who perform normally on neuropsychological tests exhibit persistent reductions in P300 amplitude in addition to latency delays (Gaetz & Weinberg, 2000; Gosselin et al., 2006), the present study sought to systematically address whether these pervasive P3 alterations are accentuated as a result of the cumulative effects of sports concussions. In addition to looking at long-term P3 alterations, the present ERP study explored whether sports concussions sustained years earlier would exert persistent alterations of the N2pc component. The use of ERPs to investigate visual-spatial attention in concussed athletes stemmed from three main observations: 1) The deployment of visual-spatial attention for object detection in space is particularly important in contact sports, such that elite athletes usually perform significantly better than non-athletes on spatial attention tasks (Lum, Enns, & Pratt, 2002; McAuliffe, 2004); 2) ERPs provide unmatched sensitivity to subtle cognitive dysfunctions in asymptomatic concussed athletes (Gaetz &

Weinberg, 2000; Gosselin et al., 2006); and finally 3) a relatively new ERP component, namely the N2pc, provides an electrophysiological index of the moment-to-moment deployment of visual-spatial attention (Eimer, 1996; Luck, Chelazzi, Hillyard, & Desimone, 1997; Luck & Hillyard, 1994a, 1994b). In short, persistent N2pc alterations after sports concussions potentially exacerbated with recurrent concussions could be of significant clinical value because relying on altered visual-spatial attention skills could reduce an athlete's ability to locate and track the position of teammates and opponents.

1.6.2. Experiment 2

Long-term and cumulative effects of sports concussion on motor cortex inhibition (published in *Neurosurgery*, 2007).

Only recently has the investigation of motor system abnormalities come to the forefront of the sports concussion literature in spite of the fact that transient balance impairments represent a reliable on-field predictor of post-concussion syndrome (McCrea et al., 2003). This lack of interest from the part of sports concussion researchers partly stemmed from the long-standing bias in the very definition of sports concussion that primarily focuses on mental status and cognitive functions alterations immediately after the injury (Aubry et al., 2002; P. R. McCrory et al., 2005). However, alarming findings from studies conducted with retired professional boxers raised awareness about the long-term repercussions of repeated blows to the head on the integrity of the motor system. A recent epidemiological study showed that nearly 17% of retired professional boxers go on to develop chronic TBI (dementia pugilistica) for which the earliest clinical manifestation is

ataxia symptoms (Rabadi & Jordan, 2001). In sum, these findings show that together with inducing quickly subsiding unsteadiness, the accumulation of repeated concussive and subconcussive injuries can lead to catastrophic motor functions impairments later in life.

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 (Abbruzzese & Trompetto, 2002; Cantello, 2002; Cantello, Tarletti, & Civardi, 2002; Reynolds & Pearson, 1993), transcranial magnetic stimulation (TMS) represents a particularly pertinent research tool to investigate persistent, modulatory effects of single/multiple concussive events on the motor system. The application of TMS to sports concussion is supported by previous findings that showed altered excitability of the motor system in the acute phase following a minor head injury (Chistyakov et al., 2001).

Where current evidence about the long-term neuropathophysiology of sports concussions is scarce — negative MRI findings in most cases (Aubry et al., 2002), equivocal evidence of diffuse axonal injury (Iverson, 2005) and neurometabolic balance typically restored within 10 days (Giza & Hovda, 2001) — changes in motor cortex excitability consecutive to sports concussions would suggest that its neurophysiological underpinnings contribute to the pervasiveness of post-concussion sequelae. Finally, in order to partially address the issue of cause and effect — namely that abnormalities in motor cortex function could have been a premorbid characteristic that may have rendered

concussed athletes more at risk of sustaining sports concussions - that cannot be excluded in retrospective studies of this nature, we sought to prospectively investigate whether sustaining another concussion would result in worsened motor system abnormalities, thereby providing further support for the contention that the effects of concussions are cumulative.

1.6.3. Experiment 3

Persistent Motor System Abnormalities in Active Concussed Athletes (accepted in *Journal of Athletic Training, 2010*)

Having shown in Experiment 2 that sports concussions induced significant deleterious effects on motor cortex inhibition mechanisms that were exacerbated with recurrent concussions, the present study sought to further investigate motor system integrity consecutive to single versus multiple concussions by simultaneously looking at dynamic motor functions in relation to M1 inhibitory mechanisms.

To date, three aspects of dynamic motor functions have been introduced to the field of sports concussions: i) Postural stability; ii) Gait stability; and iii) Motor execution speed. Among the three, postural stability has perhaps been the most extensively studied partly due to the frequent gross balance deficits observed immediately after a sports concussion. However, the investigation of balance control recovery has strictly been limited to four days post-injury at which point concussed athletes are still showing significantly reduced COP oscillations randomness relative to their own baseline standards

(Cavanaugh et al., 2006). One objective of this third experiment was therefore to explore whether having sustained a concussion more than nine months prior to testing in active University football players who have long return to competition still exert significant reductions in COP oscillations randomness relative to unconcussed teammates. Although the functional significance of enhanced COP oscillation regularity with regards to postural stability is not fully understood, previous studies suggested that it represents an adaptive compensatory mechanism put forth by concussed athletes to cope with postural stability losses (Cavanaugh et al., 2006).

Furthermore, knowing that sports concussion induce clear gait stability losses that persist beyond the acute post-concussion phase (Catena et al., 2007a, 2007b), a recent gait stability study extended this finding as it showed significantly reduced walking velocity in concussed athletes when having to concurrently perform a secondary cognitive task (Parker et al., 2006). To our knowledge, this study was among the first in the sports concussion literature to document motor execution slowness consecutive to sports concussions. Adding to this indirect measure of walking velocity slowness, a recent study showed that traumatic brain injury patients who performed normally on neuropsychological tests showed persistent motor execution slowness (or bradykinesia) when compared to matched controls on simple and complex reaction time tasks (Gray, Cantagallo, Della Sala, & Basaglia, 1998). Knowing that sports concussions represent a mild form of traumatic brain injury, the second objective of the present study aimed to explore whether sports concussions also result in long-term motor execution slowness (bradykinesia) on a rapid

alternating movement task specifically selected for its proven sensitivity to detect bradykinesia symptoms (Beuter, de Geoffroy, & Edwards, 1999).

In parallel, this study also sought to further validate the neurophysiological underpinnings of the previously demonstrated M1 inhibitory mechanisms alterations. More specifically, results from Experiment 2 revealed excessive M1 inhibition using a TMS-induced cortical silent period (CSP) paradigm. While most studies point to $GABA_B$ receptors activity (Macdonell et al., 2001; Pierantozzi et al., 2004; Siebner, Dressnandt, Auer, & Conrad, 1998; Werhahn, Kunesch, Noachtar, Benecke, & Classen, 1999), the underlying neurophysiological substrates of the CSP have been debated over recent years (McDonnell, Orekhov, & Ziemann, 2006). Whereas several pharmacological studies have suggested that the late part of the CSP was caused by long-lasting cortical inhibition mediated by $GABA_B$ receptors (Macdonell et al., 2001; Pierantozzi et al., 2004; Siebner et al., 1998; Werhahn et al., 1999), a recent study showed no specific effect of a selective $GABA_B$ receptor agonist (Baclofen) on CSP duration (McDonnell et al., 2006). However, the latter experiment shed light on another TMS paradigm that specifically responded to Baclofen. Baclofen intake resulted in a significant increase in LICI. The use of TMS-induced LICI may therefore be instrumental to delineate whether selective $GABA_B$ alterations are implicated in the long-term pathophysiology of sports concussions. The final objective of the present study was to investigate the potential adverse repercussions of these abnormal M1 inhibitory mechanisms on dynamic motor functions of contact sports athletes who have long returned to competition.

In sum, identifying persistent dynamic motor functions alterations in concussed athletes who have long returned to competition is important considering that it could negatively impact the practice of contact sports and possibly increase their susceptibility to subsequent concussions. Of great clinical relevance, confirming the implication of abnormal $GABA_B$ receptor activity in the long-term pathophysiology of sports concussions together with validating its adverse impact on dynamic motor functions would emphasize the pertinence of implementing existent interventions known to modulate intracortical inhibition (Khedr, Rothwell, Ahmed, Shawky, & Farouk, 2007; Ziemann, 2003) in an attempt to alleviate the long-term deleterious effects of sports concussions.

1.6.4. Experiment 4

Brain Function Decline in Healthy Retired Athletes who Sustained their Last Sports Concussion in Early Adulthood (published in Brain, 2009)

This experiment sought to complete the cross-sectional investigation of lifelong changes on cognitive and motor functions with former, late adulthood athletes who sustained their last concussion more than 30 years prior to testing. Considering the recently demonstrated relationship between sports concussions sustained in young athletes and the increased prevalence of mild cognitive impairment (MCI) later in life (Guskiewicz et al., 2005), study objectives aimed to answer two distinct hypotheses:

i. The effects of sports concussions on cognitive and motor system functions observed in active athletes with concussions (as revealed on measures from Experiments 1 & 2) are lifelong;

ii. The combined detrimental effects of sports concussions and aging on cognition would be associated with reduced performance on neuropsychological tests selected for their sensitivity to detect early signs of MCI.

A third, secondary objective was to validate whether the joint detrimental effects of aging and sports concussions found on cognition would similarly affect a dynamic motor function that was found to be unaltered in young concussed athletes (Experiment 3).

2. Experiment 1

De Beaumont, L., Brisson, B., Lassonde, M. & Jolicoeur, P (2007). Suppression of P3 amplitude in multiply concussed athletes years following the injury. Brain Injury , 21, 631-644.

Long-term electrophysiological changes in athletes with a history of multiple concussions

Abstract

Primary objective: This event-related potentials study investigated the long term effects associated with a history of one or multiple concussions on the N2pc and P3 components using a visual search oddball paradigm. **Methods and Procedure:** A total of 47 university football players were assigned to three experimental groups based on prior concussion history: Athletes with a history of one concussion (Single-concussion group); Athletes with two or more concussions (Multi-concussion group); Non-concussed athletic controls. The average post-concussion period was 31 months for athletes in the multi-concussion group and 59 months for the single-concussion group. **Results:** We found significantly suppressed P3 amplitude in the multi-concussed athletes group compared to the single-concussion and non-concussed athletes even when using the time since the latest concussion as a covariate. **Conclusion:** This finding suggests that the multi-concussed athletes group showed long-lasting P3 amplitude suppression when compared with single-concussion or non-concussed athletes despite equivalent neuropsychological test scores and post-concussion symptoms self-reports. This pattern of results is important because it shows that "old" concussions do not cause general or ubiquitous electrophysiological

suppression. The specificity of the long-term effects of previous concussions to the P3, along with an intact N2pc response, suggests that further work may allow to pinpoint the cognitive system that is specifically affected by multiple concussions.

Background

The reported incidence of sports concussions has grown at an accelerated pace over the last 15 years [1]. In fact, the Centers for Disease Control and Prevention (1997) [2] estimate that in the United States only, 50,000 to 300,000 contact sports athletes sustain a concussion during the course of a single year. According to the Summary and Agreement Statement of the 2nd International Conference on Concussion in Sport (2004) [3], sports concussions are subdivided into two main categories: 1) Simple concussion and 2) Complex concussion, the former representing the most common form of this injury. Studies have repeatedly demonstrated that apart from limiting playing or training while symptomatic, athletes who suffer from a Simple concussion need no further intervention during the recovery period, and the athlete typically resumes playing without further problem. Complex concussion, however, is associated with persistent symptoms (including persistent symptom recurrence with exertion), specific sequelae (such as concussive convulsions), prolonged loss of consciousness (more than one minute), or prolonged cognitive impairment after the injury. This group also includes athletes who suffer multiple concussions over time or where repeated concussions occur with progressively less impact force [3]. Since most concussion research conducted to date has aimed to improve return-to-play decisions for the majority of athletes, who typically sustain Simple concussions, fewer studies have investigated the consequences of complex concussions.

Despite the limited literature on Complex concussions, the effects of multiple concussions have raised significant interest over the last few years. Perhaps the most

compelling study on the topic included nearly 3000 football players from the National Collegiate Athletic Association (NCAA). This epidemiological study showed that contact sports athletes with a prior history of concussions are three times more likely to sustain subsequent concussions compared to players with no prior history of concussion [4]. Along the same line, a recent two-year prospective study reported that the risk of sustaining a concussion in football was 5.8 times greater if the athlete had already sustained a concussion [5].

In parallel, a growing body of evidence supports an association between recurrent concussion and increased symptomatology. A recent study conducted with high school football players found that athletes with a prior history of sports concussions are 9.3 times more at risk of showing signs in three out of the four concussion severity markers (loss of consciousness (LOC), anterograde amnesia, retrograde amnesia, and confusion) than athletes with no prior history of concussion [6]. In addition, recent data suggest that athletes with a history of more than three concussions recover significantly slower from the adverse effects of concussions than athletes who had sustained only one concussion at the time of testing [4].

Neuropsychological studies have looked at the additive deleterious impact of multiple concussions on cognitive measures immediately after a new concussion. Iverson et al. (2004) showed that when tested two days post-injury, athletes with a history of multiple concussions scored significantly lower on memory tests than those who had sustained only one concussion [7]. In addition, multi-concussed athletes were 7.7 times more likely to show a drop in memory performance in the acute phase immediately following the injury than other concussed athletes with no prior history of concussion [7].

Despite accumulating evidence for increased symptomatology and vulnerability to subsequent concussions in athletes with a history of multiple concussions, most athletes

receive medical clearance within a few days or weeks post-injury based on return-to-baseline neuropsychological test scores and post-concussion self-reports. Turning to more fine-tuned brain investigation methods might help uncover residual brain function alterations that are not detected by standard return-to-play assessment protocols.

Among alternative methods, electrophysiological recordings have been used extensively to investigate cognitive function abnormalities resulting from mild traumatic brain injury (MTBI) [37-48]. A review on the clinical usefulness of electrophysiological procedures for the assessment of MTBI suggested that event-related potentials (ERPs) provide perhaps the most promising alternative to detect subtle changes in brain function following the injury [8]. ERPs are averaged electrical brain responses that allow us to determine the time course of higher level processes such as attention and memory updating in the human brain [9]. The ERP measure represents the averaged EEG signal time-locked to the stimulus presented and consists of different components labelled by their polarity (e.g., P for positive and N for negative) and temporal range in milliseconds or the ordinal number of major components [10]. Among the many ERP components identified in the literature, the P3 has been widely applied to study cognitive dysfunctions in various neurological and psychiatric illnesses [11][12][13]. Oddball tasks are particularly useful in order to elicit a P3 response. The paradigm typically involves the presentation of two stimuli displayed in a random order, with one occurring more frequently than the other. The subject is required to discriminate an infrequent target stimulus from the frequent standard stimulus by responding covertly or overtly to the target [14][15]. A typical overt response would be to press a button when a target is detected in the presentation sequence; a typical covert response would be to count the number of targets during the presentation sequence (and to report the total at the end of the sequence. The oddball effect on the P3 has been observed with visual [11] and auditory stimuli [13]. The P3 is usually quantified

by measuring the amplitude (size) and latency (timing) of the component. P3 amplitude is thought to index memory updating [16][17], subjective significance [18] and stimulus probability[19][16]. Furthermore, P3 amplitude was shown to be positively correlated with the amount of attentional resources allocated to a particular task [20][21], and greater P3 amplitude is associated with better performance on memory tasks[22][23]. P3 amplitude can therefore be viewed as a measure of central nervous system activity that occurs when stimulus memory representations are generated, with component size reflecting the degree to which information is processed [24].

P3 latency is thought to be a measure of stimulus classification speed [25][26], which is unrelated to response selection processes [27][28] and independent of behavioral response time [29][30]. Peak latency is negatively correlated with mental efficiency, as shorter latencies are associated with better performance on neuropsychological tests that assess how rapidly attentional resources can be allocated for memory processing[31][32][33][34].

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. The appeal of measuring P3 component size and latency lies mostly in the ability to index changes in cognitive efficiency following a concussion. However, evidence of P3 changes following MTBI has been inconsistent. Many factors contribute to inconsistencies in the findings. Among them, uncontrolled intersubject variability — that is, uncontrolled concussion severity, time elapsed since the accident when tested, etiology, age, level of education — and the lack of a standard method for the acquisition of the P3 component account for some of the conflicting results observed in the existing ERPs and MTBI literature. However, the few ERP studies that specifically looked at P3 changes elicited by visual oddball paradigms in MTBI patients

have provided somewhat more reliable findings. Indeed, an ERP study showed that a visual oddball paradigm yielded more pronounced P3 component differences between patients presenting with mild cognitive complaints and controls than its auditory counterpart [35]. Moreover, the cumulative effects of concussion have been demonstrated using a visual oddball paradigm. In this study, subjects who had experienced three or more concussions had significantly longer P3 latencies than individuals who had never sustained a concussion and the P3 delay was significantly correlated with Post-concussion symptoms (PCS) taken at the time of testing [36]. In the same vein, Dupuis, Johnston, Lavoie et al. (2000) showed that the size of the P3 component elicited by a visual oddball paradigm was significantly smaller in concussed patients than controls or asymptomatic athletes [37]. Another study using the visual oddball paradigm showed that the P3 component amplitude was significantly suppressed in symptomatic athletes and that its size was negatively correlated with post-concussion symptoms severity [38].

While some studies conducted with TBI victims could not detect P3 changes in auditory oddball paradigms [39][40][41], other studies of patients with even mild head injury have disclosed small but significant auditory P3 latency and/or amplitude changes, at least during the acute phase of the injury[35][42][43]. Overt (active) oddball paradigms rather than covert (passive) ones seem to be even more sensitive to the effects of MTBIs. In fact, P3 responses to an auditory oddball task were significantly smaller in MTBI patients when they had to process stimuli that had to be actively analysed and rejected as task irrelevant [44]. Similarly, the same authors showed that when mTBI patients had to detect rare target tones while withholding responses to other equiprobable rare non-targets, the amplitude of their P3 was significantly suppressed when compared to that of controls [45]. A more recent study using a paradigm similar to the latter disclosed significantly attenuated P3 amplitude in asymptomatic athletes who had sustained a concussion more than 3 weeks

prior to testing [46]. Thus, it seems that active visual oddball paradigms would yield optimal sensitivity in the investigation of the long-term impact of sports concussions in asymptomatic athletes who sustained their latest injury years prior to testing.

In addition to looking at long-term P3 alterations, the present ERP study explored whether sports concussions sustained years earlier would exert persistent alterations in the N2pc component. This component is thought to provide a continuous measure of the allocation of visual-spatial attention across the left-right visual fields by virtue of its lateralized (contralateral relative to target location) and very posterior scalp distribution, and the use of visual displays that are balanced across the visual fields in terms of non-attentional factors [47][48]. Moreover, the N2pc component has been related to the covert orienting of visual attention during visual search [49].

Our interest in the use of ERPs to explore visual-spatial attention in concussed athletes comes from three main observations: 1) The deployment of visual-spatial attention is thought to be a fundamental skill to achieve high levels of performance in contact sports, such that athletes usually perform significantly better than non-athletes on spatial attention tasks [50][51]; 2) unmatched sensitivity to subtle cognitive dysfunctions in asymptomatic concussed athletes is achieved using ERPs [46][38]; and finally 3) a relatively new ERP component, namely the N2pc, provides an electrophysiological index of the moment-to-moment deployment of visual-spatial attention [47][48][52][53]. In short, the demonstration of persistent alterations of the N2pc component in sports concussions could be of significant clinical value because a suboptimal deployment of visual-spatial attention could impair an athlete's ability to locate and track the position of teammates and opponents. Such a deficit could put concussed athletes at an increased risk of suffering an unexpected impact with another player, thus increasing their vulnerability to subsequent concussions.

The primary hypothesis of the present study is that the P3 component elicited by an active visual oddball task will be significantly different in athletes who sustained their latest concussion years prior to testing when compared to control athletes with no prior concussion history. Secondly, in light of abovementioned findings on the cumulative effects of sports concussions, we also hypothesized that athletes with a history of recurrent concussions would show greater electrophysiological alterations than those who sustained only one concussion. Thirdly, by including two different electrophysiological measures, namely the N2pc and the P3, we sought to discover whether different forms of attention-related processing could be dissociated in terms of their likelihood of showing residual abnormalities as a function of concussion history.

METHODS

Participants

All 51 participants in this study were active players from a Canadian university football team recruited with the help of the team physician and tested from June to mid-August 2004, which correspond to the three-month period just preceding the training camp. Athletes who took part in this study were those who were not rejected after having been screened for the following exclusion criteria: A history of alcohol and/or substance abuse, psychiatric illness, learning disability, neurological history (seizure, central nervous system neoplasm, or brain tumour) and a history of traumatic brain injury unrelated to contact sports. Four concussed athletes were excluded from this study as they reported experiencing persistent post-concussion symptoms at the time of testing on the Post-Concussion Symptoms scale (PCS, see Results below). Finally, two participants were rejected from further analysis based on pre-determined data contamination criteria (refer to

Recording and Data analysis 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 $30 Canadian for their participation.

Three experimental groups were included in this study (refer to Table 1). The first group consisted of 15 asymptomatic athletes who experienced two or more sports concussions that occurred at least 9 months prior to testing. Sports concussion was defined according to the criteria proposed by the practice parameters of the American Academy of Neurology (1997). A Grade 1 concussion corresponded to a trauma-induced alteration in mental status causing transient confusion for less than 15 minutes, without loss of consciousness. Grade 2 concussions were trauma-induced alterations in mental status that lasted for more than 15 minutes but without loss of consciousness. Finally, Grade 3 concussions involved alteration in mental status accompanied with either brief or prolonged loss of consciousness. The number of concussions sustained ranged from 2 to 7 and the time elapsed since their latest concussion ranged from 9 months up to 81 months with a mean time since the latest concussion of 31 months (31.47 SD 22.03) (see Table 1). The second experimental group consisted of 15 athletes who reported only one sports concussion that also had to occur more than nine months prior to testing. In this second experimental group, the time elapsed since the latest concussion ranged from 9 months up to 285 months with a mean time since the latest concussion of 56 months (56.07 SD 70.84) (see Table 1). The Results section describes how the between-group difference on the mean time since the last concussion was statistically taken into account. The time elapsed since the latest concussion was not significant (F (1, 28) = 1.518; MSE = 4177.20; $p > .22$) between the concussion groups although multi-concussed athletes tended to have sustained their latest concussion closer to the date of testing than athletes with a history of only one concussion. The third, control, group also consisted of 15 university football players who

reported no prior history of sports concussion or neurological insult (e.g., motor vehicle accident) at the time of testing. All three experimental groups were equivalent according to age (F (2, 43) = 0.367; MSE = 2.682; $p > .69$) and level of education (F (2, 43) = 1.357; MSE = 3.989; $p > .26$) (refer to Table 1).

Procedure

Concussion history and post-concussion symptoms

A standardized concussion history form was administered to obtain detailed information about the number of previous concussions (if any), the approximate date of each concussion, the description of the accident, the nature and duration of on-field post-concussion severity markers (confusion and/or disorientation, retrograde and/or anterograde amnesia, and loss of consciousness, LOC). As predicted, the total number of times athletes in the multi-concussion group sustained a concussion that involved anterograde amnesia (AGA) and retrograde amnesia (RGA) was greater than for athletes in the single-concussion group (Total AGA multi =18, Total AGA single = 7; Total RGA multi = 17, Total RGA single = 5), whereas the number of episodes of LOC was similar in both groups (Total LOC multi = 4, Total LOC single = 3). Concussion severity ratings went from Grade 1 (confusion for less than 15 minutes without amnesia, no LOC) to Grade 3 (LOC, either brief (seconds) or prolonged (minutes)) according to the American Academy of Neurology practice parameters (1997) and they were all classified as mTBI on the Glasgow Coma Scale (scoring between 13 to 15) [54]. All reported concussions were classified by a sports physician using the practice parameter of the American Academy of Neurology (1997) [54].

---------- Insert Table 1 about here ----------

The Post-Concussion Symptoms scale (PCS) was then used to assess the presence/absence and intensity of reported symptoms at the time of testing. This questionnaire asks players to rate themselves on a scale from 0 (no symptom) to 6 (severe symptom) on a series of 19 common post-concussion symptoms for a total possible score of 114. Three categories of symptoms are identified: 1) somatic symptoms, such as headaches, dizziness, balance problems, or nausea; 2) neuropsychiatric symptoms, such as anxiety, depression, or irritability; and 3) cognitive symptoms, such as impairment of attention, memory impairment, or reduced processing speed [55]. None of the participants included in the present study reported still experiencing symptoms related to their last concussion (see Table 1).

Neuropsychological assessment

Neuropsychological tests of the National Football League Neuropsychological Testing Program were used to assess multiple aspects of cognitive functioning [56]. This battery consists of the Hopkins Verbal learning Test (assessing memory for words and delayed memory for a previously learned word list); the Brief Visuospatial Memory Test — Revised (assessing immediate/delayed visuospatial memory); the Symbol Digit Modalities (assessing visual scanning and attention); Controlled Oral Word Association Test (assessing word fluency and word retrieval); Color Trails (assessing visual scanning, mental flexibility); Pennsylvania State University Cancellation Test (assessing information processing speed and visual attention). Previous research has outlined the reliability, validity, and sensitivity of these classic neuropsychological tests to assess the specific cognitive areas associated with mTBI in the general population [57][58]. Neuropsychological testing was completed by a trained neuropsychology student. The

administration and test procedures were standardized and uniform across participants. Between-group comparisons on neuropsychological test scores are presented in Table 2.

---------- Insert Table 2 about here ----------

Event-related potentials (ERPs)

Each participant performed one practice block of 48 trials followed by 5 experimental blocks of 96 trials. Each trial was initiated by pressing the "N" and "V" keys simultaneously with the right and left index fingers respectively. A fixation point appeared for the remainder of the trial at the centre of the computer screen, and participants were instructed to maintain central fixation. Five hundred milliseconds later, a 100 ms bilateral visual display was presented and participants had 5 seconds to provide their response (see below). The trial sequence is presented in Figure 1.

----------Insert Figure 1 about here ----------

We modified a visual search task originally designed by Brisson and Jolicoeur (in press) so as to introduce an oddball condition that is known to elicit the classic P3 component [59]. This experimental paradigm includes four coloured squares (two on each side of fixation) with a gap in one of their sides (different for each square) and a fixation point (see Figure 1). All four squares in the visual display subtended a visual angle of 1˚ × 1˚ and the gaps were 0.33˚. The centre of the squares nearest to fixation was 1.5˚ below and 3.5˚ to the left or the right of fixation. The centre of the far squares was 3˚ below and 5˚ to the left or right of fixation. The target stimulus was red amongst green distractors for about half of the participants in each group and green amongst red distractors for the others.

Target squares were presented with equal probability to all four possible positions (near-left of fixation, near-right of fixation; far-left of fixation; far-right of fixation). The colours of the squares were adjusted to be approximately equiluminant using a chromameter (Minolta CS100) to control for low-level sensory responses. Although the probability of each gap location (top, bottom, left, right) was the same across trials for the target square, when the target square (unique colour square) had a gap on its left, right, or upper side (75% of trials; frequent response condition), participants were instructed to press the "V" key, whereas they had to press the "N" key only when the target square had a gap on the bottom side (25% of trials, rare response condition). Response assignment for the frequent and rare conditions (pressing the "V" key or the "N" key) and which colour was the target colour (red or green) were counterbalanced across subjects within each experimental groups (athletic controls; single concussion; multiple concussions) such that these factors could not produce differences across groups.

Electrophysiological recordings and data analysis.

The electroencephalogram (EEG) was recorded from 64 active Ag/AgCl electrodes (Biosemi Active Two system) 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 [60]. The horizontal electrooculogram (HEOG), recorded as the voltage difference between electrodes placed lateral to the external canthi, was used to measure horizontal eye movements. The vertical electrooculogram (VEOG), recorded as the voltage difference between two electrodes placed above and below the left eye, was used to detect eye blinks. The EEG and EOG were digitized at 256 Hz and low-pass filtered at 67 Hz during the recording. These signals were then high-pass filtered at 0.01 Hz and averaged offline. Trials with artefacts at electrode sites of interest (Cz, Pz, PO7, PO8), eye

blinks (VEOG > 100 μV) and large horizontal eye movements (HEOG > 35 μV) were excluded from the analysis.

Using the procedure described in Woodman and Luck (2003) [49], two participants with residual eye movements that deviated more than 0.2° (i.e., average HEOG for left or right targets > 3.2 μV) towards the target after ocular artefact rejection were rejected from the analysis.

In order to obtain the N2pc component waveform, EEG epochs of 700 ms (including 200 ms pre-stimulus onset) were averaged after artefact rejection, separately for trials with a left visual field target and trials with a right visual field target, and baseline corrected based on the 200 ms pre-target period. To isolate the N2pc component from non-lateralized perceptual processes, averaged ipsilateral waveforms (activity over the left hemisphere when the target stimulus was presented in the left visual field and activity over the right hemisphere when the target was presented in the right visual-field) were subtracted from those averaged contralateral waveforms (activity over left hemisphere to a right visual-field target and activity over right hemisphere to a left visual-field target). N2pc measurements (mean amplitude recorded during the 180—260 ms post-stimulus time window) were then made on the contralateral minus ipsilateral difference waveforms. The jackknife-based method proposed by Miller, Patterson, and Ulrich (1998) [61] was used in order to determine the N2pc latency offset according to the following parameters: fixed N2pc amplitude criteria set at -0.8 μV; beginning at 230 ms post-stimulus.

We also computed separate average ERP waveforms for trials with the more frequent response and trials with the less frequent response. EEG epochs of 1000 ms (including a 200 pre-stimulus period) were averaged after artefact rejection and baseline corrected based on mean amplitude of the activity recorcing during the 200 ms immediately

prior to stimulus onset. The P3 size was then quantified as the mean amplitude during the 500–800 ms time window post-stimulus onset. In accordance with most previous studies on the P3 and mTBIs, we determined the latency of the P3 as the latency of the most positive sample point recorded within the pre-defined time window of the P3 component. Pz and Cz electrodes, which have been shown to record maximal P3 deflection [16], were kept for further analyses. All ERP averages (both for the N2pc and P3 components) were based on a minimum of 75 trials for any given participant.

Statistical analyses

EEG and behavioural data from the visual search task used for event-related potentials recordings, neuropsychological test scores, post-concussion symptoms ratings, and demographic information were subjected to standard descriptive statistics and later tested with ANOVA. We also computed a 2-tailed Pearson correlation to look at the relationship between the size of the P3 component with the number of concussions, the time elapsed since the last concussion and concussion severity markers (LOC, retrograde and anterograde amnesia).

RESULTS

Neuropsychological and behavioural results

Neuropsychological results are presented in Table 2. The level of performance was equivalent across groups on each neuropsychological test used to assess various cognitive functions (Table 2).

Behavioural results on the target detection task are presented in Table 3. Only correct trials were included in analyses of reaction times. As expected, all groups were faster (F (2, 43) = 37.12; MSE = 34859.214; $p < .0001$) and more accurate (F (2, 43) =

64.29; *MSE* = 0.2156; $p < .0001$) for frequent stimuli relative to infrequent stimuli. There was no group difference in response accuracy either in the rare (F (2, 43) = 0.56; *MSE* = .005; $p > .575$) or the frequent response condition (F (2, 43) = 0.46; *MSE* = 0.000; $p > .634$). Similarly, reaction time scores were equivalent across groups for both frequent (F (2, 43) = 0.23; *MSE* = 1480.68; $p > .797$) and rare response conditions (F (2, 43) = 0.27; *MSE* = 2302.16; $p > .765$). Furthermore, RT variability was comparable in all three experimental groups for both frequent (F (2, 43) = 0.18; *MSE* = 395.13; $p > .837$) and rare stimuli (F (2, 43) = 0.12; *MSE* = 297.94 $p > .888$).

----------Insert Table 3 about here ----------

Electrophysiological results

Between-group comparisons on N2pc measurements recorded at PO7/PO8 electrode site were not found to be significant for either amplitude (F (2, 43) = 0.15; *MSE* = 0.082; $p > .862$) or latency of N2pc offset (F (2, 43) = 0.12; $p > .947$) (Figure 2).

----------Insert Figure 2 about here ----------

Figure 3 depicts averaged P3 waveforms recorded at Pz and Cz for each group when presented frequent stimuli, rare stimuli, and after having subtracted brain responses to frequent stimuli from those of rare stimuli. Table 4 also provides mean P3 latency and amplitude values recorded at Pz and Cz in each group. Whereas no group difference was revealed on the mean P3 amplitude elicited by frequent stimuli either at Pz (F (2, 43) = 1.92; *MSE* = 14.542; $p > .159$) or at Cz (F (2, 43) = 0.80; *MSE* = 11.440; $p > .457$), we found a significant between-group effect on the mean P3 amplitude evoked by rare stimuli

at both Pz (F (2, 43) = 4.00; MSE = 58.631; $p < .026$) and Cz (F (2, 43) = 3.30; MSE = 61.641; $p < .047$) (Figure 3). Then, Tukey post-hoc analysis revealed that the mean amplitude of the P3 component for rare stimuli was significantly suppressed at both Pz and Cz in the group of athletes presenting with multiple concussions when contrasted with that of the control athletes group ($p < .04$) and the single concussion group ($p < .04$). When we subtracted the mean P3 amplitude difference between ERPs elicited by frequent stimuli from that elicited by rare stimuli, we found a similar between-group effect at Pz (F (2, 43) = 3.30; MSE = 12.167; $p < .05$) and at Cz (F (2, 43) = 4.98; MSE = 17.33; $p < .02$) (Figure 3). A Tukey HSD post-hoc analysis revealed that the mean P3 amplitude difference between that elicited by rare and frequent stimuli was significantly smaller in multiple-concussion athletes in comparison to those who presented no prior history of concussion ($p < .037$) at both Pz and Cz, whereas a trend toward significance was observed when we contrasted the multi-concussed athletes group with the single-concussion group on the latter measure at Pz ($p < .093$).

None of the between-group comparisons computed on the latency of the P3 component were significant either at Pz (Rare stimulus condition (F (2, 43) = 1.06; MSE = 4761.63; $p > .355$); Frequent stimulus condition (F (2, 43) = 0.02; MSE = 57.318; $p > .983$); and Rare-Frequent difference wave (F (2, 43) = 0.11; MSE = 595.103; $p > .900$)) or at Cz (Rare stimulus condition (F (2, 43) = 1.23; MSE = 4914.41; $p > .318$); Frequent stimulus condition (F (2, 43) = 0.03; MSE = 81.976; $p > .913$); and Rare-Frequent difference wave (F (2, 43) = 0.23; MSE = 1304.752; $p > .816$)).

----------Insert Figure 3 about here ----------

----------Insert Table 4 about here----------

Two-tailed Pearson correlations drawn between P3 amplitude recorded at Pz – after having subtracted ERPs elicited by frequent stimuli from those of rare stimuli – and the athlete's reported history of anterograde amnesia (correlation coefficient (r) = -0.06; p = 0.76), retrograde amnesia (correlation coefficient (r) = 0.12; p = 0.52), and loss of consciousness (correlation coefficient (r) = -0.19; p = 0.33) were not significant (see Table 5). A two-tailed Pearson correlation drawn between P3 amplitude recorded at Pz, after having subtracted brain activity elicited by frequent stimuli from that of rare stimuli, and the number of concussion(s) sustained (correlation coefficient (r) = 0.11; $p > .56$) was not found to be significant (see Table 5). Although not reaching significance, a two-tailed Pearson correlation revealed that P3 amplitude tended to be correlated with the time elapsed since the last concussion (correlation coefficient (r)= -0.31; $p > .091$), such that greater attenuation of the P3 component seems to be associated with recent rather than remote concussions.

Knowing that multi-concussion athletes had sustained on average their latest concussion 25 months earlier than single concussion athletes, this raised the possibility that the effects of multiple concussions on the amplitude of the P3 component might have been confounded by the time since their latest concussion. To address this issue, we computed an ANCOVA to remove the effects of the time elapsed since the last concussion as a covariate on the amplitude of the P3 component. This additional analysis showed that the amplitude of the P3 component was still significantly attenuated in multi-concussion athletes despite having removed the effect of the time elapsed since the latest concussion as a covariate ($F(2, 43) = 3.08$, $MSE = 14.116$; $p < .038$) at Pz and ($F(2, 43) = 2.99$ $MSE = 11.731$; $p < .041$) .

----------Insert Table 5 about here----------

DISCUSSION

The present study shows that asymptomatic multiple-concussion athletes who sustained their latest concussion on average 3 years prior to testing still show significantly suppressed P3 amplitude for rare stimuli in an oddball paradigm when compared to athletes who experienced just one or no concussion despite equivalent neuropsychological test scores. These findings suggest that when using an active visual oddball paradigm, the P3 amplitude attenuation observed a few weeks post-injury in asymptomatic concussed athletes [46] persists even years post-injury in those who have sustained more than one concussion.

However, post-hoc correlations revealed that the association between the number of concussion(s) sustained and P3 amplitude attenuation was weak. This finding suggests that factors other than those associated with the mere accumulation of concussions affect the size of the P3 component in multi-concussion athletes. In contrast, it was found that the magnitude of the P3 amplitude tended to be positively correlated with the time elapsed since the latest concussion. Importantly, we still observed a significant P3 amplitude suppression in multi-concussion athletes after having statistically controlled the influence of time since the last concussion. Other alternatives to explain the observed P3 amplitude attenuation in the multi-concussed athletes group is that as the number of concussions increases, so too does the possibility for covert characteristics, such as traumatic axonal injury (TAI) or alterations in brain metabolism, to influence neural activity. The presence of these characteristics will largely be determined by the type of force (linear or rotational), the intensity of the blow, and location of the impact [3]. For example, in rotational force injury, shearing and tearing is more likely [62]. Shutter, Tong, Lee, Holshouser (2006)

showed that shearing and tearing is correlated with an early spike in choline levels associated with poor recovery [63]. One possibility to explain P3 amplitude alterations could be that multi-concussed athletes are at an increased risk of sustaining persistent axonal degeneration that might, in turn, affect information processing through impaired cellular transmission. Studies that look at residual pathophysiological changes in concussed athletes in relation with P3 component waveforms are necessary in order to address this issue.

Among other potential contributing factors to the observed reduction in P3 size that could be examined within the context of the present study, post-hoc correlations between self-reported concussion severity markers and the size of the P3 component were computed. This is based on the observation that a vast literature has attempted to delineate which of these common concussion severity markers best predicted later outcome. To date, evidence has been inconclusive. For instance, one recent study described an association of loss of consciousness and post-traumatic amnesia with specific early deficits on neuropsychological measures [64], while another group did not find any relationship between LOC and neuropsychological functioning in mTBIs who were still presenting performance differences on a more extensive neuropsychological assessment battery [65]. For the purpose of this study, we attempted to establish a relationship between the number of times athletes had suffered AGA, RGA and LOC with the size of the P3 component. None of the Pearson correlations coefficients were found to be significant between the size of the P3 and the number of episodes of anterograde amnesia, retrograde amnesia and loss of consciousness immediately after the injury. However, due to the fact that most concussed athletes in this study reported relatively minor accidents — only five out of 30 concussed athletes reported symptoms associated with Grade 3 concussions — few athletes

showed signs of concussion severity markers, which in turn, lessened our ability to uncover significant correlations with P3 amplitude. Further studies including a more extensive sample of athletes presenting with a broader history of concussions are therefore needed if we are to delineate the potential relationship between concussion severity markers and pervasive P3 amplitude suppression.

ERP studies conducted with MTBIs have reported a P3 amplitude reduction when performing an oddball task despite normal behavioral measures (i.e., mean reaction time and mean accuracy). Such P3 amplitude attenuation has typically been attributed to reduced cognitive efficiency related to attention-mediated and immediate memory processes [24]. Given that standard neuropsychological tests could not detect residual effects of sports concussion that occurred years prior to testing while event-related potentials did, it is possible that the latter investigation alternative provides added sensitivity to the long term effects of sports concussion. On the other hand, some might argue that our inability to find overt neurocognitive changes in asymptomatic concussed athletes undermines the clinical significance of the observed P3 changes. These subtle alterations in brain activity could be interpreted as irrelevant for the athlete's cognitive function. Interestingly, several functional imaging studies showed that mTBI patients display different brain activation patterns while achieving performance levels similar to those of controls [66][67]. These findings suggest that the injured brain of mTBIs can compensate for depleted mental efficiency possibly through the recruitment of additional brain resources. Future studies using more refined neuropsychological measures are therefore needed in order to determine the clinical relevance of changes in the amplitude of the P3 found years post-injury in otherwise asymptomatic concussed athletes. More difficult experimental tasks, such as dual tasks, might be a good alternative given that

Bernstein (2002) [68] recently showed dual task decrements in a sample of undergraduate students tested on average eight years post-TBI.

Using the N2pc, we sought to discover whether visual spatial attention was disturbed nine months after athletes had sustained their latest sports concussion. At least under present conditions — namely in a relatively easy task with a relatively low attentional load and nine months post-concussion — sports concussions did not induce long term deficits in the early deployment of visual-spatial attention. These results contrast with the persistent attenuation of P3 amplitude following multiple concussions. This pattern of results is important because it shows that "old" concussions do not cause general or ubiquitous electrophysiological suppression. The specificity of the long-term effects of previous concussions to the P3, along with an intact N2pc response, suggests that further work may allow us to pinpoint the cognitive system that is specifically affected by multiple concussions, and perhaps the underlying neural causes of this persistent P3 suppression.

If we are to investigate the impact of historically remote concussions on on-field attention requirements, experimental designs in which ongoing central attention and visual-spatial attention resources are solicited represent an appealing alternative. Since emerging studies have demonstrated that central attention can exert significant interference on the control of visual-spatial attention [59][69][70][71][72], it would be interesting for future studies to investigate how the history of concussion might influence one's ability to perform a visual search task while having to process interfering central attention stimuli. Another possibility would be to use a more difficult form of visual search (e.g., conjunction search or search in displays with visual noise) to verify whether a prior history of

concussion can predict one's ability to perform a visual search involving greater attention load.

The main limitation of the present study is that standard tests did not allow us to identify observable cognitive symptoms associated with the reduction in P3 size in concussed athletes. Future studies looking much more closely at the modulation of the P3 component waveform according to various concussion characteristics — clinical manifestations (confusion, memory problems, loss of consciousness), anatomical localization (such as cerebral versus brainstem), biomechanical impact (rotational versus linear force), genetic phenotype (apolipoprotein epsilon 4 (ApoE4) positive versus ApoE4 negative, and neuropathological changes (structural injury vs. no structural injury) [3] — would be helpful. Secondly, having to rely on concussion history self-reports as opposed to medical records to address consequences of sports concussion that occurred years prior to testing is not optimal. Prospective studies conducted with young athletes followed longitudinally are therefore required to validate the residual effects of concussions observed in the present study.

FIGURE CAPTIONS

Figure 1. Trial sequence of the visual search paradigm used for ERPs recordings.

Figure 2. Grand average N2pc component recorded at PO7/PO8 across groups (Control athletes group: Thick black trace; Single concussion group: Thick grey trace; Multiple concussion group: Thin black line trace).

Figure 3. ERPs were recorded at **1)** Cz & **2)** Pz. Grand average ERP **A)** To rare stimuli for each experimental group; **B)** To frequent stimuli across groups; & **C)** When brain activity evoked by frequent stimuli is subtracted from that elicited by rare stimuli (Control athletes group: Thick black trace; Single concussion group: Thick grey trace; Multiple concussion group: Thin black trace).

ACKNOWLEDGEMENTS

This study was supported by the Natural Sciences and Engineering Research Council of Canada and the Canada Research Chairs Program.

Disclosure: The authors have reported no conflicts of interest.

Experiment 1, Table 1

Groups	Age	Education (years)	Time since last concussion (mo)	# concussions sustained	Concussion severity markers			Post-Concussion symptoms scale		
					LOC	AGA	RGA	Somatic	Neuropsychiatric	Cognitive complaints
Control	22.50 (2.53)	17.00 (1.68)	-	-	-	-	-	0.19 (0.2)	0.43 (0.3)	0.38 (0.2)
Single	23 (2.93)	17.75 (1.61)	56.07 (70.84)	1	3	7	5	0.22 (0.1)	0.6 (0.4)	0.3 (0.2)
Multiple	23.46 (2.67)	17.94 (1.73)	31.47 (22.03)	2.80 (1.32)	4	18	17	0.20 (0.2)	0.45 (0.3)	0.35 (0.2)

Table 1. Between-group comparisons (group of control athletes with no history of concussion, single concussion group and multiple concussion group) on demographic, concussion severity markers and Post-concussion symptoms subscales. Values under each concussion severity marker reflects the total number of times athletes in each group sustained a concussion that involved anterograde amnesia (AGA), retrograde amnesia (RGA) and loss of consciousness (LOC). Values are expressed as means (standard deviation).

Experiment 1, Table 2

Tests	Condition	Group	Mean	Mean ± SD	*F*	*p*
Hopkins	Immediate Recall	Control	25.78 SD 4.11	25,78±4,11	0.198	> .82
		Single	24.88 SD 2.85	24.88±2.85		
		Multiple	25.87 SD 3.94	25.87±3.94		
Hopkins	Delayed Recall	Control	9.83 SD 2.46	9,83±2,46	0.335	> .71
		Single	9.22 SD 1.79	9.22±1.79		
		Multiple	9.25 SD 1.75	9.25±1.75		
Symbol Digit	Total Correct	Control	58.94 SD 9.82	58,94±9,82	0.205	> .81
		Single	58.11 SD 10.13	58.11±10.13		
		Multiple	56.25 SD 9.79	56.25±9.79		
Verbal Fluency	Total Correct	Control	34.72 SD 10.06	34,72±10,06	0.537	> .59
		Single	38.89 SD 10.26	38.89±10.26		
		Multiple	35.75 SD 9.00	35.75±9.00		
PSU	Total Correct	Control	42.33 SD 7.32	42,33±7,32	0.024	> .97
		Single	42.78 SD 5.87	42.78±5.87		
		Multiple	42.00 SD 8.94	42.00±8.94		
BVMT	Total Correct	Control	29.72 SD 4.16	29,72±4,16	0.909	> .41
		Single	27.44 SD 3.09	27.44±3.09		
		Multiple	28.25 SD 5.78	28.25±5.78		
BVMT	Delayed Recall	Control	11.67 SD 0.49	11,67±0,49	1.307	> .28
		Single	11.00 SD 1.50	11.00±1.50		
		Multiple	11.25 SD 1.39	11.25±1.39		
Color Trails A	Completion Time	Control	27.61 SD 7.85	27,61±7,85	0.610	> .55
		Single	25.78 SD 6.69	25.78±6.69		
		Multiple	24.38 SD 5.85	24.38±5.85		
Color Trails B	Completion Time	Control	66.44 SD 22.16	66,44±22,16	0.621	> .54
		Single	58.5 SD 11.65	58.5±11.65		
		Multiple	62.62 SD 7.58	62.62±7.58		

Table 2. Performance on neuropsychological measures across groups (Normal control group vs Single concussion group vs Multiple concussion group).

Experiment 1, Table 3

Measures	Experimental Conditions	Groups	Mean	*F*	*p*
Mean Reaction Time (ms)	Rare	Controls	581 SD 58	0.27	> .76
		Single	604 SD 112		
		Multiple	596 SD 100		
	Frequent	Controls	549 SD 66	0.23	> .79
		Single	547 SD 77		
		Multiple	565 SD 97		
Mean Accuracy (% correct)	Rare	Controls	86.9 SD 10.8	0.56	> .57
		Single	90.2 SD 6.6		
		Multiple	87.7 SD 9.8		
	Frequent	Controls	97.9 SD 1.6	0.46	> .63
		Single	98.2 SD 1.6		
		Multiple	97.5 SD 2.9		

Table 3. Between-group comparisons on behavioral scores for the experimental task performed during the EEG recordings.

Experiment 1, Table 4

		Mean P3 amplitude ± SD			Mean P3 latency ± SD		
Condition	**Electrode**	**Controls**	**Single**	**Multiple**	**Controls**	**Single**	**Multiple**
Frequent	Cz	6.77 SD 3.13	7.82 SD 4.92	6.89 SD 3.77	540 SD 96	559 SD 103	575 SD 97
	Pz	4.52 SD 2.90	4.52 SD 2.90	3.46 SD 1.30	558 SD 100	550 SD 91	570 SD 89
Rare	Cz	10.40 SD 4.21	10.61 SD 5.27	7.00 SD 3.24	540 SD 97	548 SD 108	570 SD 100
	Pz	11.05 SD 3.82	11.05 SD 3.82	11.16 SD 4.90	556 SD 101	543 SD 88	574 SD 97
Rare-Frequent	Cz	4.05 SD 0.68	2.94 SD 1.62	1.90 SD 0.89	581 SD 86	557 SD 83	588 SD 106
	Pz	4.50 SD 2.79	4.50 SD 2.79	3.71 SD 1.56	590 SD 73	614 SD 75	574 SD 74

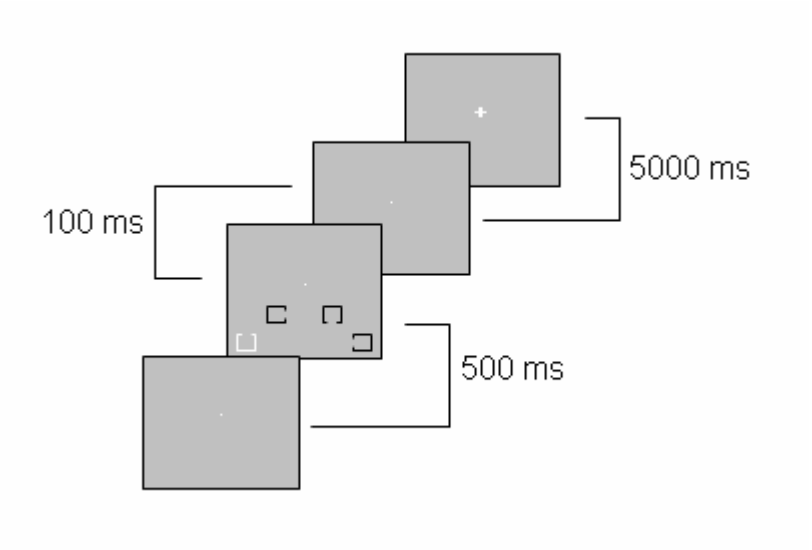
Table 4. Between-group difference on the mean P3 amplitude (in μV) and latency (ms) recorded at Pz and Cz in the 500–800 ms post-stimulus time window when presented rare stimuli, frequent stimuli, and after having subtracted mean P3 amplitude elicited by frequent stimuli from that elicited by rare stimuli.

Experiment 1, Table 5

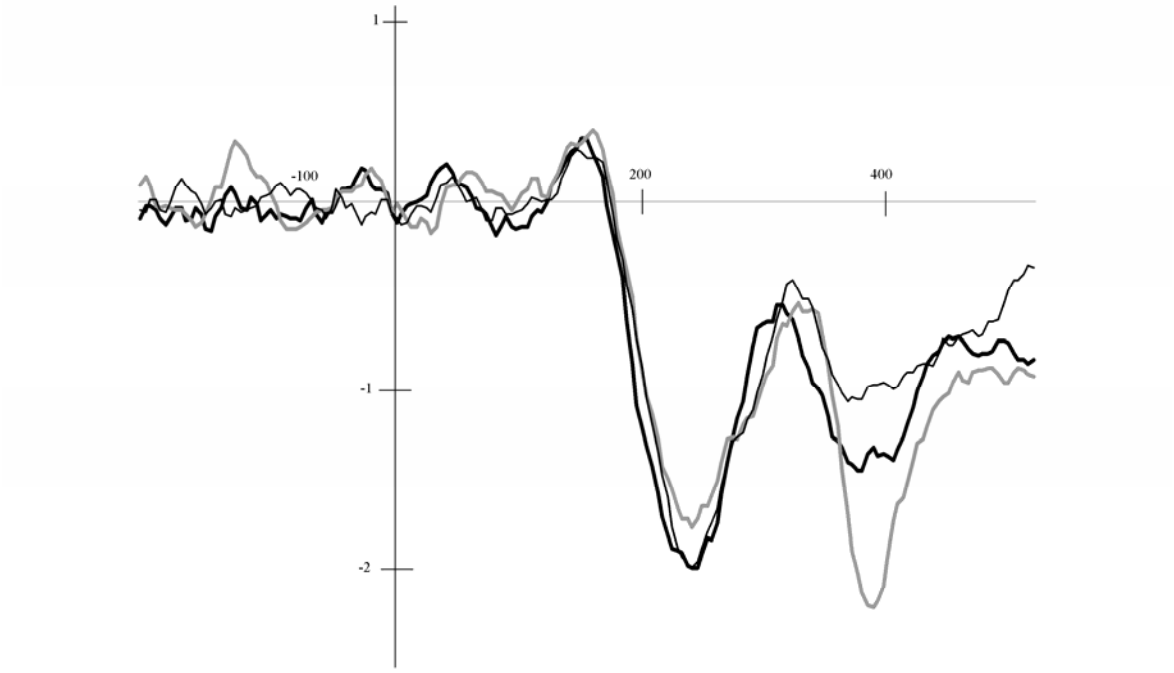
		Correlation Coefficient (*r*)	*p*
Concussion History	**Time since last concussion**	-0.31	> .091
	# of concussions sustained	0.11	> .56
Concussion Severity	**Anterograde amnesia**	-0.09	> .59
	Retrograde amnesia	-0.05	> .77
	Loss of consciousness	0.02	> .91

Table 5. Two-tailed Pearson correlations between concussion history information (Time since last concussion, Number of concussions), concussion severity markers (Anterograde amnesia, Retrograde amnesia, Loss of consciousness) and P3 amplitude difference between rare stimuli and frequent stimuli. P3 amplitude was taken at Pz.

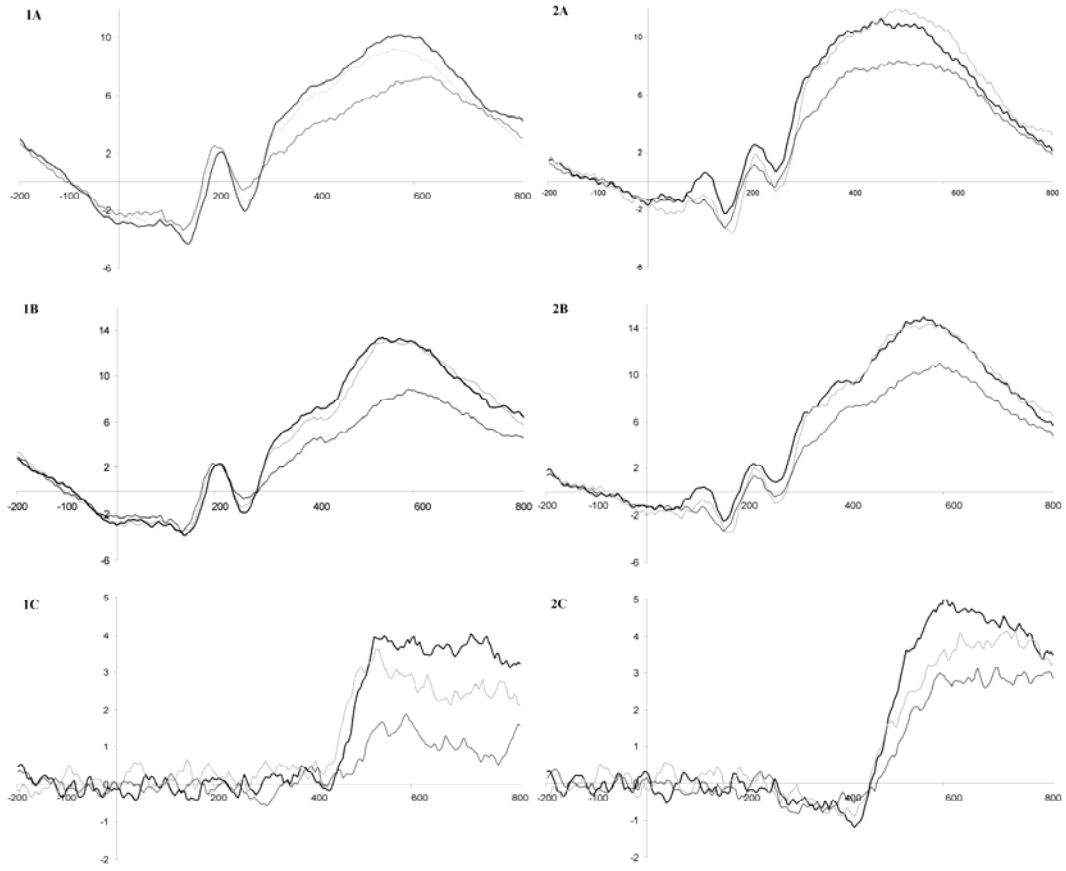
Experiment 1, Figure 1



Experiment 1, Figure 2



Experiment 1, Figure 3



3. Experiment 2

De Beaumont, L., Lassonde, M., Leclerc, S. & Théoret, H. (2007). Impaired cortical inhibition in Sports Concussions. Neurosurgery , 61, 329-336

Long Term and Cumulative Effects of Sports Concussions on Motor Cortex Inhibition

Abstract

Objectives: Using transcranial magnetic stimulation (TMS) paradigms, this study investigated motor cortex integrity as a function of an athlete's prior history of concussions. **Methods:** Motor cortex excitatory and inhibitory mechanisms were studied using 4 different TMS protocols: 1) Resting motor threshold; 2) Intracortical inhibition and intracortical facilitation in a paired-pulse paradigm; 3) Excitability of the corticospinal system using an input/output curve; and 4) Intracortical inhibition (ICI) in a cortical silent period (CSP) paradigm. Motor-evoked potentials were recorded from the first dorsal interosseous muscle of the right hand. **Results:** CSP duration in multiple concussion athletes was prolonged when compared to that of normal controls. Linear regressions suggested severity of concussions was the main factor explaining motor cortex dysfunction. Moreover, upon retesting, the CSP was further prolonged in the athletes who sustained another concussion after baseline testing. **Conclusion:** Findings from this study show that sports concussions result in long term motor system dysfunctions that seem to be attributable to subclinical intracortical inhibitory systems abnormalities. This study also

shows that sustaining subsequent concussions exacerbates this deficit, thus providing further support for the contention that the adverse effects of sports concussions on intracortical inhibitory systems are cumulative.

INTRODUCTION

Only in the United States, an estimated 50,000 to 300,000 contact sports athletes sustain a concussion during the course of a sports season (6). Over the last 15 years, the exponentially growing prevalence of sports concussions has greatly promoted research efforts dedicated to the diagnosis, treatment, and recovery process of traumatic brain injuries (TBI), as it is now considered a major public health concern (19). Although decades of research have looked for the existence of pervasive impairments in brain function following TBI, very few conclusive evidence have been provided, especially with regards to mild TBI. In fact, most neuropsychological studies (4)(10)(11)(17) suggest fully recovered cognitive function in mild head injury patients within 2-10 days following the accident.

Despite the seemingly scarce effects of mild TBI on cognitive function, recent data provide strong evidence that the effects of concussions are cumulative. A recent National Collegiate Athletic Association (NCAA) study showed that contact sports athletes with a prior history of concussions are three times more likely to sustain subsequent concussions than athletes with no prior concussion history (15). This study also showed that athletes with a history of more than 3 concussions recovered more slowly than those who sustained

only one concussion. In the same vein, high school football players who previously sustained a severe concussion involving loss of consciousness were found to be four times more likely to suffer subsequent Grade 3 concussions than players who had never lost consciousness as a result of brain trauma (13). Another study showed that athletes with a prior history of sports concussions are 9.3 times more at risk of showing signs in three out of the four concussion severity markers (positive LOC, anterograde amnesia, retrograde amnesia, and confusion) than others with no prior history of concussion (9). Taken together, these data show that multiple concussion athletes are more vulnerable to subsequent concussions and that they suffer more severe post-concussion symptoms than athletes with no prior history of concussion.

With regard to the growing literature on the cumulative effects of concussion, recent studies sought to explore its potential long term impact on brain function. Among them, a wide epidemiological study recently demonstrated that retired football players had a fivefold prevalence of mild cognitive impairments (MCI) diagnosis, a condition characterized by early memory impairments that convert at a rate of about 10-20% per year into Alzheimer's disease (16). Other studies conducted with professional and amateur boxers provided additional evidence for the existence of severe long-term sequelae associated with recurrent concussive and subconcussive blows to the head. As a direct consequence of sustaining recurrent concussions throughout their career, it was found that approximately 17% of retired professional boxers developed early symptoms of mild confusion and ataxia quickly progressing to a "Parkinsonian" cognitive decline. In fact, abnormal performance on memory tests, increased motor and speech latencies, dysarthria, pyramidal tract dysfunction, tremor in the head and upper extremities, and behavioral

changes are common features associated with what has often been referred to as Dementia Pugilistica or chronic TBI (27), a brain pathology that has solely been described in boxers. Whereas recent event-related potentials studies revealed persistent subclinical attention and working memory abnormalities in asymptomatic concussed athletes (14)(21), no study to date has looked for motor system abnormalities in this population. Considering that motor symptoms are typically the earliest clinical manifestation of chronic TBI (27), it seems plausible that the motor system could have been affected by repeated concussive blows to the head. In order to address this issue, transcranial magnetic stimulation (TMS) represents a particularly pertinent alternative due to its unprecedented sensitivity to central inhibitory/excitatory mechanisms of the motor system (1). Indeed, altered excitability of the motor system in the acute phase following a minor head injury was recently demonstrated as higher thresholds to single-pulse TMS were reported (7).

The present study was conducted to evaluate whether young asymptomatic concussed athletes for whom negative MRI results are reliably reported across studies (3)(8) will show subclinical motor cortex dysfunction years following their last concussion. In light of abovementioned neuropsychological data on the cumulative effects of sports concussions, we hypothesized that athletes with a history of recurrent concussions would show greater subclinical motor system abnormalities than those who sustained only one concussion. Finally, in order to partially address the issue of cause and effect ─ namely that abnormalities in motor cortex function were a premorbid characteristic and may have played a causal role in sustaining sports concussions - that cannot be excluded in retrospective studies of this nature, we sought to prospectively investigate whether

sustaining another concussion would result in worsened motor system abnormalities, thereby providing further support for the contention that the effects of concussions are cumulative.

METHODS

Participants

All 45 participants in this study were active players from a Canadian University Football team recruited with the help of the Montreal Carabins' team physician. Athletes who took part in this study were those who were not rejected after having been screened for the following exclusion criteria: A history of alcohol and/or substance abuse, psychiatric illness, learning disability, neurological history (seizure disorder or concussion-related seizures, central nervous system neoplasm or brain tumor) and a history of traumatic brain injury unrelated to contact sports. None of the athletes who took part in this study were taking medications at the time of testing. Three experimental groups were included in this study. The first group consisted of 15 asymptomatic athletes with a history of two or more sports concussions that occurred more than 9 months prior to testing. The number of concussions sustained ranged from 2 to 5. The second experimental group consisted of 15 athletes with a history of only one sports concussion that also had to occur more than nine months prior to testing. These two concussion groups were equivalent for the time elapsed since their last concussion (F (1, 28) = 2.38; $p > .13$) (see Table 1). Concussion severity was assessed by the team physician. It varied from Grade 1 (confusion for less than 15 minutes without amnesia, no LOC) to Grade 3 (LOC, either brief (seconds) or prolonged (minutes)) according to the American Academy of Neurology (2) and they were all

considered as minor head injuries on the Glasgow Coma Scale (scoring between 13 to 15). The third, control, group also consisted of 15 university football players with no history of neurological insult at the time of testing. All three experimental groups were equivalent according to age (F (2, 43) = 0.46; $p > .63$) and level of education (F (2, 43) = 1.51; $p > .23$) (refer to Table 1). A standardized concussion history form was administered to obtain detailed information about the number of previous concussions (if any), the approximate date of each concussion (s), the description of the accident, the nature and the duration of relevant post-concussion symptoms (confusion and/or disorientation, retrograde and/or anterograde amnesia, and loss of consciousness), neuroimaging results (if any), and number of days before returning to play (if any). Grade of previous concussion were classified by a sports physician using the practice parameter of the American Academy of Neurology.

----------Insert Table 1 about here----------

Materials and Procedure

Neuropsychological Assessment

Neuropsychological tests of the National Football League Neuropsychological Testing Program were used to assess multiple aspects of cognitive functioning (25). This battery includes classic neuropsychological tests selected to evaluate attentional processes (PSU cancellation task); Visual scanning and information processing (Color Trails A and B, Symbol Digit Modality Test (SDMT); Visual memory (Brief test of Visual Memory (BTVM), incidental memory recall of SDMT); Verbal memory (Hopkins verbal learning

test); Visual-motor coordination (BTVM, copy); & Speech fluency (Verbal fluency, phonemic). Neuropsychological testing was completed by a trained neuropsychology student. The administration and test procedures were standardized and uniform across participants. All scores were within normal ranges and between-group comparisons on neuropsychological test scores revealed no differences among the groups.

Transcranial magnetic stimulation recordings

All participants completed four TMS paradigms administered in a single 1-hour session at the University of Montreal Neuropsychology laboratory. Subjects were seated in a comfortable chair. EMG recordings were obtained from electrodes placed on the right first dorsal interosseus (index finger) muscle using a belly-tendon montage and were amplified using a BioPac MP150 system (Biopac Systems, Goleta, CA), with a 20 Hz to 1 KHz band pass filter. The signal was processed on a G4 MacIntosh computer using Acqknowledge System software (Biopac Systems, Goleta, CA). A Mag Pro transcranial magnetic stimulator (Medtronic, Minneapolis, MN) was connected to a 8 cm diameter figure-of–eight coil. The coil was positioned over the optimal coil position for eliciting contralateral MEPs at a 45˚ angle from the midline. For each subject, the optimal coil position for eliciting reproducible MEPs was obtained by slowly moving the coil in 1-cm steps over the preferred area of stimulation of the contralateral motor cortex. This optimal site was marked using a washable marker to make sure that the coil was held in the same position throughout the experiment. The following TMS parameters were measured: 1) Resting motor threshold; 2) EMG response to paired TMS stimulation; 3) EMG response to single TMS pulse of varying stimulus intensities (Input/Output curves); and 4) duration of the cortical silent period.

Resting Motor Threshold: Several TMS parameters have been developed to assess the overall excitability of the corticospinal system. The resting motor threshold reflects the minimum TMS intensity (usually expressed as a percentage of maximum stimulator output) resulting in MEPs in a fully relaxed target muscle in 5 out of 10 consecutive trials. Pharmacological studies have recently suggested that the resting motor threshold reflected neuronal membrane excitability, which is highly dependent on ion channel conductivity (32). The motor threshold at rest was calculated as the minimal stimulation intensity evoking a MEP of at least 50μV in 5 out of 10 consecutive trials when TMS was applied to the contralateral M1. In most cases, the resting motor threshold was measured by a reduction from slightly supra-threshold intensities (starting at 60% of the maximum stimulator output) in 1% steps. However, when participants presented with resting motor threshold higher than 60% of the maximum stimulator output, the resting motor threshold was obtained by increasing stimulation intensity in 3% steps until recorded reproducible MEPs were recorded. Then, the resting motor threshold was obtained by reducing intensity from these slightly supra-threshold values in 1% steps. A typical motor evoked potential elicited by a single pulse is illustrated in Figure 1A.

Paired-Pulse TMS paradigm (ICF and ICI): Intracortical inhibition resulting in suppressed motor evoked potentials is obtained in a paired-pulse TMS paradigm when a sub-threshold conditioning stimulus over the motor cortex precedes a supra-threshold stimulation by 1 to 6 milliseconds. The maximum suppression is induced by conditioning stimulus intensities ranging from 70% to 90% of the resting motor threshold, whereas higher stimulation intensities engenders less inhibition and often facilitation (1). Based on previous animal studies, Kujirai et al. (1993) (20) suggested that this suppression in motor activity is mainly

the result of the activation of intracortical GABA-ergic interneurons of the primary motor cortex. A typical MEP resulting from ICI in a paired-pulse paradigm is illustrated in Figure 1B. On the contrary, when the sub-threshold conditioning stimulus precedes the supra-threshold stimulus (test stimulus) by 8-20 ms, the motor evoked potentials elicited by the test stimulus are facilitated when the target muscle is at rest. Although the mechanisms responsible for ICF are not fully understood, MEP facilitation assessed by the ICF paradigm seems to be mediated by synaptic glutamatergic transmission (22) (32). Possibly, horizontally arranged cortico-cortical projecting pyramidal cells located in superficial cortical layers mediate ICF (31).

For the purpose of this study, we used short interstimulus intervals (ISIs) of 1, 2 and 3 ms to test intracortical inhibition and long ISIs of 6, 9, 12 and 15 ms to study intracortical facilitation according to the method of Kujirai et al. (1993) (20). A sub-threshold conditioning stimulus set at 80% of the resting motor threshold preceded a supra-threshold test stimulus. This test stimulus was adjusted to produce an average MEP of 1 mV peak-to-peak amplitude (20). The conditioning stimulus preceded the test stimulus according to seven random inter-stimulus intervals (1ms, 2ms, 3ms, 6ms, 9ms, 12ms and 15ms). We also included a test stimulus-alone condition set at approximately 120% of the resting motor threshold to obtain baseline measurements. Ten consecutive trials were collected for each interstimulus interval and for the test stimulus alone condition. Interpulse interval was 6-8 seconds. A typical MEP resulting from ICF in a paired-pulse paradigm is illustrated in Figure 1C.

Input-Output curves: Input-Output curves are thought reflect the strength of corticospinal projections, being steeper in muscles with a large motor cortex representation (1).

Corticospinal excitability was assessed using single TMS pulses of increasing intensities (80%, 90%, 100%, 110%, 115%, 120%, 130%, 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 seconds.

Cortical Silent Period: When TMS is delivered over the motor cortex while the subjects maintain a voluntary muscle contraction, a pause in ongoing EMG activities follows the MEP, which is called the silent period (28). The level of muscle contraction was found to have negligible effects on the duration of the cortical silent period, whereas the intensity of the test stimulus is positively correlated with the duration of this silent period. Studies on the mechanism of the cortical silent period (CSP) tend to suggest that its duration is influenced by several factors. The initial phase of the silent period has often be explained by segmental factors such as the H reflex and the refractory period of the pyramidal tract neurons. However, segmental factors are too short to explain the extended duration of the silent period that often last for more than a few hundred milliseconds. Activation of intracortical inhibition interneurons mediated by GABA-b receptors located in the motor cortex seems to explain the late phase of the cortical silent period (30). Ten single-pulse stimulations (120% MT intensity) were applied to the left M1 while participants maintained a voluntary isometric muscle contraction of the right FDI at approximately 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 approximately 15 seconds. The intensity of the muscle contraction was digitized so that participants could regulate their exerted strength to a relatively constant level. The duration

of the CSP was calculated with a graphical method as previously described by Garvey et al. (2001) (12) and was defined as the period from the onset of EMG suppression until the resumption of sustained post-stimulus EMG activity (A typical CSP is illustrated in Figure 1D).

---------- Insert Figure 1 about here ----------

Retest

Five athletes from the multiple concussion group sustained a concussion after they had been tested for the initial purpose of this study. They all agreed to be retested with the same experimental protocol between six and fifteen months after their injury to prospectively investigate the pervasive effects of sustaining incident concussions on motor system function.

Statistical analyses

All values are expressed as means ± SD. EMG data obtained from consecutive recordings were subjected to standard descriptive statistics and later tested with ANOVA in all four TMS paradigms. 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. Greenhouse-Geisser correction for multiple comparisons was applied to both paired-pulse and input/output paradigms. We also computed a series of 2-tailed Pearson correlations between cortical silent period duration and concussion history information collected for each participant included in this study (time elapsed since the last concussion, concussion severity rated according to AAN standards, number of concussions sustained). Finally, we computed a linear regression from which we obtained the coefficient of the linear equation (βeta coefficient) that

provides an estimate of the variable(s) (in this study, the number of concussions sustained or the concussion severity) that best predict(s) the abnormal cortical silent lengthening in concussed athletes

RESULTS

Resting Motor threshold

There was no group difference for MT (F (2, 43) = 0.20; $p > .81$). Mean resting MT was 53% (SD = 9.53%), 56% (SD = 18.27%) and 53% (SD = 7.19%) for the control, single concussion athletes and multiple concussion athletes groups, respectively (Figure 1, A).

Paired pulse TMS

Intracortical inhibition condition

Paired-pulse TMS curves in both groups were normal in configuration. In both groups, short ISIs (1, 2, 3 ms) inhibited the response to the test stimulus. There was no significant interaction between groups (concussed or controls) and inter-stimulus interval duration for short ISIs eliciting intracortical inhibition (1ms, 2ms, 3ms) (F (1, 44) = 1.75; $p > .14$) after Greenhouse-Geisser correction. MEP sizes were not found to be significantly different across the three groups for intracortical inhibition conditions (F (2, 43) = 0.14; $p > .86$). As expected, tests of within-subject effects yielded a significant difference in MEP sizes elicited by the 3 different ISIs of the intracortical inhibition condition (1, 2 and 3 ms) (F (1, 44) = 5.32; $p < .01$).

Intracortical facilitation condition

The interaction between groups and inter-stimulus interval duration for longer ISIs (6ms, 9ms, 12ms, 15ms) eliciting intracortical facilitation was not significant (F (1, 44) = 1.72; p > .12) (Figure 1, D). MEP sizes for the ICF condition were not statistically different between the three groups (F (2, 43) = 0.42; p > .65). Tests of within-subject effects showed a significant difference between ISIs yielding intracortical facilitation (F (1, 44) = 12.19; p < .01).

Input/Output curves

Input-output curves were normal in configuration. In all three groups, EMG response was higher as TMS intensity increased. The interaction between groups (concussed or controls) and TMS intensities (90%, 100%, 105%, 110%, 115%, 120%, 130% and 140% of resting motor threshold) was not found to be significant (F (1, 44) = 1.73; p > .14) after Greenhouse-Geisser correction for multiple comparisons was applied. Test of within-subject effect showed that all three groups had significantly greater MEPs as the intensity of the TMS increased (F (1, 44) = 36.39; p < .001) (Figure 1, C).

Cortical silent period duration

Two raters (both blind to diagnosis) measured CSP durations for all subjects. The length of the silent period was measured from the beginning of the MEP until the onset of on-going EMG activity. An intraclass correlation coefficient was calculated to determine the inter-rater reliability for CSP durations. A 0.96 correlation coefficient was obtained. A One-way ANOVA yielded a significant between-group effect (F (2, 43) = 5.12; p< .01). Then, Tukey HSD post-hoc analysis revealed that the cortical silent period duration was

significantly prolonged in the group of athletes presenting with recurrent concussions when contrasted with that of the normal control group ((Normal control group (100.53 ± 26.09 ms)) vs (Multiple concussion group (127.55 ± 26.86 ms)) ; $p < .01$) (Figure 1, B), whereas other between-group comparisons did not reach significance.

----------Insert Figure 2 about here----------

We computed two-tailed Pearson correlations to investigate whether the length of the silent period appeared to be affected by concussion history information markers such as the time elapsed since the last concussion, the number of concussion(s) sustained and the severity of concussions sustained. Among those concussion history markers, it was found that sustaining rather severe concussions was significantly correlated with cortical silent period lengthening (2-tailed Pearson correlation = 0.45; $p < .02$; n = 15) in concussed athletes. Other correlations drawn between the TMS-induced cortical silent period and concussion history information were not significant (Table 2).

----------Insert Table 2 about here----------

Finally, a linear regression was computed to assess what variable between prior history of concussions and severity of the accident best predicted the observed abnormal cortical silent period duration in multiple concussion athletes. This analysis revealed that the severity of concussions sustained, as rated according to the AAN in contact sports, was a better predictor of abnormal cortical silent period lengthening observed in multiple concussion athletes than the number of concussions per se (β for concussion **Groups** = 0.08 ; $p > .637$); (β for concussion **Severity** = 0.435 ; $p < .019$)) (Figure 1E).

Retest

While repeated-measure ANOVAs revealed equivalent resting motor threshold ($F(1, 4) = 0.38$; $p > .57$), paired-pulse intracortical inhibition ($F(1, 4) = 1.31$; $p > .32$) and facilitation ($F(1, 4) = 1.61$; $p > 0.25$), input/output curves ($F(1, 4) = 2.82$; $p > .11$), and neuropsychological test scores at testing date 1 (Time 1) comparable with those obtained at testing date 2 (Time 2), the length of the cortical silent period was found to be significantly prolonged as a result of the incident concussion ($F(1, 4) = 8.80$; $p < .05$) (Table 3).

----------Insert Table 3 about here----------

DISCUSSION

Results from this study suggest for the first time that sports concussions result in chronic subclinical motor system dysfunctions that are linked to intracortical inhibitory systems abnormalities. Three main sources of evidence are provided in the present study to support this finding: 1) The duration of the cortical silent period was significantly prolonged in those athletes with a history of concussions; 2) Sustaining subsequent concussions exacerbates cortical silent period abnormalities; and 3) CSP duration is positively correlated with the severity of concussions sustained.

The primary objective of this study was to investigate the excitability of the primary motor cortex as a function of an athlete's prior history of concussions. Using TMS, we found a prolonged cortical silent period duration in asymptomatic athletes who presented with a history of recurrent concussions. However, when computing linear regressions in order to

determine the variable that best predicted the observed cortical silent period lengthening in multiple concussion athletes, we found that most of this abnormality could be attributed to the severity of concussions rather than belonging to the single or the multiple concussion groups. These linear regressions were performed as our data showed that athletes with a history of multiple concussions tended to have sustained more severe concussions than the single concussion group.

When we prospectively examined the effects of recurrent concussions in a small group of multiple concussion athletes who were retested with the same experimental protocol, we found that the cortical silent period was significantly prolonged after having sustained another concussion, suggesting that intracortical inhibitory interneurons receptors of the motor system may be particularly vulnerable to the effects of sports concussions.

Another major finding was that the observed cortical silent period duration lengthening in multiple concussion athletes seemed to remain unaffected by the time elapsed since the last accident, as evidenced by a near zero Pearson correlation value obtained between these two variables. This strongly suggests that the underlying intracortical inhibitory mechanism that is currently thought to modulate the duration of the cortical silent period remains significantly altered in asymptomatic young athletes regardless of the time elapsed since the last concussion. Taken together, these results suggest that sustaining concussions of a more severe nature exerts significant abnormalities in motor cortex functioning that persist far beyond the acute phase of the injury.

One possible neurophysiological substrate of silent period duration increases in concussed athletes may lie in an impaired GABA-b receptor system. The latter part of the silent period has been attributed to activity of intracortical inhibitory systems of the primary motor cortex, whereas spinal inhibition contributes to its early part (18). Evidence that the late part of the silent period is caused by long-lasting cortical inhibition mediated by GABA-b receptors comes from pharmacological studies. Tiagabine, a GABA re-uptake inhibitor lengthens the silent period (29). Furthermore, L-DOPA and dopamine agonists also appear to lengthen SP duration (26), strengthening the claim that GABA receptors, and particularly GABA-b, are crucial for the determination of silent period duration. Based on these findings, it would appear that concussions alter the efficacy of GABA-b receptor systems, perhaps contributing to rendering the brain more vulnerable to subsequent traumatic events. However, a recent pharmacological study showed no specific effect of having ingested a selective GABA-b receptor agonist on the modulation of the cortical silent period (23). In light of emerging findings suggesting that CSP abnormalities constitute a particularly sensitive measure of motor system dysfunctions observed in various brain pathologies, it strengthens the need to gain a better grasp at the underlying mechanisms of the CSP.

In a previous study conducted by Chistyakov et al. (2001) (7), CSP was also found to be significantly prolonged in mild to moderate head injury patients when compared to matched controls two weeks following the accident. However, results from that study suggested that the CSP duration was not altered in concussed patients who sustained minor head injuries, this severity grading being equivalent to that of concussed athletes recruited in the present study. This discrepancy could be explained by a variety of factors such as

different methodologies (different TMS intensity used to measure CSP duration and the use of a circular coil), differing patient populations (concussed university football players versus head injury patients recruited as they were seeking medical attention for their head injury in a health care facility) and different time of testing (9 months following the injury vs within 2 weeks of the injury). On the other hand, it raises the intriguing possibility that CSP prolongation could be triggered later following head trauma. Contrary to Chistyakov et al.'s findings (2001) (7), our study did not reveal differences in corticospinal system excitability based on resting motor threshold measurements between concussed athletes and controls. One way to explain this failure to replicate Chistyakov et al.'s findings (7) could be that concussed athletes recruited in our study had sustained their injury more than nine months prior to testing, whereas the minor-to-moderate head injury patients from the latter study were tested 2 weeks following their injury. When results from Chistyakov et al.'s work (7) and those obtained in the present study are taken together, one might speculate that the motor threshold paradigm is especially sensitive to the metabolic imbalances that are known to take place in the acute effects of concussions (24), while this motor system abnormality may return to normal functioning after having benefited from spontaneous recovery.

Interestingly, recent neuropsychological and event-related potentials (ERP) studies found that asymptomatic concussion athletes showed altered cognitive function despite normal results on classic neuropsychological tests used as the gold standard in the assessment of cognitive function following sports concussion (5)(14). Similarly, the altered cortical silent period duration found in this study in asymptomatic concussed athletes presenting with normal scores on neuropsychological tests adds further support for the contention that

sports concussion result in persistent brain function alterations that cannot be detected by standard neuropsychological tests. Future studies using more refined motor tasks are needed in order to determine the clinical significance of these TMS findings.

An important limitation to the present study is the lack of imaging results. In fact, one possibility to explain the present findings could be that the prolongation of the CSP is the result of structural damage rather than that of sports concussions. However, knowing that only 10% of all minor/mild head injury patients show MRI abnormalities related to trauma (3)(7), it is highly improbable that structural damage alone could explain the observed CSP prolongation in all five patients who sustained a subsequent concussion within the study period. Nonetheless, the addition of structural imaging would be instrumental in future studies to systematically address this issue.

Findings from this study show that sports concussions result in long term motor system dysfunctions that seem to be attributable to subclinical intracortical inhibitory systems abnormalities. This study also shows that sustaining subsequent concussions exacerbates this deficit, thus providing further support for the contention that the adverse effects of sports concussions on intracortical inhibitory systems are cumulative.

FIGURE CAPTIONS

Figure 1: 1A) A typical motor evoked potential elicited by a single pulse; **1B)** A typical MEP resulting from intracortical inhibition (ICI) in a paired-pulse paradigm; **1C)** A typical MEP resulting from intracortical facilitation (ICF) in a paired-pulse paradigm; & **1D)** A typical CSP when TMS is delivered over the motor cortex while the subjects maintain a voluntary muscle contraction.

Figure 2: (A) Resting motor threshold values expressed as a percentage of the maximum stimulator output for all three experimental groups (normal control group, single concussion group and multiple concussion group); **(B)** Cortical silent period duration (in ms) when the three experimental groups exert a voluntary isometric muscle contraction of the first dorsal interosseus muscle of the right hand at approximately 10% of maximum strength; **(C)** Input/Output curves for all three experimental groups showing the average MEP amplitude (in mV) when increasing TMS intensities (90%, 100%, 105% 110%, 115%, 120%, 130%, 140%), expressed as a percentage of the resting motor threshold, are applied to the motor cortex; **(D)** Paired-pulse paradigm showing the average MEP amplitude (in mV) for all three experimental groups when increasing interstimulus interval duration (1, 2, 3, 6, 9, 12, and 15) (in ms) separate the conditioning stimulus from the test stimulus; **(E)** Pearson correlations between the duration of the silent period (in ms) and concussion severity (Grade 1 to Grade 3) in concussed athletes. Error bars illustrated in Figure 1A, 1B, 1C, 1D represent standard error values (SE).

ACKNOWLEDGEMENTS

This study was supported by the Natural Sciences and Engineering Research Council of Canada, the Fonds de Recherche en Santé du Québec and the Canada Foundation for Innovation.

Disclosure: The authors have reported no conflicts of interest.

Experiment 2, Table 1

Variables	GROUPS	Mean ± SD	F	*p*
Age	Control	22.50± 2.53	0.461	> .63
	Single	22.94± 2.84		
	Multiple	23.38± 2.63		
Education (years)	Control	17.00± 1.68	1.511	> .23
	Single	17.75± 1.612		
	Multiple	17.94± 1.73		
Time since last concussion (months)	Control	-	2.379	> .13
	Single	59.12±69.52		
	Multiple	31.00± 22.08		
# concussions sustained	Control	-	29.4	< .001
	Single	1± 0		
	Multiple	2.75±1.29		
Concussion Severity	Control	-	1.923	> .17
	Single	1.81± 0.75		
	Multiple	2.13± 0.50		

Table 1: Between-group comparisons (group of control athletes with no history of concussion, single concussion group and multiple concussion group) on demographic and concussion history information.

Experiment 2, Table 2

Concussion history marker	Condition	Correlations	*p*
Concussion History	# of concussions	0.133	> .48
Concussion Severity	AANPP Grades	0.448	< .02*
Concussion Date	Date of last Concussion	-0.169	> .37

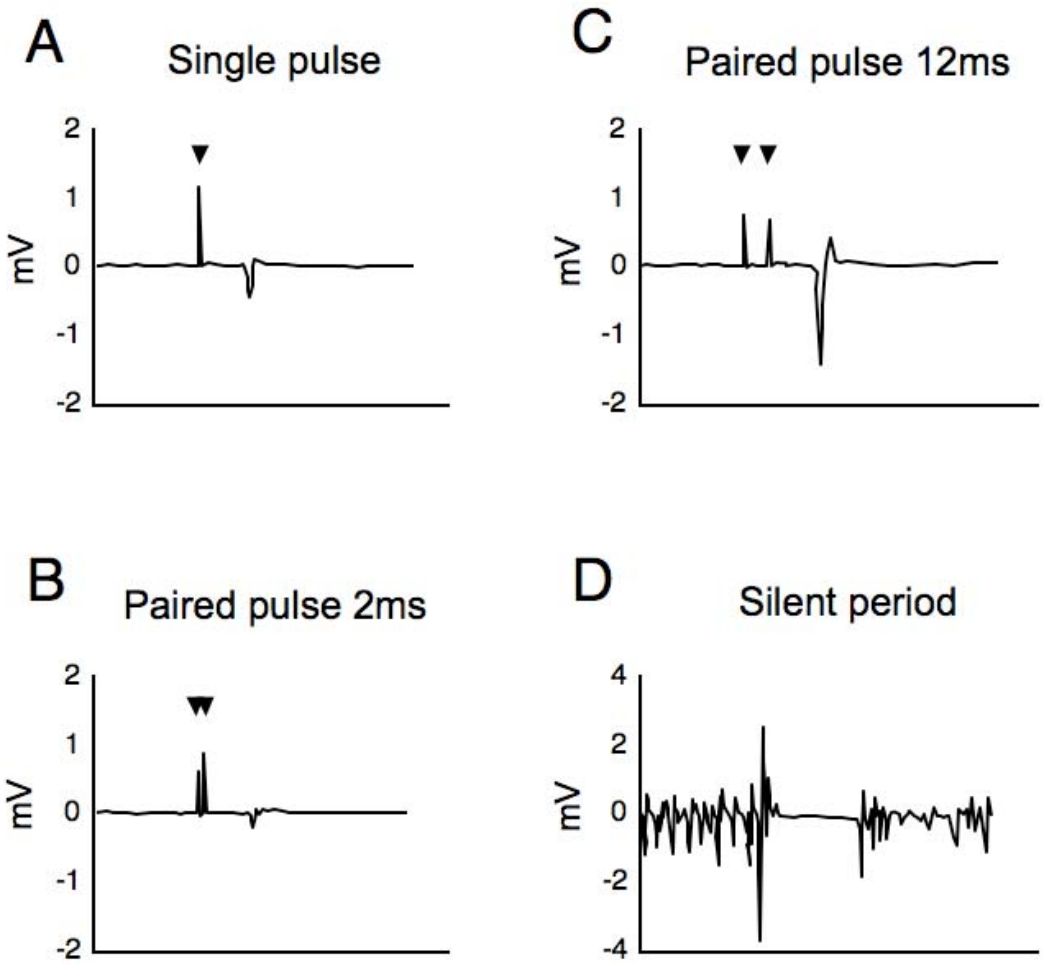
Table 2: Correlations between concussion history information and the duration of the cortical silent period (in ms) in concussed athletes.

Experiment 2, Table 3

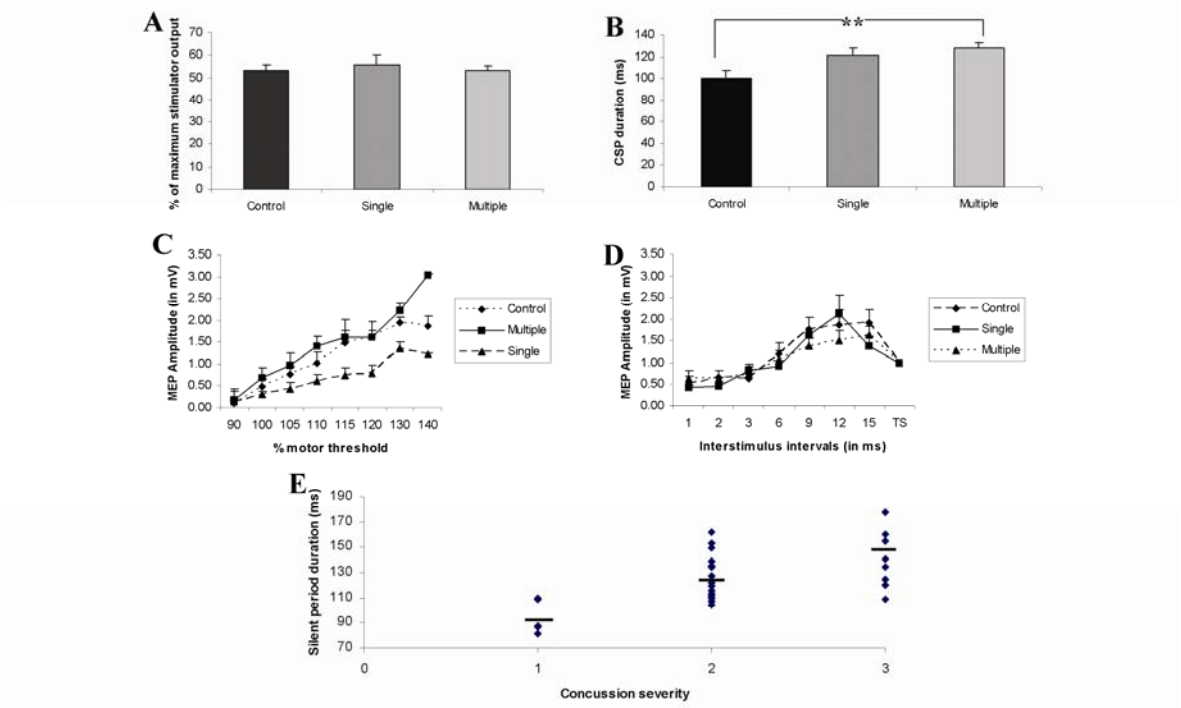
Subject	Number of concussions	Time elapsed (in months)	Severity	Time 1	Time 2
1	3	7	3	120.80±11.27	132.30±12.76
2	5	6	2	207.65±14.85	214.75±16.04
3	3	7	3	90.15±10.80	118.62±8.43
4	4	7	1	154.20±11.27	158.51±10.77
5	3	15	2	144.26±10.73	155.30±9.52

Table 3: Length of the cortical silent period (CSP) at Time 1 and Time 2 (at retest) with concussion history information.

Experiment 2, Figure 1



Experiment 2, Figure 2



4. Experiment 3

De Beaumont, L., Mongeon, D., Tremblay, S., Messier, J., Prince, F., Leclerc, S., Lassonde, M., & Théoret, H. Neurophysiological and motor function changes in asymptomatic concussed athletes. Journal of Athletic Training (accepted)

Persistent Motor System Abnormalities in Active Concussed Athletes

Abstract

Context: Balance problems have been found in the acute post-concussion phase following a concussion while abnormal motor cortex excitability was related to slowed motor execution in a group of former athletes with concussions sustained more than three decades ago. **Objective:** This study seeks to identify persistent motor function alterations in concussed University football players who had returned to competition more than 9 months prior to testing. **Design and Participants:** Twenty-one active university-level football players with concussions were compared to 15 unconcussed university football players. **Setting and Main outcome Measures:** A force platform was used to record centre-of-pressure (COP) displacement and COP oscillation regularity (approximate entropy) as measures of postural stability in an upright position. A rapid alternating movement task (RAM) was also used to assess motor execution speed. Transcranial magnetic stimulation (TMS) over the motor cortex was used to measure long-interval intracortical inhibition and cortical silent period, presumably reflecting $GABA_B$ mediated intracortical inhibition. **Results:** Relative to controls, concussed athletes showed: 1) persistent decrease of COP oscillation randomness; 2) normal performance on a RAM task; 3) significant excess of intracortical inhibition in M1 that was related to the number of previous concussions. **Conclusions:** This study shows that sports concussions induce pervasive changes in postural control through increased COP oscillation regularity as well as enhanced intracortical inhibition in M1, possibly reflecting abnormal $GABA_B$ receptor activity. These

data provide neurophysiological and behavioral markers of sub-clinical motor dysfunction several months following a concussion.

BACKGROUND

The reported incidence of sports concussions has substantially increased over the last 15 years and it is now considered a major public health concern with an estimated 50,000 to 300,000 new cases occurring every year in the United States (Thurman, Branche, & Sniezek, 1998). Only recently has the investigation of motor system abnormalities come to the forefront of the sports concussion literature with transient balance impairments now recognized as a reliable on-field predictor of the post-concussion syndrome (McCrea et al., 2003). The existence of pervasive motor dysfunction was further supported by evidence of motor cortex excitability changes in athletes tested on average three years after their last concussion (De Beaumont, Lassonde, Leclerc, & Theoret, 2007) as well as more than three decades post-concussion [4]. Of considerable clinical relevance, it has been shown that duration of the cortical silent period (CSP), a TMS measure of primary motor cortex (M1) inhibition, is closely related to significant motor execution slowness in former concussed athletes performing a rapid alternating movement task (RAM) (De Beaumont et al., 2009). Significantly, performance on the RAM task has been shown to be altered in traumatic brain injury patients who performed normally on neuropsychological tests (Gray et al., 1998).

Besides motor execution speed, the study of balance control has been used to investigate the effect of sports concussions on motor function. Assessment of postural stability when

standing still was originally integrated into clinical practice to assist clinicians in determining when concussed athletes who experienced balance problems after injury could safely return to play (Guskiewicz et al., 1996). The recent addition of approximate entropy calculation as a non-linear dynamic measure of postural control has revealed increased sensitivity to subtle physiological alterations associated with sports concussions. This measure was introduced to detect changes in centre-of-pressure (COP) oscillation randomness while subjects attempt to stand as steadily as possible on a force platform. While postural stability typically returns to baseline levels within a few days post-concussion on conventional COP displacement measures (Cavanaugh et al., 2006; Cavanaugh, Guskiewicz, & Stergiou, 2005; McCrea et al., 2003), centre-of-pressure (COP) oscillation abnormalities were found to persist 96 hours post-injury (Cavanaugh et al., 2006). Interestingly, concussed athletes whose COP oscillation regularity most augmented from baseline levels tended to obtain lower equilibrium scores (postural instability)(Cavanaugh et al., 2006). While studies have advocated that non-linear approximate entropy measures of postural stability provides a valuable measurement alternative that may prove useful in reducing uncertainty in return-to-play decisions (Cavanaugh et al., 2006), not knowing about the persistence of COP oscillation abnormalites beyond the acute post-concussion phase considerably undermines its clinical utility. This is especially relevant considering that the recovery pattern of balance control during gait was found to level off from day 4 to day 28 post-concussion and remained significantly altered relative to unconcussed teammates (Parker, Osternig, van Donkelaar, & Chou, 2007).

The present study sought to explore whether the increase in COP oscillation regularity found 4 days post-concussion (Cavanaugh et al., 2006), along with slowed motor execution previously reported in former concussed athletes(De Beaumont et al., 2009), are still present after players return to play and if they are concomitant with known alterations of M1 intracortical inhibition. Furthermore, in light of recent contradictory evidence regarding the neurophysiological underpinnings of the CSP (McDonnell et al., 2006), the present study introduced the more widely accepted and less empirically debated long-interval intracortical inhibition (LICI) TMS paradigm (McDonnell et al., 2006) to detect persistent dysfunction in M1 inhibitory function. Finally, TMS measures of M1 inhibition were used to verify the contention that the detrimental effects of sports concussions are cumulative (De Beaumont, Lassonde et al., 2007; Gaetz et al., 2000; Guskiewicz et al., 2003; Iverson et al., 2004).

METHODS

Participants

All 36 participants were active players from Canadian university football teams aged between 19 and 26 years (mean age of 22.3 years SD 3.45). Participants were included if they met all of the following criteria: no history of alcohol and/or substance abuse; no medical condition requiring daily medication; no previous history of psychiatric illness, learning disability, neurological history or traumatic brain injury unrelated to contact sports. 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 $50 CDN for their participation.

The study included two groups. The first group consisted of 21 university level football players who had sustained their last sports concussion more than nine months prior to testing. The number of concussions ranged from 1 to 5 (mean 2.65; SD 1.45) and the time elapsed since the last concussion ranged from 9 months up to 34 months (mean 19.03; SD 13.77). Concussion severity was assessed by the team physician and ranged from Grade 1 to Grade 3 according to the American Academy of Neurology practice parameters (American Academy of Neurology Practice, 1997). At the time of testing, concussed athletes were asymptomatic, reporting very few, if any, symptoms on the Post-concussion symptom scale (mean 2.15; SD 2.08)(Maroon et al., 2000). The second, control, group consisted of 15 university football players who reported no prior history of sports concussion or neurological insult. The two groups were equivalent according to age (F (1, 34) = 0.58; $p > .05$), post-concussion symptoms (F (1, 34) = 0.02; $p > .05$) and level of education (F (1, 34) = 0.21; $p > .05$).

Procedure

The experiment consisted of two one-hour testing sessions that took place 1 to 5 weeks apart. The first session included the administration of a concussion history questionnaire, a general health questionnaire, the Post-Concussion Symptoms scale (PCS) (refer to this previously published paper (De Beaumont et al., 2009)to obtain more details on these questionnaires), and the TMS protocol. The second session consisted of the rapid alternating movement task (RAM) and the assessment of postural control.

Postural Control Paradigm

Participants were instructed to stand as steadily as possible in an upright position on a force platform (Advance Mechanical Technology,INC., MA, USA) with their eyes open and their feet side-by-side, parallel at pelvis width. A total of two trials separated by a 60-second resting period were recorded and each trial lasted 30 seconds. Analyses were computed on the first trial except for two participants for whom we used the second trial due to data recording failures. Postural stability referred to the root mean square amplitude (RMS) of centre-of-pressure (COP) displacement in both mediolateral (ML) and anteroposterior (AP) directions. Approximate entropy values were computed on test trials for ML and AP components of the COP coordinates (Cavanaugh et al., 2006).

Rapid Alternating Movement (RAM) task

Participants were seated on a straight back chair and kept elbows close to the trunk and flexed at an angle of 90º. Participants were instructed to rotate two hand-held spheres as fast as possible with maximal movement amplitude (complete pronation-supination at the wrist). Hand position and orientation in 3D space was recorded with four infrared light-emitting diodes placed on the spheres and later analyzed with a 3D motion analysis system (Optotrak Certus, Northern Digital inc.). Two periods of 15 seconds were recorded (separated by a pause of 2 minutes) for each of the three conditions: both hands, left hand only, right hand only. Further analyses were computed with the first trial except in three cases where 3D motion recordings had failed.

Three main performance measures were computed using the algorithms developed by Okada and Okada (1983): velocity, sharpness and bimanual coordination. Velocity is a

composite measure of Range/Duration (i.e.; average angular displacement for a pronation-supination cycle / time per cycle). Sharpness reflects the delays associated with changes of direction (more delays reflect less sharp pronation-supination turns). Finally, bimanual coordination refers to movement synchrony between hands (smaller values reflect better synchrony) (see (Okada & Okada, 1983) for a detailed description of these performance measures).

TMS recordings and data analysis

Transcranial magnetic stimulation (TMS) was performed using a figure-of-eight coil positioned over the optimal position to elicit motor evoked potentials in the right first dorsal interosseus (FDI) muscle. Cortical silent period duration was calculated at three TMS intensities. Five single-pulse stimulations for each of three TMS intensities (110%, 120%, 130% of the predefined resting motor threshold (rMT) intensity) were applied to the left M1 while participants maintained a voluntary isometric muscle contraction of the right FDI at approximately 10% of their maximum strength. The duration of the CSP was calculated with the graphical method described by Garvey and colleagues (2001). An interstimulus interval of 100 ms was used to assess long-interval intracortical inhibition (LICI)LICI (McDonnell et al., 2006). The intensity of the conditioning stimulus (CS) was set at 120% of the rMT and the test stimulus (TS) intensity was adjusted to induce motor evoked potentials (MEPs) of approximately 1mV peak-to-peak amplitude. Fifteen MEPs were collected for the TS alone and CS-TS. LICI was presented as the ratio CS-TS/TS.

Statistical analyses

All values are expressed as means plus/minus standard deviations (SD). Demographic information, TMS data, postural stability scores, and approximate entropy values were subjected to standard descriptive statistics and ANOVAs. Contrast analyses were computed to assess between-group differences for CSP across TMS intensities. Two-tailed Pearson correlations were computed between LICI and CSP values of concussed athletes as well as between the number of previous concussions and LICI, CSP and postural stability values. Tukey's corrections for multiple comparisons were subsequently applied.

RESULTS

Postural control results

Approximate entropy values were significantly lower (more regular) in asymptomatic concussed athletes relative to controls in the AP direction (F (1, 35) = 8.90; $p < .05$) while that in the ML direction was not significant (F (1, 35) = 1.48; $p > .05$) *(see Figure 1A)*. In contrast, between-group ANOVA was not significant for RMS amplitude of COP displacement in both ML (F (1, 35) = 1.48; $p > .05$) and AP (F (1, 35) = 1.210; $p > .05$) directions *(see Figure 1B*).

-------- Insert Figure 1 about here --------

RAM task results

When computing a 2 (Groups) X 4 (Hand conditions) two-way ANOVA for velocity, the Group * Hand condition interaction was not significant F (3, 28) = 1.91; $p > .05$). In sharp contrast to what had been found in former athletes with concussion, young concussed

athletes performed pronation-supination cycles with significantly greater velocity than controls (F (1, 35) = 8.78; $p < .05$). As expected, the main effect of Hand condition was significant F (3, 35) = 7.07; $p < .05$). However, controls tended to display better bimanual coordination (F (1, 35) = 2.28; $p < .15$). The computation of an overall performance score at the RAM task that put equal weight on velocity and bimanual coordination (Velocity score X (1/ bimanual coordination score)), groups were found to be equivalent (F (1, 35) = 1.01; $p > .05$).

When computing the 2 (Groups) X 4 (Hand conditions) two-way ANOVA for sharpness, the Group * Hand condition interaction did not reach statistical significance F(3, 28) = 2.18; $p > .05$) . Groups did not differ according to sharpness (F (1, 35) = 3.11; $p > .05$). Finally, the main effect of hand condition did not reveal to be significant F (3, 35) = 1.0; $p > .05$).

TMS results

Relative to controls, a one-factor between-group ANOVA revealed that concussed athletes exhibited significantly increased LICI ratios (F (1, 35) = 5.96; $p < .03$) *(see Figure 2B)*. When computing a 2 (Groups) X 3 (stimulation intensity) two-way ANOVA for CSP, the Group * Intensity interaction was not significant F (2, 30) = 1.17; $p > .05$). More importantly, the main effect of Group revealed that concussed athletes exhibited significant CSP prolongation relative to controls (F (1, 35) = 15.61; $p < .001$) *(see Figure 2A)*. As expected, the main effect of Intensity yielded a significant difference in CSP duration across all groups F (2, 35) = 80.11; $p < .001$).

-------- Insert Figure 2 about here --------

Furthermore, LICI ratio in concussed athletes was found to significantly correlate with the duration of the CSP elicited when pulses were delivered at intensities of 120% and 130% of the resting MT (at 120%: r = 0.479; $p < .05$; at 130%: r = 0.501; $p < .05$) while similar Pearson correlation computed with CSP at 110% failed to reach statistical significance (r = 0.214; $p > .05$).

Two-tailed Pearson correlations between the number of previous concussions and LICI ratio values were significantly correlated ($r = 0.47$; $p < .05$). Similarly, CSP duration was found to significantly correlate with the number of previous concussions for both 120% ($r = 0.52$; $p < .05$) and 130% of rMT conditions ($r = 0.49$; $p < .05$). COP oscillation regularity also tended to correlate with the number of previous concussions but this correlation failed to reach significance ($r = 0.261$; $p < .15$). Finally, velocity scores on the RAM task were not correlated with the number of previous concussions ($r = -0.114$; $p < .05$).

DISCUSSION

The current study revealed four main findings about concussed athletes who returned to competition nine months prior to testing: 1) they exhibit a persistent decrease of COP oscillation randomness; 2) they perform normally on a rapid alternating movement task; 3) they display a significant excess of intracortical inhibition in M1; and 4) the extent of M1 inhibition increases as a function of the number of previous concussions.

The presence of increased COP oscillation regularity in the anterior/posterior (A/P) direction despite normal scores on conventional measures of postural stability in active players who returned to competition more than nine months prior to testing closely resembles that found 4 days post-concussion (Cavanaugh et al., 2006). This suggests that augmented COP oscillation regularity may be an early and persistent manifestation of dynamic motor function abnormality among concussed football players who have long returned to competition. Furthermore, the persistence of abnormal COP oscillation regularity long after players have received medical clearance according to typical criteria significantly restricts its utility for return-to-play decisions. Although the functional significance of enhanced COP oscillation regularity with regards to postural stability is still largely unknown, previous studies suggest that it represents an adaptive compensatory mechanism put forth by concussed athletes to achieve postural stability (Cavanaugh et al., 2006; Geurts, de Haart, van Nes, & Duysens, 2005). More specifically, knowing that ankle muscles dominate the regulation of postural stability in the A/P direction (Termoz et al., 2008), contracting these muscles has been shown to enhance control over postural sway and consequently decrease COP oscillation randomness (Cavanaugh et al., 2006; Geurts et al., 2005). One possible explanation for increased COP oscillation regularity could therefore be that concussed athletes deliberately increase co-contraction of the lower extremity musculature to compensate for postural stability losses (Cavanaugh et al., 2006). Another possibility would be that concussive injuries result in stiffened lower extremity musculature. However, acquired lower musculature stiffness post-concussion is at odds with concussed athletes' excessive M1 intracortical inhibition considering that spasticity has been associated with reduced M1 inhibition (Cantello, Tarletti, Varrasi, Cecchin, & Monaco, 2007; Tinazzi et al., 2005).

In sharp contrast with former concussed athletes who exhibited significant motor execution slowness at the rapid alternating movement task (RAM), young concussed athletes obtained significantly better scores than controls. However, when equal weight was attributed to velocity and bimanual coordination precision, performance was equivalent across groups. Relative to controls, concussed athletes appear to favor speed over movement accuracy while controls tend to be more coordinated. This qualitatively distinct performance pattern is most likely mediated by factors extraneous to concussions. Greater performance motivation when more emphasis is placed on speed rather than movement precision could partly explain this finding knowing that concussed athletes are highly motivated to undermine the effects of injury (McCrea et al., 2004; P. R. McCrory, 1999). Unlike former, older, concussed athletes who displayed significant CSP prolongation strongly correlating with motor execution slowness (De Beaumont et al., 2009), the present study finds prolonged CSP duration without motor execution slowness. This suggests that aging with concussion could differentially affect various brain systems, including intracortical inhibition, interacting to underlie motor execution slowness. Considering that many professional athletes retire in their late thirties, longitudinal studies are needed to determine the typical age of concussion-related motor execution slowness onset. In addition, in light of slowed motor execution associated with aging (De Beaumont et al., 2009), longitudinal follow-ups into late adulthood are needed to seek for potential adverse repercussions of enhanced COP oscillation regularity found in young concussed athletes.

Among active university football players, those presenting with a prior history of sports concussion showed significantly enhanced LICI along with significantly prolonged CSP

duration relative to their unconcussed counterparts. In accordance with numerous studies suggesting that CSP and LICI reflect similar M1 intracortical inhibitory mechanisms (Abbruzzese & Trompetto, 2002; Lang, Sueske, Hasan, Paulus, & Tergau, 2006; Mohammadi et al., 2006), LICI ratios were found to correlate significantly with CSP duration. Furthermore, alterations of M1 intracortical inhibition were shown to be exacerbated as a function of the number of previous concussions. Gaining from the recent demonstration of a direct increase in LICI with the intake of $GABA_B$ agonist *Baclofen (McDonnell et al., 2006)*, results from the present study provide compelling support suggesting that sports concussions induce long-lasting alterations of intracortical inhibition at least partially mediated by $GABA_B$ receptor activity (Macdonell et al., 2001; Moller et al., 2007; Pierantozzi et al., 2004; Siebner et al., 1998; Werhahn et al., 1999). Although these findings argue in favor of the potential implication of $GABA_B$ mediated intracortical inhibition in the neuropathophysiology of sports concussions, the moderate positive correlation found between CSP/LICI and the number of previous concussive events strongly suggests that other intervening factors contribute to the known long-term and cumulative effects of sports concussions. The absence of correlations between COP oscillation regularity and CSP/LICI in concussed athletes also points to the complexity of the pathophysiology of concussion. This is in line with recommendations formulated by the Second Summary and Agreement Statement on Concussion in Sport (P. McCrory et al., 2005) suggesting that multidisciplinary assessments should benefit the management of concussion cases.

In sum, we show that sports concussions induce pervasive changes in postural control as well as enhanced M1 intracortical inhibition possibly occuring through $GABA_B$ receptor

activity, providing neurophysiological and behavioral markers of sub-clinical motor dysfunction in concussed athletes. The absence of significant impairments on the rapid alternating movement task suggests that slowed motor execution found in former athletes 30 years post-concussion (De Beaumont et al., 2009) reflects the combined detrimental impact of aging with a history of sports concussions.

FIGURE CAPTIONS

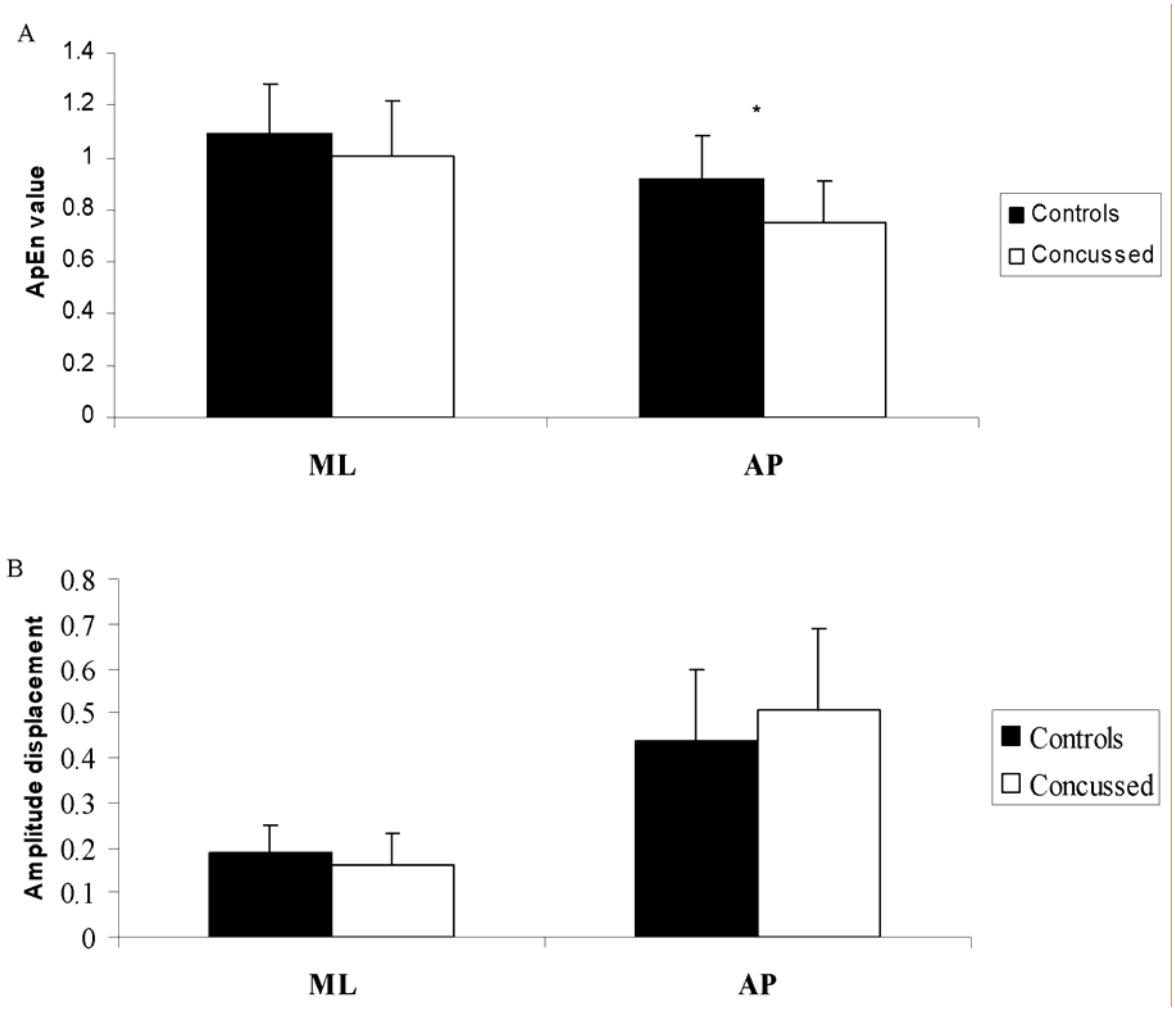
Figure 1: A) Approximate entropy values expressed as the COP oscillation regularity (from 0 to 2) on both mediolateral and anteroposterior directions. Greater approximate entropy values reflect more COP oscillation randomness; B) Root mean square amplitude of COP displacement for both mediolateral (ML) and anteroposterior (AP) directions. Smaller COP displacement amplitude reflects better postural stability.

Figure 2: A) Cortical silent period duration (in ms) when TMS of three different intensities (110%, 120%, 130%), expressed as a percentage of the resting motor threshold, are applied to the vertex while participants in each experimental group exert a voluntary isometric muscle contraction of the first dorsal interosseus muscle of the right hand at approximately 10% of maximum strength; B) Long interval intracortical inhibition LICI was expressed as the ratio CS-TS/TS. The intensity of the conditioning stimulus (CS) was set at 120% of the resting motor threshold and the test stimulus (TS) intensity was adjusted to induce motor evoked potentials (MEPs) of approximately 1mv peak-to-peak amplitude.

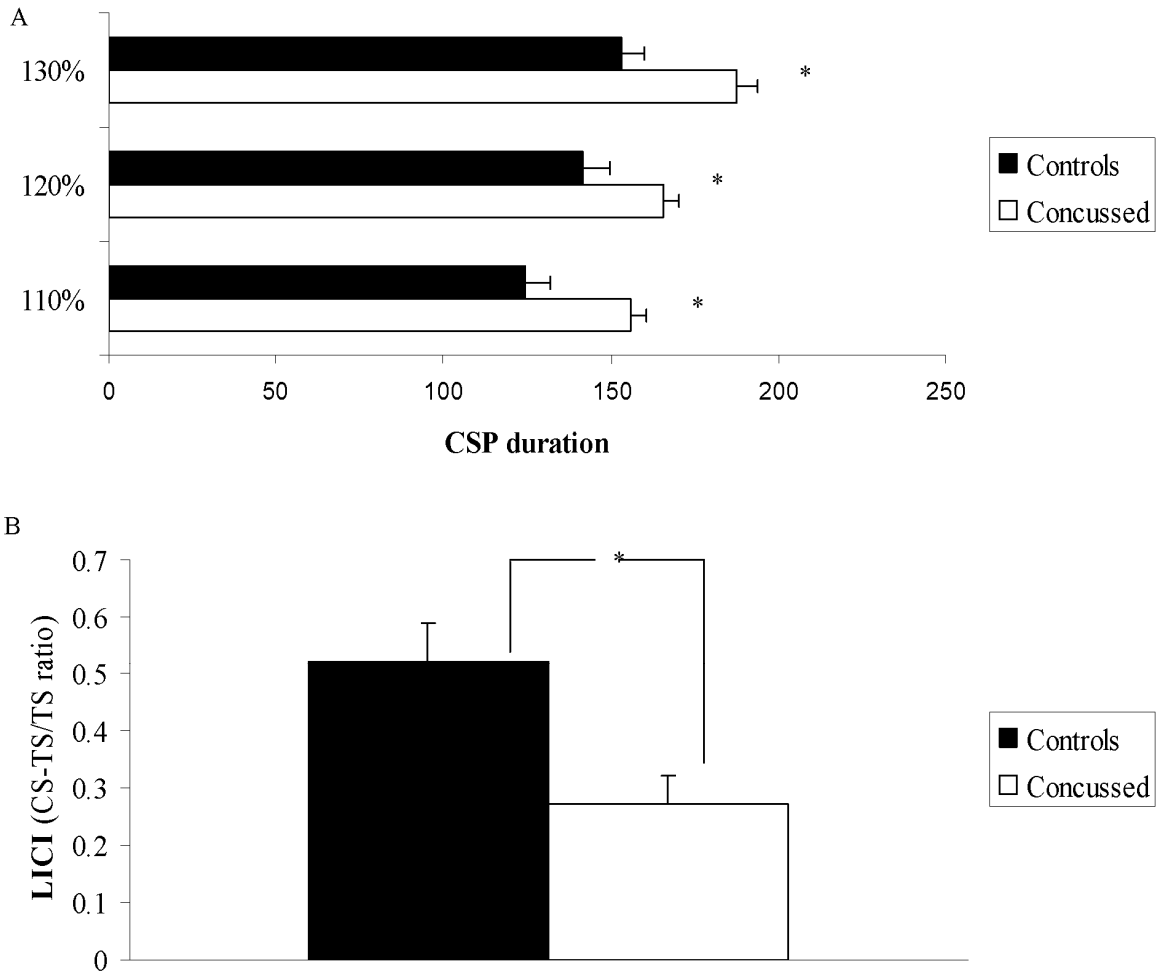
ACKNOWLEDGMENTS

This research was funded by grants from the Natural Sciences and Engineering Research Council of Canada (NSERC) (ML, HT), by support from the Canada Research Chairs program (ML) and by Canadian Institutes of Health Research (CIHR) postgraduate scholarships awarded to LDB.

Experiment 3, Figure 1



Experiment 3, Figure 2



5. Experiment 4

De Beaumont, L., Théoret, H., Mongeon, D., Messier, J., Leclerc, S., Tremblay, S., Ellemberg, D., & Lassonde, M. (2009). Brain Function Decline in Healthy Retired University Level Athletes with Concussions. Brain, 132, 695-708.

Brain Function Decline in Healthy Retired Athletes who Sustained their Last Sports Concussion in Early Adulthood

Abstract

Objectives: 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. Methods: Nineteen healthy former athletes in late adulthood (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 (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: 1) Resting motor threshold; 2) Paired-pulse intracortical inhibition and intracortical facilitation; 3) Input/output curve; and 4) Cortical silent period (CSP). A rapid alternating movement task was also used to characterize motor system dysfunctions. Results: Relative to controls, former athletes with a history of concussion had: 1) Lower performance on neuropsychological tests of episodic memory and response inhibition; 2) Significantly delayed and attenuated P3a/P3b components; 3) Significantly

prolonged CSP; and 4) Significantly reduced movement velocity (bradykinesia). Interpretation: 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.

BACKGROUND

The growing scientific interest for sports concussion 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 to 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 (P. R. McCrory 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 (Collins et al., 2002;

Gerberich et al., 1983; 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 fivefold prevalence of mild cognitive impairment (MCI) (a condition that converts at a rate of about 10-20% annually into dementia) compared with retirees without a history of concussion. Moreover, they observed an earlier onset of Alzheimer's disease (AD) in the concussed retirees than in the general American male population. In fact, TBI has been described as the most robust environmental AD risk factor in the general population (Guo et al., 2000; Heyman et al., 1984; Mortimer et al., 1985; 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 (Dupuis et al., 2000; Gosselin et al., 2006; Lavoie et al., 2004; Potter et al., 2001; Reinvang et al., 2000; Solbakk et al., 1999; Werner & Vanderzant, 1991). Recent studies specifically conducted with asymptomatic concussed athletes showed persistent P300 latency delays (Gaetz & Weinberg, 2000) and amplitude attenuation (De Beaumont, Brisson, Lassonde, & Jolicoeur, 2007; Gosselin et al., 2006). Reductions in the amplitude of the P300 component are thought to index memory updating (Donchin & Coles, 1988; Picton, 1992), subjective significance (Duncan-Johnson & Donchin, 1977) and stimulus probability (Donchin & Coles, 1988; Johnson & Donchin, 1978), whereas P300 latency delays are associated with reduced performance on

neuropsychological tests that assess how rapidly attentional resources can be allocated for memory processing (Emmerson et al., 1989; Polich et al., 1983; Reinvang, 1999). De Beaumont and collaborators (2007) 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, Reinvang, & Andersson, 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 & 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 (Kopp, Tabeling, Moschner, & Wessel, 2006; Nordby, Hugdahl, Jasiukaitis, & Spiegel, 1999).

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 AD (Fjell & Walhovd, 2004; Golob, Irimajiri, & Starr, 2007; Polich, 2004), 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 & 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, Ridderinkhof, Eckerle, & Manning, 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 & 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 fueled 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 & 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 (Abbruzzese & Trompetto, 2002; Cantello, 2002; Cantello et al., 2002; Reynolds & Pearson, 1993), 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 three years prior to testing still exhibited a significantly prolonged cortical silent period (CSP) when compared to controls (De Beaumont, Lassonde et al., 2007). Furthermore, De Beaumont and colleagues (2007) showed that the time elapsed since the last sports concussion did not influence the duration of the cortical silent period, 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 cortical silent period remain debated, research has typically attributed it to changes in intracortical inhibitory systems of the motor cortex mediated by GABA-b interneurons receptors (McDonnell et al., 2006; Moller et al., 2007; Pierantozzi et al., 2004; Siebner et al., 1998; Werhahn et al., 1999). 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 & 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 traumatic brain injury. Deficits in gait stability was found to persist at least 30 days post-injury in sports concussion victims (Slobounov, 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 (Catena et al., 2007b; Parker et al., 2006). The second dynamic motor function alteration found in traumatic brain injury victims is motor speed. Traumatic brain injury 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 traumatic brain injury, 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 three 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, Brisson et al., 2007; De Beaumont, Lassonde et al., 2007), we hypothesized that former athletes who sustained their last concussion more than 30 years ago would exhibit significantly prolonged TMS-induced cortical silent period 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 & 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 (Rey-Osterrieth Complex Figure Test) and attention/executive functions (arrow flanker task) that were found to be highly sensitive to MCI and early onset AD. Knowing that successful inhibitions on incongruent trials of a modified Flanker arrow test were associated with greater P3a amplitude in the general population (Liotti, Pliszka, Perez, Kothmann, & Woldorff, 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 (Kramer & Strayer, 1988; Wickens, Kramer, Vanasse, & Donchin, 1983), we hypothesized that former concussed athletes who would perform more poorly at the Rey-Osterrieth Complex Figure Test 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 traumatic brain injury 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 cortical silent period and several movement disorders for which bradykinesia is a cardinal symptom (Cantello, 2002; Cantello et al., 2002; Reynolds & Pearson, 1993), we further

hypothesized that former concussed athletes with a more prolonged cortical silent period 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 varsity hockey team while the remaining six former athletes had played for the varsity 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 traumatic brain injury unrelated to contact sports. Likewise, participants included in the present study had no history of sports concussion after their years spent playing for the varsity 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 ten 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 CND 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 minutes, 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 to 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 ($F(1, 39) = 1.348$; $p > .05$) and level of education ($F(1, 39) = 0.019$; $p > .05$).

Procedure

The experiment consisted of two three-hour testing sessions that took place 1 to 5 weeks apart. The first session included the administration of a concussion history questionnaire, the Mini-Mental Status Examination, 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 loss of consciousness (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 Mini-Mental Status Examination (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, Folstein, & McHugh, 1975). The maximum score is 30 and the total completion time ranged from 5 to 10 minutes. 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, Laake, & Engedal, 1995), especially with highly educated participants (Crum, Anthony, Bassett, & Folstein, 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 Rey-Osterrieth Complex Figure Test (RCFT) was administered to assess incidental learning and visual memory (Lezak, 1995). Participants were asked to draw from memory a complex figure at 3 minutes (immediate

memory) and 30 minutes (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-minute 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 & 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 seconds 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 & Eriksen, 1974; Eriksen & Schultz, 1979). A recent study using an arrow flanker task showed that MCI patients performed significantly worse than controls when flankers signaled an incongruent response (Wylie et al., 2007). The administration and test procedures were standardized and uniform across participants.

Event-Related Potentials (ERPs)

The 3-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 & Corey-Bloom, 2005). This auditory oddball paradigm consisted of three different stimuli presented in a random order: (a) A standard 1000 Hz tone presented in 80% of trials; (b) A deviant 2000 Hz target tone presented in 10% of trials; and (c) 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 5 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, Osselton, & Shaw, 1980). A ground electrode was included in the montage and its impedance was kept below 5 kΩ. 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 μV) 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 & 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 Analyzer 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 & Polich, 1999).

TMS recordings and data analysis

Transcranial magnetic stimulation (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 50μV in 5 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%, 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 seconds. According to the method of Kujirai and colleagues (Kujirai et al., 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 sub-threshold conditioning stimulus set at 80% of the resting motor threshold 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 approximately 120% of the resting motor threshold to obtain baseline measurements. Ten consecutive trials were collected for each interstimulus interval and for the test stimulus alone condition. Interpulse interval was 6-8 seconds. Finally, the duration of the cortical silent period was calculated at three TMS intensities. Five single-pulse stimulations for each of the three TMS intensities (110%, 120%, 130% of MT intensity) were applied to the left M1 while participants maintained a voluntary isometric muscle contraction of the right FDI at approximately 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 approximately 15 seconds. 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 90º. 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 seconds were recorded (separated by a pause of 2 minutes) 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 plus/minus standard deviations (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 cortical silent period 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 Mini-Mental Status Examination (MMSE) to that of former athletes with no prior history of concussion ($F (1, 38) = 0.51$; $p > .05$). 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 Rey-Osterrieth Complex Figure Test (RCFT) ($F (1, 38) = 5.76$; $p < .05$) after Greenhouse-Geisser corrections were applied. While the two groups produced equivalent initial copy performances ($F (1, 38) = 0.47$; $p > .05$), both immediate recall ($F (1, 38) = 2.90$; $p < .10$) and delayed recall ($F (1, 38) = 2.85$; $p < .10$) 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 ($F = (1, 39) = 6.80$; $p < .05$) after Greenhouse-Geisser correction while reaction time scores on the incongruent flanker condition did not differ between the two groups ($F = (1, 39) = 0.03$; $p > .05$). The flanker interference effect calculated for accuracy scores was also found to be significantly greater in former concussed athletes relative to controls ($F (1, 39) = 5.66$; $p < .03$), while that computed for reaction time scores did not differ across groups ($F (1, 39) = 0.61$; $p > .05$). As expected, accuracy as well as reaction time scores were found to be equivalent across groups on both congruent ((Accuracy ($F (1, 39) = 0.18$; $p > .05$); Reaction time ($F (1, 39) = 0.01$; $p > .05$))

and no flanker ((Accuracy (F (1, 39) = 0.27; $p > .05$); Reaction time (F (1, 39) = 0.11; $p > .05$)) conditions.

-------- Insert Table 1 about here --------

Electrophysiological results

Figure 1 depicts averaged P3a component waveform at Fz and averaged P3b waveforms at both Cz and Pz. Event-related potentials analyses were computed from predetermined electrodes known to record maximal P3b (Cz, Pz) and P3a (Fz) brain responses in this 3-tone auditory oddball paradigm (Comerchero & 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; $p > .05$) and response accuracy to the target stimulus (F (1, 37) = 2.12; $p > .05$) of the auditory oddball task, former athletes with a history of concussion showed significant P3a latency delays (F (1, 37) = 4.43; $p < .05$) along with significant amplitude reductions (F (1, 37) = 5.66; $p < .05$) when contrasted with those of controls after Greenhouse-Geisser corrections were applied. Similar between-group effects on the latency of the P3b component were found at both Cz (F (1, 37) = 6.47; $p < .05$) and Pz (F (1, 37) = 5.58; $p < .05$) 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; $p < .12$).

-------- Insert Figure 1 about here --------

-------- Insert Table 2 about here --------

While none of the two-tailed Pearson correlations computed between P3a amplitude/latency and the Rey-Osterrieth Complex figure test 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; $p < .006$) 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; $p < .001$) 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 cortical silent period was found to be altered in former athletes with a prior history of concussion relative to controls (F (1, 37) = 8.18; $p < .01$). 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; $p < .01$); (At 120%: F (1, 37) = 7.54; $p < .01$); & (At 130%: F (1, 37) = 6.17; $p < .02$)] (see *Figure 2B*). There was no group difference in motor threshold (F (1, 38) = 0.16; $p > .05$) (see *Figure 2A*), intracortical inhibition (F (1, 38) = .02; $p > .05$) (see *Figure 2D* – interstimulus intervals of 2 and 3 ms), intracortical facilitation (F (1, 38) = 0.78; $p > .05$) (see *Figure 2D* – interstimulus intervals

of 9 and 12 ms), and input-output curves (F (1, 38) = 2.21; $p > .05$) (see *Figure 2C*) after Greenhouse-Geisser corrections were applied.

--------Insert Figure 2 about here --------

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; $p < .01$). 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 this between-group difference did not reach significance (F (1, 32) = 2.190; $p < .12$) (see *Figure 3*).

--------Insert Figure 3 about here --------

The duration of the cortical silent period elicited by TMS delivered at 120% and 130% of the resting motor threshold was highly correlated with motor execution velocity when the dominant hand was rotating with the non-dominant hand immobile (at 120%: r = -0.669; $p < .01$; at 130%: r = -0.564; $p < .02$) as well as when both hands were simultaneously performing pronation-supination cycles (at 120%: r = -0.567; $p < .03$; at 130%: r =-0.501; $p < .02$) 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: 1) 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, Brisson et al., 2007; De Beaumont, Lassonde et al., 2007); 2) 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 AD; 3) Display significant motor execution slowness on a diadochokinesia task that significantly correlated with the duration of the TMS-induced cortical silent period.

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, Brisson et al., 2007). 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 & Donchin, 1981; Pfefferbaum, Christensen, Ford, & Kopell, 1986) and independent of behavioral response time (Duncan-Johnson & Donchin, 1980; Ilan & Polich, 1999). P3 latency is rather considered as a measure of stimulus classification speed (Kutas, McCarthy, & Donchin, 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 (Emmerson et al., 1989; Polich et al., 1983; 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 to controls. Previous studies demonstrated that the latter P300 component reflects memory updating (Johnson & Donchin, 1978) such that greater P3b amplitude is associated with better performance on memory tasks (Kramer & Strayer, 1988; Wickens et al., 1983). 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 & Polich, 1999; Kopp et al., 2006; Nordby et al., 1999; Polich, 2004). 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 Rey-Osterrieth Complex Figure Test (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 (AD) (Selkoe, 1991). Clinical symptoms of AD have been shown to correlate with the distribution of NFT (Arriagada,

Marzloff, & Hyman, 1992; Delacourte et al., 1999). NFT initially develop in a subregion of the perirhinal cortex corresponding to Brodmann area 35 (Braak & Braak, 1991; Van Hoesen, Hyman, & Damasio, 1991). Animal studies have shown severe visual recognition memory impairments consecutive to perirhinal cortex lesion (Meunier, Bachevalier, Mishkin, & Murray, 1993; Squire & Zola, 1996), while hippocampal damage did not impair performance (Murray & Mishkin, 1998). Similar visual recognition memory sparing was found in a patient with damage limited to the hippocampus (Mayes, Holdstock, Isaac, Hunkin, & Roberts, 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 (P. R. McCrory 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 event-related potentials and classic neuropsychological tests particularly sensitive to MCI and early-onset AD.

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 (Borenstein, Copenhaver, & Mortimer, 2006; Lindsay et al., 2002).

The TMS assessment of motor cortex excitability performed in this study showed that the cortical silent period (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, Lassonde et al., 2007). 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, Shivitz, & Bronte-Stewart, 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). Motor threshold, 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 (McDonnell et al., 2006; Moller et al., 2007; Pierantozzi et al., 2004; Siebner et al., 1998; Werhahn et al., 1999). The CSP has proven to be sensitive to various neurological conditions such as sports concussions (De Beaumont, Lassonde et al., 2007), cerebellar ataxia (Restivo et al., 2004), stroke (Catano, Houa, & Noel, 1997), Parkinson's disease (Cantello et al., 2002), epilepsy (Macdonell et al., 2001; Tataroglu, Ozkiziltan, & Baklan, 2004), and others (Lefaucheur et al., 2006;

Tinazzi et al., 2005). Among those brain pathologies, sports concussions and cerebellar ataxia have both been associated with slowness of movement (Oechsner & 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 (DTI) study (M. F. Kraus, Susmaras, T, Caughlin, B P, Walker, C J, Sweeney, J A, Little, D M., 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 loss of consciousness 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 Grade 2 or Grade 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 Grade 2 or Grade 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.

FIGURE CAPTIONS

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.

Figure 2: (A) Resting motor threshold 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) Cortical silent period duration (in ms) when TMS of three different intensities (110%, 120%, 130%), expressed as a percentage of the resting motor threshold, are applied to the vertex while participants in each experimental group exert a voluntary isometric muscle contraction of the first dorsal interosseus muscle of the right hand at approximately 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%, 140%), expressed as a percentage of the resting motor threshold, are applied to the vertex; (D) Paired-pulse paradigm showing the ratio between MEP amplitude elicited when increasing interstimulus interval duration (2, 3, 9, 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 Figure 2A, 2B, 2C, 2D represent standard error values (SE). * $p < .05$; ** $p < .01$.

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 & 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 Figure 3A, 3B, 3C, 3D represent standard deviation values (SD). * $p < .05$; ** $p < .01$.

ACKNOWLEDGEMENTS

This research was funded by grants from the Natural Sciences and Engineering Research Council of Canada (NSERC) (ML, HT), by support from the Canada Research Chairs program (ML) and by Canadian Institutes of Health Research (CIHR) postgraduate scholarships awarded to LDB.

Experiment 4, Table 1

Measures	Controls	Concussed	F	*P*
MMSE				
Global Score	29.0 SD 1.0	29.3 SD 0.9	0.51	> .05
Rey Complex Figure				
Copy	34.66 SD 2.5	34.08 SD 2.87	0.47	> .05
Immediate recall	23.0 SD 6.6	19.4 SD 6.7	2.85	< .1
Delayed recall	22.4 SD 6.4	18.9 SD 6.5	2.76	< .1
Recognition	21.3 SD 1.9	19.7 SD 2.0	5.76	**< .05**
Flanker				
No Flanker RT	507.2 SD 77.9	515.7 SD 81.7	0.11	> .05
No Flanker Accuracy	98.8 SD 1.96	99.12 SD 1.50	0.27	> .05
Congruent RT	549.7 SD 104.6	546.8 SD 82.0	0.01	> .05
Congruent Accuracy	96.5 SD 3.5	95.6 SD 8.6	0.18	> .05
Incongruent RT	603.0 SD 117.2	610.1 SD 127.3	0.03	> .05
Incongruent Accuracy	95.1 SD 3.1	87.9 SD 13.7	6.80	**< .05**

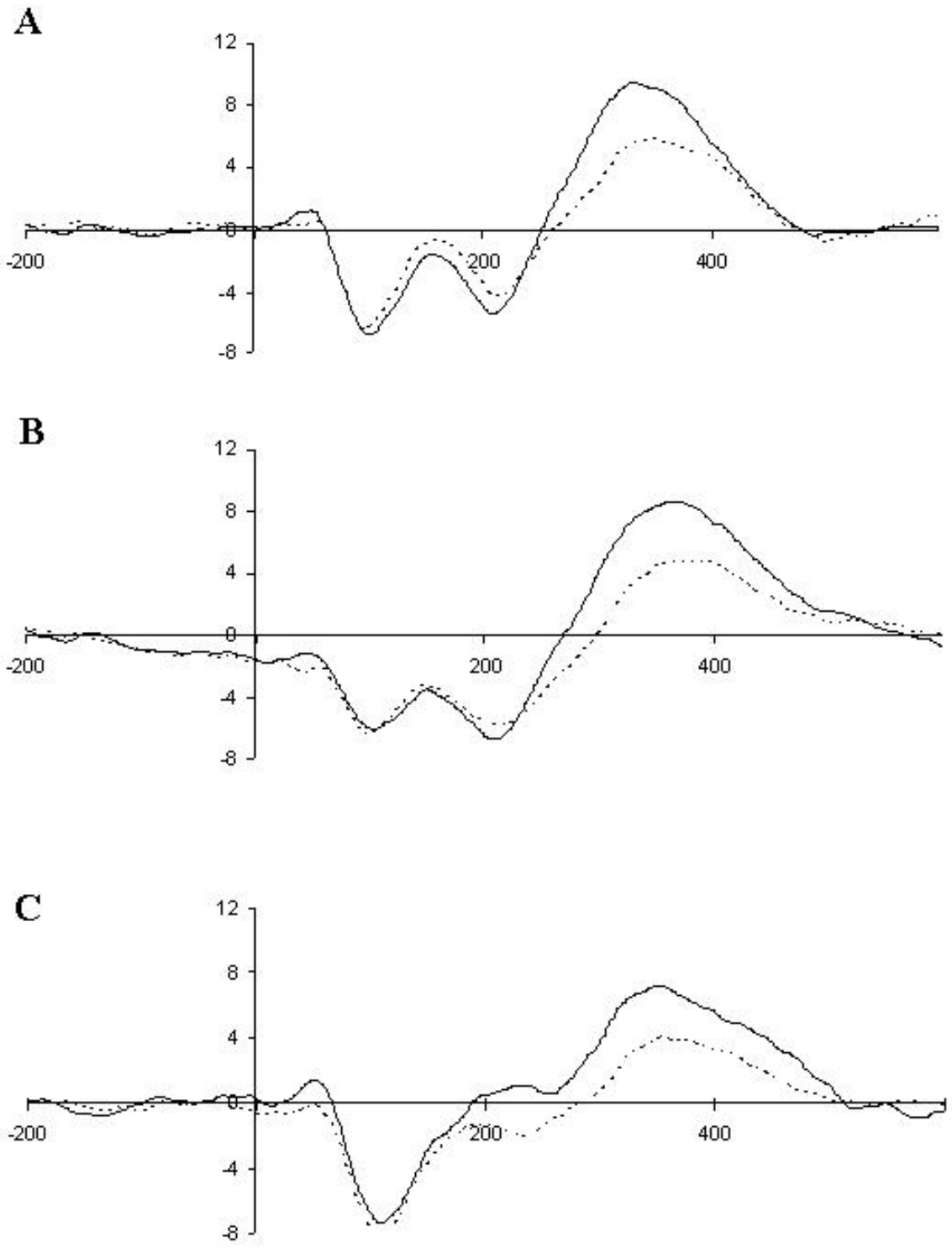
Table 1. Between-group difference on neuropsychological measures of memory and attention after Greenhouse-Geisser corrections for multiple comparisons were applied.

Experiment 4, Table 2

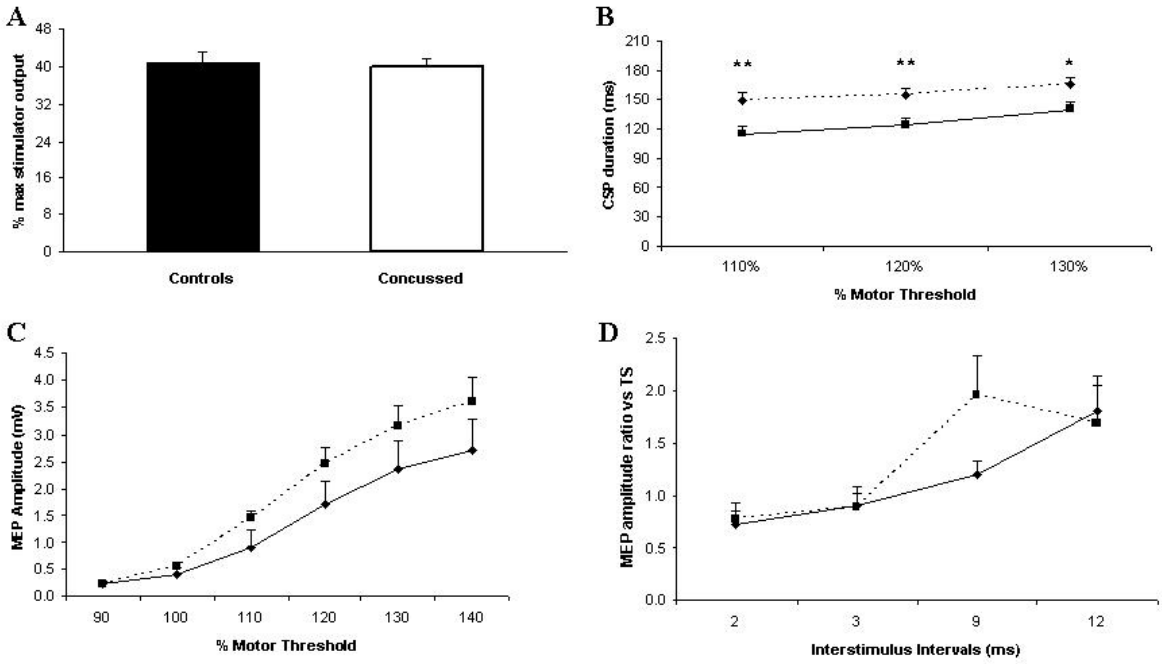
Measures	Controls	Concussed	F	*P*
P3a				
Amplitude	4.50 SD 2.32	2.94 SD 1.67	5.67	**< .05**
Latency	359.6 SD 35.5	387.2 SD 44.9	4.43	**< .05**
P3b				
Amplitude	5.25 SD 2.11	4.18 SD 1.99	2.57	> .05
Latency	362.9 SD 28.9	397.6 SD 57.0	5.58	**< .05**

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

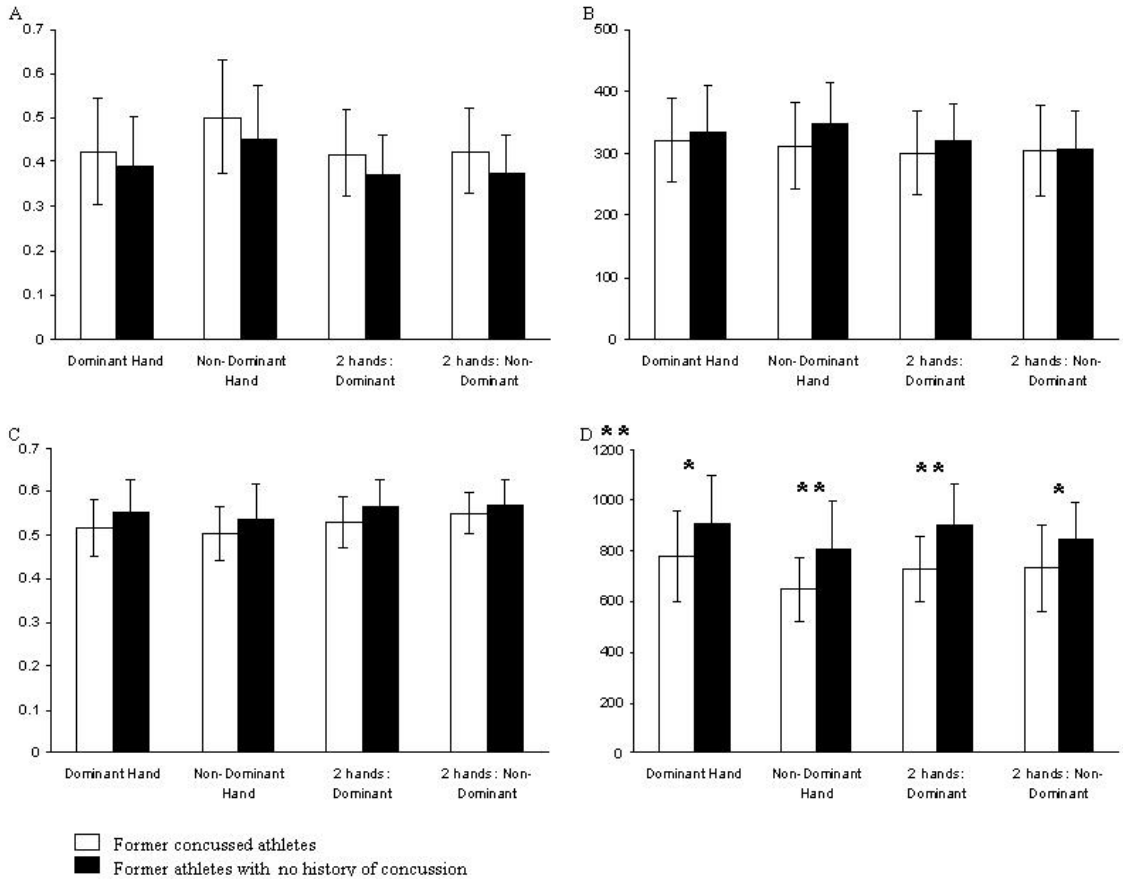
Experiment 4, Figure 1



Experiment 4, Figure 2



Experiment 4, Figure 3



6. DISCUSSION

6.1. MAIN THESIS FINDINGS

The main findings of this thesis reveal: 1) that sports concussions induce persistent subclinical alterations of cognitive and motor systems functions in young athletes who have returned to competition more than nine months prior to testing; 2) that the detrimental effects of sports concussions on cognitive and motor systems functions are cumulative with recurrent concussions; and 3) that having sustained only one or two concussions in early adulthood has the potential for observable, quantifiable cognitive and motor functions alterations in late adulthood.

6.1.1. Experiment 1: Main findings

Experiment 1 sought to investigate the long-term and cumulative effects of sports concussions on an electrophysiological index of attention/memory functions in concussed athletes who did not report post-concussion symptoms over an averaged period of three years. The main findings of Experiment 1 was that asymptomatic multiple-concussion athletes who sustained their latest concussion on average 3 years prior to testing still show significantly suppressed P3 amplitude for rare stimuli in an oddball paradigm when compared to athletes who experienced just one or no concussion despite equivalent neuropsychological test scores. These findings suggest that when using an active visual oddball paradigm, the P3 amplitude attenuation observed a few weeks post-injury in asymptomatic concussed athletes (Gosselin et al., 2006) persists even years post-injury in

those who have sustained more than one concussion. However, post-hoc correlations revealed that the association between the number of concussion(s) sustained and P3 amplitude attenuation was weak. This finding suggests that factors other than those associated with the mere accumulation of concussions affect the size of the P3 component in multi-concussion athletes. Further correlational analyses showed that the number of occurrences of typical concussion severity markers (LOC, anterograde amnesia, retrograde amnesia) was not predictive of the extent of P300 amplitude suppression in concussed athletes. It therefore seems that typical concussion severity markers as well as concussion history characteristics (number of previous concussions and the time elapsed since the last accident) cannot readily explain this significant P3 amplitude suppression found in multiply-concussed athletes. However, unexplored interindividual factors such as the magnitude of diffuse axonal injury, the type of impact to the head (linearly or rotationally applied forces), genotypic predispositions to head injuries, could have intervened to induce significant P3 amplitude suppression in multiply-concussed athletes. For instance, it stands to reason that having sustained multiple concussions increases one's probability to have withstood excessively harmful rotational blows to the head in addition to having accumulated more extensive diffuse axonal injury.

Given that standard neuropsychological tests could not detect residual effects of sports concussion that occurred years prior to testing while event-related potentials did, it is possible that the latter investigation alternative provides added sensitivity to the long-term effects of sports concussion. However, linking these P300 amplitude reductions to overt, clinically recognized measures of cognitive functions appear imperative to validate their clinical significance.

Finally, at least under present conditions — namely in a relatively easy task with a relatively low attentional load and nine months post-concussion — sports concussions were not associated with long term visuo-spatial attention alterations. These results contrast with the persistent attenuation of P3 amplitude following multiple concussions. This pattern of results is important because it shows that "old" concussions do not cause general or ubiquitous electrophysiological suppression. The specificity of the long-term effects of previous concussions to the P3, along with an intact N2pc response, suggests that further work may allow us to pinpoint the cognitive system that is specifically affected by multiple concussions, and perhaps the underlying neural causes of this persistent P3 suppression.

6.1.2. Experiment 2: Main Findings

Experiment 2 aimed to investigate the long-term and cumulative effects of sports concussions on primary motor cortex excitatory/inhibitory mechanisms in concussed athletes that had been asymptomatic for over nine months. Results from this study suggest that the effects of sports concussions induce significant motor cortex intracortical inhibitory mechanisms abnormalities. This was derived from two main findings: 1) the duration of the cortical silent period was significantly prolonged in multiply concussed athletes relative to unconcussed teammates; and 2) the prospective investigation of the effects of sustaining another concussion revealed further lengthening of the cortical silent period in all six athletes with recurrent concussions retested during the study period.

When we computed linear regressions to determine which variable between having sustained multiple concussions and injury severity best predicted CSP lengthening, it was

found that most of this abnormality could be attributed to the severity of concussions rather than belonging to the single or the multiple concussion groups. These linear regressions were computed because multiply concussed athletes tended to have sustained more severe concussions than the single concussion group.

The systematic CSP prolongation found prospectively in all six recurrent concussion athletes who were allowed nine months to recover from their subsequent concussions provided robust evidence for the cumulative, detrimental effects of sports concussion on motor cortex inhibition.

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 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). Motor threshold, 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 (McDonnell et al., 2006; Moller et al., 2007; Pierantozzi et al., 2004; Siebner et al., 1998; Werhahn et al., 1999).

Finally, another important finding was that the mere passage of time, which is to this day the most commonly prescribed treatment for uncomplicated cases of sports concussions, had no beneficial effect on significantly prolonged cortical silent period duration, as evidenced by a near zero Pearson correlation value obtained between these two variables. This suggests that altered neurophysiological mechanisms that lengthen the CSP in concussed athletes remains significantly altered in asymptomatic young concussed athletes regardless of the time elapsed since the last concussion.

6.1.3. Experiment 3: Main findings

Experiment 3 was conducted to identify persistent motor function alterations more than nine months post-concussion in University football players who have long returned to play. Specifically, we wished to determine whether sports concussions altered neurophysiological markers of $GABA_B$ receptor activity and induced related changes in postural stability, in addition to motor execution speed. In addition to showing that sports concussions exert persistent and cumulative alterations of $GABA_B$ –mediated intracortical inhibition of the motor cortex (M1), this study found that postural control is still altered in concussed athletes tested more than nine months post-injury while performance on a rapid alternating movement task was normal.

Active University Football players who sustained sports concussions that occurred more than nine months prior to testing exhibited significantly augmented $GABA_B$–mediated intracortical inhibition of M1 as revealed on a TMS-induced long interval intracortical inhibition (LICI) paradigm. LICI increases were also found to augment as a function of the number of previous sports concussions. These findings provided

preliminary evidence supporting the implication of abnormal $GABA_B$ activity in the neuropathophysiology of sports concussions. Moreover, the significant relationship found between the number of previous sports concussions and the magnitude of $GABA_B$ mediated intracortical inhibition changes also suggest that LICI represents a clinically valid marker of the cumulative effects of sports concussion.

Secondly, Experiment 3 replicated CSP lengthening in concussed athletes from Experiment 2. Perhaps more importantly, the duration of the CSP was found to correlate significantly with LICI ratio values, thereby supporting the notion that $GABA_B$ receptor activity at least partially influences the duration of the CSP (Macdonell et al., 2001; Moller et al., 2007; Pierantozzi et al., 2004; Siebner et al., 1998; Werhahn et al., 1999).

Another main finding from Experiment 3 demonstrated that the increased COP oscillation regularity previously found in concussed athletes tested at four days post-concussion (Cavanaugh et al., 2006) was also present in concussed athletes tested more than nine months after having returned to competition. This increased COP oscillation regularity was proposed to act as a compensatory mechanism put forth by concussed athletes to restore normal balance control (Cavanaugh et al., 2006). This is supported by previous evidence suggesting that increased COP oscillation regularity consecutive to the deliberate contraction of ankle muscles improved control over postural sway (Termoz et al., 2008) in stroke patients experiencing significant balance impairments (Geurts et al., 2005).

Finally, contrary to our expectations, concussed athletes were significantly faster than the group of athletes with no prior history of concussion at performing pronation-

supination cycles on a rapid alternating movement (RAM) task. However, athletes with no prior concussion tended to show better bimanual coordination than concussed athletes. Thus, when equal weight was attributed to velocity and bimanual coordination, performance was equivalent across groups. This qualitatively distinct performance pattern is most likely mediated by factors extraneous to concussions. Greater performance motivation when more emphasis is placed on speed rather than movement precision could partly explain this finding knowing that concussed athletes are highly motivated to undermine the effects of their injury (McCrea et al., 2004; P. R. McCrory, 1999).

In sum, Experiment 3 showed that sports concussions induce pervasive increases in $GABA_B$ mediated intracortical inhibition of M1 and pervasive changes in postural control mechanisms via increased COP oscillation regularity, providing neurophysiological and behavioral markers of subclinical motor dysfunction in concussed athletes.

6.1.4. Experiment 4: Main findings

This experiment concluded our cross-sectional investigation of the long-term effects of sports concussions on cognitive and motor systems functions along with a preliminary assessment of the functional consequences of the aging process on the remotely concussed brain.

More specifically, Experiment 4 was conducted to assess whether the effects of sports concussions on electrophysiological and TMS measures of cognitive and motor system functions observed in active athletes with concussions are also found in former athletes who sustained their last sports concussion more than three decades ago. In

addition, this study sought to assess the repercussions of aging with a history of sports concussions on cognitive and motor functions measures particularly sensitive to the effects of MCI and more severe forms of traumatic brain injury, respectively. Results form this study revealed that former athletes with concussions exhibited similar P300 (Experiment 1) and CSP (Experiment 2) alterations as those found in asymptomatic concussed athletes who sustained their last concussion on average three years prior to testing. Moreover, relative to former athletes with no prior history of sports concussions, former athletes with concussions showed 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 AD. Thirdly, former athletes with concussion displayed significant motor execution slowness on a RAM task that was found to be unaltered in young concussed athletes tested more than nine months after they had returned to competition (Experiment 3).

P300 abnormalities in former athletes with concussion tested more than 30 years after their last concussion that closely resemble those found in young concussed athletes provided compelling evidence that the detrimental effects of sports concussions on cognitive functions are chronic. Perhaps equally important in ascertaining the clinical significance of these electrophysiological measures to index factual cognitive functions alterations were the significant correlations drawn between P3a/P3b components amplitude and performance scores of former concussed athletes on neuropsychological measures of executive functions and episodic memory, respectively. To our knowledge, this was the first electrophysiological study of sports concussion to demonstrate well-established associations between suppressed P3a amplitude and reduced frontal lobe efficiency (Liotti

et al., 2005) together with attenuated P3b amplitude and reduced performance on memory tasks (Kramer & Strayer, 1988; Wickens et al., 1983).

Similarly to what we had found in young concussed athletes (Experiment 1), the duration of the CSP was significantly prolonged in former athletes who had sustained their last concussion more than three decades ago. Intracortical inhibitory mechanisms of the primary motor cortex at least partially mediated by $GABA_B$ receptors activity therefore seemed to have been chronically altered as a consequence of sustaining sports concussions in young adulthood. Of great clinical significance, this CSP prolongation was found to be strongly correlated with motor execution slowness in former concussed athletes, such that those exhibiting more prolonged CSP duration were slower at executing pronation-supination cycles of maximal wrist amplitude. This finding is providing preliminary evidence that $GABA_B$ mediated intracortical inhibition abnormalities consecutive to sports concussions sustained in early adulthood seem to contribute among biological bases to early symptoms of motor execution slowness in otherwise healthy late adulthood former athletes.

In addition to these lifelong neurophysiological alterations of cognitive and motor systems functions, this study also reveals that former athletes with concussions experience observable, quantifiable performance alterations on neuropsychological tests selected for their sensitivity to MCI and early onset AD. These findings are in sharp contrast with previous neuropsychological studies of sports concussion typically demonstrating normal performance scores on neuropsychological tests when young athletes are tested beyond 10-14 days post-injury (McCrea et al., 2003). Episodic memory decline in former athletes

with concussion relative to controls was found at the recognition condition of the Rey-Osterrieth Complex Figure Test (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). 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 study therefore demonstrated that former athletes with concussions share similar patterns of early neuropsychological alterations with those of mild cognitive impairments patients.

Finally, Experiment 4 also revealed that former athletes with concussion exhibited significant motor execution slowness 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). Interestingly, young concussed athletes who had returned to competition more than nine months prior to testing did not show this significant movement slowness when performing the same RAM task

(Experiment 3) despite exhibiting significantly prolonged CSP. In light of these results, it stands to reason that the combined, detrimental effects of sports concussions and aging are necessary to induce motor execution slowness.

6.2. OVERALL THESIS DISCUSSION

The main objectives of the present thesis were twofold:

i. To cross-sectionally investigate lifelong changes in cognitive and motor systems functions using methods sensitive to the effects of mild TBI that outlasted the acute post-injury phase;
ii. To systematically study the cumulative detrimental effects of recurrent sports concussions on cognitive and motor systems functions.

This thesis demonstrated that concussed athletes experience subclinical alterations of cognitive and motor systems functions more than nine months after having received medical clearance to return to competition. Moreover, these subclinical cognitive and functional motor systems alterations were found to have worsened in young athletes presenting a history of recurrent sports concussions. These results were obtained in asymptomatic, single / multiple concussions athletes who performed normally on neuropsychological tests classically used to assess post-concussion recovery as well as on postural stability and motor execution speed tasks that revealed to be sensitive to the effects of sports concussion during the acute post-concussion phase.

In parallel, our cross-sectional thesis design allowed us to demonstrate that these subclinical alterations of cognitive and motor systems functions found in young concussed athletes were chronic. In addition, observable, quantifiable decline on neuropsychological as well as on rapid alternating movement (RAM) tasks reflected clinically significant cognitive and motor systems alterations specific to the combined detrimental effects of sports concussions and aging. This functional decline on cognitive and motor functions measures found in former athletes tested more than 30 years after their last concussions were strongly correlated with lifelong subclinical alterations of ERPs as well as TMS measures consecutive to sports concussions.

The following sections will provide an integrated discussion of our thesis findings highlighting their respective contribution to the field of sports concussions both in terms of the advancement of knowledge on the long-term effects of sports concussions and their ability to orient ensuing research.

6.2.1. Alterations of cognitive functions after sports concussions

This thesis showed that P300 components amplitude of event-related potentials (ERP) were chronically altered after sports concussions and that the latter P300 attenuation was accentuated in multiply concussed athletes. Up to now, very little clinical significance has been granted to P300 amplitude reductions found in concussed athletes as the expert panel from the last Summary and Agreement Statement on sports concussions has yet to recognize ERPs as a useful tool for the management of sports concussions cases (P. R. McCrory et al., 2005). One of the main issues restraining the application of ERPs to current return-to-play protocols is our inability to relate these persistent P300 components

alterations to neither self-reported cognitive symptoms or performance alterations on validated neuropsychological measures of memory/attention functions beyond the acute post-concussion phase. Another major limitation is that although highly sensitive to the effects of sports concussions, the specificity of the P300 component to sports concussions is relatively poor. In fact, P300 components alterations have been found in various clinical populations including schizophrenia, alcoholism, depression, attention deficits disorders, epilepsy, Alzheimer's disease and others (Polich, 2004). This is particularly problematic with concussed athletes whose P300 components alterations are not tied to observable/reported cognitive difficulties as one might argue that factors extraneous to the damaging impact of sports concussions on brain functions could just as well have influenced the size and latency of the P300 component. Moreover, without supporting evidence from prospective studies looking at P300 components changes relative to concussed athletes' own baseline measurements, we cannot ascertain that these P300 components alterations are a consequence of sports concussions rather than a premorbid characteristic of athletes who are more at risk of sustaining sports concussions. Although not addressing the issue of cause and effect, evidence for the clinical significance of chronic P300 components alterations after sports concussions was revealed in a group of former athletes with concussions who obtained reduced performance scores on neuropsychological tests that significantly correlated with P3a/P3b components amplitude attenuations. This finding confirms that concussion-related P300 components attenuations are associated with worsened performance on neuropsychological tests of episodic memory and executive functions as athletes get older and that the more P300 components are suppressed, the greater cognitive decline are to be expected.

The concept of cognitive reserve is very useful to help explain the resurgence of neuropsychological tests performance decrements when tested more than 30 years post-injury. The central element to the cognitive reserve concept is that resilience to neuropathological damage resides in the way the brain uses its damaged resources. It therefore represents the ability to optimize or maximize performance through differential recruitment of brain networks and/or alternative cognitive strategies. Another important aspect to the concept of cognitive reserve is that damage from various environmental, developmental and genotypic sources accumulates throughout the lifespan to reduce cognitive reserve. The progressive reduction of cognitive reserve via the accumulation of brain damaging experiences and slowly depleting health condition throughout the lifespan was particularly useful to explain widespread cognitive functions decline characterizing the aging process (F. I. Craik & Bialystok, 2006; F. I. Craik & Salthouse, 1999). When applied to the present thesis findings, it appears that young concussed athletes who showed persistent P300 components alterations relied on cognitive reserve that allowed the recovery of baseline performance levels on neuropsychological tests after the acute post-concussion phase had subsided. The functional magnetic resonance imaging (fMRI) and concussion literature provides further support for cognitive reserve as a potential explanation to normal behavioural output in young concussed athletes despite altered neurophysiological indexes of cognitive functions. Recent fMRI findings indicated that the concussed brain recruited additional brain resources outside of the typical region of interest when performing a visual WM task despite achieving normal performance (J. K. Chen et al., 2004; Jantzen, Anderson, Steinberg, & Kelso, 2004; McAllister et al., 2001) . These findings could suggest that this BOLD response increase outside of typical regions of interest found after sports concussion when performing a higher-order cognitive task is put forth by the concussed brain to compensate for depleted neurophysiological efficiency.

However, when the chronic, deleterious effects of sports concussions on cognitive functions were combined to the known age-related cognitive decline, ensuing cognitive reserve of former athletes with concussions relative to that of former athletes without concussions could no longer maintain optimal performance levels on neuropsychological

tests of episodic memory and executive functions selected for their sensitivity to early symptoms of MCI.

Of great clinical relevance, former athletes with concussions performed significantly worse than their unconcussed counterparts on cognitive functions measures that have recently revealed to be affected in the very early stages of MCI (Barbeau et al., 2004). Most notably, while immediate and delayed recall scores at the Rey-Osterrieth Complex Figure Test (RCFT) were not statistically different across groups, former athletes with concussions obtained significantly worse performance scores at the recognition condition of the RCFT. Interestingly, visual recognition memory impairments were recently found early in the course of patients with MCI (Barbeau et al., 2004) as its acute sensitivity was found to stem from the distribution of neurofibrillary tangles (NFT) that initially develop in a subregion of the perirhinal cortex corresponding to Brodmann area 35 (Braak & 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 & Zola, 1996), while hippocampal damage did not impair performance (Murray & Mishkin, 1998). 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 which could coincide with the installation of MCI. Future neuroimagery studies should attempt to shed some light on potential perirhinal cortex lesions in former athletes with concussion while also comparing patterns of volumetric atrophy of parahippocampal structures between former athletes with concussions, MCI patients and former athletes without concussion.

This association between having sustained sports concussion and mild cognitive impairments has recently earned compelling support from epidemiological data showing that former athletes who suffered multiple sports concussions had a fivefold prevalence of developing mild cognitive impairment (MCI) (a condition that converts at a rate of about 10-20% annually into dementia) compared with retirees without a history of concussion (Guskiewicz et al., 2005). Moreover, they observed an earlier onset of Alzheimer's disease (AD) in concussed retirees than in the general American male population (Guskiewicz et al., 2005). In keeping with these findings, previous reports have identified TBI as the single most robust environmental AD risk factor in the general population (Guo et al., 2000; Heyman et al., 1984; Mortimer et al., 1985; Plassman et al., 2000). However, specification of whether and how TBI may trigger a long-term process of neurodegeneration ultimately leading to dementia is still largely unknown (Levin, 1995). Recent advances have recently demonstrated that severe traumatic brain injury (TBI) was associated with elevated Alzheimer's amyloid peptide A beta 1-42 in human CSF coupled with an increased prevalence of AD (Emmerling et al., 2000). In addition to replicating abnormal A beta 1-42 in human CSF of traumatic brain injury victims, a recent study also found elevated CSF tau protein level, another hallmark of Alzheimer's disease neuropathology (Selkoe, 1991), beyond two weeks post-accident and suggested that A beta 1-42 and tau may play a role in the pathophysiology of TBI. Furthermore, the results of this study suggest that A beta 1-42 may be a supportive early predictor for recovery after severe head injury. Turning to mild TBI, Uryu and collaborators (2002) studied neuropathological and behavioral consequences of single versus repetitive mild TBI in transgenic mice that expressed mutant human Aβ precursor protein. Neurobehavioral results showed that

transgenic mice subjected to repetitive mTBI displayed altered ability to learn a visuospatial task relative to sham-injured transgenic mice as well as to single mTBI transgenic mice. These findings indicated that the detrimental effects of mTBI on mice's cognitive functions were cumulative when measured at 16 weeks after the last injury. Equally important, Aβ burden in repetitive mTBI mice was modest at 9 weeks after injury, but only at 16 weeks (in 12 month-old transgenic mice) was the Aβ burden significantly increased in both single and repetitive mTBI mice relative to sham-treated transgenic mice. These data provided the first compelling mechanistic linkage between previous episodes of mild TBI and subsequent amyloidosis accompanied by cognitive impairments in mice. Furthermore, this study showed that repetitive mTBI augmented key pathological features found in the brains of AD patients (Uryu et al., 2002). These findings stress the need to investigate the potential role of AD hallmarks in the neuropathophysiology of sports concussions in relation with both the onset and the severity of AD/MCI-related symptoms.

In addition to sharing similar key pathological features with those of AD patients, apolipoprotein E epsilon 4 (ApoE ε4), which is the main known genetic risk factor for Alzheimer's disease (Poirier et al., 1993), was recently shown to be a risk factor for adverse outcome after all levels of traumatic brain injury (Liberman, Stewart, Wesnes, & Troncoso, 2002; Nicoll, Roberts, & Graham, 1995; G. M. Teasdale, Nicoll, Murray, & Fiddes, 1997) in addition to being associated with an increased likelihood of developing chronic traumatic brain injury in boxers (Jordan et al., 1997). In parallel, a recent study conducted with non-demented participants from the general population established an association between carrying the ApoE ε4 allele, right hippocampal atrophy and lower performance on a recognition memory test (Lind et al., 2006). Interestingly, this recognition memory

alteration in AD-symptom-free carriers of the ApoE ε4 allele is highly similar to what we have found in former athletes with concussions relative to unconcussed counterparts. In light of this similarity in cognitive alterations pattern between non-demented carriers of the ApoE ε4 allele and former athletes with concussion, future studies conducted with former concussed athletes should systematically screen for the presence of ApoE ε4 allele in an attempt to uncover its potential synergistic effects with sports concussions. Furthermore, this study also calls for a systematic assessment of hippocampal volumetric changes in former athletes with concussions who show altered recognition memory performance.

6.2.2. Alterations of motor system functions after sports concussions

The present thesis showed that sports concussions induce lifelong alterations of $GABA_B$ mediated intracortical inhibition of the motor cortex that was found to be: 1) significantly modulated by the number of previous sports concussions; and 2) related to significant motor execution slowness in former athletes who sustained their last concussion more than three decades prior to testing. The use of TMS was instrumental to uncover persistent subclinical alterations of motor cortex excitability after sports concussions. Similarly to subclinical P300 amplitude reductions in young concussed athletes performing normally on related neuropsychological tests, TMS detected pervasive motor cortex excitability changes on both CSP and LICI measures despite unaltered performance on dynamic motor functions sensitive to the acute post-concussion phase. However, our cross-sectional thesis design allowed us to show that former athletes with concussion exhibited significant motor execution slowness on a RAM task whereas young, active University football players with concussions did not. The concept of cognitive reserve – with the only amendment made to its name to more generally refer to brain reserve – discussed

earlier to explain the reappearance of neuropsychological tests deficits in former athletes with concussions relative to unconcussed counterparts could just as well apply to bradykinesia symptoms coming to surface three decades post-concussion. In fact, the resilience of the young concussed brain to adapt to abnormal intracortical inhibition of the motor cortex was sufficient to maintain normal performance on dynamic motor functions tasks while that of the aging brain who had sustained prior concussions could no longer enable optimal performance levels.

Besides depleted *brain* reserve, results collected for the purpose of this thesis do not allow us to exclude the possibility that former athletes with concussions were experiencing early symptoms of a neurodegenerative disease affecting motor system functions. In keeping with this notion, repetitive subconcussive and concussive blows to the head in boxing were shown to induce a neurodegenerative condition that has catastrophic consequences on long-term motor system functions. Recent studies established that approximately 17% of retired professional boxers developed early symptoms of mild confusion and ataxia quickly progressing to a "Parkinsonian" cognitive decline. In fact, abnormal performance on memory tests, increased motor and speech latencies, dysarthria, pyramidal tract dysfunction, tremor in the head and upper extremities, and behavioral changes are common features associated with what has often been referred to as Dementia Pugilistica or chronic TBI (Rabadi & Jordan, 2001). Of great clinical relevance, motor symptoms of chronic TBI are typically the earliest clinical manifestations of this neurodegenerative condition (Rabadi & Jordan, 2001). Among cardinal motor impairments of chronic TBI, ataxia and motor execution slowness (bradykinesia) have both been related to significantly prolonged CSP duration in other neurodegenerative conditions. In fact,

previous studies conducted with cerebellar ataxia (Restivo et al., 2004) and Huntingdon's disease (Lefaucheur et al., 2006) patients have found excessive CSP alongside bradykinesia / ataxia symptoms. Knowing that former athletes with concussions from Experiment 4 experienced motor execution slowness strongly correlating with significant CSP prolongation, it would be pertinent to assess the potential implication of $GABA_B$ receptors activity in the neuropathophysiology of chronic TBI. Contrasting the effects of chronic TBI with those of fewer remote concussions from Experiment 4 on interplaying $GABA_B$ mediated intracortical inhibition anomalies and associated motor symptoms could also help establish the clinical significance of lifelong TMS-induced CSP and LICI anomalies after sports concussions. Based on the contention that shared pathophysiological characteristics across neurological conditions could influence the development of common symptomatology, the association between prolonged CSP and ataxia symptoms should also be investigated in former athletes with concussions.

6.2.3. Clinical implications of excessive intracortical inhibition in M1

The discovery of lifelong $GABA_B$ mediated intracortical inhibition alterations of M1 gives rise to extensive ramifications for future clinical studies of sports concussions on associated functional losses and potential treatment alternatives. The following subsections will be detailing potential clinical applications derived from our discovery of excessive intracortical inhibition mechanisms of M1 mediated by $GABA_B$ receptors activity.

i. Excessive $GABA_B$ receptors activity and depressed synaptic plasticity

It has been shown that synaptic plasticity occurring through long-term potentiation (LTP) is an essential part of motor learning. In animal preparations, motor learning

strengthens primary motor cortex (M1) synaptic efficacy (Rioult-Pedotti, Friedman, Hess, & Donoghue, 1998) and prevents subsequent LTP (Rioult-Pedotti, Friedman, & Donoghue, 2000) from occurring. Pharmacological studies also indicate that $GABA_B$ receptors play an important role in LTP (Davies, Starkey, Pozza, & Collingridge, 1991) and learning (McNamara & Skelton, 1996). Recent advances in TMS research have enabled the non-invasive induction of LTP in human M1 to study its role in skill acquisition. In paired associative stimulation (PAS), stimulation of the median nerve is repetitively paired with TMS of the homotopic representation in M1 (Stefan, Kunesch, Cohen, Benecke, & Classen, 2000) resulting in increased motor cortex excitability. It is reversible, topographically specific and is dependent on NMDA receptors (Stefan, Kunesch, Benecke, Cohen, & Classen, 2002; Stefan et al., 2000). Similarly to what has been shown in animals (Rioult-Pedotti et al., 2000), a period of motor learning prevents LTP-like plasticity from occurring following PAS (Ziemann, Ilic, Pauli, Meintzschel, & Ruge, 2004), suggesting that motor learning occurs more easily in a system where LTP induction is easily achieved. Since the $GABA_B$ receptor agonist baclofen suppresses PAS-induced LTP-like plasticity (McDonnell, Orekhov, & Ziemann, 2007), it has been proposed that increases in $GABA_B$ receptors activity prevent LTP-dependent motor learning (McDonnell et al., 2007). Significantly, it has been shown that practice effects following sports concussion are significantly reduced (Bleiberg et al., 2004; Collins, Lovell et al., 1999). Taken together, these data suggest that abnormalities in $GABA_B$ transmission in the motor cortex of concussed athletes may underlie motor dysfunctions and reduce the probability of LTP induction, resulting in impaired motor learning. Knowing that sports concussions induce significant excess of $GABA_B$ receptors activity, future studies should directly assess the

ability of the concussed brain to produce LTP in M1 via PAS and determine how LTP interacts with motor learning.

ii. Interventions to alleviate excessive $GABA_B$ receptors activity of M1

In addition to assessing the functionality of the circuitry and connectivity of the brain, TMS delivered repetitively (repetitive TMS) can exert longer lasting changes in brain activity. Because repetitive TMS is non-invasive, painless, and free from side effects, its application has become increasingly popular to various psychiatric as well as neurological conditions (Derejko, Niewiadomska, & Rakowicz, 2005). Studies specifically pertaining to motor system functions have revealed that repetitive TMS can induce durable increases or decreases of corticospinal or corticocortical pathways excitability depending on the intensity of stimulation, coil orientation and frequency of stimulation (Fitzgerald, Fountain, & Daskalakis, 2006). A recent rapid-rate TMS study revealed promising results supporting its potential application to sports concussions. In fact, this study showed that a single rapid-rate TMS session (1500 subthreshold pulses at 25 Hz) could reduce CSP duration while increasing motor cortex excitability for more than 30 minutes post-stimulation (Khedr et al., 2007). Relying on repetitive TMS rather than conventional pharmacotherapy to reinstate pre-concussion motor cortex excitability levels is desirable mostly because of its targeted effects on the excitability of the motor system rather than inducing inevitable side effects associated with diffusing medication through the central nervous system. Moreover, from an ethical standpoint, the application of non-invasive, painless, outpatient procedure, highly targeted, free from side-effects repetitive TMS could reveal to be the most suitable treatment alternative to motor cortex excitability alterations in young concussed athletes whose motor symptoms are most typically mild enough to be

unnoticed or neglected. Conducting a large-scale double-blind sham-controlled study is clearly needed before we are to introduce repetitive TMS to the management of sports concussion cases.

In parallel, directly manipulating $GABA_B$ receptors activity with specific $GABA_B$ antagonists like *Saclofen* (Heinmiller, Ting, Vargas-Perez, Yeh, & van der Kooy, 2009) or Phaclofen (Marazioti, Spyraki, & Thermos, 2009) in animal models of single/recurrent mTBI (Laurer et al., 2001) should be envisaged especially in relation to late-life motor function impairments.

iii. Concussion-related $GABA_B$ receptors activity alterations outside of M1

One particularly pertinent query that arises from our findings is whether sports concussions induce M1-specific abnormalities of $GABA_B$ receptors activity as opposed to inducing diffuse, widespread damage to the GABAergic system dispersed throughout the brain. Although not reflecting whole-brain GABAergic system alterations, a recent TMS study has recently demonstrated the existence of intracortical inhibitory and excitatory circuits in parietal somatosensory cortex in humans similar to those found in M1. Applying paired-pulse TMS paradigms known to elicit intracortical inhibition (ICI) of M1 to the parietal cortex revealed to exert significant reductions of contralateral tactile perception while paired-pulse TMS paradigms involving intracortical facilitation in M1improved performance on the tactile discrimination task (Oliveri et al., 2000). Similarly, short afferent inhibition (SAI), generated when peripheral afferent inputs relayed to the somatosensory cortex (S1) precede a TMS pulse delivered to M1 approximately 20 ms later, was shown to inhibit motor cortex excitability via direct sensorimotor ICI

mechanisms (Udupa, Ni, Gunraj, & Chen, 2009). Moreover, this study showed that afferent stimulation that produced SAI decreased LICI, which was found to be affected in concussed athletes. This suggests that LICI in M1 and SAI in S1 have inhibitory interactions (Udupa et al., 2009). Using a SAI protocol together with paired-pulse TMS applied over the hand representation of S1 with concussed athletes could provide a first glimpse at $GABA_B$ mediated intracortical inhibition alterations outside of M1. In parallel, investigating performance of concussed athletes on diverse brain functions (cognitive, motor, perceptual, affective) in relation to magnetic resonance spectroscopy aiming to assess the integrity of the GABAergic system through whole-brain/regions of interest GABA concentration levels (Snyder, Hanstock, & Wilman, 2009) could also reveal to be fruitful.

iv. Potential concussion-related causes of lifelong $GABA_B$ receptors anomalies

Although CSP duration abnormalities have been described in numerous neurological conditions such as sports concussions (De Beaumont, Lassonde et al., 2007; De Beaumont et al., 2009), 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), Huntington's disease (Lefaucheur et al., 2006), and dystonia (Tinazzi et al., 2005), it is interesting to note that alterations in motor cortex excitability were limited to CSP duration whereas other TMS paradigm were unaltered. The selective impairment in motor cortex excitability reported in the present thesis suggests that the long-term effects of concussions are restricted to specific mechanisms within the motor cortex that preferentially involve $GABA_B$ receptors. No study to date has applied current knowledge about the pathophysiology of sports concussions to explain seemingly

permanent alterations of $GABA_B$ mediated intracortical inhibition mechanisms. Theoretically, however, the well-known neurometabolic cascade triggered by concussive injury, which involves a profound shift in the neurochemical balance of the concussed brain (Giza & Hovda, 2001), could very well have contributed to induce permanent detrimental effects on $GABA_B$ receptors functions. Immediately after the accident, research has shown that neurotransmitters are indiscriminately released and uncontrolled ionic fluxes ensue (Giza & Hovda, 2001). In particular, the binding of excitatory neurotransmitters, such as glutamate, to the N-methyl-D-aspartate (NMDA) receptor initiates sustained cell depolarization characterized by potassium (K^+) ions rushing out of the cells, shortly followed by an influx of both sodium (Na^+) and calcium (Ca^+). Due to severe disruptions in ionic gradients, ion-specific pumps are activated by the cells so as to restore resting membrane potential. Because these ion-specific pumps require much energy to operate, a dramatic increase in glucose consumption ensues. Importantly, this hypermetabolism occurs in the context of diminished cerebral blood flow, and the disparity between glucose supply and demand triggers a cellular energy crisis. The rapid exhaustion of glucose supply causes the concussed brain to undergo a period of depressed metabolism which no longer suffices to reinstate resting membrane potential of depolarized cells. Knowing about the hyperpolarizing role of metabotropic $GABA_B$ receptors, which provide sustained input for the opening of K^+ channels (K. Chen, Li, Ye, Zhang, & Wang, 2005), one might speculate that the lingering exposure to sustained excitotoxicity could alter exceeded $GABA_B$ receptors continuously working to stimulate the opening of K^+ channels under short energy supplies. More research is clearly needed if we are to delineate what renders $GABA_B$ receptors particularly vulnerable to the effects of sports concussions.

6.2.4. Postural stability changes after sports concussions

Postural stability changes after sports concussions was a late addition to the present thesis that has not been subjected to our original cross-sectional experimental design. We nonetheless found that asymptomatic concussed athletes tested more than nine months post-injury showed enhanced COP oscillation regularity in the anteroposterior (AP) direction concomitant with normal postural stability on conventional, linear displacement measures. This extends previous prospective data from a recent study that found fully recovered postural stability on linear displacement measures at day 4 post-concussion despite abnormally enhanced COP oscillation regularity (Cavanaugh et al., 2006). Interestingly, when tested in the first few hours after the accident, concussed athletes who displayed greater COP oscillations regularity tended to obtain lower equilibrium scores (postural instability) on standard balance control measures. In fact, concussed athletes who exhibited better postural control in quiet standing were those who displayed relatively unconstrained, more irregular patterns of motor output (Cavanaugh et al., 2006). Although action mechanisms underlying this persistent COP oscillation randomness reduction are still largely unknown, it has been suggested that it represents an adaptive compensatory mechanism put forth by concussed athletes to maintain postural stability (Cavanaugh et al., 2006). More specifically, knowing that ankle muscles dominate the regulation of postural stability in the anterior/posterior (A/P) direction (Termoz et al., 2008), increasing contraction of these muscles has been shown to improve postural stability in stroke patients (Geurts et al., 2005). In keeping with this notion, a recent study demonstrated that introducing a demanding cognitive task in order to redirect attention away from the main postural stability task significantly compromised balance control in stroke patients (Hyndman, Ashburn, Yardley, & Stack, 2006). Assuming that the concussed brain

consciously commands co-contraction of lower extremity muscles to alleviate balance control losses (Cavanaugh et al., 2006), the introduction of a secondary, demanding cognitive task in a postural stability paradigm could interfere with conscious co-contraction of lower extremity muscles so as to give access to uncompensated postural stability. In addition, ecological validity would considerably benefit from the combination of cognitive and postural stability tasks as it more accurately replicates in-game settings. Finally, balance control should be investigated in former athletes with concussions to examine whether age-related depleted brain reserve is associated with postural stability losses on standard, linear displacement measures.

6.3. MAIN THESIS LIMITATIONS

The retrospective nature of studies included in the present thesis is undeniably the main limitation restraining the clinical significance of our findings. Although we clearly agree that prospective experimental designs are needed to validate our findings, the cross-sectional experimental design used for the purpose of this thesis nonetheless informs us about shared cognitive and motor system functions alterations in both active and former University-level concussed athletes. The introduction of a fairly stringent set of inclusion criteria for former athletes to take part in our study added significant robustness to our findings as the latter were required to have maintained an active lifestyle throughout their life while having been exempt from medical conditions or illnesses known to affect central nervous system functions. However, this stringent set of exclusion criteria limits the generalization of our findings to a subset of the population of former athletes with a prior history of concussion. Further prospective replications of the present thesis findings with

broader samples of active and 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. Finally, the lack of structural imaging information also damper the interpretation of our findings. This is especially problematic in former concussed athletes in late adulthood when latent structural damage coming to surface in aging is documented in mild TBI victims (Umile, Sandel, Alavi, Terry, & Plotkin, 2002).

OVERALL THESIS CONCLUSION

With the demonstration of lifelong, cumulative cognitive and motor system functions alterations after sports concussions, this thesis raised awareness over the contention that their damaging effects could no longer be underestimated and that more research efforts should be invested to deepen our understanding of the long-term pathophysiology of sports concussions. To this end, our findings stress the need to turn to more refined brain investigation tools if we are to delineate the underlying causes and associated action mechanisms causing the brain never to fully recover from the seemingly benign adverse effects of sports concussions. This is especially called for if we are to move from return-to-play management currently based mostly on expert opinion to an evidence-based medicine approach. Finally, our findings also highlight the importance of implementing longitudinal follow-up studies with former concussed athletes, whose cognitive and motor systems functions alterations may possibly evolve into more severe, perhaps debilitating difficulties impairing their daily functions.

7. References

7.1. Introduction

Abbruzzese, G., & Trompetto, C. (2002). Clinical and research methods for evaluating cortical excitability. *J Clin Neurophysiol, 19*(4), 307-321.

American Academy of Neurology Practice. (1997). Practice parameter: the management of concussion in sports (summary statement). Report of the Quality Standards Subcommittee. *Neurology, 48*(3), 581-585.

Arriagada, P. V., Marzloff, K., & Hyman, B. T. (1992). Distribution of Alzheimer-type pathologic changes in nondemented elderly individuals matches the pattern in Alzheimer's disease. *Neurology, 42*(9), 1681-1688.

Aubry, M., Cantu, R. C., Dvorak, J., Graf-Baumann, T., Johnston, K., Kelly, J., et al. (2002). Summary and agreement statement of the First International Conference on Concussion in Sport, Vienna 2001. Recommendations for the improvement of safety and health of athletes who may suffer concussive injuries. *Br J Sports Med, 36*(1), 6-10.

Awasthi, D., Church, D. F., Torbati, D., Carey, M. E., & Pryor, W. A. (1997). Oxidative stress following traumatic brain injury in rats. *Surg Neurol, 47*(6), 575-581; discussion 581-572.

Barbeau, E., Didic, M., Tramoni, E., Felician, O., Joubert, S., Sontheimer, A., et al. (2004). Evaluation of visual recognition memory in MCI patients. *Neurology, 62*(8), 1317-1322.

Barth, J., Alves, W., Ryans, T., Macchiocchi, S., Rimel, R., Jane, J., et al. (1989). Mild head injury in sports: neuropsychological sequelae and recovery of function. *J Cogn Neurorehab, 26*, 451-478.

Bayly, P. V., Black, E. E., Pedersen, R. C., Leister, E. P., & Genin, G. M. (2006). In vivo imaging of rapid deformation and strain in an animal model of traumatic brain injury. *J Biomech, 39*(6), 1086-1095.

Bayly, P. V., Cohen, T. S., Leister, E. P., Ajo, D., Leuthardt, E. C., & Genin, G. M. (2005). Deformation of the human brain induced by mild acceleration. *J Neurotrauma, 22*(8), 845-856.

Besenski, N. (2002). Traumatic injuries: imaging of head injuries. *Eur Radiol, 12*(6), 1237-1252.

Besenski, N., Broz, R., Jadro-Santel, D., Pavic, D., & Mikulic, D. (1996). The course of the traumatising force in acceleration head injury: CT evidence. *Neuroradiology, 38 Suppl 1*, S36-41.

Beuter, A., de Geoffroy, A., & Edwards, R. (1999). Analysis of rapid alternating movements in Cree subjects exposed to methylmercury and in subjects with neurological deficits. *Environ Res, 80*(1), 64-79.

Bleiberg, J., Cernich, A. N., Cameron, K., Sun, W., Peck, K., Ecklund, P. J., et al. (2004). Duration of cognitive impairment after sports concussion. *Neurosurgery, 54*(5), 1073-1078; discussion 1078-1080.

Borenstein, A. R., Copenhaver, C. I., & Mortimer, J. A. (2006). Early-life risk factors for Alzheimer disease. *Alzheimer Dis Assoc Disord, 20*(1), 63-72.

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol, 82*(4), 239-259.

Braekhus, A., Laake, K., & Engedal, K. (1995). A low, 'normal' score on the Mini-Mental State Examination predicts development of dementia after three years. *J Am Geriatr Soc, 43*(6), 656-661.

Broglio, S. P., Sosnoff, J. J., Shin, S., He, X., Alcaraz, C., & Zimmerman, J. (2009). Head impacts during high school football: a biomechanical assessment. *J Athl Train, 44*(4), 342-349.

Cantello, R. (2002). Applications of transcranial magnetic stimulation in movement disorders. *J Clin Neurophysiol, 19*(4), 272-293.

Cantello, R., Tarletti, R., & Civardi, C. (2002). Transcranial magnetic stimulation and Parkinson's disease. *Brain Res Brain Res Rev, 38*(3), 309-327.

Cantello, R., Tarletti, R., Varrasi, C., Cecchin, M., & Monaco, F. (2007). Cortical inhibition in Parkinson's disease: new insights from early, untreated patients. *Neuroscience, 150*(1), 64-71.

Cantu, R. C. (1992). Cerebral concussion in sport. Management and prevention. *Sports Med, 14*(1), 64-74.

Cantu, R. C. (1998). Second impact syndrome. *Clinical Journal of Sports Medicine, 17*(1), 37-44.

Catano, A., Houa, M., & Noel, P. (1997). Magnetic transcranial stimulation: clinical interest of the silent period in acute and chronic stages of stroke. *Electroencephalogr Clin Neurophysiol, 105*(4), 290-296.

Catena, R. D., van Donkelaar, P., & Chou, L. S. (2007a). Altered balance control following concussion is better detected with an attention test during gait. *Gait Posture, 25*(3), 406-411.

Catena, R. D., van Donkelaar, P., & Chou, L. S. (2007b). Cognitive task effects on gait stability following concussion. *Exp Brain Res, 176*(1), 23-31.

Cavanaugh, J. T., Guskiewicz, K. M., Giuliani, C., Marshall, S., Mercer, V., & Stergiou, N. (2005). Detecting altered postural control after cerebral concussion in athletes with normal postural stability. *Br J Sports Med, 39*(11), 805-811.

Cavanaugh, J. T., Guskiewicz, K. M., Giuliani, C., Marshall, S., Mercer, V. S., & Stergiou, N. (2006). Recovery of postural control after cerebral concussion: new insights using approximate entropy. *J Athl Train, 41*(3), 305-313.

Cavanaugh, J. T., Guskiewicz, K. M., & Stergiou, N. (2005). A nonlinear dynamic approach for evaluating postural control: new directions for the management of sport-related cerebral concussion. *Sports Med, 35*(11), 935-950.

Chen, J. K., Johnston, K. M., Frey, S., Petrides, M., Worsley, K., & Ptito, A. (2004). Functional abnormalities in symptomatic concussed athletes: an fMRI study. *Neuroimage, 22*(1), 68-82.

Chen, K., Li, H. Z., Ye, N., Zhang, J., & Wang, J. J. (2005). Role of GABAB receptors in GABA and baclofen-induced inhibition of adult rat cerebellar interpositus nucleus neurons in vitro. *Brain Res Bull, 67*(4), 310-318.

Chistyakov, A. V., Soustiel, J. F., Hafner, H., Trubnik, M., Levy, G., & Feinsod, M. (2001). Excitatory and inhibitory corticospinal responses to transcranial magnetic stimulation in patients with minor to moderate head injury. *J Neurol Neurosurg Psychiatry, 70*(5), 580-587.

Cohen, J., & Polich, J. (1997). On the number of trials needed for P300. *Int J Psychophysiol, 25*(3), 249-255.

Collins, M. W., Grindel, S. H., Lovell, M. R., Dede, D. E., Moser, D. J., Phalin, B. R., et al. (1999). Relationship between concussion and neuropsychological performance in college football players. *Jama, 282*(10), 964-970.

Collins, M. W., Iverson, G. L., Lovell, M. R., McKeag, D. B., Norwig, J., & Maroon, J. (2003). On-field predictors of neuropsychological and symptom deficit following sports-related concussion. *Clin J Sport Med, 13*(4), 222-229.

Collins, M. W., Lovell, M. R., Iverson, G. L., Cantu, R. C., Maroon, J. C., & Field, M. (2002). Cumulative effects of concussion in high school athletes. *Neurosurgery, 51*(5), 1175-1179; discussion 1180-1171.

Collins, M. W., Lovell, M. R., & McKeag, D. B. (1999). Current issues in managing sports-related concussion. *Jama, 282*(24), 2283-2285.

Comerchero, M. D., & Polich, J. (1999). P3a and P3b from typical auditory and visual stimuli. *Clin Neurophysiol, 110*(1), 24-30.

Control, N. C. f. I. P. a. (2003). Report to Congress on Mild Traumatic Brain Injury in the United States: Steps to Prevent a Serious Public Health Problem. . In. Atlanta: Centers for Disease Control and Prevention.

Cooper, R., Osselton, J. W., & Shaw, J. C. (1980). *EEG Technology (3rd edn)*. London: Butterworths.

Courville, C. B. (1953). The functional and structural bases for psychic phenomena consequent to cerebral concussion. *J Nerv Ment Dis, 118*(5), 447-454.

Craik, F. I., & Bialystok, E. (2006). Cognition through the lifespan: mechanisms of change. *Trends Cogn Sci, 10*(3), 131-138.

Craik, F. I., & Salthouse, T. A. (1999). *The Handbook of Aging and Cognition* (2nd edition ed.). Mahwah: Lawrence Erlbaum Associates

Crum, R. M., Anthony, J. C., Bassett, S. S., & Folstein, M. F. (1993). Population-based norms for the Mini-Mental State Examination by age and educational level. *Jama, 269*(18), 2386-2391.

Davies, C. H., Starkey, S. J., Pozza, M. F., & Collingridge, G. L. (1991). GABA autoreceptors regulate the induction of LTP. *Nature, 349*(6310), 609-611.

De Beaumont, L., Brisson, B., Lassonde, M., & Jolicoeur, P. (2007). Long-term electrophysiological changes in athletes with a history of multiple concussions. *Brain Inj, 21*(6), 631-644.

De Beaumont, L., Lassonde, M., Leclerc, S., & Theoret, H. (2007). Long-term and cumulative effects of sports concussion on motor cortex inhibition. *Neurosurgery, 61*(2), 329-336; discussion 336-327.

De Beaumont, L., Theoret, H., Mongeon, D., Messier, J., Leclerc, S., Tremblay, S., et al. (2009). Brain function decline in healthy retired athletes who sustained their last sports concussion in early adulthood. *Brain, 132*(Pt 3), 695-708.

Delacourte, A., David, J. P., Sergeant, N., Buee, L., Wattez, A., Vermersch, P., et al. (1999). The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. *Neurology, 52*(6), 1158-1165.

Delaney, J. S. (2004). Head injuries presenting to emergency departments in the United States from 1990 to 1999 for ice hockey, soccer, and football. *Clin J Sport Med, 14*(2), 80-87.

Delaney, J. S., Lacroix, V. J., Leclerc, S., & Johnston, K. M. (2000). Concussions during the 1997 Canadian Football League season. *Clin J Sport Med, 10*(1), 9-14.

Delaney, J. S., Lacroix, V. J., Leclerc, S., & Johnston, K. M. (2002). Concussions among university football and soccer players. *Clin J Sport Med, 12*(6), 331-338.

Deng, Y., Thompson, B. M., Gao, X., & Hall, E. D. (2007). Temporal relationship of peroxynitrite-induced oxidative damage, calpain-mediated cytoskeletal degradation and neurodegeneration after traumatic brain injury. *Exp Neurol, 205*(1), 154-165.

Derejko, M., Niewiadomska, M., & Rakowicz, M. (2005). [The diagnostic and therapeutic application of transcranial magnetic stimulation]. *Neurol Neurochir Pol, 39*(5), 389-396.

Donchin, E., & Coles, M. (1988). Is the P300 component a manifestation of context updating? *Behavior and Brain Science, 11*, 357-374.

Duncan-Johnson, C. C., & Donchin, E. (1977). On quantifying surprise: the variation of event-related potentials with subjective probability. *Psychophysiology, 14*(5), 456-467.

Duncan-Johnson, C. C., & Donchin, E. (1980). The relation of P300 latency to reaction time as a function of expectancy. *Prog Brain Res, 54*, 717-722.

Dupuis, F., Johnston, K. M., Lavoie, M., Lepore, F., & Lassonde, M. (2000). Concussions in athletes produce brain dysfunction as revealed by event-related potentials. *Neuroreport, 11*(18), 4087-4092.

Echemendia, R. J. (Ed.). (2006). *Sports Neuropsychology* (1 ed. Vol. 1). New York: Guilford Press.

Echemendia, R. J., Putukian, M., Mackin, R. S., Julian, L., & Shoss, N. (2001). Neuropsychological test performance prior to and following sports-related mild traumatic brain injury. *Clin J Sport Med, 11*(1), 23-31.

Eimer, M. (1996). The N2pc component as an indicator of attentional selectivity. *Electroencephalogr Clin Neurophysiol, 99*(3), 225-234.

Emmerling, M. R., Morganti-Kossmann, M. C., Kossmann, T., Stahel, P. F., Watson, M. D., Evans, L. M., et al. (2000). Traumatic brain injury elevates the Alzheimer's amyloid peptide A beta 42 in human CSF. A possible role for nerve cell injury. *Ann N Y Acad Sci, 903*, 118-122.

Emmerson, R. Y., Dustman, R. E., Shearer, D. E., & Turner, C. W. (1989). P3 latency and symbol digit performance correlations in aging. *Exp Aging Res, 15*(3-4), 151-159.

Eriksen, C. W., & Eriksen, B. A. (1974). Effects of noise letters upon the identification letter in a nonsearch task. *Perception & Psychophysics, 16*, 143-149.

Eriksen, C. W., & Schultz, D. W. (1979). Information processing in visual search: a continuous flow conception and experimental results. *Percept Psychophys, 25*(4), 249-263.

Fitzgerald, P. B., Fountain, S., & Daskalakis, Z. J. (2006). A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clin Neurophysiol, 117*(12), 2584-2596.

Fjell, A. M., & Walhovd, K. B. (2004). Life-span changes in P3a. *Psychophysiology, 41*(4), 575-583.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res, 12*(3), 189-198.

Gaetz, M., & Bernstein, D. M. (2001). The current status of electrophysiologic procedures for the assessment of mild traumatic brain injury. *J Head Trauma Rehabil, 16*(4), 386-405.

Gaetz, M., Goodman, D., & Weinberg, H. (2000). Electrophysiological evidence for the cumulative effects of concussion. *Brain Inj, 14*(12), 1077-1088.

Gaetz, M., & Weinberg, H. (2000). Electrophysiological indices of persistent post-concussion symptoms. *Brain Inj, 14*(9), 815-832.

Garvey, M. A., Ziemann, U., Becker, D. A., Barker, C. A., & Bartko, J. J. (2001). New graphical method to measure silent periods evoked by transcranial magnetic stimulation. *Clin Neurophysiol, 112*(8), 1451-1460.

Gentry, L. R. (1994). Imaging of closed head injury. *Radiology, 191*(1), 1-17.

Gentry, L. R., Godersky, J. C., & Thompson, B. (1988). MR imaging of head trauma: review of the distribution and radiopathologic features of traumatic lesions. *AJR Am J Roentgenol, 150*(3), 663-672.

Gerberich, S. G., Priest, J. D., Boen, J. R., Straub, C. P., & Maxwell, R. E. (1983). Concussion incidences and severity in secondary school varsity football players. *Am J Public Health, 73*(12), 1370-1375.

Gessel, L. M., Fields, S. K., Collins, C. L., Dick, R. W., & Comstock, R. D. (2007). Concussions among United States high school and collegiate athletes. *J Athl Train, 42*(4), 495-503.

Geurts, A. C., de Haart, M., van Nes, I. J., & Duysens, J. (2005). A review of standing balance recovery from stroke. *Gait Posture, 22*(3), 267-281.

Giza, C. C., & Hovda, D. A. (2001). The Neurometabolic Cascade of Concussion. *J Athl Train, 36*(3), 228-235.

Golob, E. J., Irimajiri, R., & Starr, A. (2007). Auditory cortical activity in amnestic mild cognitive impairment: relationship to subtype and conversion to dementia. *Brain, 130*(Pt 3), 740-752.

Gosselin, N., Theriault, M., Leclerc, S., Montplaisir, J., & Lassonde, M. (2006). Neurophysiological anomalies in symptomatic and asymptomatic concussed athletes. *Neurosurgery, 58*(6), 1151-1161; discussion 1151-1161.

Gray, C., Cantagallo, A., Della Sala, S., & Basaglia, N. (1998). Bradykinesia and bradyphrenia revisited: patterns of subclinical deficit in motor speed and cognitive functioning in head-injured patients with good recovery. *Brain Inj, 12*(5), 429-441.

Greenwald, R. M., Gwin, J. T., Chu, J. J., & Crisco, J. J. (2008). Head impact severity measures for evaluating mild traumatic brain injury risk exposure. *Neurosurgery, 62*(4), 789-798; discussion 798.

Guo, Z., Cupples, L. A., Kurz, A., Auerbach, S. H., Volicer, L., Chui, H., et al. (2000). Head injury and the risk of AD in the MIRAGE study. *Neurology, 54*(6), 1316-1323.

Guskiewicz, K. M. (2002). No evidence of impaired neurocognitive performance in collegiate soccer players. *Am J Sports Med, 30*(4), 630.

Guskiewicz, K. M., Marshall, S. W., Bailes, J., McCrea, M., Cantu, R. C., Randolph, C., et al. (2005). Association between recurrent concussion and late-life cognitive impairment in retired professional football players. *Neurosurgery, 57*(4), 719-726; discussion 719-726.

Guskiewicz, K. M., McCrea, M., Marshall, S. W., Cantu, R. C., Randolph, C., Barr, W., et al. (2003). Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA Concussion Study. *Jama, 290*(19), 2549-2555.

Guskiewicz, K. M., Perrin, D. H., & Gansneder, B. M. (1996). Effect of Mild Head Injury on Postural Stability in Athletes. *J Athl Train, 31*(4), 300-306.

Guskiewicz, K. M., Ross, S. E., & Marshall, S. W. (2001). Postural Stability and Neuropsychological Deficits After Concussion in Collegiate Athletes. *J Athl Train, 36*(3), 263-273.

Guskiewicz, K. M., Weaver, N. L., Padua, D. A., & Garrett, W. E., Jr. (2000). Epidemiology of concussion in collegiate and high school football players. *Am J Sports Med, 28*(5), 643-650.

Hashimoto, T., Nakamura, N., Richard, K. E., & Frowein, R. A. (1993). Primary brain stem lesions caused by closed head injuries. *Neurosurg Rev, 16*(4), 291-298.

Heinmiller, A., Ting, A. K. R., Vargas-Perez, H., Yeh, A., & van der Kooy, D. (2009). Tegmental pedunculopontine glutamate and GABA-B synapses mediate morphine reward. *Behav Neurosci, 123*(1), 145-155.

Heyman, A., Wilkinson, W. E., Stafford, J. A., Helms, M. J., Sigmon, A. H., & Weinberg, T. (1984). Alzheimer's disease: a study of epidemiological aspects. *Ann Neurol, 15*(4), 335-341.

Hinton-Bayre, A. D., & Geffen, G. (2002). Severity of sports-related concussion and neuropsychological test performance. *Neurology, 59*(7), 1068-1070.

Hovda, D. A., Lee, S. M., Smith, M. L., Von Stuck, S., Bergsneider, M., Kelly, D., et al. (1995). The neurochemical and metabolic cascade following brain injury: moving from animal models to man. *J Neurotrauma, 12*(5), 903-906.

Hyndman, D., Ashburn, A., Yardley, L., & Stack, E. (2006). Interference between balance, gait and cognitive task performance among people with stroke living in the community. *Disabil Rehabil, 28*(13-14), 849-856.

Ilan, A. B., & Polich, J. (1999). P300 and response time from a manual Stroop task. *Clin Neurophysiol, 110*(2), 367-373.

Iverson, G. L. (2005). Outcome from mild traumatic brain injury. *Curr Opin Psychiatry, 18*(3), 301-317.

Iverson, G. L. (2007). Predicting slow recovery from sport-related concussion: the new simple-complex distinction. *Clin J Sport Med, 17*(1), 31-37.

Iverson, G. L., Gaetz, M., Lovell, M. R., & Collins, M. W. (2004). Cumulative effects of concussion in amateur athletes. *Brain Inj, 18*(5), 433-443.

Jantzen, K. J., Anderson, B., Steinberg, F. L., & Kelso, J. A. (2004). A prospective functional MR imaging study of mild traumatic brain injury in college football players. *AJNR Am J Neuroradiol, 25*(5), 738-745.

Johnson, R., Jr., & Donchin, E. (1978). On how P300 amplitude varies with the utility of the eliciting stimuli. *Electroencephalogr Clin Neurophysiol, 44*(4), 424-437.

Jordan, B. D., Relkin, N. R., Ravdin, L. D., Jacobs, A. R., Bennett, A., & Gandy, S. (1997). Apolipoprotein E epsilon4 associated with chronic traumatic brain injury in boxing. *Jama, 278*(2), 136-140.

Kandel, E., Schwartz, J., & Jessell, T. (2000). *Principles of Neural Science* (4th ed.). New York: McGraw-Hill.

Kasai, M., Meguro, K., Hashimoto, R., Ishizaki, J., Yamadori, A., & Mori, E. (2006). Non-verbal learning is impaired in very mild Alzheimer's disease (CDR 0.5): normative data from the learning version of the Rey-Osterrieth Complex Figure Test. *Psychiatry Clin Neurosci, 60*(2), 139-146.

Kelly, J. P. (1999). Traumatic brain injury and concussion in sports. *Jama, 282*(10), 989-991.

Khedr, E. M., Rothwell, J. C., Ahmed, M. A., Shawky, O. A., & Farouk, M. (2007). Modulation of motor cortical excitability following rapid-rate transcranial magnetic stimulation. *Clin Neurophysiol, 118*(1), 140-145.

Kobori, N., & Dash, P. K. (2006). Reversal of brain injury-induced prefrontal glutamic acid decarboxylase expression and working memory deficits by D1 receptor antagonism. *J Neurosci, 26*(16), 4236-4246.

Koop, M. M., Shivitz, N., & Bronte-Stewart, H. (2008). Quantitative measures of fine motor, limb, and postural bradykinesia in very early stage, untreated Parkinson's disease. *Mov Disord, 23*(9), 1262-1268.

Kopp, B., Tabeling, S., Moschner, C., & Wessel, K. (2006). Fractionating the neural mechanisms of cognitive control. *J Cogn Neurosci, 18*(6), 949-965.

Kramer, A. F., & Strayer, D. L. (1988). Assessing the development of automatic processing: an application of dual-task and event-related brain potential methodologies. *Biol Psychol, 26*(1-3), 231-267.

Kraus, J. F., & Nourjah, P. (1988). The epidemiology of mild, uncomplicated brain injury. *J Trauma, 28*(12), 1637-1643.

Kraus, M. F., Susmaras, T, Caughlin, B P, Walker, C J, Sweeney, J A, Little, D M. (2007). White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain, 130*, 2508-2519.

Kujirai, T., Caramia, M. D., Rothwell, J. C., Day, B. L., Thompson, P. D., Ferbert, A., et al. (1993). Corticocortical inhibition in human motor cortex. *J Physiol, 471*, 501-519.

Kutas, M., McCarthy, G., & Donchin, E. (1977). Augmenting mental chronometry: the P300 as a measure of stimulus evaluation time. *Science, 197*(4305), 792-795.

Lang, N., Sueske, E., Hasan, A., Paulus, W., & Tergau, F. (2006). Pregabalin exerts oppositional effects on different inhibitory circuits in human motor cortex: a double-blind, placebo-controlled transcranial magnetic stimulation study. *Epilepsia, 47*(5), 813-819.

Langlois, J. A., Rutland-Brown, W., & Wald, M. M. (2006). The epidemiology and impact of traumatic brain injury: a brief overview. *J Head Trauma Rehabil, 21*(5), 375-378.

Laurer, H. L., Bareyre, F. M., Lee, V. M., Trojanowski, J. Q., Longhi, L., Hoover, R., et al. (2001). Mild head injury increasing the brain's vulnerability to a second concussive impact. *J Neurosurg, 95*(5), 859-870.

Lavoie, M. E., Dupuis, F., Johnston, K. M., Leclerc, S., & Lassonde, M. (2004). Visual p300 effects beyond symptoms in concussed college athletes. *J Clin Exp Neuropsychol, 26*(1), 55-73.

Lefaucheur, J. P., Menard-Lefaucheur, I., Maison, P., Baudic, S., Cesaro, P., Peschanski, M., et al. (2006). Electrophysiological deterioration over time in patients with Huntington's disease. *Mov Disord, 21*(9), 1350-1354.

Levin, H. S. (1995). Neurobehavioral outcome of closed head injury: implications for clinical trials. *J Neurotrauma, 12*(4), 601-610.

Lezak, M. D. (1995). *Neuropsychyological Assessment (3rd edition)*. New York: Oxford University Press.

Liberman, J. N., Stewart, W. F., Wesnes, K., & Troncoso, J. (2002). Apolipoprotein E epsilon 4 and short-term recovery from predominantly mild brain injury. *Neurology, 58*(7), 1038-1044.

Lind, J., Larsson, A., Persson, J., Ingvar, M., Nilsson, L. G., Backman, L., et al. (2006). Reduced hippocampal volume in non-demented carriers of the apolipoprotein E epsilon4: relation to chronological age and recognition memory. *Neurosci Lett, 396*(1), 23-27.

Lindsay, J., Laurin, D., Verreault, R., Hebert, R., Helliwell, B., Hill, G. B., et al. (2002). Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol, 156*(5), 445-453.

Liotti, M., Pliszka, S. R., Perez, R., Kothmann, D., & Woldorff, M. G. (2005). Abnormal brain activity related to performance monitoring and error detection in children with ADHD. *Cortex, 41*(3), 377-388.

Lovell, M. R., Iverson, G. L., Collins, M. W., McKeag, D., & Maroon, J. C. (1999). Does loss of consciousness predict neuropsychological decrements after concussion? *Clin J Sport Med, 9*(4), 193-198.

Lovell, M. R., Pardini, J. E., Welling, J., Collins, M. W., Bakal, J., Lazar, N., et al. (2007). Functional brain abnormalities are related to clinical recovery and time to return-to-play in athletes. *Neurosurgery, 61*(2), 352-359; discussion 359-360.

Luck, S. J., Chelazzi, L., Hillyard, S. A., & Desimone, R. (1997). Neural mechanisms of spatial selective attention in areas V1, V2, and V4 of macaque visual cortex. *J Neurophysiol, 77*(1), 24-42.

Luck, S. J., & Hillyard, S. A. (1994a). Electrophysiological correlates of feature analysis during visual search. *Psychophysiology, 31*(3), 291-308.

Luck, S. J., & Hillyard, S. A. (1994b). Spatial filtering during visual search: evidence from human electrophysiology. *J Exp Psychol Hum Percept Perform, 20*(5), 1000-1014.

Lum, J., Enns, J. T., & Pratt, J. (2002). Visual orienting in college athletes: explorations of athlete type and gender. *Res Q Exerc Sport, 73*(2), 156-167.

Mac Donald, C. L., Dikranian, K., Song, S. K., Bayly, P. V., Holtzman, D. M., & Brody, D. L. (2007). Detection of traumatic axonal injury with diffusion tensor imaging in a mouse model of traumatic brain injury. *Exp Neurol, 205*(1), 116-131.

Macdonell, R. A., King, M. A., Newton, M. R., Curatolo, J. M., Reutens, D. C., & Berkovic, S. F. (2001). Prolonged cortical silent period after transcranial magnetic stimulation in generalized epilepsy. *Neurology, 57*(4), 706-708.

Maddocks, D. L., Dicker, G. D., & Saling, M. M. (1995). The assessment of orientation following concussion in athletes. *Clin J Sport Med, 5*(1), 32-35.

Marazioti, A., Spyraki, C., & Thermos, K. (2009). GABA antagonists reverse the somatostatin dependent attenuation of rat locomotor activity. *Neuropeptides, 43*(3), 207-212.

Maroon, J. C., Lovell, M. R., Norwig, J., Podell, K., Powell, J. W., & Hartl, R. (2000). Cerebral concussion in athletes: evaluation and neuropsychological testing. *Neurosurgery, 47*(3), 659-669; discussion 669-672.

Mayers, L. (2008). Return-to-play criteria after athletic concussion: a need for revision. *Arch Neurol, 65*(9), 1158-1161.

Mayes, A. R., Holdstock, J. S., Isaac, C. L., Hunkin, N. M., & Roberts, N. (2002). Relative sparing of item recognition memory in a patient with adult-onset damage limited to the hippocampus. *Hippocampus, 12*(3), 325-340.

McAllister, T. W., Sparling, M. B., Flashman, L. A., Guerin, S. J., Mamourian, A. C., & Saykin, A. J. (2001). Differential working memory load effects after mild traumatic brain injury. *Neuroimage, 14*(5), 1004-1012.

McAuliffe, J. (2004). Differences in attentional set between athletes and nonathletes. *J Gen Psychol, 131*(4), 426-437.

McCarthy, G., & Donchin, E. (1981). A metric for thought: a comparison of P300 latency and reaction time. *Science, 211*(4477), 77-80.

McCrea, M., Guskiewicz, K. M., Marshall, S. W., Barr, W., Randolph, C., Cantu, R. C., et al. (2003). Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. *Jama, 290*(19), 2556-2563.

McCrea, M., Hammeke, T., Olsen, G., Leo, P., & Guskiewicz, K. (2004). Unreported concussion in high school football players: implications for prevention. *Clin J Sport Med, 14*(1), 13-17.

McCrea, M., Kelly, J. P., Kluge, J., Ackley, B., & Randolph, C. (1997). Standardized assessment of concussion in football players. *Neurology, 48*(3), 586-588.

McCrea, M., Kelly, J. P., Randolph, C., Cisler, R., & Berger, L. (2002). Immediate neurocognitive effects of concussion. *Neurosurgery, 50*(5), 1032-1040; discussion 1040-1032.

McCrea, M., Kelly, J. P., Randolph, C., Kluge, J., Bartolic, E., Finn, G., et al. (1998). Standardized assessment of concussion (SAC): on-site mental status evaluation of the athlete. *J Head Trauma Rehabil, 13*(2), 27-35.

McCrory, P. R. (1999). You can run but you can't hide: the role of concussion severity scales in sport. *Br J Sports Med, 33*(5), 297-298.

McCrory, P. R. (2000). Headaches and exercise. *Sports Med, 30*(3), 221-229.

McCrory, P. R. (2001a). Does second impact syndrome exist? *Clin J Sport Med, 11*(3), 144-149.

McCrory, P. R. (2001b). Headache in sport. *Br J Sports Med, 35*(5), 286-287.

McCrory, P. R., Ariens, T., & Berkovic, S. F. (2000). The nature and duration of acute concussive symptoms in Australian football. *Clin J Sport Med, 10*(4), 235-238.

McCrory, P. R., & Berkovic, S. F. (1998). Second impact syndrome. *Neurology, 50*(3), 677-683.

McCrory, P. R., Johnston, K., Meeuwisse, W., Aubry, M., Cantu, R., Dvorak, J., et al. (2005a). Summary and agreement statement of the 2nd International Conference on Concussion in Sport, Prague 2004. *Br J Sports Med, 39*(4), 196-204.

McCrory, P. R., Johnston, K., Meeuwisse, W., Aubry, M., Cantu, R. C., Dvorak, J., et al. (2005b). Summary and agreement statement of the 2nd International Conference on Concussion in Sport, Prague 2004. *Clin J Sport Med, 15*(2), 48-55.

McCrory, P. R., Meeuwisse, W., Johnston, K., Dvorak, J., Aubry, M., Molloy, M., et al. (2009). Consensus statement on concussion in sport: the 3rd International Conference on Concussion in Sport held in Zurich, November 2008. *J Athl Train, 44*(4), 434-448.

McDonnell, M. N., Orekhov, Y., & Ziemann, U. (2006). The role of GABA(B) receptors in intracortical inhibition in the human motor cortex. *Exp Brain Res, 173*(1), 86-93.

McDonnell, M. N., Orekhov, Y., & Ziemann, U. (2007). Suppression of LTP-like plasticity in human motor cortex by the GABAB receptor agonist baclofen. *Exp Brain Res, 180*(1), 181-186.

McIntosh, T. K., Smith, D. H., Meaney, D. F., Kotapka, M. J., Gennarelli, T. A., & Graham, D. I. (1996). Neuropathological sequelae of traumatic brain injury: relationship to neurochemical and biomechanical mechanisms. *Lab Invest, 74*(2), 315-342.

McNamara, R. K., & Skelton, R. W. (1996). Baclofen, a selective GABAB receptor agonist, dose-dependently impairs spatial learning in rats. *Pharmacol Biochem Behav, 53*(2), 303-308.

Meunier, M., Bachevalier, J., Mishkin, M., & Murray, E. A. (1993). Effects on visual recognition of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkeys. *J Neurosci, 13*(12), 5418-5432.

Mohammadi, B., Krampfl, K., Petri, S., Bogdanova, D., Kossev, A., Bufler, J., et al. (2006). Selective and nonselective benzodiazepine agonists have different effects on motor cortex excitability. *Muscle Nerve, 33*(6), 778-784.

Moller, B., Light, G. A., Fitzgerald, P. B., Snyder, J. S., Chen, R., & Daskalakis, Z. J. (2007). Relationship between P50 suppression and the cortical silent period. *Neuroreport, 18*(14), 1503-1506.

Mortimer, J. A., French, L. R., Hutton, J. T., & Schuman, L. M. (1985). Head injury as a risk factor for Alzheimer's disease. *Neurology, 35*(2), 264-267.

Moser, R. S., Iverson, G. L., Echemendia, R. J., Lovell, M. R., Schatz, P., Webbe, F. M., et al. (2007). Neuropsychological evaluation in the diagnosis and management of sports-related concussion. *Arch Clin Neuropsychol, 22*(8), 909-916.

Murray, E. A., & Mishkin, M. (1998). Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. *J Neurosci, 18*(16), 6568-6582.

Nicoll, J. A., Roberts, G. W., & Graham, D. I. (1995). Apolipoprotein E epsilon 4 allele is associated with deposition of amyloid beta-protein following head injury. *Nat Med, 1*(2), 135-137.

Nordby, H., Hugdahl, K., Jasiukaitis, P., & Spiegel, D. (1999). Effects of hypnotizability on performance of a Stroop task and event-related potentials. *Percept Mot Skills, 88*(3 Pt 1), 819-830.

Oechsner, M., & Zangemeister, W. H. (1999). Prolonged postexcitatory inhibition after transcranial magnetic stimulation of the motor cortex in patients with cerebellar ataxia. *J Neurol Sci, 168*(2), 107-111.

Okada, M., & Okada, M. (1983). A method for quantification of alternate pronation and supination of forearms. *Comput Biomed Res, 16*(1), 59-78.

Oliveri, M., Caltagirone, C., Filippi, M. M., Traversa, R., Cicinelli, P., Pasqualetti, P., et al. (2000). Paired transcranial magnetic stimulation protocols reveal a pattern of inhibition and facilitation in the human parietal cortex. *J Physiol, 529 Pt 2*, 461-468.

Ommaya, A. K., Goldsmith, W., & Thibault, L. (2002). Biomechanics and neuropathology of adult and paediatric head injury. *Br J Neurosurg, 16*(3), 220-242.

Ommaya, A. K., Rockoff, S. D., & Baldwin, M. (1964). Experimental Concussion; a First Report. *J Neurosurg, 21*, 249-265.

Pandya, D. N., & Yeterian, E. H. (1996). Comparison of prefrontal architecture and connections. *Philos Trans R Soc Lond B Biol Sci, 351*(1346), 1423-1432.

Parizel, P. M., Ozsarlak, Van Goethem, J. W., van den Hauwe, L., Dillen, C., Verlooy, J., et al. (1998). Imaging findings in diffuse axonal injury after closed head trauma. *Eur Radiol, 8*(6), 960-965.

Parker, T. M., Osternig, L. R., Van Donkelaar, P., & Chou, L. S. (2006). Gait stability following concussion. *Med Sci Sports Exerc, 38*(6), 1032-1040.

Parker, T. M., Osternig, L. R., van Donkelaar, P., & Chou, L. S. (2007). Recovery of cognitive and dynamic motor function following concussion. *Br J Sports Med, 41*(12), 868-873; discussion 873.

Pascual, J. M., Solivera, J., Prieto, R., Barrios, L., Lopez-Larrubia, P., Cerdan, S., et al. (2007). Time course of early metabolic changes following diffuse traumatic brain injury in rats as detected by (1)H NMR spectroscopy. *J Neurotrauma, 24*(6), 944-959.

Paterakis, K., Karantanas, A. H., Komnos, A., & Volikas, Z. (2000). Outcome of patients with diffuse axonal injury: the significance and prognostic value of MRI in the acute phase. *J Trauma, 49*(6), 1071-1075.

Pettus, E. H., Christman, C. W., Giebel, M. L., & Povlishock, J. T. (1994). Traumatically induced altered membrane permeability: its relationship to traumatically induced reactive axonal change. *J Neurotrauma, 11*(5), 507-522.

Pfefferbaum, A., Christensen, C., Ford, J. M., & Kopell, B. S. (1986). Apparent response incompatibility effects on P3 latency depend on the task. *Electroencephalogr Clin Neurophysiol, 64*(5), 424-437.

Picton, T. W. (1992). The P300 wave of the human event-related potential. *J Clin Neurophysiol, 9*(4), 456-479.

Pierantozzi, M., Marciani, M. G., Palmieri, M. G., Brusa, L., Galati, S., Caramia, M. D., et al. (2004). Effect of Vigabatrin on motor responses to transcranial magnetic stimulation: an effective tool to investigate in vivo GABAergic cortical inhibition in humans. *Brain Res, 1028*(1), 1-8.

Plassman, B. L., Havlik, R. J., Steffens, D. C., Helms, M. J., Newman, T. N., Drosdick, D., et al. (2000). Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. *Neurology, 55*(8), 1158-1166.

Poirier, J., Davignon, J., Bouthillier, D., Kogan, S., Bertrand, P., & Gauthier, S. (1993). Apolipoprotein E polymorphism and Alzheimer's disease. *Lancet, 342*(8873), 697-699.

Polich, J. (1986). Normal variation of P300 from auditory stimuli. *Electroencephalogr Clin Neurophysiol, 65*(3), 236-240.

Polich, J. (1988). Bifurcated P300 peaks: P3a and P3b revisited? *J Clin Neurophysiol, 5*(3), 287-294.

Polich, J. (2004). Clinical application of the P300 event-related brain potential. *Phys Med Rehabil Clin N Am, 15*(1), 133-161.

Polich, J., & Corey-Bloom, J. (2005). Alzheimer's disease and P300: review and evaluation of task and modality. *Curr Alzheimer Res, 2*(5), 515-525.

Polich, J., Howard, L., & Starr, A. (1983). P300 latency correlates with digit span. *Psychophysiology, 20*(6), 665-669.

Potter, D. D., Bassett, M. R., Jory, S. H., & Barrett, K. (2001). Changes in event-related potentials in a three-stimulus auditory oddball task after mild head injury. *Neuropsychologia, 39*(13), 1464-1472.

Povlishock, J. T., Becker, D. P., Cheng, C. L., & Vaughan, G. W. (1983). Axonal change in minor head injury. *J Neuropathol Exp Neurol, 42*(3), 225-242.

Povlishock, J. T., & Katz, D. I. (2005). Update of neuropathology and neurological recovery after traumatic brain injury. *J Head Trauma Rehabil, 20*(1), 76-94.

Rabadi, M. H., & Jordan, B. D. (2001). The cumulative effect of repetitive concussion in sports. *Clin J Sport Med, 11*(3), 194-198.

Reinvang, I. (1999). Cognitive event-related potentials in neuropsychological assessment. *Neuropsychol Rev, 9*(4), 231-248.

Reinvang, I., Nordby, H., & Nielsen, C. S. (2000). Information processing deficits in head injury assessed with ERPs reflecting early and late processing stages. *Neuropsychologia, 38*(7), 995-1005.

Reis, J., Swayne, O. B., Vandermeeren, Y., Camus, M., Dimyan, M. A., Harris-Love, M., et al. (2008). Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. *J Physiol, 586*(2), 325-351.

Restivo, D. A., Lanza, S., Giuffrida, S., Le Pira, F., Drago, M. T., Di Mauro, R., et al. (2004). Cortical silent period prolongation in spinocerebellar ataxia type 2 (SCA2). *Funct Neurol, 19*(1), 37-41.

Reynolds, G. P., & Pearson, S. J. (1993). Neurochemical-clinical correlates in Huntington's disease--applications of brain banking techniques. *J Neural Transm Suppl, 39*, 207-214.

Riis, J. L., Chong, H., Ryan, K. K., Wolk, D. A., Rentz, D. M., Holcomb, P. J., et al. (2008). Compensatory neural activity distinguishes different patterns of normal cognitive aging. *Neuroimage, 39*(1), 441-454.

Rioult-Pedotti, M. S., Friedman, D., & Donoghue, J. P. (2000). Learning-induced LTP in neocortex. *Science, 290*(5491), 533-536.

Rioult-Pedotti, M. S., Friedman, D., Hess, G., & Donoghue, J. P. (1998). Strengthening of horizontal cortical connections following skill learning. *Nat Neurosci, 1*(3), 230-234.

Ruff, R. (2005). Two decades of advances in understanding of mild traumatic brain injury. *J Head Trauma Rehabil, 20*(1), 5-18.

Sackett, D. L., Rosenberg, W. M., Gray, J. A., Haynes, R. B., & Richardson, W. S. (1996). Evidence based medicine: what it is and what it isn't. *Bmj, 312*(7023), 71-72.

Selkoe, D. J. (1991). Alzheimer's disease. In the beginning. *Nature, 354*(6353), 432-433.

Shaw, N. A. (2002). The neurophysiology of concussion. *Prog Neurobiol, 67*(4), 281-344.

Shibata, Y., Matsumura, A., Meguro, K., & Narushima, K. (2000). Differentiation of mechanism and prognosis of traumatic brain stem lesions detected by magnetic resonance imaging in the acute stage. *Clin Neurol Neurosurg, 102*(3), 124-128.

Siebner, H. R., Dressnandt, J., Auer, C., & Conrad, B. (1998). Continuous intrathecal baclofen infusions induced a marked increase of the transcranially evoked silent period in a patient with generalized dystonia. *Muscle Nerve, 21*(9), 1209-1212.

Slobounov, S., Slobounov, E, Sebastianelli, W, Cao, C, Newell, K. (2007). Differential rate of recovery in athletes after first and second concussion episodes. *Neurosurgery, 61*(2), 338-344.

Snyder, J., Hanstock, C. C., & Wilman, A. H. (2009). Spectral editing of weakly coupled spins using variable flip angles in PRESS constant echo time difference spectroscopy: Application to GABA. *J Magn Reson*.

Solbakk, A. K., Reinvang, I., & Andersson, S. (2002). Assessment of P3a and P3b after moderate to severe brain injury. *Clin Electroencephalogr, 33*(3), 102-110.

Solbakk, A. K., Reinvang, I., Nielsen, C., & Sundet, K. (1999). ERP indicators of disturbed attention in mild closed head injury: a frontal lobe syndrome? *Psychophysiology, 36*(6), 802-817.

Squire, L. R., & Zola, S. M. (1996). Structure and function of declarative and nondeclarative memory systems. *Proc Natl Acad Sci U S A, 93*(24), 13515-13522.

Stefan, K., Kunesch, E., Benecke, R., Cohen, L. G., & Classen, J. (2002). Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation. *J Physiol, 543*(Pt 2), 699-708.

Stefan, K., Kunesch, E., Cohen, L. G., Benecke, R., & Classen, J. (2000). Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain, 123 Pt 3*, 572-584.

Tataroglu, C., Ozkiziltan, S., & Baklan, B. (2004). Motor cortical thresholds and cortical silent periods in epilepsy. *Seizure, 13*(7), 481-485.

Teasdale, G., & Jennett, B. (1974). Assessment of coma and impaired consciousness. A practical scale. *Lancet, 2*(7872), 81-84.

Teasdale, G. M., Nicoll, J. A., Murray, G., & Fiddes, M. (1997). Association of apolipoprotein E polymorphism with outcome after head injury. *Lancet, 350*(9084), 1069-1071.

Termoz, N., Halliday, S. E., Winter, D. A., Frank, J. S., Patla, A. E., & Prince, F. (2008). The control of upright stance in young, elderly and persons with Parkinson's disease. *Gait Posture, 27*(3), 463-470.

Thurman, D. J., Branche, C. M., & Sniezek, J. E. (1998). The epidemiology of sports-related traumatic brain injuries in the United States: recent developments. *J Head Trauma Rehabil, 13*(2), 1-8.

Tinazzi, M., Farina, S., Edwards, M., Moretto, G., Restivo, D., Fiaschi, A., et al. (2005). Task-specific impairment of motor cortical excitation and inhibition in patients with writer's cramp. *Neurosci Lett, 378*(1), 55-58.

Udupa, K., Ni, Z., Gunraj, C., & Chen, R. (2009). Interactions between short latency afferent inhibition and long interval intracortical inhibition. *Exp Brain Res*.

Uryu, K., Laurer, H., McIntosh, T., Pratico, D., Martinez, D., Leight, S., et al. (2002). Repetitive mild brain trauma accelerates Abeta deposition, lipid peroxidation, and

cognitive impairment in a transgenic mouse model of Alzheimer amyloidosis. *J Neurosci, 22*(2), 446-454.

Vagnozzi, R., Tavazzi, B., Signoretti, S., Amorini, A. M., Belli, A., Cimatti, M., et al. (2007). Temporal window of metabolic brain vulnerability to concussions: mitochondrial-related impairment--part I. *Neurosurgery, 61*(2), 379-388; discussion 388-379.

Van Hoesen, G. W., Hyman, B. T., & Damasio, A. R. (1991). Entorhinal cortex pathology in Alzheimer's disease. *Hippocampus, 1*(1), 1-8.

Ward, A. A., Jr. (1964). The physiology of concussion. *Clin Neurosurg, 12*, 95-111.

Werhahn, K. J., Kunesch, E., Noachtar, S., Benecke, R., & Classen, J. (1999). Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. *J Physiol, 517 (Pt 2)*, 591-597.

Werner, R. A., & Vanderzant, C. W. (1991). Multimodality evoked potential testing in acute mild closed head injury. *Arch Phys Med Rehabil, 72*(1), 31-34.

Wickens, C., Kramer, A., Vanasse, L., & Donchin, E. (1983). Performance of concurrent tasks: a psychophysiological analysis of the reciprocity of information-processing resources. *Science, 221*(4615), 1080-1082.

Wilson, J. R., Foresman, B. H., Gamber, R. G., & Wright, T. (1998). Hyperbaric oxygen in the treatment of migraine with aura. *Headache, 38*(2), 112-115.

Wylie, S. A., Ridderinkhof, K. R., Eckerle, M. K., & Manning, C. A. (2007). Inefficient response inhibition in individuals with mild cognitive impairment. *Neuropsychologia, 45*(7), 1408-1419.

Zemper, E. D. (2003). Two-year prospective study of relative risk of a second cerebral concussion. *Am J Phys Med Rehabil, 82*(9), 653-659.

Ziemann, U. (2003). Pharmacology of TMS. *Suppl Clin Neurophysiol, 56*, 226-231.

Ziemann, U. (2004). TMS and drugs. *Clin Neurophysiol, 115*(8), 1717-1729.

Ziemann, U., Ilic, T. V., Pauli, C., Meintzschel, F., & Ruge, D. (2004). Learning modifies subsequent induction of long-term potentiation-like and long-term depression-like plasticity in human motor cortex. *J Neurosci, 24*(7), 1666-1672.

7.2. Experiment 1

[1] Kelly J. Traumatic brain injury and concussion in sports. Journal of the American Medical Association 1999; 282: 989-991.

[2] Centers for Disease Control and Prevention. Sports-related recurrent brain injuries--United States. Journal of the American Medical Association 1997; 277: 1190-1.

[3] McCrory P, Johnston K, Meeuwisse W, Aubry M, Cantu R, Dvorak J, Graf-Baumann T, Kelly J, Lovell M, Schamasch P; International Symposium on Concussion in Sport. Summary and agreement statement of the 2nd International Conference on Concussion in Sport, Prague 2004. Clinical Journal of Sports Medicine 2005; 15: 48-55.

[4] Guskiewicz KM, McCrea M, Marshall SW, Cantu RC, Randolph C, Barr W, Onate JA, Kelly JP. Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA concussion study. Journal of the American Medical Association 2003; 290: 2549-55.

[5] Zemper ED. Two-year prospective study of relative risk of a second cerebral concussion. American Journal of Physical Medicine and Rehabilitation 2003; 82: 653-9.

[6] Collins MW, Lovell MR, Iverson GL, Cantu RC, Maroon JC, Field M. Cumulative effects of concussions in high school athletes. Neurosurgery 2002; 51: 1175-81.

[7] Iverson GL, Gaetz M, Lovell MR, Collins MW. Two-year prospective study of relative risk of a second cerebral concussion. American Journal of Physical Medicine and Rehabilitation 2004; 82: 653-9.

[8] Gaetz M, Bernstein DM. The current status of eletrophysiologic procedures for the assessment of mild traumatic brain injury. Brain Injury 2001; 14: 386-405.

[9] Coles MGH, Ruggs MD (1995). Event-related potentials: An introduction. In Ruggs MD & Coles MGH, editors. Electrophysiology of mind: Event-related potentials and cognition; New York, NY: Oxford Psychology Series; 1995. pp 86-125.

[10] Donchin E. A multivariate approach to the analysis of average evoked potentials. IEEE Transformation Biomedical Engineering 1966; 13: 131-9.

[11] Rodriguez Holguin S, Porjesz B, Chorlian DB, Polich J, Begleiter H. Visual P3a in male alcoholics and controls. Alcoholism, Clinical and Experimental Research 1999; 23: 582-9.

[12] Sawaki R, Katayama J. Severity of AD/HD symptoms and efficiency of attentional resource allocation. Neuroscience Letters 2006; 407: 86-90.

[13] Polich J. P300 from a passive auditory paradigm. Electroencephalography and Clinical Neurophysiology 1989; 74: 312-20.

[14] Picton TW. The P300 wave of the human event-related potential. Journal of Clinical Neurophysiology 1992; 9: 456-79.

[15] Polich J. P300 clinical utility and control of variability. Journal of Clinical Neurophysiology 1998; 15: 14-33.

[16] Donchin E, Coles M. Is the P300 component a manifestation of context updating? Behavior and Brain Science 1988; 11: 357-74.

[17] Picton TW. The P300 wave of the human event-related potential. Journal of Clinical Neurophysiology 1992; 9: 456-79.

[16] Duncan-Johnson CC, Donchin E. On quantifying surprise: the variation of event-related potentials with subjective probability. Psychophysiology 1977; 14: 456-67.

[17] Johnson R Jr, Donchin E. On how P300 amplitude varies with the utility of the eliciting stimuli. Electroencephalography and Clinical Neurophysiology 1978; 44: 424-37.

[18] Polich J. Bifurcated P300 peaks: P3a and P3b revisited. Journal of Clinical Neurophysiology 1988; 5: 287-94.

[19] Duncan-Johnson CC. Young Psychophysiologist Award address, 1980. P300 latency: a new metric of information processing. Psychophysiology 1981; 18: 207-15.

[20] Kramer AF, Strayer DL. Assessing the development of automatic processing: an application of dual-task and event-related brain potential methodologies. Biological Psychology 1988; 26: 231-67.

[21] Wickens C, Kramer A, Vanasse L, Donchin E. Performance of concurrent tasks: a psychophysiological analysis of the reciprocity of information-processing resources. Science 1983; 221: 1080-2.

[22] Fabiani M, Karis D, Donchin E. Effects of mnemonic strategy manipulation in a Von Restorff paradigm. Electroencephalography and Clinical Neurophysiology 1990; 75: 22-35.

[23] Johnson R Jr. On the neural generators of the P300: evidence from temporal lobectomy patients. Electroencephalography and Clinical Neurophysiology Supplements 1995; 44: 110-29.

[24] Polich J. Clinical application of the P300 event-related brain potential. Physical Medicine and Rehabilitation Clinics of North America 2004;15: 133-61.

[25] Kutas M, McCarthy G, Donchin E. Augmenting mental chronometry: the P300 as a measure of stimulus evaluation time. Science 1977; 197: 792-5.

[26] Polich J. Attention, probability, and task demands as determinants of P300 latency from auditory stimuli. Electroencephalography and Clinical Neurophysiology 1986; 63: 251-9.

[27] McCarthy G, Donchin E. A metric for thought: a comparison of P300 latency and reaction time. Science 1981; 211: 77-80.

[28] Pfefferbaum A, Christensen C, Ford JM, Kopell BS. Apparent response incompatibility effects on P3 latency depend on the task. Electroencephalography and Clinical Neurophysiology 1986; 64: 424-37.

[29] Duncan-Johnson CC, Donchin E. The relation of P300 latency to reaction time as a function of expectancy. Progress in brain research 1980; 54: 717-22.

[30] Ilan AB, Polich J. P300 and response time from a manual Stroop task. Clinical Neurophysiology 1999; 110: 367-73.

[31] Emmerson RY, Dustman RE, Shearer DE, Turner CW. P3 latency and symbol digit performance correlations in aging. Experimental Aging Research 1989; 15: 151-9.

[32] Polich J, Howard L, StarrA. P300 latency correlates with digit span. Psychophysiology 1983; 20: 665-9.

[33] Polich J. On the clinical application of P300. Biological Psychiatry 1992; 31: 647-9.

[34] Reinvang I. Cognitive event-related potentials in neuropsychological assessment. Neuropsychological Review 1999; 9: 231-48.

[35] Sangal RB, Sangal JM. Closed head injury patients with mild cognitive complaints without neurological or psychiatric findings have abnormal visual P300 latencies. Biological Psychiatry 1996; 39: 305-7.

[36] Gaetz M, Goodman D, Weinberg H. Electrophysiological evidence for the cumulative effects of concussion. Brain Injury 2000; 14: 1077-88.

[37] Dupuis F, Johnston KM, Lavoie M, Lepore F, Lassonde M. Concussions in athletes produce brain dysfunction as revealed by event-related potentials. Neuroreport 2000; 11: 4087-92.

[38] Lavoie ME, Dupuis F, Johnston KM, Leclerc S, Lassonde M. Visual P300 effects beyond symptoms in concussed college athletes. Journal of Clinical and Experimental Neuropsychology 2004; 26: 55-73.

[39] Potter DD, Bassett MR, Jory SH, Barrett K. Changes in event-related potentials in a three-stimulus auditory oddball task after mild head injury. Neuropsychologia 2001; 39: 1464-72.

[40] Werner RA, Vanderzant CW. Multimodality evoked potential testing in acute mild closed head injury. Archives of Physical Medicine and Rehabilitation 1991; 72: 31-4.

[41] von Bierbrauer A, Weissenborn K. P300 after minor head injury (a follow-up examination). Acta Neurologica Belgica 1998; 98: 21-6.

[42] Ford MR, Khalil M. Evoked potentials findings in mild traumatic brain injury 1: middle latency component augmentation and cognitive component attenuation. Journal of Head Trauma Rehabilitation 1996; 11: 1-15.

[43] Solbakk AK, Reinvang I, Nielsen C, Sundet K. ERP indicators of disturbed attention in mild closed head injury: a frontal lobe syndrome? Psychophysiology 1999; 36: 802-17.

[44] Reinvang I, Nordby H, Nielsen C. Information processing deficits in head injury assessed with ERPs reflecting early and late processing stages. Neuropsychologia 2000; 38: 995-1005.

[45] Solbakk AK, Reinvang I, Nielsen CS. ERP indices of resource allocation difficulties in mild head injury. Journal of Clinical Experimental Neuropsychology 2000; 22: 743-60.

[46] Gosselin N, Thériault M, Johnston KM, Leclerc S, Montplaisir J, Lassonde M. Neurophysiological anomalies in symptomatic and asymptomatic concussed athletes. Neurosurgery 2006; 58: 1151-61.

[47] Luck SJ, Hillyard SA. Spatial filtering during visual search: evidence from human electrophysiology. Journal of Experimental Psychology: Human Perception and Performance 1994a; 20: 1000-14.

[48] Luck SJ, Hillyard SA. Electrophysiological correlates of feature analysis during visual search. Psychophysiology 1994b; 31: 291-308.

[49] Woodman GF, Luck SJ. Serial deployment of attention during visual search. Journal of Experimental Psychology: Human Perception and Performance 2003; 29: 121–38.

[50] Lum J, Enns JT, Pratt J. Visual orienting in college athletes: explorations of athlete type and gender. Research quarterly for exercise and sport 2002; 73: 156-67.

[51] McAuliffe J. Differences in attentional set between athletes and nonathletes. The Journal of General Psychology 2004; 131: 426-37.

[52] Eimer M. The N2pc component as an indicator of attentional selectivity. Electroencephalography and Clinical Neurophysiology 1996; 99: 225-34.

[53] Luck SJ, Girelli M, McDermott MT, Ford MA. Bridging the gap between monkey neurophysiology and human perception: an ambiguity resolution theory of visual selective attention. Cognitive Psychology 1997; 33: 64-87.

[54] American Academy of Neurology Practice. Practice parameter : the management of concussion in sports (summary statement). Neurology 1997; 48: 581-5.

[55] Maroon JC, Lovell MR, Norwig J, Podell K, Powell JW, Hartl R. Cerebral concussion in athletes: evaluation and neuropsychological testing. Neurosurgery 2000; 47: 659-69.

[56] Pellman EJ, Lovell MR, Viano DC, Casson IR, Tucker AM. Concussion in professional football: neuropsychological testing-part 6. Neurosurgery 2004; 55: 1290-303.

[57] Dikmen SS, Mclean A, Temkin N. Neuropsychological and psychosocial consequences of minor head injury. Journal of Neurology Neurosurgery and Psychiatry 1986; 49: 1227-32.

[58] Rimel RW, Giordani B, Barth JT, Boll TJ, Jane JA. Disability caused by minor head injury. Neurosurgery 1981; 9: 221-8.

[59] Brisson B, Jolicoeur P. Electrophysiological evidence of central interference on the control of visual-spatial attention. Psychonomics Bulletin Review, (in-press).

[60] Cooper R, Osselton JW, Shaw JC. EEG Technology, (3rd edn). Butterworths, London, 1980.

[61] Miller J, Patterson T, Ulrich R. Jackknife-based method for measuring LRP onset latency differences. Psychophysiology 1998; 35: 99-115.

[62] Holbourn AHS. Mechanisms of head injury. Lancet 1943; 2: 438-41.

[63] Shutter MD, Tong KA, Lee A, Holshouser BA. Prognostic role of proton magnetic resonance spectroscopy in acute traumatic brain injury. Journal of head trauma rehabilitation 2006; 21: 334-49.

[64] McCrea M, Kelly JP, Randolph C, Cisler R, Berger L. Immediate neurocognitive effects of concussion. Neurosurgery 2002; 50: 1032-40.

[65] Lovell MR, Iverson GL, Collins MW, McKeag D, Maroon JC. Does loss of consciousness predict neuropsychological decrements after concussion? Clinical Journal of Sports Medicine 1999; 9: 193-8.

[66] McAllister TW, Sparling MB, Flashman LA, Guerin SJ, Mamourian AC, Saykin AJ. Differential working memory load effects after mild traumatic brain injury. Neuroimage 2001; 14: 1004-12.

[67] Jantzen KJ, Anderson B, Steinberg FL, Kelso JA. A prospective functional MR imaging study of mild traumatic brain injury in college football players. AJNR. American Journal of Neuroradiology 2004; 25: 738-45.

[68] Bernstein DM. Information processing difficulty long after self-reported concussion. Journal of the International Neuropsychological Society 2002; 8: 673-82.

[69]Brisson B, Jolicoeur P. A psychological refractory period in access to visual short-term memory and the deployment of visual-spatial attention: Multitasking processing deficits revealed by event-related potentials. Psychophysiology, (in-press).

[70] Dell'Acqua R, Sessa P, Jolicoeur P, Robitaille N. Spatial attention freezes during the attentional blink. Psychophysiology 2006; 43: 394-400.

[71] Jolicoeur P, Sessa P, Dell'Acqua R, Robitaille N. On the control of visual spatial attention: Evidence from human electrophysiology. Psychological Research 2006a; 70: 414-24.

[72] Jolicoeur P, Sessa P, Dell'Acqua R, Robitaille N. Attentional control and capture in the attentional blink paradigm: Evidence from human electrophysiology. European Journal of Cognitive Psychology 2006b; 18: 560-78.

7.3. Experiment 2

1 Abbruzzesse G & Trompetto C. Clinical and research methods for evaluating cortical excitability. **J Clin Neurophysiol** 19: 307-321, 2002.

2 American Academy of Neurology Practice. Practice parameter : the management of concussion in sports (summary statement). **Neurology** 48: 581-585, 1997.

3 Aubry M, Cantu R, Dvorak J, Graf-Baumann T, Johnston KM, Kelly J, Lovell M, McCrory P, Meeuwisse WH, & Schamasch P; Concussion in Sport (CIS) Group. Summary and agreement statement of the 1st International Symposium on Concussion in Sport, Vienna 2001. **Clin J Sport Med 12 :** 6–11, 2002.

4 Barth JV, Alves WM, Ryans TV, Macchiocchi SN, Rimel RE, Jane JA, & Nelson WE. Mild head injury in sports: neuropsychological sequelae and recovery of function. **J Cogn Neurorehab** 26: 451-478, 1989.

5 Bernstein DM. Information processing difficulty long after self-reported concussion. **J Int Neuropsychol Soc** 8:673–682, 2002.

6 Centers for Disease Control and Prevention. Sports-related recurrent brain injuries--United States. **JAMA** 277: 1190-1191, 1997.

7 Chistyakov AV, Soustiel JF, Hafner H, Trubnik M, Levy G, & Feinsod M. Excitatory and inhibitory corticospinal responses to transcranial magnetic stimulation in patients with moderate head injury. **J Neurol Neurosurg Psychiatry** 70: 580-587, 2001.

8 Chen JK, Johnston KM, Frey S, Petrides M, Worsley K, & Ptito A. Functional abnormalities in symptomatic concussed athletes: an fMRI study. **Neuroimage** 22: 68-82, 2003.

9 Collins MW, Lovell MR, Iverson GL, Cantu RC, Maroon JC, & Field M. Cumulative effects of concussions in high school athletes. **Neurosurgery** 51: 1175-1181, 2002.

10 Dikmen SS, Mclean A & Temkin N. Neuropsychological and psychosocial consequences of minor head injury. **J Neurol Neurosurg Psychiatry** 49: 1227-1232, 1986.

11 Echemendia RJ, Putukian M, Mackin RS, Julian L, & Shoss N. Neuropsychological test performance prior to and following sport-related mild traumatic brain injury. **Clin J Sport Med** 11: 23-31, 2001.

12 Garvey MA, Ziemann U, Becker DA, Barker CA, & Bartko JJ. New graphical method to measure silent periods evoked by transcranial magnetic stimulation. **Clin Neurophysiol** 112: 1451–1460, 2001.

13 Gerberich SG, Priest JD, Boen JR, Straub CP, & Maxwell RE. Concussion incidences and severity in secondary school varsity football players. **Am J Public Health** 73: 1370-1375, 1983.

14 Gosselin N, Thériault M, Johnston KM, Leclerc S, Montplaisir J & Lassonde M. Neurophysiological anomalies in symptomatic and asymptomatic concussed athletes. **Neurosurgery** 58: 1151-1161, 2006.

15 Guskiewicz KM, McCrea M, Marshall SW, Cantu RC, Randolph C, Barr W, Onate JA, & Kelly JP. Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA concussion study. **JAMA** 290: 2549-2555, 2003.

16 Guskiewicz KM, Marshall SW, Bailes J, McCrea M, Cantu RC, Randolph C, & Jordan BD. Association between recurrent concussion and late-life cognitive impairment in retired professional football players, **Neurosurgery** 57: 719-726, 2005.

17 Hinto-Bayre AD & Geffen G. Severity of sport-related concussion and neuropsychological test performance. **Neurology** 59: 1068-1070, 2002.

18 Inghilleri M, Berardelli A, Cruccu G & Manfredi M. Silent period evoked by transcranial stimulation of the human cortex and cervicomedullary junction. **J Physiol** 466: 521-534, 1993.

19 Kelly J. Traumatic brain injury and concussion in sports. **JAMA** 282: 989-991, 1999.

20 Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P, & Marsden CD. Corticocortical inhibition in human motor cortex. **J Physiol** 471: 501-519, 1993.

21 Lavoie ME, Dupuis F, Johnston KM, Leclerc S, & Lassonde M. Visual p300 effects beyond symptoms in concussed college athletes. **J Clin Exp Neuropsychol** 26: 55-73, 2004.

22 Liepert J, Schwenkreis P, Tegenthoff M, & Malin JP. The glutamate antagonist riluzole suppresses intracortical facilitation. **J Neural Transm** 104:1207-14, 1997.

23 McDonnell MN, Orekhov Y & Ziemann U. The role of $GABA_B$ receptors in intracortical inhibition in the human cortex. **Exp Brain Res** 173: 86-93, 2006.

24 Mendez CV, Hurley RA, Lassonde M, Zhang L, & Taber KH. Mild traumatic brain injury: neuroimaging of sports-related concussion. **J Neuropsychiatry Clin Neurosci**; 17: 297-303, 2005.

25 Pellman EJ, Lovell MR, Viano DC, Casson IR, & Tucker AM. Concussion in professional football: neuropsychological testing-part 6. **Neurosurgery** 55: 1290-1303, 2004.

26 Priori A, Berardelli A, Inghilleri M, Accornero N & Manfredi M. Motor cortical inhibition and the dopaminergic system. Pharmacological changes in the silent period after transcranial brain stimulation in normal subjects, patients with Parkinson's disease and drug-induced parkinsonism. **Brain** 117: 317-323, 1994.

27 Rabadi MH & Jordan BD. The cumulative effect of repetitive concussion in sports. **Clin J Sport Med** 11: 194-198, 2001.

28 Terao Y & Ugawa Y. Basic mechanisms of TMS. **J Clin Neurophysiol** 19:322-43, 2002.

29 Werhahn KJ, Kunesch E, Noachtar S, Benecke R, & Classen J. Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. **J Physiol** 517: 591-597, 1999.

30 Ziemann U, Netz J, Szelenyi A, & Homberg V. Spinal and supraspinal mechanisms contribute to the silent period in the contracting soleus muscle after transcranial magnetic stimulation of human motor cortex. **Neurosci lett** 156: 167-171, 1993.

31 Ziemann U, Lonnecker S, Steinhoff BJ, & Paulus W. Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. **Ann Neurol** 40: 344-345, 1996.

32 Ziemann U, Tergau F, Wischer S, Hildebrandt J, & Paulus W. Pharmacological control of facilitatory I-wave interaction in the human motor cortex. A paired transcranial magnetic stimulation study. **Electroencephalogr Clin Neurophysiol** 109: 321-330, 1998.

7.4. Experiment 3

1. Thurman DJ, Branche CM, Sniezek JE. The epidemiology of sports-related traumatic brain injuries in the United States: recent developments. *J Head Trauma Rehabil.* Apr 1998;13(2):1-8.

2. McCrea M, Guskiewicz KM, Marshall SW, et al. Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. *Jama.* Nov 19 2003;290(19):2556-2563.

3. De Beaumont L, Lassonde M, Leclerc S, Theoret H. Long-term and cumulative effects of sports concussion on motor cortex inhibition. *Neurosurgery.* Aug 2007;61(2):329-336; discussion 336-327.

4. De Beaumont L, Theoret H, Mongeon D, et al. Brain function decline in healthy retired athletes who sustained their last sports concussion in early adulthood. *Brain.* Mar 2009;132(Pt 3):695-708.

5. Gray C, Cantagallo A, Della Sala S, Basaglia N. Bradykinesia and bradyphrenia revisited: patterns of subclinical deficit in motor speed and cognitive functioning in head-injured patients with good recovery. *Brain Inj.* May 1998;12(5):429-441.

6. Guskiewicz KM, Perrin DH, Gansneder BM. Effect of Mild Head Injury on Postural Stability in Athletes. *J Athl Train.* Oct 1996;31(4):300-306.

7. Cavanaugh JT, Guskiewicz KM, Stergiou N. A nonlinear dynamic approach for evaluating postural control: new directions for the management of sport-related cerebral concussion. *Sports Med.* 2005;35(11):935-950.

8. Cavanaugh JT, Guskiewicz KM, Giuliani C, Marshall S, Mercer VS, Stergiou N. Recovery of postural control after cerebral concussion: new insights using approximate entropy. *J Athl Train.* Jul-Sep 2006;41(3):305-313.

9. Parker TM, Osternig LR, van Donkelaar P, Chou LS. Recovery of cognitive and dynamic motor function following concussion. *Br J Sports Med.* Dec 2007;41(12):868-873; discussion 873.

10. McDonnell MN, Orekhov Y, Ziemann U. The role of GABA(B) receptors in intracortical inhibition in the human motor cortex. *Exp Brain Res.* Aug 2006;173(1):86-93.

11. Gaetz M, Goodman D, Weinberg H. Electrophysiological evidence for the cumulative effects of concussion. *Brain Inj.* Dec 2000;14(12):1077-1088.

12. Guskiewicz KM, McCrea M, Marshall SW, et al. Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA Concussion Study. *Jama.* Nov 19 2003;290(19):2549-2555.

13. Iverson GL, Gaetz M, Lovell MR, Collins MW. Cumulative effects of concussion in amateur athletes. *Brain Inj.* May 2004;18(5):433-443.

14. American Academy of Neurology Practice. Practice parameter: the management of concussion in sports (summary statement). Report of the Quality Standards Subcommittee. *Neurology.* Mar 1997;48(3):581-585.

15. Maroon JC, Lovell MR, Norwig J, Podell K, Powell JW, Hartl R. Cerebral concussion in athletes: evaluation and neuropsychological testing. *Neurosurgery.* Sep 2000;47(3):659-669; discussion 669-672.

16. Okada M, Okada M. A method for quantification of alternate pronation and supination of forearms. *Comput Biomed Res.* Feb 1983;16(1):59-78.

17. Garvey MA, Ziemann U, Becker DA, Barker CA, Bartko JJ. New graphical method to measure silent periods evoked by transcranial magnetic stimulation. *Clin Neurophysiol.* Aug 2001;112(8):1451-1460.

18. Geurts AC, de Haart M, van Nes IJ, Duysens J. A review of standing balance recovery from stroke. *Gait Posture.* Nov 2005;22(3):267-281.

19. Termoz N, Halliday SE, Winter DA, Frank JS, Patla AE, Prince F. The control of upright stance in young, elderly and persons with Parkinson's disease. *Gait Posture.* Apr 2008;27(3):463-470.

20. Cantello R, Tarletti R, Varrasi C, Cecchin M, Monaco F. Cortical inhibition in Parkinson's disease: new insights from early, untreated patients. *Neuroscience.* **21.** Tinazzi M, Farina S, Edwards M, et al. Task-specific impairment of motor

cortical excitation and inhibition in patients with writer's cramp. *Neurosci Lett.* Apr 11 2005;378(1):55-58.

22. McCrea M, Hammeke T, Olsen G, Leo P, Guskiewicz K. Unreported concussion in high school football players: implications for prevention. *Clin J Sport Med.* Jan 2004;14(1):13-17.

23. McCrory PR. You can run but you can't hide: the role of concussion severity scales in sport. *Br J Sports Med.* Oct 1999;33(5):297-298.

24. Abbruzzese G, Trompetto C. Clinical and research methods for evaluating cortical excitability. *J Clin Neurophysiol.* Aug 2002;19(4):307-321.

25. Lang N, Sueske E, Hasan A, Paulus W, Tergau F. Pregabalin exerts oppositional effects on different inhibitory circuits in human motor cortex: a double-blind, placebo-controlled transcranial magnetic stimulation study. *Epilepsia.* May 2006;47(5):813-819.

26. Mohammadi B, Krampfl K, Petri S, et al. Selective and nonselective benzodiazepine agonists have different effects on motor cortex excitability. *Muscle Nerve.* Jun 2006;33(6):778-784.

27. Macdonell RA, King MA, Newton MR, Curatolo JM, Reutens DC, Berkovic SF. Prolonged cortical silent period after transcranial magnetic stimulation in generalized epilepsy. *Neurology.* Aug 28 2001;57(4):706-708.

28. Moller B, Light GA, Fitzgerald PB, Snyder JS, Chen R, Daskalakis ZJ. Relationship between P50 suppression and the cortical silent period. *Neuroreport.* Sep 17 2007;18(14):1503-1506.

29. Pierantozzi M, Marciani MG, Palmieri MG, et al. Effect of Vigabatrin on motor responses to transcranial magnetic stimulation: an effective tool to investigate in vivo GABAergic cortical inhibition in humans. *Brain Res.* Nov 26 2004;1028(1):1-8.

30. Siebner HR, Dressnandt J, Auer C, Conrad B. Continuous intrathecal baclofen infusions induced a marked increase of the transcranially evoked silent period in a patient with generalized dystonia. *Muscle Nerve.* Sep 1998;21(9):1209-1212.

31. Werhahn KJ, Kunesch E, Noachtar S, Benecke R, Classen J. Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. *J Physiol.* Jun 1 1999;517 (Pt 2):591-597.

32. McCrory PR, Johnston K, Meeuwisse W, et al. Summary and agreement statement of the 2nd International Conference on Concussion in Sport, Prague 2004. *Br J Sports Med.* Apr 2005;39(4):196-204.

7.5. Experiment 4

Abbruzzese G, Trompetto C. Clinical and research methods for evaluating cortical excitability. J Clin Neurophysiol 2002; 19: 307-21.

American Academy of Neurology Practice. Practice parameter: the management of concussion in sports (summary statement). Report of the Quality Standards Subcommittee. Neurology 1997; 48: 581-5.

Arriagada PV, Marzloff K, Hyman BT. Distribution of Alzheimer-type pathologic changes in nondemented elderly individuals matches the pattern in Alzheimer's disease. Neurology 1992; 42: 1681-8.

Barbeau E, Didic M, Tramoni E, Felician O, Joubert S, Sontheimer A, et al. Evaluation of visual recognition memory in MCI patients. Neurology 2004; 62: 1317-22.

Barth J, Alves W, Ryans T, Macchiocchi S, Rimel R, Jane J, et al. Mild head injury in sports: neuropsychological sequelae and recovery of function. J Cogn Neurorehab 1989; 26: 451-478.

Beuter A, de Geoffroy A, Edwards R. Analysis of rapid alternating movements in Cree subjects exposed to methylmercury and in subjects with neurological deficits. Environ Res 1999; 80: 64-79.

Borenstein AR, Copenhaver CI, Mortimer JA. Early-life risk factors for Alzheimer disease. Alzheimer Dis Assoc Disord 2006; 20: 63-72.

Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 1991; 82: 239-59.

Braekhus A, Laake K, Engedal K. A low, 'normal' score on the Mini-Mental State Examination predicts development of dementia after three years. J Am Geriatr Soc 1995; 43: 656-61.

Cantello R. Applications of transcranial magnetic stimulation in movement disorders. J Clin Neurophysiol 2002; 19: 272-93.

Cantello R, Tarletti R, Civardi C. Transcranial magnetic stimulation and Parkinson's disease. Brain Res Brain Res Rev 2002; 38: 309-27.

Catano A, Houa M, Noel P. Magnetic transcranial stimulation: clinical interest of the silent period in acute and chronic stages of stroke. Electroencephalogr Clin Neurophysiol 1997; 105: 290-6.

Catena RD, van Donkelaar P, Chou LS. Cognitive task effects on gait stability following concussion. Exp Brain Res 2007; 176: 23-31.

Chistyakov AV, Soustiel JF, Hafner H, Trubnik M, Levy G, Feinsod M. Excitatory and inhibitory corticospinal responses to transcranial magnetic stimulation in patients with minor to moderate head injury. J Neurol Neurosurg Psychiatry 2001; 70: 580-7.

Cohen J, Polich J. On the number of trials needed for P300. Int J Psychophysiol 1997; 25: 249-55.

Collins MW, Lovell MR, Iverson GL, Cantu RC, Maroon JC, Field M. Cumulative effects of concussion in high school athletes. Neurosurgery 2002; 51: 1175-9; discussion 1180-1.

Comerchero MD, Polich J. P3a and P3b from typical auditory and visual stimuli. Clin Neurophysiol 1999; 110: 24-30.

Cooper R, Osselton JW, Shaw JC. EEG Technology (3rd edn). London: Butterworths, 1980.

Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level. Jama 1993; 269: 2386-91.

De Beaumont L, Brisson B, Lassonde M, Jolicoeur P. Long-term electrophysiological changes in athletes with a history of multiple concussions. Brain Inj 2007a; 21: 631-44.

De Beaumont L, Lassonde M, Leclerc S, Theoret H. Long-term and cumulative effects of sports concussion on motor cortex inhibition. Neurosurgery 2007b; 61: 329-36; discussion 336-7.

Delacourte A, David JP, Sergeant N, Buee L, Wattez A, Vermersch P, et al. The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. Neurology 1999; 52: 1158-65.

Donchin E, Coles M. Is the P300 component a manifestation of context updating? Behavior and Brain Science 1988; 11: 357-374.

Duncan-Johnson CC, Donchin E. On quantifying surprise: the variation of event-related potentials with subjective probability. Psychophysiology 1977; 14: 456-67.

Duncan-Johnson CC, Donchin E. The relation of P300 latency to reaction time as a function of expectancy. Prog Brain Res 1980; 54: 717-22.

Dupuis F, Johnston KM, Lavoie M, Lepore F, Lassonde M. Concussions in athletes produce brain dysfunction as revealed by event-related potentials. Neuroreport 2000; 11: 4087-92.

Emmerson RY, Dustman RE, Shearer DE, Turner CW. P3 latency and symbol digit performance correlations in aging. Exp Aging Res 1989; 15: 151-9.

Eriksen CW, Eriksen BA. Effects of noise letters upon the identification letter in a nonsearch task. Perception & Psychophysics 1974; 16: 143-149.

Eriksen CW, Schultz DW. Information processing in visual search: a continuous flow conception and experimental results. Percept Psychophys 1979; 25: 249-63.

Fjell AM, Walhovd KB. Life-span changes in P3a. Psychophysiology 2004; 41: 575-83.

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189-98.

Gaetz M, Weinberg H. Electrophysiological indices of persistent post-concussion symptoms. Brain Inj 2000; 14: 815-32.

Gerberich SG, Priest JD, Boen JR, Straub CP, Maxwell RE. Concussion incidences and severity in secondary school varsity football players. Am J Public Health 1983; 73: 1370-5.

Golob EJ, Irimajiri R, Starr A. Auditory cortical activity in amnestic mild cognitive impairment: relationship to subtype and conversion to dementia. Brain 2007; 130: 740-52.

Gosselin N, Theriault M, Leclerc S, Montplaisir J, Lassonde M. Neurophysiological anomalies in symptomatic and asymptomatic concussed athletes. Neurosurgery 2006; 58: 1151-61; discussion 1151-61.

Gray C, Cantagallo A, Della Sala S, Basaglia N. Bradykinesia and bradyphrenia revisited: patterns of subclinical deficit in motor speed and cognitive functioning in head-injured patients with good recovery. Brain Inj 1998; 12: 429-41.

Guo Z, Cupples LA, Kurz A, Auerbach SH, Volicer L, Chui H, et al. Head injury and the risk of AD in the MIRAGE study. Neurology 2000; 54: 1316-23.

Guskiewicz KM. No evidence of impaired neurocognitive performance in collegiate soccer players. Am J Sports Med 2002; 30: 630.

Guskiewicz KM, Marshall SW, Bailes J, McCrea M, Cantu RC, Randolph C, et al. Association between recurrent concussion and late-life cognitive impairment in retired professional football players. Neurosurgery 2005; 57: 719-26; discussion 719-26.

Guskiewicz KM, McCrea M, Marshall SW, Cantu RC, Randolph C, Barr W, et al. Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA Concussion Study. Jama 2003; 290: 2549-55.

Heyman A, Wilkinson WE, Stafford JA, Helms MJ, Sigmon AH, Weinberg T. Alzheimer's disease: a study of epidemiological aspects. Ann Neurol 1984; 15: 335-41.

Ilan AB, Polich J. P300 and response time from a manual Stroop task. Clin Neurophysiol 1999; 110: 367-73.

Johnson R, Jr., Donchin E. On how P300 amplitude varies with the utility of the eliciting stimuli. Electroencephalogr Clin Neurophysiol 1978; 44: 424-37.

Kasai M, Meguro K, Hashimoto R, Ishizaki J, Yamadori A, Mori E. Non-verbal learning is impaired in very mild Alzheimer's disease (CDR 0.5): normative data from the learning version of the Rey-Osterrieth Complex Figure Test. Psychiatry Clin Neurosci 2006; 60: 139-46.

Kelly JP. Traumatic brain injury and concussion in sports. Jama 1999; 282: 989-91.

Kobori N, Dash PK. Reversal of brain injury-induced prefrontal glutamic acid decarboxylase expression and working memory deficits by D1 receptor antagonism. J Neurosci 2006; 26: 4236-46.

Koop MM, Shivitz N, Bronte-Stewart H. Quantitative measures of fine motor, limb, and postural bradykinesia in very early stage, untreated Parkinson's disease. Mov Disord 2008; 23: 1262-8.

Kopp B, Tabeling S, Moschner C, Wessel K. Fractionating the neural mechanisms of cognitive control. J Cogn Neurosci 2006; 18: 949-65.

Kramer AF, Strayer DL. Assessing the development of automatic processing: an application of dual-task and event-related brain potential methodologies. Biol Psychol 1988; 26: 231-67.

Kraus MF, Susmaras, T, Caughlin, B P, Walker, C J, Sweeney, J A, Little, D M. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. Brain 2007; 130: 2508-2519.

Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, et al. Corticocortical inhibition in human motor cortex. J Physiol 1993; 471: 501-19.

Kutas M, McCarthy G, Donchin E. Augmenting mental chronometry: the P300 as a measure of stimulus evaluation time. Science 1977; 197: 792-5.

Lavoie ME, Dupuis F, Johnston KM, Leclerc S, Lassonde M. Visual p300 effects beyond symptoms in concussed college athletes. J Clin Exp Neuropsychol 2004; 26: 55-73.

Lefaucheur JP, Menard-Lefaucheur I, Maison P, Baudic S, Cesaro P, Peschanski M, et al. Electrophysiological deterioration over time in patients with Huntington's disease. Mov Disord 2006; 21: 1350-4.

Lezak MD. Neuropsychyological Assessment (3rd edition). New York: Oxford University Press, 1995.

Lindsay J, Laurin D, Verreault R, Hebert R, Helliwell B, Hill GB, et al. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol 2002; 156: 445-53.

Liotti M, Pliszka SR, Perez R, Kothmann D, Woldorff MG. Abnormal brain activity related to performance monitoring and error detection in children with ADHD. Cortex 2005; 41: 377-88.

Macdonell RA, King MA, Newton MR, Curatolo JM, Reutens DC, Berkovic SF. Prolonged cortical silent period after transcranial magnetic stimulation in generalized epilepsy. Neurology 2001; 57: 706-8.

Mayes AR, Holdstock JS, Isaac CL, Hunkin NM, Roberts N. Relative sparing of item recognition memory in a patient with adult-onset damage limited to the hippocampus. Hippocampus 2002; 12: 325-40.

McCarthy G, Donchin E. A metric for thought: a comparison of P300 latency and reaction time. Science 1981; 211: 77-80.

McCrory P, Johnston K, Meeuwisse W, Aubry M, Cantu R, Dvorak J, et al. Summary and agreement statement of the 2nd International Conference on Concussion in Sport, Prague 2004. Clin J Sport Med 2005; 15: 48-55.

McDonnell MN, Orekhov Y, Ziemann U. The role of GABA(B) receptors in intracortical inhibition in the human motor cortex. Exp Brain Res 2006; 173: 86-93.

Meunier M, Bachevalier J, Mishkin M, Murray EA. Effects on visual recognition of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkeys. J Neurosci 1993; 13: 5418-32.

Moller B, Light GA, Fitzgerald PB, Snyder JS, Chen R, Daskalakis ZJ. Relationship between P50 suppression and the cortical silent period. Neuroreport 2007; 18: 1503-1506.

Mortimer JA, French LR, Hutton JT, Schuman LM. Head injury as a risk factor for Alzheimer's disease. Neurology 1985; 35: 264-7.

Murray EA, Mishkin M. Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. J Neurosci 1998; 18: 6568-82.

Nordby H, Hugdahl K, Jasiukaitis P, Spiegel D. Effects of hypnotizability on performance of a Stroop task and event-related potentials. Percept Mot Skills 1999; 88: 819-30.

Oechsner M, Zangemeister WH. Prolonged postexcitatory inhibition after transcranial magnetic stimulation of the motor cortex in patients with cerebellar ataxia. J Neurol Sci 1999; 168: 107-11.

Okada M, Okada M. A method for quantification of alternate pronation and supination of forearms. Comput Biomed Res 1983; 16: 59-78.

Parker TM, Osternig LR, Van Donkelaar P, Chou LS. Gait stability following concussion. Med Sci Sports Exerc 2006; 38: 1032-40.

Pascual JM, Solivera J, Prieto R, Barrios L, Lopez-Larrubia P, Cerdan S, et al. Time course of early metabolic changes following diffuse traumatic brain injury in rats as detected by (1)H NMR spectroscopy. J Neurotrauma 2007; 24: 944-59.

Pfefferbaum A, Christensen C, Ford JM, Kopell BS. Apparent response incompatibility effects on P3 latency depend on the task. Electroencephalogr Clin Neurophysiol 1986; 64: 424-37.

Picton TW. The P300 wave of the human event-related potential. J Clin Neurophysiol 1992; 9: 456-79.

Pierantozzi M, Marciani MG, Palmieri MG, Brusa L, Galati S, Caramia MD, et al. Effect of Vigabatrin on motor responses to transcranial magnetic stimulation: an effective tool to investigate in vivo GABAergic cortical inhibition in humans. Brain Res 2004; 1028: 1-8.

Plassman BL, Havlik RJ, Steffens DC, Helms MJ, Newman TN, Drosdick D, et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology 2000; 55: 1158-66.

Polich J. Normal variation of P300 from auditory stimuli. Electroencephalogr Clin Neurophysiol 1986; 65: 236-40.

Polich J. Bifurcated P300 peaks: P3a and P3b revisited? J Clin Neurophysiol 1988; 5: 287-94.

Polich J. Clinical application of the P300 event-related brain potential. Phys Med Rehabil Clin N Am 2004; 15: 133-61.

Polich J, Corey-Bloom J. Alzheimer's disease and P300: review and evaluation of task and modality. Curr Alzheimer Res 2005; 2: 515-25.

Polich J, Howard L, Starr A. P300 latency correlates with digit span. Psychophysiology 1983; 20: 665-9.

Potter DD, Bassett MR, Jory SH, Barrett K. Changes in event-related potentials in a three-stimulus auditory oddball task after mild head injury. Neuropsychologia 2001; 39: 1464-72.

Rabadi MH, Jordan BD. The cumulative effect of repetitive concussion in sports. Clin J Sport Med 2001; 11: 194-8.

Reinvang I. Cognitive event-related potentials in neuropsychological assessment. Neuropsychol Rev 1999; 9: 231-48.

Reinvang I, Nordby H, Nielsen CS. Information processing deficits in head injury assessed with ERPs reflecting early and late processing stages. Neuropsychologia 2000; 38: 995-1005.

Reis J, Swayne OB, Vandermeeren Y, Camus M, Dimyan MA, Harris-Love M, et al. Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. J Physiol 2008; 586: 325-51.

Restivo DA, Lanza S, Giuffrida S, Le Pira F, Drago MT, Di Mauro R, et al. Cortical silent period prolongation in spinocerebellar ataxia type 2 (SCA2). Funct Neurol 2004; 19: 37-41.

Reynolds GP, Pearson SJ. Neurochemical-clinical correlates in Huntington's disease--applications of brain banking techniques. J Neural Transm Suppl 1993; 39: 207-14.

Riis JL, Chong H, Ryan KK, Wolk DA, Rentz DM, Holcomb PJ, et al. Compensatory neural activity distinguishes different patterns of normal cognitive aging. Neuroimage 2008; 39: 441-54.

Selkoe DJ. Alzheimer's disease. In the beginning. Nature 1991; 354: 432-3.

Siebner HR, Dressnandt J, Auer C, Conrad B. Continuous intrathecal baclofen infusions induced a marked increase of the transcranially evoked silent period in a patient with generalized dystonia. Muscle Nerve 1998; 21: 1209-12.

Slobounov S, Slobounov, E, Sebastianelli, W, Cao, C, Newell, K. Differential rate of recovery in athletes after first and second concussion episodes. Neurosurgery 2007; 61: 338-344.

Solbakk AK, Reinvang I, Andersson S. Assessment of P3a and P3b after moderate to severe brain injury. Clin Electroencephalogr 2002; 33: 102-10.

Solbakk AK, Reinvang I, Nielsen C, Sundet K. ERP indicators of disturbed attention in mild closed head injury: a frontal lobe syndrome? Psychophysiology 1999; 36: 802-17.

Squire LR, Zola SM. Structure and function of declarative and nondeclarative memory systems. Proc Natl Acad Sci U S A 1996; 93: 13515-22.

Tataroglu C, Ozkiziltan S, Baklan B. Motor cortical thresholds and cortical silent periods in epilepsy. Seizure 2004; 13: 481-5.

Tinazzi M, Farina S, Edwards M, Moretto G, Restivo D, Fiaschi A, et al. Task-specific impairment of motor cortical excitation and inhibition in patients with writer's cramp. Neurosci Lett 2005; 378: 55-8.

Van Hoesen GW, Hyman BT, Damasio AR. Entorhinal cortex pathology in Alzheimer's disease. Hippocampus 1991; 1: 1-8.

Ward AA, Jr. The physiology of concussion. Clin Neurosurg 1964; 12: 95-111.

Werhahn KJ, Kunesch E, Noachtar S, Benecke R, Classen J. Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. J Physiol 1999; 517 (Pt 2): 591-7.

Werner RA, Vanderzant CW. Multimodality evoked potential testing in acute mild closed head injury. Arch Phys Med Rehabil 1991; 72: 31-4.

Wickens C, Kramer A, Vanasse L, Donchin E. Performance of concurrent tasks: a psychophysiological analysis of the reciprocity of information-processing resources. Science 1983; 221: 1080-2.

Wylie SA, Ridderinkhof KR, Eckerle MK, Manning CA. Inefficient response inhibition in individuals with mild cognitive impairment. Neuropsychologia 2007; 45: 1408-19.

Ziemann U. TMS and drugs. Clin Neurophysiol 2004; 115: 1717-29.

7.6. Discussion

Abbruzzese, G., & Trompetto, C. (2002). Clinical and research methods for evaluating cortical excitability. *J Clin Neurophysiol, 19*(4), 307-321.

American Academy of Neurology Practice. (1997). Practice parameter: the management of concussion in sports (summary statement). Report of the Quality Standards Subcommittee. *Neurology, 48*(3), 581-585.

Arriagada, P. V., Marzloff, K., & Hyman, B. T. (1992). Distribution of Alzheimer-type pathologic changes in nondemented elderly individuals matches the pattern in Alzheimer's disease. *Neurology, 42*(9), 1681-1688.

Aubry, M., Cantu, R., Dvorak, J., Graf-Baumann, T., Johnston, K., Kelly, J., et al. (2002). Summary and agreement statement of the First International Conference on Concussion in Sport, Vienna 2001. Recommendations for the improvement of safety and health of athletes who may suffer concussive injuries. *Br J Sports Med, 36*(1), 6-10.

Awasthi, D., Church, D. F., Torbati, D., Carey, M. E., & Pryor, W. A. (1997). Oxidative stress following traumatic brain injury in rats. *Surg Neurol, 47*(6), 575-581; discussion 581-572.

Barbeau, E., Didic, M., Tramoni, E., Felician, O., Joubert, S., Sontheimer, A., et al. (2004). Evaluation of visual recognition memory in MCI patients. *Neurology, 62*(8), 1317-1322.

Barth, J., Alves, W., Ryans, T., Macchiocchi, S., Rimel, R., Jane, J., et al. (1989). Mild head injury in sports: neuropsychological sequelae and recovery of function. *J Cogn Neurorehab, 26*, 451-478.

Bayly, P. V., Black, E. E., Pedersen, R. C., Leister, E. P., & Genin, G. M. (2006). In vivo imaging of rapid deformation and strain in an animal model of traumatic brain injury. *J Biomech, 39*(6), 1086-1095.

Bayly, P. V., Cohen, T. S., Leister, E. P., Ajo, D., Leuthardt, E. C., & Genin, G. M. (2005). Deformation of the human brain induced by mild acceleration. *J Neurotrauma, 22*(8), 845-856.

Besenski, N. (2002). Traumatic injuries: imaging of head injuries. *Eur Radiol, 12*(6), 1237-1252.

Besenski, N., Broz, R., Jadro-Santel, D., Pavic, D., & Mikulic, D. (1996). The course of the traumatising force in acceleration head injury: CT evidence. *Neuroradiology, 38 Suppl 1*, S36-41.

Beuter, A., de Geoffroy, A., & Edwards, R. (1999). Analysis of rapid alternating movements in Cree subjects exposed to methylmercury and in subjects with neurological deficits. *Environ Res, 80*(1), 64-79.

Bleiberg, J., Cernich, A. N., Cameron, K., Sun, W., Peck, K., Ecklund, P. J., et al. (2004). Duration of cognitive impairment after sports concussion. *Neurosurgery, 54*(5), 1073-1078; discussion 1078-1080.

Borenstein, A. R., Copenhaver, C. I., & Mortimer, J. A. (2006). Early-life risk factors for Alzheimer disease. *Alzheimer Dis Assoc Disord, 20*(1), 63-72.

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol, 82*(4), 239-259.

Braekhus, A., Laake, K., & Engedal, K. (1995). A low, 'normal' score on the Mini-Mental State Examination predicts development of dementia after three years. *J Am Geriatr Soc, 43*(6), 656-661.

Broglio, S. P., Sosnoff, J. J., Shin, S., He, X., Alcaraz, C., & Zimmerman, J. (2009). Head impacts during high school football: a biomechanical assessment. *J Athl Train, 44*(4), 342-349.

Cantello, R. (2002). Applications of transcranial magnetic stimulation in movement disorders. *J Clin Neurophysiol, 19*(4), 272-293.

Cantello, R., Tarletti, R., & Civardi, C. (2002). Transcranial magnetic stimulation and Parkinson's disease. *Brain Res Brain Res Rev, 38*(3), 309-327.

Cantello, R., Tarletti, R., Varrasi, C., Cecchin, M., & Monaco, F. (2007). Cortical inhibition in Parkinson's disease: new insights from early, untreated patients. *Neuroscience, 150*(1), 64-71.

Cantu, R. C. (1992). Cerebral concussion in sport. Management and prevention. *Sports Med, 14*(1), 64-74.

Cantu, R. C. (1998). Second impact syndrome. *Clinical Journal of Sports Medicine, 17*(1), 37-44.

Catano, A., Houa, M., & Noel, P. (1997). Magnetic transcranial stimulation: clinical interest of the silent period in acute and chronic stages of stroke. *Electroencephalogr Clin Neurophysiol, 105*(4), 290-296.

Catena, R. D., van Donkelaar, P., & Chou, L. S. (2007a). Altered balance control following concussion is better detected with an attention test during gait. *Gait Posture, 25*(3), 406-411.

Catena, R. D., van Donkelaar, P., & Chou, L. S. (2007b). Cognitive task effects on gait stability following concussion. *Exp Brain Res, 176*(1), 23-31.

Cavanaugh, J. T., Guskiewicz, K. M., Giuliani, C., Marshall, S., Mercer, V., & Stergiou, N. (2005). Detecting altered postural control after cerebral concussion in athletes with normal postural stability. *Br J Sports Med, 39*(11), 805-811.

Cavanaugh, J. T., Guskiewicz, K. M., Giuliani, C., Marshall, S., Mercer, V. S., & Stergiou, N. (2006). Recovery of postural control after cerebral concussion: new insights using approximate entropy. *J Athl Train, 41*(3), 305-313.

Cavanaugh, J. T., Guskiewicz, K. M., & Stergiou, N. (2005). A nonlinear dynamic approach for evaluating postural control: new directions for the management of sport-related cerebral concussion. *Sports Med, 35*(11), 935-950.

Chen, J. K., Johnston, K. M., Frey, S., Petrides, M., Worsley, K., & Ptito, A. (2004). Functional abnormalities in symptomatic concussed athletes: an fMRI study. *Neuroimage, 22*(1), 68-82.

Chen, K., Li, H. Z., Ye, N., Zhang, J., & Wang, J. J. (2005). Role of GABAB receptors in GABA and baclofen-induced inhibition of adult rat cerebellar interpositus nucleus neurons in vitro. *Brain Res Bull, 67*(4), 310-318.

Chistyakov, A. V., Soustiel, J. F., Hafner, H., Trubnik, M., Levy, G., & Feinsod, M. (2001). Excitatory and inhibitory corticospinal responses to transcranial magnetic stimulation in patients with minor to moderate head injury. *J Neurol Neurosurg Psychiatry, 70*(5), 580-587.

Cohen, J., & Polich, J. (1997). On the number of trials needed for P300. *Int J Psychophysiol, 25*(3), 249-255.

Collins, M. W., Grindel, S. H., Lovell, M. R., Dede, D. E., Moser, D. J., Phalin, B. R., et al. (1999). Relationship between concussion and neuropsychological performance in college football players. *Jama, 282*(10), 964-970.

Collins, M. W., Iverson, G. L., Lovell, M. R., McKeag, D. B., Norwig, J., & Maroon, J. (2003). On-field predictors of neuropsychological and symptom deficit following sports-related concussion. *Clin J Sport Med, 13*(4), 222-229.

Collins, M. W., Lovell, M. R., Iverson, G. L., Cantu, R. C., Maroon, J. C., & Field, M. (2002). Cumulative effects of concussion in high school athletes. *Neurosurgery, 51*(5), 1175-1179; discussion 1180-1171.

Collins, M. W., Lovell, M. R., & McKeag, D. B. (1999). Current issues in managing sports-related concussion. *Jama, 282*(24), 2283-2285.

Comerchero, M. D., & Polich, J. (1999). P3a and P3b from typical auditory and visual stimuli. *Clin Neurophysiol, 110*(1), 24-30.

Control, N. C. f. I. P. a. (2003). Report to Congress on Mild Traumatic Brain Injury in the United States: Steps to Prevent a Serious Public Health Problem. . In. Atlanta: Centers for Disease Control and Prevention.

Cooper, R., Osselton, J. W., & Shaw, J. C. (1980). *EEG Technology (3rd edn)*. London: Butterworths.

Courville, C. B. (1953). The functional and structural bases for psychic phenomena consequent to cerebral concussion. *J Nerv Ment Dis, 118*(5), 447-454.

Craik, F. I., & Bialystok, E. (2006). Cognition through the lifespan: mechanisms of change. *Trends Cogn Sci, 10*(3), 131-138.

Craik, F. I., & Salthouse, T. A. (1999). *The Handbook of Aging and Cognition* (2nd edition ed.). Mahwah: Lawrence Erlbaum Associates

Crum, R. M., Anthony, J. C., Bassett, S. S., & Folstein, M. F. (1993). Population-based norms for the Mini-Mental State Examination by age and educational level. *Jama, 269*(18), 2386-2391.

Davies, C. H., Starkey, S. J., Pozza, M. F., & Collingridge, G. L. (1991). GABA autoreceptors regulate the induction of LTP. *Nature, 349*(6310), 609-611.

De Beaumont, L., Brisson, B., Lassonde, M., & Jolicoeur, P. (2007). Long-term electrophysiological changes in athletes with a history of multiple concussions. *Brain Inj, 21*(6), 631-644.

De Beaumont, L., Lassonde, M., Leclerc, S., & Theoret, H. (2007). Long-term and cumulative effects of sports concussion on motor cortex inhibition. *Neurosurgery, 61*(2), 329-336; discussion 336-327.

De Beaumont, L., Theoret, H., Mongeon, D., Messier, J., Leclerc, S., Tremblay, S., et al. (2009). Brain function decline in healthy retired athletes who sustained their last sports concussion in early adulthood. *Brain, 132*(Pt 3), 695-708.

Delacourte, A., David, J. P., Sergeant, N., Buee, L., Wattez, A., Vermersch, P., et al. (1999). The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. *Neurology, 52*(6), 1158-1165.

Delaney, J. S. (2004). Head injuries presenting to emergency departments in the United States from 1990 to 1999 for ice hockey, soccer, and football. *Clin J Sport Med, 14*(2), 80-87.

Delaney, J. S., Lacroix, V. J., Leclerc, S., & Johnston, K. M. (2000). Concussions during the 1997 Canadian Football League season. *Clin J Sport Med, 10*(1), 9-14.

Delaney, J. S., Lacroix, V. J., Leclerc, S., & Johnston, K. M. (2002). Concussions among university football and soccer players. *Clin J Sport Med, 12*(6), 331-338.

Deng, Y., Thompson, B. M., Gao, X., & Hall, E. D. (2007). Temporal relationship of peroxynitrite-induced oxidative damage, calpain-mediated cytoskeletal degradation and neurodegeneration after traumatic brain injury. *Exp Neurol, 205*(1), 154-165.

Derejko, M., Niewiadomska, M., & Rakowicz, M. (2005). [The diagnostic and therapeutic application of transcranial magnetic stimulation]. *Neurol Neurochir Pol, 39*(5), 389-396.

Donchin, E., & Coles, M. (1988). Is the P300 component a manifestation of context updating? *Behavior and Brain Science, 11*, 357-374.

Duncan-Johnson, C. C., & Donchin, E. (1977). On quantifying surprise: the variation of event-related potentials with subjective probability. *Psychophysiology, 14*(5), 456-467.

Duncan-Johnson, C. C., & Donchin, E. (1980). The relation of P300 latency to reaction time as a function of expectancy. *Prog Brain Res, 54*, 717-722.

Dupuis, F., Johnston, K. M., Lavoie, M., Lepore, F., & Lassonde, M. (2000). Concussions in athletes produce brain dysfunction as revealed by event-related potentials. *Neuroreport, 11*(18), 4087-4092.

Echemendia, R. J. (Ed.). (2006). *Sports Neuropsychology* (1 ed. Vol. 1). New York: Guilford Press.

Echemendia, R. J., Putukian, M., Mackin, R. S., Julian, L., & Shoss, N. (2001). Neuropsychological test performance prior to and following sports-related mild traumatic brain injury. *Clin J Sport Med, 11*(1), 23-31.

Eimer, M. (1996). The N2pc component as an indicator of attentional selectivity. *Electroencephalogr Clin Neurophysiol, 99*(3), 225-234.

Emmerling, M. R., Morganti-Kossmann, M. C., Kossmann, T., Stahel, P. F., Watson, M. D., Evans, L. M., et al. (2000). Traumatic brain injury elevates the Alzheimer's amyloid peptide A beta 42 in human CSF. A possible role for nerve cell injury. *Ann N Y Acad Sci, 903*, 118-122.

Emmerson, R. Y., Dustman, R. E., Shearer, D. E., & Turner, C. W. (1989). P3 latency and symbol digit performance correlations in aging. *Exp Aging Res, 15*(3-4), 151-159.

Eriksen, C. W., & Eriksen, B. A. (1974). Effects of noise letters upon the identification letter in a nonsearch task. *Perception & Psychophysics, 16*, 143-149.

Eriksen, C. W., & Schultz, D. W. (1979). Information processing in visual search: a continuous flow conception and experimental results. *Percept Psychophys, 25*(4), 249-263.

Fitzgerald, P. B., Fountain, S., & Daskalakis, Z. J. (2006). A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clin Neurophysiol, 117*(12), 2584-2596.

Fjell, A. M., & Walhovd, K. B. (2004). Life-span changes in P3a. *Psychophysiology, 41*(4), 575-583.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res, 12*(3), 189-198.

Gaetz, M., & Bernstein, D. M. (2001). The current status of electrophysiologic procedures for the assessment of mild traumatic brain injury. *J Head Trauma Rehabil, 16*(4), 386-405.

Gaetz, M., Goodman, D., & Weinberg, H. (2000). Electrophysiological evidence for the cumulative effects of concussion. *Brain Inj, 14*(12), 1077-1088.

Gaetz, M., & Weinberg, H. (2000). Electrophysiological indices of persistent post-concussion symptoms. *Brain Inj, 14*(9), 815-832.

Garvey, M. A., Ziemann, U., Becker, D. A., Barker, C. A., & Bartko, J. J. (2001). New graphical method to measure silent periods evoked by transcranial magnetic stimulation. *Clin Neurophysiol, 112*(8), 1451-1460.

Gentry, L. R. (1994). Imaging of closed head injury. *Radiology, 191*(1), 1-17.

Gentry, L. R., Godersky, J. C., & Thompson, B. (1988). MR imaging of head trauma: review of the distribution and radiopathologic features of traumatic lesions. *AJR Am J Roentgenol, 150*(3), 663-672.

Gerberich, S. G., Priest, J. D., Boen, J. R., Straub, C. P., & Maxwell, R. E. (1983). Concussion incidences and severity in secondary school varsity football players. *Am J Public Health, 73*(12), 1370-1375.

Gessel, L. M., Fields, S. K., Collins, C. L., Dick, R. W., & Comstock, R. D. (2007). Concussions among United States high school and collegiate athletes. *J Athl Train, 42*(4), 495-503.

Geurts, A. C., de Haart, M., van Nes, I. J., & Duysens, J. (2005). A review of standing balance recovery from stroke. *Gait Posture, 22*(3), 267-281.

Giza, C. C., & Hovda, D. A. (2001). The Neurometabolic Cascade of Concussion. *J Athl Train, 36*(3), 228-235.

Golob, E. J., Irimajiri, R., & Starr, A. (2007). Auditory cortical activity in amnestic mild cognitive impairment: relationship to subtype and conversion to dementia. *Brain, 130*(Pt 3), 740-752.

Gosselin, N., Theriault, M., Leclerc, S., Montplaisir, J., & Lassonde, M. (2006). Neurophysiological anomalies in symptomatic and asymptomatic concussed athletes. *Neurosurgery, 58*(6), 1151-1161; discussion 1151-1161.

Gray, C., Cantagallo, A., Della Sala, S., & Basaglia, N. (1998). Bradykinesia and bradyphrenia revisited: patterns of subclinical deficit in motor speed and cognitive functioning in head-injured patients with good recovery. *Brain Inj, 12*(5), 429-441.

Greenwald, R. M., Gwin, J. T., Chu, J. J., & Crisco, J. J. (2008). Head impact severity measures for evaluating mild traumatic brain injury risk exposure. *Neurosurgery, 62*(4), 789-798; discussion 798.

Guerrero, J. L., Thurman, D. J., & Sniezek, J. E. (2000). Emergency department visits associated with traumatic brain injury: United States, 1995-1996. *Brain Inj, 14*(2), 181-186.

Guo, Z., Cupples, L. A., Kurz, A., Auerbach, S. H., Volicer, L., Chui, H., et al. (2000). Head injury and the risk of AD in the MIRAGE study. *Neurology, 54*(6), 1316-1323.

Guskiewicz, K. M. (2002). No evidence of impaired neurocognitive performance in collegiate soccer players. *Am J Sports Med, 30*(4), 630.

Guskiewicz, K. M., Marshall, S. W., Bailes, J., McCrea, M., Cantu, R. C., Randolph, C., et al. (2005). Association between recurrent concussion and late-life cognitive impairment in retired professional football players. *Neurosurgery, 57*(4), 719-726; discussion 719-726.

Guskiewicz, K. M., McCrea, M., Marshall, S. W., Cantu, R. C., Randolph, C., Barr, W., et al. (2003). Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA Concussion Study. *Jama, 290*(19), 2549-2555.

Guskiewicz, K. M., Perrin, D. H., & Gansneder, B. M. (1996). Effect of Mild Head Injury on Postural Stability in Athletes. *J Athl Train, 31*(4), 300-306.

Guskiewicz, K. M., Ross, S. E., & Marshall, S. W. (2001). Postural Stability and Neuropsychological Deficits After Concussion in Collegiate Athletes. *J Athl Train, 36*(3), 263-273.

Guskiewicz, K. M., Weaver, N. L., Padua, D. A., & Garrett, W. E., Jr. (2000). Epidemiology of concussion in collegiate and high school football players. *Am J Sports Med, 28*(5), 643-650.

Hashimoto, T., Nakamura, N., Richard, K. E., & Frowein, R. A. (1993). Primary brain stem lesions caused by closed head injuries. *Neurosurg Rev, 16*(4), 291-298.

Heinmiller, A., Ting, A. K. R., Vargas-Perez, H., Yeh, A., & van der Kooy, D. (2009). Tegmental pedunculopontine glutamate and GABA-B synapses mediate morphine reward. *Behav Neurosci, 123*(1), 145-155.

Heyman, A., Wilkinson, W. E., Stafford, J. A., Helms, M. J., Sigmon, A. H., & Weinberg, T. (1984). Alzheimer's disease: a study of epidemiological aspects. *Ann Neurol, 15*(4), 335-341.

Hinton-Bayre, A. D., & Geffen, G. (2002). Severity of sports-related concussion and neuropsychological test performance. *Neurology, 59*(7), 1068-1070.

Hovda, D. A., Lee, S. M., Smith, M. L., Von Stuck, S., Bergsneider, M., Kelly, D., et al. (1995). The neurochemical and metabolic cascade following brain injury: moving from animal models to man. *J Neurotrauma, 12*(5), 903-906.

Hyndman, D., Ashburn, A., Yardley, L., & Stack, E. (2006). Interference between balance, gait and cognitive task performance among people with stroke living in the community. *Disabil Rehabil, 28*(13-14), 849-856.

Ilan, A. B., & Polich, J. (1999). P300 and response time from a manual Stroop task. *Clin Neurophysiol, 110*(2), 367-373.

Iverson, G. L. (2005). Outcome from mild traumatic brain injury. *Curr Opin Psychiatry, 18*(3), 301-317.

Iverson, G. L. (2007). Predicting slow recovery from sport-related concussion: the new simple-complex distinction. *Clin J Sport Med, 17*(1), 31-37.

Iverson, G. L., Gaetz, M., Lovell, M. R., & Collins, M. W. (2004). Cumulative effects of concussion in amateur athletes. *Brain Inj, 18*(5), 433-443.

Jantzen, K. J., Anderson, B., Steinberg, F. L., & Kelso, J. A. (2004). A prospective functional MR imaging study of mild traumatic brain injury in college football players. *AJNR Am J Neuroradiol, 25*(5), 738-745.

Johnson, R., Jr., & Donchin, E. (1978). On how P300 amplitude varies with the utility of the eliciting stimuli. *Electroencephalogr Clin Neurophysiol, 44*(4), 424-437.

Jordan, B. D., Relkin, N. R., Ravdin, L. D., Jacobs, A. R., Bennett, A., & Gandy, S. (1997). Apolipoprotein E epsilon4 associated with chronic traumatic brain injury in boxing. *Jama, 278*(2), 136-140.

Kandel, E., Schwartz, J., & Jessell, T. (2000). *Principles of Neuroscience* (4th ed.). New York: McGraw-Hill.

Kasai, M., Meguro, K., Hashimoto, R., Ishizaki, J., Yamadori, A., & Mori, E. (2006). Non-verbal learning is impaired in very mild Alzheimer's disease (CDR 0.5): normative data from the learning version of the Rey-Osterrieth Complex Figure Test. *Psychiatry Clin Neurosci, 60*(2), 139-146.

Kelly, J. P. (1999). Traumatic brain injury and concussion in sports. *Jama, 282*(10), 989-991.

Khedr, E. M., Rothwell, J. C., Ahmed, M. A., Shawky, O. A., & Farouk, M. (2007). Modulation of motor cortical excitability following rapid-rate transcranial magnetic stimulation. *Clin Neurophysiol, 118*(1), 140-145.

Kobori, N., & Dash, P. K. (2006). Reversal of brain injury-induced prefrontal glutamic acid decarboxylase expression and working memory deficits by D1 receptor antagonism. *J Neurosci, 26*(16), 4236-4246.

Koop, M. M., Shivitz, N., & Bronte-Stewart, H. (2008). Quantitative measures of fine motor, limb, and postural bradykinesia in very early stage, untreated Parkinson's disease. *Mov Disord, 23*(9), 1262-1268.

Kopp, B., Tabeling, S., Moschner, C., & Wessel, K. (2006). Fractionating the neural mechanisms of cognitive control. *J Cogn Neurosci, 18*(6), 949-965.

Kramer, A. F., & Strayer, D. L. (1988). Assessing the development of automatic processing: an application of dual-task and event-related brain potential methodologies. *Biol Psychol, 26*(1-3), 231-267.

Kraus, J. F., & Nourjah, P. (1988). The epidemiology of mild, uncomplicated brain injury. *J Trauma, 28*(12), 1637-1643.

Kraus, M. F., Susmaras, T, Caughlin, B P, Walker, C J, Sweeney, J A, Little, D M. (2007). White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain, 130*, 2508-2519.

Kujirai, T., Caramia, M. D., Rothwell, J. C., Day, B. L., Thompson, P. D., Ferbert, A., et al. (1993). Corticocortical inhibition in human motor cortex. *J Physiol, 471*, 501-519.

Kutas, M., McCarthy, G., & Donchin, E. (1977). Augmenting mental chronometry: the P300 as a measure of stimulus evaluation time. *Science, 197*(4305), 792-795.

Lang, N., Sueske, E., Hasan, A., Paulus, W., & Tergau, F. (2006). Pregabalin exerts oppositional effects on different inhibitory circuits in human motor cortex: a double-blind, placebo-controlled transcranial magnetic stimulation study. *Epilepsia, 47*(5), 813-819.

Langlois, J. A., Rutland-Brown, W., & Wald, M. M. (2006). The epidemiology and impact of traumatic brain injury: a brief overview. *J Head Trauma Rehabil, 21*(5), 375-378.

Laurer, H. L., Bareyre, F. M., Lee, V. M., Trojanowski, J. Q., Longhi, L., Hoover, R., et al. (2001). Mild head injury increasing the brain's vulnerability to a second concussive impact. *J Neurosurg, 95*(5), 859-870.

Lavoie, M. E., Dupuis, F., Johnston, K. M., Leclerc, S., & Lassonde, M. (2004). Visual p300 effects beyond symptoms in concussed college athletes. *J Clin Exp Neuropsychol, 26*(1), 55-73.

Lefaucheur, J. P., Menard-Lefaucheur, I., Maison, P., Baudic, S., Cesaro, P., Peschanski, M., et al. (2006). Electrophysiological deterioration over time in patients with Huntington's disease. *Mov Disord, 21*(9), 1350-1354.

Levin, H. S. (1995). Neurobehavioral outcome of closed head injury: implications for clinical trials. *J Neurotrauma, 12*(4), 601-610.

Lezak, M. D. (1995). *Neuropsychyological Assessment (3rd edition)*. New York: Oxford University Press.

Liberman, J. N., Stewart, W. F., Wesnes, K., & Troncoso, J. (2002). Apolipoprotein E epsilon 4 and short-term recovery from predominantly mild brain injury. *Neurology, 58*(7), 1038-1044.

Lind, J., Larsson, A., Persson, J., Ingvar, M., Nilsson, L. G., Backman, L., et al. (2006). Reduced hippocampal volume in non-demented carriers of the apolipoprotein E epsilon4: relation to chronological age and recognition memory. *Neurosci Lett, 396*(1), 23-27.

Lindsay, J., Laurin, D., Verreault, R., Hebert, R., Helliwell, B., Hill, G. B., et al. (2002). Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol, 156*(5), 445-453.

Liotti, M., Pliszka, S. R., Perez, R., Kothmann, D., & Woldorff, M. G. (2005). Abnormal brain activity related to performance monitoring and error detection in children with ADHD. *Cortex, 41*(3), 377-388.

Lovell, M. R., Iverson, G. L., Collins, M. W., McKeag, D., & Maroon, J. C. (1999). Does loss of consciousness predict neuropsychological decrements after concussion? *Clin J Sport Med, 9*(4), 193-198.

Lovell, M. R., Pardini, J. E., Welling, J., Collins, M. W., Bakal, J., Lazar, N., et al. (2007). Functional brain abnormalities are related to clinical recovery and time to return-to-play in athletes. *Neurosurgery, 61*(2), 352-359; discussion 359-360.

Luck, S. J., Chelazzi, L., Hillyard, S. A., & Desimone, R. (1997). Neural mechanisms of spatial selective attention in areas V1, V2, and V4 of macaque visual cortex. *J Neurophysiol, 77*(1), 24-42.

Luck, S. J., & Hillyard, S. A. (1994a). Electrophysiological correlates of feature analysis during visual search. *Psychophysiology, 31*(3), 291-308.

Luck, S. J., & Hillyard, S. A. (1994b). Spatial filtering during visual search: evidence from human electrophysiology. *J Exp Psychol Hum Percept Perform, 20*(5), 1000-1014.

Lum, J., Enns, J. T., & Pratt, J. (2002). Visual orienting in college athletes: explorations of athlete type and gender. *Res Q Exerc Sport, 73*(2), 156-167.

Mac Donald, C. L., Dikranian, K., Song, S. K., Bayly, P. V., Holtzman, D. M., & Brody, D. L. (2007). Detection of traumatic axonal injury with diffusion tensor imaging in a mouse model of traumatic brain injury. *Exp Neurol, 205*(1), 116-131.

Macdonell, R. A., King, M. A., Newton, M. R., Curatolo, J. M., Reutens, D. C., & Berkovic, S. F. (2001). Prolonged cortical silent period after transcranial magnetic stimulation in generalized epilepsy. *Neurology, 57*(4), 706-708.

Maddocks, D. L., Dicker, G. D., & Saling, M. M. (1995). The assessment of orientation following concussion in athletes. *Clin J Sport Med, 5*(1), 32-35.

Marazioti, A., Spyraki, C., & Thermos, K. (2009). GABA antagonists reverse the somatostatin dependent attenuation of rat locomotor activity. *Neuropeptides, 43*(3), 207-212.

Maroon, J. C., Lovell, M. R., Norwig, J., Podell, K., Powell, J. W., & Hartl, R. (2000). Cerebral concussion in athletes: evaluation and neuropsychological testing. *Neurosurgery, 47*(3), 659-669; discussion 669-672.

Mayers, L. (2008). Return-to-play criteria after athletic concussion: a need for revision. *Arch Neurol, 65*(9), 1158-1161.

Mayes, A. R., Holdstock, J. S., Isaac, C. L., Hunkin, N. M., & Roberts, N. (2002). Relative sparing of item recognition memory in a patient with adult-onset damage limited to the hippocampus. *Hippocampus, 12*(3), 325-340.

McAllister, T. W., Sparling, M. B., Flashman, L. A., Guerin, S. J., Mamourian, A. C., & Saykin, A. J. (2001). Differential working memory load effects after mild traumatic brain injury. *Neuroimage, 14*(5), 1004-1012.

McAuliffe, J. (2004). Differences in attentional set between athletes and nonathletes. *J Gen Psychol, 131*(4), 426-437.

McCarthy, G., & Donchin, E. (1981). A metric for thought: a comparison of P300 latency and reaction time. *Science, 211*(4477), 77-80.

McCrea, M., Guskiewicz, K. M., Marshall, S. W., Barr, W., Randolph, C., Cantu, R. C., et al. (2003). Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. *Jama, 290*(19), 2556-2563.

McCrea, M., Hammeke, T., Olsen, G., Leo, P., & Guskiewicz, K. (2004). Unreported concussion in high school football players: implications for prevention. *Clin J Sport Med, 14*(1), 13-17.

McCrea, M., Kelly, J. P., Kluge, J., Ackley, B., & Randolph, C. (1997). Standardized assessment of concussion in football players. *Neurology, 48*(3), 586-588.

McCrea, M., Kelly, J. P., Randolph, C., Cisler, R., & Berger, L. (2002). Immediate neurocognitive effects of concussion. *Neurosurgery, 50*(5), 1032-1040; discussion 1040-1032.

McCrea, M., Kelly, J. P., Randolph, C., Kluge, J., Bartolic, E., Finn, G., et al. (1998). Standardized assessment of concussion (SAC): on-site mental status evaluation of the athlete. *J Head Trauma Rehabil, 13*(2), 27-35.

McCrory, P. (2000). Headaches and exercise. *Sports Med, 30*(3), 221-229.

McCrory, P. (2001a). Does second impact syndrome exist? *Clin J Sport Med, 11*(3), 144-149.

McCrory, P. (2001b). Headache in sport. *Br J Sports Med, 35*(5), 286-287.

McCrory, P., Johnston, K., Meeuwisse, W., Aubry, M., Cantu, R., Dvorak, J., et al. (2005). Summary and agreement statement of the 2nd International Conference on Concussion in Sport, Prague 2004. *Br J Sports Med, 39*(4), 196-204.

McCrory, P. R. (1999). You can run but you can't hide: the role of concussion severity scales in sport. *Br J Sports Med, 33*(5), 297-298.

McCrory, P. R., Ariens, T., & Berkovic, S. F. (2000). The nature and duration of acute concussive symptoms in Australian football. *Clin J Sport Med, 10*(4), 235-238.

McCrory, P. R., & Berkovic, S. F. (1998). Second impact syndrome. *Neurology, 50*(3), 677-683.

McCrory, P. R., Johnston, K., Meeuwisse, W., Aubry, M., Cantu, R. C., Dvorak, J., et al. (2005). Summary and agreement statement of the 2nd International Conference on Concussion in Sport, Prague 2004. *Clin J Sport Med, 15*(2), 48-55.

McCrory, P. R., Meeuwisse, W., Johnston, K., Dvorak, J., Aubry, M., Molloy, M., et al. (2009). Consensus statement on concussion in sport: the 3rd International Conference on Concussion in Sport held in Zurich, November 2008. *J Athl Train, 44*(4), 434-448.

McDonnell, M. N., Orekhov, Y., & Ziemann, U. (2006). The role of GABA(B) receptors in intracortical inhibition in the human motor cortex. *Exp Brain Res, 173*(1), 86-93.

McDonnell, M. N., Orekhov, Y., & Ziemann, U. (2007). Suppression of LTP-like plasticity in human motor cortex by the GABAB receptor agonist baclofen. *Exp Brain Res, 180*(1), 181-186.

McIntosh, T. K., Smith, D. H., Meaney, D. F., Kotapka, M. J., Gennarelli, T. A., & Graham, D. I. (1996). Neuropathological sequelae of traumatic brain injury:

relationship to neurochemical and biomechanical mechanisms. *Lab Invest, 74*(2), 315-342.

McNamara, R. K., & Skelton, R. W. (1996). Baclofen, a selective GABAB receptor agonist, dose-dependently impairs spatial learning in rats. *Pharmacol Biochem Behav, 53*(2), 303-308.

Meunier, M., Bachevalier, J., Mishkin, M., & Murray, E. A. (1993). Effects on visual recognition of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkeys. *J Neurosci, 13*(12), 5418-5432.

Mohammadi, B., Krampfl, K., Petri, S., Bogdanova, D., Kossev, A., Bufler, J., et al. (2006). Selective and nonselective benzodiazepine agonists have different effects on motor cortex excitability. *Muscle Nerve, 33*(6), 778-784.

Moller, B., Light, G. A., Fitzgerald, P. B., Snyder, J. S., Chen, R., & Daskalakis, Z. J. (2007). Relationship between P50 suppression and the cortical silent period. *Neuroreport, 18*(14), 1503-1506.

Mortimer, J. A., French, L. R., Hutton, J. T., & Schuman, L. M. (1985). Head injury as a risk factor for Alzheimer's disease. *Neurology, 35*(2), 264-267.

Moser, R. S., Iverson, G. L., Echemendia, R. J., Lovell, M. R., Schatz, P., Webbe, F. M., et al. (2007). Neuropsychological evaluation in the diagnosis and management of sports-related concussion. *Arch Clin Neuropsychol, 22*(8), 909-916.

Murray, E. A., & Mishkin, M. (1998). Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. *J Neurosci, 18*(16), 6568-6582.

Nicoll, J. A., Roberts, G. W., & Graham, D. I. (1995). Apolipoprotein E epsilon 4 allele is associated with deposition of amyloid beta-protein following head injury. *Nat Med, 1*(2), 135-137.

Nordby, H., Hugdahl, K., Jasiukaitis, P., & Spiegel, D. (1999). Effects of hypnotizability on performance of a Stroop task and event-related potentials. *Percept Mot Skills, 88*(3 Pt 1), 819-830.

Oechsner, M., & Zangemeister, W. H. (1999). Prolonged postexcitatory inhibition after transcranial magnetic stimulation of the motor cortex in patients with cerebellar ataxia. *J Neurol Sci, 168*(2), 107-111.

Okada, M., & Okada, M. (1983). A method for quantification of alternate pronation and supination of forearms. *Comput Biomed Res, 16*(1), 59-78.

Oliveri, M., Caltagirone, C., Filippi, M. M., Traversa, R., Cicinelli, P., Pasqualetti, P., et al. (2000). Paired transcranial magnetic stimulation protocols reveal a pattern of inhibition and facilitation in the human parietal cortex. *J Physiol, 529 Pt 2*, 461-468.

Ommaya, A. K., Goldsmith, W., & Thibault, L. (2002). Biomechanics and neuropathology of adult and paediatric head injury. *Br J Neurosurg, 16*(3), 220-242.

Ommaya, A. K., Rockoff, S. D., & Baldwin, M. (1964). Experimental Concussion; a First Report. *J Neurosurg, 21*, 249-265.

Pandya, D. N., & Yeterian, E. H. (1996). Comparison of prefrontal architecture and connections. *Philos Trans R Soc Lond B Biol Sci, 351*(1346), 1423-1432.

Parizel, P. M., Ozsarlak, Van Goethem, J. W., van den Hauwe, L., Dillen, C., Verlooy, J., et al. (1998). Imaging findings in diffuse axonal injury after closed head trauma. *Eur Radiol, 8*(6), 960-965.

Parker, T. M., Osternig, L. R., Van Donkelaar, P., & Chou, L. S. (2006). Gait stability following concussion. *Med Sci Sports Exerc, 38*(6), 1032-1040.

Parker, T. M., Osternig, L. R., van Donkelaar, P., & Chou, L. S. (2007). Recovery of cognitive and dynamic motor function following concussion. *Br J Sports Med, 41*(12), 868-873; discussion 873.

Pascual, J. M., Solivera, J., Prieto, R., Barrios, L., Lopez-Larrubia, P., Cerdan, S., et al. (2007). Time course of early metabolic changes following diffuse traumatic brain injury in rats as detected by (1)H NMR spectroscopy. *J Neurotrauma, 24*(6), 944-959.

Paterakis, K., Karantanas, A. H., Komnos, A., & Volikas, Z. (2000). Outcome of patients with diffuse axonal injury: the significance and prognostic value of MRI in the acute phase. *J Trauma, 49*(6), 1071-1075.

Pettus, E. H., Christman, C. W., Giebel, M. L., & Povlishock, J. T. (1994). Traumatically induced altered membrane permeability: its relationship to traumatically induced reactive axonal change. *J Neurotrauma, 11*(5), 507-522.

Pfefferbaum, A., Christensen, C., Ford, J. M., & Kopell, B. S. (1986). Apparent response incompatibility effects on P3 latency depend on the task. *Electroencephalogr Clin Neurophysiol, 64*(5), 424-437.

Picton, T. W. (1992). The P300 wave of the human event-related potential. *J Clin Neurophysiol, 9*(4), 456-479.

Pierantozzi, M., Marciani, M. G., Palmieri, M. G., Brusa, L., Galati, S., Caramia, M. D., et al. (2004). Effect of Vigabatrin on motor responses to transcranial magnetic stimulation: an effective tool to investigate in vivo GABAergic cortical inhibition in humans. *Brain Res, 1028*(1), 1-8.

Plassman, B. L., Havlik, R. J., Steffens, D. C., Helms, M. J., Newman, T. N., Drosdick, D., et al. (2000). Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. *Neurology, 55*(8), 1158-1166.

Poirier, J., Davignon, J., Bouthillier, D., Kogan, S., Bertrand, P., & Gauthier, S. (1993). Apolipoprotein E polymorphism and Alzheimer's disease. *Lancet, 342*(8873), 697-699.

Polich, J. (1986). Normal variation of P300 from auditory stimuli. *Electroencephalogr Clin Neurophysiol, 65*(3), 236-240.

Polich, J. (1988). Bifurcated P300 peaks: P3a and P3b revisited? *J Clin Neurophysiol, 5*(3), 287-294.

Polich, J. (2004). Clinical application of the P300 event-related brain potential. *Phys Med Rehabil Clin N Am, 15*(1), 133-161.

Polich, J., & Corey-Bloom, J. (2005). Alzheimer's disease and P300: review and evaluation of task and modality. *Curr Alzheimer Res, 2*(5), 515-525.

Polich, J., Howard, L., & Starr, A. (1983). P300 latency correlates with digit span. *Psychophysiology, 20*(6), 665-669.

Potter, D. D., Bassett, M. R., Jory, S. H., & Barrett, K. (2001). Changes in event-related potentials in a three-stimulus auditory oddball task after mild head injury. *Neuropsychologia, 39*(13), 1464-1472.

Povlishock, J. T., Becker, D. P., Cheng, C. L., & Vaughan, G. W. (1983). Axonal change in minor head injury. *J Neuropathol Exp Neurol, 42*(3), 225-242.

Povlishock, J. T., & Katz, D. I. (2005). Update of neuropathology and neurological recovery after traumatic brain injury. *J Head Trauma Rehabil, 20*(1), 76-94.

Rabadi, M. H., & Jordan, B. D. (2001). The cumulative effect of repetitive concussion in sports. *Clin J Sport Med, 11*(3), 194-198.

Reinvang, I. (1999). Cognitive event-related potentials in neuropsychological assessment. *Neuropsychol Rev, 9*(4), 231-248.

Reinvang, I., Nordby, H., & Nielsen, C. S. (2000). Information processing deficits in head injury assessed with ERPs reflecting early and late processing stages. *Neuropsychologia, 38*(7), 995-1005.

Reis, J., Swayne, O. B., Vandermeeren, Y., Camus, M., Dimyan, M. A., Harris-Love, M., et al. (2008). Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. *J Physiol, 586*(2), 325-351.

Restivo, D. A., Lanza, S., Giuffrida, S., Le Pira, F., Drago, M. T., Di Mauro, R., et al. (2004). Cortical silent period prolongation in spinocerebellar ataxia type 2 (SCA2). *Funct Neurol, 19*(1), 37-41.

Reynolds, G. P., & Pearson, S. J. (1993). Neurochemical-clinical correlates in Huntington's disease--applications of brain banking techniques. *J Neural Transm Suppl, 39*, 207-214.

Riis, J. L., Chong, H., Ryan, K. K., Wolk, D. A., Rentz, D. M., Holcomb, P. J., et al. (2008). Compensatory neural activity distinguishes different patterns of normal cognitive aging. *Neuroimage, 39*(1), 441-454.

Rioult-Pedotti, M. S., Friedman, D., & Donoghue, J. P. (2000). Learning-induced LTP in neocortex. *Science, 290*(5491), 533-536.

Rioult-Pedotti, M. S., Friedman, D., Hess, G., & Donoghue, J. P. (1998). Strengthening of horizontal cortical connections following skill learning. *Nat Neurosci, 1*(3), 230-234.

Ruff, R. (2005). Two decades of advances in understanding of mild traumatic brain injury. *J Head Trauma Rehabil, 20*(1), 5-18.

Ryu, W. H., Feinstein, A., Colantonio, A., Streiner, D. L., & Dawson, D. R. (2009). Early identification and incidence of mild TBI in Ontario. *Can J Neurol Sci, 36*(4), 429-435.

Sackett, D. L., Rosenberg, W. M., Gray, J. A., Haynes, R. B., & Richardson, W. S. (1996). Evidence based medicine: what it is and what it isn't. *Bmj, 312*(7023), 71-72.

Selkoe, D. J. (1991). Alzheimer's disease. In the beginning. *Nature, 354*(6353), 432-433.

Shaw, N. A. (2002). The neurophysiology of concussion. *Prog Neurobiol, 67*(4), 281-344.

Shibata, Y., Matsumura, A., Meguro, K., & Narushima, K. (2000). Differentiation of mechanism and prognosis of traumatic brain stem lesions detected by magnetic resonance imaging in the acute stage. *Clin Neurol Neurosurg, 102*(3), 124-128.

Siebner, H. R., Dressnandt, J., Auer, C., & Conrad, B. (1998). Continuous intrathecal baclofen infusions induced a marked increase of the transcranially evoked silent period in a patient with generalized dystonia. *Muscle Nerve, 21*(9), 1209-1212.

Slobounov, S., Slobounov, E, Sebastianelli, W, Cao, C, Newell, K. (2007). Differential rate of recovery in athletes after first and second concussion episodes. *Neurosurgery, 61*(2), 338-344.

Snyder, J., Hanstock, C. C., & Wilman, A. H. (2009). Spectral editing of weakly coupled spins using variable flip angles in PRESS constant echo time difference spectroscopy: Application to GABA. *J Magn Reson*.

Solbakk, A. K., Reinvang, I., & Andersson, S. (2002). Assessment of P3a and P3b after moderate to severe brain injury. *Clin Electroencephalogr, 33*(3), 102-110.

Solbakk, A. K., Reinvang, I., Nielsen, C., & Sundet, K. (1999). ERP indicators of disturbed attention in mild closed head injury: a frontal lobe syndrome? *Psychophysiology, 36*(6), 802-817.

Squire, L. R., & Zola, S. M. (1996). Structure and function of declarative and nondeclarative memory systems. *Proc Natl Acad Sci U S A, 93*(24), 13515-13522.

Stefan, K., Kunesch, E., Benecke, R., Cohen, L. G., & Classen, J. (2002). Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation. *J Physiol, 543*(Pt 2), 699-708.

Stefan, K., Kunesch, E., Cohen, L. G., Benecke, R., & Classen, J. (2000). Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain, 123 Pt 3*, 572-584.

Tataroglu, C., Ozkiziltan, S., & Baklan, B. (2004). Motor cortical thresholds and cortical silent periods in epilepsy. *Seizure, 13*(7), 481-485.

Teasdale, G., & Jennett, B. (1974). Assessment of coma and impaired consciousness. A practical scale. *Lancet, 2*(7872), 81-84.

Teasdale, G. M., Nicoll, J. A., Murray, G., & Fiddes, M. (1997). Association of apolipoprotein E polymorphism with outcome after head injury. *Lancet, 350*(9084), 1069-1071.

Termoz, N., Halliday, S. E., Winter, D. A., Frank, J. S., Patla, A. E., & Prince, F. (2008). The control of upright stance in young, elderly and persons with Parkinson's disease. *Gait Posture, 27*(3), 463-470.

Thurman, D. J., Branche, C. M., & Sniezek, J. E. (1998). The epidemiology of sports-related traumatic brain injuries in the United States: recent developments. *J Head Trauma Rehabil, 13*(2), 1-8.

Tinazzi, M., Farina, S., Edwards, M., Moretto, G., Restivo, D., Fiaschi, A., et al. (2005). Task-specific impairment of motor cortical excitation and inhibition in patients with writer's cramp. *Neurosci Lett, 378*(1), 55-58.

Udupa, K., Ni, Z., Gunraj, C., & Chen, R. (2009). Interactions between short latency afferent inhibition and long interval intracortical inhibition. *Exp Brain Res*.

Umile, E. M., Sandel, M. E., Alavi, A., Terry, C. M., & Plotkin, R. C. (2002). Dynamic imaging in mild traumatic brain injury: support for the theory of medial temporal vulnerability. *Arch Phys Med Rehabil, 83*(11), 1506-1513.

Uryu, K., Laurer, H., McIntosh, T., Pratico, D., Martinez, D., Leight, S., et al. (2002). Repetitive mild brain trauma accelerates Abeta deposition, lipid peroxidation, and cognitive impairment in a transgenic mouse model of Alzheimer amyloidosis. *J Neurosci, 22*(2), 446-454.

Vagnozzi, R., Tavazzi, B., Signoretti, S., Amorini, A. M., Belli, A., Cimatti, M., et al. (2007). Temporal window of metabolic brain vulnerability to concussions: mitochondrial-related impairment--part I. *Neurosurgery, 61*(2), 379-388; discussion 388-379.

Van Hoesen, G. W., Hyman, B. T., & Damasio, A. R. (1991). Entorhinal cortex pathology in Alzheimer's disease. *Hippocampus, 1*(1), 1-8.

Ward, A. A., Jr. (1964). The physiology of concussion. *Clin Neurosurg, 12*, 95-111.

Werhahn, K. J., Kunesch, E., Noachtar, S., Benecke, R., & Classen, J. (1999). Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. *J Physiol, 517 (Pt 2)*, 591-597.

Werner, R. A., & Vanderzant, C. W. (1991). Multimodality evoked potential testing in acute mild closed head injury. *Arch Phys Med Rehabil, 72*(1), 31-34.

Wickens, C., Kramer, A., Vanasse, L., & Donchin, E. (1983). Performance of concurrent tasks: a psychophysiological analysis of the reciprocity of information-processing resources. *Science, 221*(4615), 1080-1082.

Wilson, J. R., Foresman, B. H., Gamber, R. G., & Wright, T. (1998). Hyperbaric oxygen in the treatment of migraine with aura. *Headache, 38*(2), 112-115.

Wylie, S. A., Ridderinkhof, K. R., Eckerle, M. K., & Manning, C. A. (2007). Inefficient response inhibition in individuals with mild cognitive impairment. *Neuropsychologia, 45*(7), 1408-1419.

Zemper, E. D. (2003). Two-year prospective study of relative risk of a second cerebral concussion. *Am J Phys Med Rehabil, 82*(9), 653-659.

Ziemann, U. (2003). Pharmacology of TMS. *Suppl Clin Neurophysiol, 56*, 226-231.

Ziemann, U. (2004). TMS and drugs. *Clin Neurophysiol, 115*(8), 1717-1729.

Ziemann, U., Ilic, T. V., Pauli, C., Meintzschel, F., & Ruge, D. (2004). Learning modifies subsequent induction of long-term potentiation-like and long-term depression-like plasticity in human motor cortex. *J Neurosci, 24*(7), 1666-1672.