

**THE NEUROPSYCHIATRIC SEQUELAE OF CONCUSSION:
TOWARDS AN UNDERSTANDING OF THE NEUROBIOLOGY**

THE NEUROPSYCHIATRIC SEQUELAE OF CONCUSSION: TOWARDS
AN UNDERSTANDING OF THE NEUROBIOLOGY

By

MELISSA DANIELLE MCCRADDEN, Hons. BA

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AUTHOR: Melissa Danielle McCradden, Hons.BA (McMaster
University)

SUPERVISOR: Doctor Michael Mazurek

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Abstract

Concussion/mild traumatic brain injury (mTBI) is a significant public health concern, particularly for young individuals and athletes. While the vast majority recover quickly and without lasting consequences, some will suffer from potentially long-term neuropsychiatric sequelae. These sequelae have been investigated in mTBI samples consisting largely of motor vehicle-related injuries, but very few have examined these following sport-related concussion (SRC). Further, new evidence indicates that participation in contact sports alone can result in similar problems with cognition and mood/anxiety. This thesis investigates neuropsychiatric sequelae in youth and young adults with concussion and who participate in contact sports.

The hippocampus is known to be vulnerable to head injury, and animal models indicate that mTBI impairs hippocampal neurogenesis — the process of the growth, maturation, and integration of adult-born neurons. Hippocampal neurogenesis is well-recognized for its importance to cognition, and has more recently been linked to mood and anxiety. Accumulating evidence indicates that a test involving a component of high memory interference, the mnemonic similarity test (MST), is sensitive to neurogenesis-dependent conditions in humans. To the best of our knowledge, this thesis is the first to investigate whether the MST is sensitive to concussion, contact sport participation, and athletic anxiety.

This thesis describes: (1) a critical review of the literature regarding the psychiatric sequelae of concussion, followed by (2) clinical profiles derived from

retrospective data which document the new onset of immediate psychiatric problems in youth, and delayed psychiatric problems in youth with persistent concussion symptomology; that (3) anxiety is the most common and persistent psychiatric symptom in youth with concussion; that (4) concussion and contact sport participation negatively affect performance on the MST; that (5) a reprieve from contact sport participation is associated with an improvement in MST performance; that (6) these negative effects on the MST are not seen with other injuries; that (7) athletic anxiety impairs performance on the MST. Taken together, this thesis provides evidence that psychiatric problems can present immediately after concussion in persons without identifiable risk factors, and that concussion, contact sport participation, and athletic anxiety affect performance on a putatively neurogenesis-linked test. These results may implicate impaired hippocampal neurogenesis in postconcussion sequelae.

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I would first and foremost like to thank my supervisor, Dr. Michael Mazurek, for his guidance, knowledge, and support. His unique method of allowing me to sort out problems on my own while also giving me context and clues to find the answers I needed allowed me to grow as a student researcher and an academic. I have benefited immensely from his seemingly unending supply of knowledge, and have always appreciated how he cares about his students as people first, and students second. Dr. Rosebush has similar been a source of support and guidance, and I have immensely enjoyed learning from her. Dr. Rosebush's understanding of psychiatric patients has provided me with incredible insights into the complex dynamics of these conditions and the people who experience them. Dr. Suzanna Becker came onto my committee to lend her expertise particularly in regards to the prospective component of this thesis, and her contribution has been absolutely invaluable. It has been a pleasure working with my committee, and I am forever grateful for their support and guidance. My entire supervisory committee has made me feel supported as a student and as a mother, and have shown by example and in their guidance that balancing family and academic life is not only possible, but beneficial.

This thesis could never have been completed without the incredible, unfailing, and relentless support from my husband, Joel McCradden. He has been with me the whole way through my graduate adventure, and, especially once our son Oscar was born, has continually given me the support and advice that I

needed. At this point, I think he might know more about hippocampal neurogenesis than any of my graduate peers, because of how much he has heard me talk about it (and how well he listened to me). And although he works in computer science, his ability to absorb information and problem-solve outside of his field allowed him to help me through some of the toughest spots.

I would like to acknowledge Stephanie Vivier, who unwillingly and unfortunately provided me with the motivation to start this project. She is one of the strongest women I know and how she suffered after her concussion was the impetus for me to pursue this project and attempt to understand postconcussion syndrome. If positive attitude were all it took, she would have healed in seconds. She continues to be a source of inspiration to me for her strength, perseverance, and loving heart.

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To my son, Oscar, who so beautifully behaves as to have allowed me to get all my work done, and to my daughter, Addison, who stayed in her little home just long enough for me to submit this thesis.

Preface

This thesis includes three original articles describing investigations of postconcussion and subconcussion sequelae. The 3rd chapter is a critical literature review of post-mTBI psychiatric sequelae and reports on retrospective data derived from the clinical patient records of Drs Mazurek and Rosebush. Chapters 4 and 5 describe a prospective study involving McMaster varsity athletes and are written as primary research papers.

The original idea that concussion might impair neurogenesis was conceived by Dr. Michael Mazurek. Melissa McCradden was responsible for the background research that led us to the mnemonic similarity test (MST), programming the test, study design, ethics approval, recruiting and running the experiment, data collection, and analysis in addition to writing all three manuscripts. The writing of chapters 4 and 5 involved the valuable editorial assistance of Drs Mazurek and Becker, and chapter 3 was written with the much appreciated input and guidance from Dr Rosebush.

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LIST OF ABBREVIATIONS

<u>Abbreviations</u>	<u>Meaning</u>
ACL	Anterior cruciate ligament
ADHD	Attention deficit with hyperactivity disorder
ATP	Adenosine triphosphate
BDNF	Brain-derived neurotrophic factor
BDI-II	Beck Depression Inventory-II
BOLD	Blood oxygen level dependent
BrdU	Bromodeoxyuridine
BPSM	Biopsychosocial model
CA	Cornu ammonis
CBF	Cerebral blood flow
CD/ODD	Conduct disorder/Oppositional defiant disorder
Cho	Choline
CHR	Clinical high risk
Cr	Creatine
CSAI-2	Competitive sport anxiety inventory-2
CT	Computed tomography
CTE	Chronic traumatic encephalopathy
CVLT	California verbal learning test
DG	Dentate gyrus
DLPFC	Dorsolateral prefrontal cortex
DSM	Diagnostic and Statistical Manual
DTI	Diffusion tensor imaging
EEG	Electroencephalography
EPM	Elevated plus maze
ERP	Event-related potential
ED	Emergency department
FA	Fractional anisotropy
FMRI	Functional magnetic resonance imaging
FNSD	Functional neurological symptom disorder
GABA	Gamma-aminobutyric acid
GAD	Generalized anxiety disorder
GC	Granule cell
GCL	Granule cell layer
GCS	Glasgow Coma Scale
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Depression Rating Scale
HMO	Health maintenance organization
ImPACT	Immediate postconcussion assessment and

LC	cognitive test
LOC	Locus coeruleus
MDE	Loss of consciousness
MR	Major depression episode
MRI	Magnetic resonance
MRS	Magnetic resonance imaging
MST	Magnetic resonance spectroscopy
MTBI	Mnemonic similarity test
MVA	Mild traumatic brain injury
NAA	Motor vehicle accident
NCAA	N-acetylaspartatic acid
NFL	National collegiate athletic association
NHL	National Football League
NMDA	National Hockey League
NPD	N-methyl-D-aspartate
NSC	New psychiatric disorder
QEEG	Neural stem cell
OCD	Quantitative electroencephalography
OFC	Obsessive-compulsive disorder
PCS	Orbitofrontal cortex
PCSS	Postconcussion syndrome
PHG	Postconcussion Symptom Scale
POMS	Parahippocampal gyrus
PTA	Profile of Mood States
PTE	Posttraumatic amnesia
PTSD	Posttraumatic epilepsy
rACC	Posttraumatic stress disorder
RHI	Rostral anterior cingulate cortex
SAI	Repetitive head impacts
SCAT	State Anxiety Inventory
SCID	Sport Competition Anxiety Test
SGZ	Structured Clinical Interview for DSM
SRC	Subgranular zone
TBI	Sport-related concussion
TUNEL	Traumatic brain injury
	Terminal deoxynucleotidyl transferase
	dUTP nick-end labeling
VEP	Visual evoked potential

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CHAPTER ONE: SUMMARY OF RATIONALE AND OBJECTIVES

1.1 Rationale

Concussion/mild traumatic brain injury (mTBI) is recognized as a prevalent and significant public health concern, particularly among athletes and youth. Despite such widespread recognition, neurobiological substrates which may influence the development of symptoms such as memory impairment and mood-related changes remain unclear. The hippocampus is known to be vulnerable to head injury, and hippocampal neurogenesis — the process of the growth, maturation, and integration of adult-born neurons — is impaired following experimental mTBI in animal models. Reductions of neurogenesis levels have been linked with memory and mood changes, similar to those observed as part of the postconcussion sequelae. The central aim of this thesis was to investigate the neuropsychiatric sequelae of concussion with the hypothesis that hippocampal neurogenesis might be impaired following concussion.

It has only recently been recognized that concussion in athletes results in significant mood changes that are likely separate from the psychological reactions to sustaining an injury. While much research has been conducted into the frequency of psychiatric complaints following mTBI, virtually none have looked at such sequelae in athletes with concussion. Accordingly, I reviewed a large cohort of concussion patients presenting to a neurology clinic to assess the prevalence and clinical profiles of psychiatric sequelae of concussion.

A test involving a component of high memory interference, the mnemonic similarity test (MST), has shown promise for detecting putatively neurogenesis-linked changes in performance. It has recently been demonstrated that MST performance deteriorates with age, elevated stress, depression, and binge drinking levels, all of which are associated with lower neurogenesis in rodents. To investigate its potential link to head injury, I assessed concussed and nonconcussed athletes at multiple time points. In addition, I explored performance on the MST throughout a single season of a high contact sport (rugby).

Anxiety in particular has been linked with reductions in neurogenesis, and is a well recognized symptom in a sizeable minority of concussion patients. Recently, anxiety has been hypothesized to be linked with reductions of neurogenesis. Athletes in organized sports offer a unique look at how anxiety might affect performance on the MST, since they typically experience high levels of stress (anti-neurogenic) but also engage in similar levels of exercise (pro-neurogenic). Accordingly, I studied how anxiety in athletes influences performance on the MST.

1.2 Objectives

- ◆ To investigate the potential psychiatric sequelae of concussion (Chapter 3).

Specifically, to:

- review the literature that has previously investigated post-concussion psychiatric problems and identify significant limitations
 - investigate the prevalence of new onset psychiatric problems in a sample of youth patients presenting to a neurology clinic with concussion symptoms
 - characterize the clinical profile of how these problems arise and persist in relation to concussion symptoms
- ◆ To investigate whether concussion and contact sport participation might affect performance on a high memory interference test (Chapter 4). Specifically, to:
 - assess baseline, acute concussion, and recovery performance on the MST
 - compare concussed athletes with those with orthopedic injuries on the MST
 - assess performance on the MST across a single season of contact sport in nonconcussed athletes
 - ◆ To investigate whether anxiety might be linked with impaired neurogenesis (Chapter 5). Specifically, to:
 - assess MST performance in a group of anxious athletes, compared with non-anxious athletes and physically active controls
 - investigate potential modifiers of anxiety, such as self-confidence

1.3 Thesis structure

This thesis has been structured in a “sandwich thesis” format, consisting of a common introduction followed by three publication-ready chapters, and a closing discussion. The papers are at various stages of the publication process, as indicated on each chapter’s title page.

The reader should note that the title of this thesis uses the term ‘concussion’ to refer to a biomechanical injury sustained to the head which resulted in symptoms such as headache, balance problems, cognitive difficulties, and emotional lability. In general, it is believed that all concussions are mild traumatic brain injuries (mTBIs). However, in the sport literature ‘concussion’ is typically the preferred term due to a perceived distinction between a mTBI sustained in sport participation versus the general public. The majority of literature on mTBI (non-sport head injuries) is derived from motor vehicle accidents, in which a substantial majority of mTBI subjects experience loss of consciousness (LOC; <30 minutes) and/or posttraumatic amnesia (PTA). This contrasts with the sport literature, where only a minority of subjects experience LOC of 1-5 minutes at most. While some argue that concussion is distinct from mTBI (McCrory et al., 2013), there remains to be seen whether this distinction has any clinical or neuropathological significance. Chapter 3 includes a literature review of the psychiatric sequelae of mild head injuries, and the choice of term used therein (concussion/mTBI) reflects the choice of the original study’s authors. The presentation of clinical data which follows consists of a sample of individuals

who overwhelming were involved in SRCs (85%), and chapters 3 and 4 the study population included solely SRCs; for these samples, the term ‘concussion’ is used.

Melissa McCradden is the primary author on all papers included within this thesis. Her contributions include the study design, selection of psychometrics, programming of the MST, testing participants, chart review, data collection and analysis. She drafted and edited all three manuscripts with the much appreciated input and editorial guidance of Drs Mazurek, Rosebush, and Becker.

CHAPTER TWO: GENERAL INTRODUCTION

"You get a concussion, they've got to take you out of the game. So if you can hide it and conceal it as much as possible, you pay for it the next day, but you'll be able to ... stay in the game."

- Washington Redskins fullback Mike Sellers

2.1 CONCUSSION/MILD TRAUMATIC BRAIN INJURY

2.1.1 Introduction

Homer's *The Iliad* contains one of the first recorded accounts of concussion, when, in the epic Battle of Troy, Hektor is hit by a rock and collapses, briefly losing consciousness. His compatriots believe him to be dead, but to their surprise he quickly awakens - groggy, clumsy, confused, and with cloudy vision. His eventual recovery allows him to return to battle, seemingly no worse for wear. Our modern conception of concussion is nearly identical — a disturbance in cerebral function, largely without overt signs of injury, remains the generic description of concussion. But while it was previously believed to be a transient state of cerebral dysfunction, the past two decades of research have caused us to reconsider the cost of this seemingly innocuous injury.

Concussion's 'renaissance' is owed largely to the athletes who have suffered at the hands of their sports, whereby, before return-to-play protocols and concussion lawsuits, concussion was thought of as a 'bell ringer.' Like Hektor, without a second thought these athletes were allowed to continue playing. We now know that concussions can result in a host of potential sequelae from the relatively

mild (such as prolonged concussion symptoms) to the highly detrimental (neurodegenerative diseases). We also know that this so-called invisible injury may not be so invisible; sophisticated neuroimaging tests have indicated deficiencies of the the compromised. In addition to concussion itself, the notion of ‘subconcussive hits’ has gained traction with the discovery that participation in contact sports alone can result in neurological changes. While this incredible surge in research has offered a plethora of information, there are still many unanswered questions and many individuals without sufficient treatment.

2.1.2 The impact of concussion

Concussion was recognized to be an imminent threat to the healthcare system over a decade ago, when the toll was estimated to be 441.7\$ million per year in indirect costs such as those incurred by lost wages for individuals on disability (Smart Risk, Ministry of Health and Long Term Care, 1999). Sport-related concussions (SRCs) can affect between 1.6 and 3.8 million individuals in the United States each year (Langlois, Rutland-Brown, & Wald, 2006). Canada has recently deemed concussion a priority area and pledged \$1.4 million to focus on athlete and student return-to-play and return-to-learn protocols, as well as to improve concussion education (Government of Canada, 2016).

Current epidemiological reports of the impact of concussion vary widely, and are limited substantially by the near 50% which are not reported to medical personnel (McCrea et al., 2004). Football, the sport with the highest overall

number of concussions (Zuckerman et al., 2015), has yielded as many as 19 concussions per team per 100 games played in the National Football League each year (Casson et al, 2010). Concussions are most prevalent among collegiate-level football players, where football yields as many as 55% of all collegiate SRCs (Hootman, Dick, & Agel, 2007). A confidential survey given to high school football players revealed that 30% reported at least one previous concussion; only 47.3% reported the concussion to a coach or medical personnel (McCrea et al., 2004). A 4-year National Collegiate Athletic Association (NCAA) Injury Surveillance Program reviewed the incidence of concussion by sport for each gender, and revealed that men and women show similar rates of concussion per athletic exposure (presented in Table 1; Zuckerman et al., 2015). The study reveals that men's wrestling and men's and women's ice hockey have the highest concussion rates when the number of concussions reported is calculated by athlete exposure (defined as one athlete participating in one practice or one competitive event). However, it is noteworthy that the sum of concussions in a single year among the 3 sports does not equal the total number of concussions sustained in one year of football alone, due to the number of athletes who participate in football as compared with other sports. The study also demonstrates that when comparing individual sports by gender, women appear to suffer more concussions than men. While several mechanisms have been suggested such as weaker neck muscles (Zuckerman et al., 2015), greater effect of biomechanical forces (Tierney, 2005), or

larger ball-to-head size (Barnes et al., 1998), it is also possible that women simply report concussion more often (Llewellyn et al., 2012; Torres et al., 2013).

Table 1: Concussion rates among NCAA athletes between 2009-2013 competition season (from Zuckerman et al., 2015).

<i>Sport</i>	<u>Rate per 10,000 athlete-exposures*</u>		
	<i>Competition</i>	<i>Practice</i>	<i>Overall</i>
Men's wrestling	55.46	5.68	10.92
Men's ice hockey	24.89	2.51	7.91
Women's ice hockey	20.10	3.00	7.50
Men's football	30.07	4.20	6.71
Women's soccer	19.38	2.14	6.31
Women's basketball	10.92	4.43	5.95
Women's lacrosse	13.08	3.30	5.21
Women's field hockey	11.10	1.77	4.02
Men's basketball	5.60	3.42	3.89
Women's volleyball	5.75	2.69	3.57
Men's soccer	9.69	1.75	3.44
Women's softball	5.61	1.75	3.28
Men's lacrosse	9.31	1.95	3.18
Women's gymnastics	4.83	2.43	2.65
Men's sports total	9.35	1.63	3.23
Women's sports total	10.81	1.99	3.94

*Based on total number of reported concussions by sport and gender to the NCAA injury surveillance program, calculated as rate per 10,000 exposures (1 exposure = 1 athlete participating in 1 practice or 1 competitive event. The overall rate calculated the number of practice and competition concussions per 10,000 exposures. Only varsity-level scheduled practices and competitive events were included (individual and conditioning training sessions omitted).

Despite the notion that athletes may be somewhat protected from long-

term sequelae of mTBI (Rabinowitz, Li, & Levin, 2014), evidence indicates that athletes may incur steeper penalties for incurring multiple head injuries over the years. Retired football players are at significant risk for depression later in life independent of other risk factors and increasing with the number of self-reported concussions (Didehbani et al., 2013; Guskiewicz et al., 2007a; Hart et al., 2013). Repeated mTBI (as is observed in contact sports) has also been associated with an increased risk for development of neurodegenerative diseases such as Alzheimer's (Jellinger, 2004; Jiang et al., 2013; Lye & Shores, 2000), and chronic traumatic encephalopathy (CTE; McKee et al., 2009; Omalu et al., 2005, 2006).

2.1.3 The clinical picture of concussion

The International Consensus on Sport defines concussion as the presence of an observed or reported biomechanical force to the head accompanied by one or more of the following: loss of consciousness (LOC) with a maximum time of 15 minutes; post traumatic amnesia (PTA) under 24 hours; focal neurological deficits; concussion symptoms such as headache, dizziness, confusion, or balance disturbances. These symptoms will usually correspond to a Glasgow Coma Score (GCS) of 13 at the lowest, which describes a patient who is fairly responsive, but perhaps confused or disorientated. The definition of mTBI most widely used in the literature is that of the American Congress for Rehabilitation Medicine, where the only difference is the allowance for LOC of up to 30 minutes (Kay et al., 1993).

It has long been recognized that approximately 90% of collegiate athletes report full symptom recovery within 1 week of sustaining a concussion, which coincides with a return to baseline performance on computerized neuropsychological tests (McCrea 2003, 2005). Children typically require longer to recover, and take around 3 weeks until they report no symptoms at rest and nearly 3 months before they can be considered fully recovered (Purcell *et al.*, 2014). In the initial stage, the most common symptom by far is headache, with dizziness, fatigue, sleep disturbance, nausea, and cognitive problems presenting in a majority of individuals (Guskiewicz *et al.*, 2000; McCrea *et al.*, 2003). However, a given individual may experience a variety of symptoms that may not present at exactly the same time — some symptoms appear initially and resolve quickly while others seem to present later, such as when the patient returns to a more cognitively demanding environment (i.e., school, athletic pursuits). The range of concussion symptoms is presented in Table 2. It is not currently known why some individuals sustain a concussion while others do not, in a similar context. The advent of helmet accelerometers has taught us that there are substantial inter-individual differences in the forces one can stand without exhibiting neurological dysfunction or sustaining a concussion (Guskiewicz *et al.*, 2007b; McCaffrey *et al.*, 2007).

Table 2: Symptoms of Concussion	
PHYSICAL/SOMATIC Headache Nausea/vomiting Dizziness Visual disturbances Photophobia, phonophobia Loss of balance or poor coordination Decreased playing ability	AFFECTIVE Irritability Emotional lability Sadness Anxiety Inappropriate affect Emotional outbursts Spontaneous crying
COGNITIVE Trouble concentrating Trouble remembering Confusion Feeling ‘in a fog’ Slow reaction times	SLEEP Drowsiness Fatigue Hypersomnia Hypsomnia

2.1.4 Potential sequelae of mTBI

The range and risk of complications after concussion/mTBI continue to be elucidated. Post-concussion syndrome (PCS), post traumatic epilepsy, and chronic traumatic encephalopathy (CTE) are all potential consequences of sustaining one or more concussions in one’s lifetime.

Post concussion syndrome

Post-concussion syndrome (PCS) has been a topic of considerable debate for over a century (summarized in Taylor, 1967). First described in the DSM-IV as ‘post-concussional disorder,’ PCS is diagnosed when a patient experiences ongoing symptoms that are deemed to be the direct consequence of concussion. The debate largely centres around whether these persistent symptoms are the direct result of the brain injury and are indicative of persistent neurological dysfunction,

the uncovering of a psychological problem masquerading as post-concussion symptoms, or whether individuals are malingering for secondary gain (Bigler, 2013).

Consistently, prospective, consecutive case-control studies have documented that approximately 15% of patients (young and adult) will experience symptoms persisting beyond 3 months of the initial mTBI (Barlow et al., 2010; Eisenberg et al., 2013). Some have argued that PCS symptoms are not specific to mTBI, and that over time mTBI becomes less predictive of the presence of PCS symptoms than do other factors (i.e., depression symptoms; Iverson, 2006). Arguably, one could reasonably contend that pre-existing factors are frequently not accounted for in the literature, which casts doubt on the causative link between the mTBI itself and persistent neuropsychiatric and neurocognitive problems. But even when factors such as litigation, effort on neuropsychological testing, and pre-existing depression are controlled for, persistent problems with residual concussion symptoms continue to be observed in a sizeable, but consistent minority of patients with mTBI (Dean & Sterr, 2013; Hanten et al., 2012; Heitger et al., 2009).

Psychiatric disorders

A recent committee panel conducting the largest systematic review of published, peer-reviewed literature to date concluded that substantial evidence exists to support an association between mTBI and the 6-month or more development of newly presenting postinjury mood and anxiety disorders

(Hesdorffer, Rauch, & Taminga, 2009). Although this evidence is derived largely from prospective studies of individuals presenting to emergency rooms or primary care clinics, several studies have indicated that concussed athletes show increases in anxiety and mood disruption that are distinct from orthopedically-injured and uninjured athletes (Chen et al., 2008; Hutchison et al., 2009; Kontos et al., 2012; Mainwaring et al., 2010; Meier et al., 2015; Roiger, Weidauer, & Kern, 2015). These anxiety- and mood-related disturbances are transient and largely parallel symptomatic recovery from concussion; they have also been demonstrated to be quantitatively different from the emotional responses to orthopedic injuries (Hutchison et al., 2009; Mainwaring et al., 2010). A full review of the psychiatric sequelae of SRC and mTBI is presented in Chapter 3 of this thesis.

Chronic traumatic encephalopathy (CTE)

Chronic traumatic encephalopathy (CTE) has been re-introduced with a renewed interest owing largely to the efforts of Dr. Ann McKee and Dr. Robert Omalu, who began to describe and define the disorder histopathologically and clinically (McKee et al., 2009; 2013; Omalu et al., 2005, 2006). CTE is an Alzheimers-like progressive dementing disorder associated with significant neuropsychiatric symptomatology, particularly in the later stages. High prevalence rates have been described in samples of former professional athletes, particular in boxing, football, hockey, and wrestling, as well as among military personnel (believed to have suffered blast-induced TBIs; for an excellent review, see McKee & Robinson, 2014). While the evidence supports the general notion that CTE is

linked with repetitive head impacts, it is still largely unknown how CTE develops, as well as its precise link to concussions or subconcussive impacts, and why there appears to be a latency period between the cessation of sport participation and symptom onset (for an excellent review, see Meehan et al., 2015). Further, the population samples collected in the above studies were exclusively from individuals who had directed their brains in the interest of research into concussion-related sequelae, indicating a potentially significant sampling bias. Nonetheless, the early onset of the disorder coupled with the severity and swiftness of neuropsychiatric symptoms are ample reasons to aggressively research sequelae associated with head trauma.

2.1.5 Neuropathology

A core feature of the so-called “mild” traumatic brain injury has been a lack of positive findings on traditional neuroimaging tests such as CT or MRI, leading to the description of mTBI as a ‘functional’ injury. However, more sophisticated neuroimaging techniques have allowed us to visualize changes in the brains of individuals with acute concussion and also in those with chronic concussion symptoms (reviewed in Bigler, 2013).

During a traumatic event, the brain is subject to acceleration, rotational, and angular forces. These forces result in shearing and tensile strain imposed on axonal tissue, and, while mTBI injuries differ in the precise biomechanics, in general the forces are most impactful to long-range axonal tracts such as the

corpus callosum and corona radiata (Bayly et al., 2012; Chatelin et al., 2011; McAllister et al., 2012b), as well as long tracts such as the longitudinal fasciculus (Shenton et al., 2012). Postmortem studies of individuals sustaining mTBI but dying by other injuries have observed myelin destruction, axonal retraction bulbs, microhemorrhages, hemosiderin deposits, and macrophages (Bigler, 2004; Bigler & Maxwell, 2012). These trauma-induced microhemorrhages can develop from hours to days following a mild head injury (Bigler, 2013; Yuh et al., 2010).

Some of the most common neuroimaging findings indicate contusions occurring at the brain-skull interface, while petechial hemorrhages often occur at the intersection of gray and white matter (Gean & Fischbein, 2010; Kim & Gean, 2011), which may co-occur with diffuse or focal edema. These positive findings on MRI have been noted in 27% of mTBI samples with normal CT findings and a GCS score of 15 (Yuh et al., 2010). Among those with persistent symptoms, diffusion tensor imaging (DTI) has detected abnormalities of the superior longitudinal fasciculus, region of the forceps minor of the corpus callosum, superior frontal gyrus, insula, and fornix (Wada, Asano, & Shinoda, 2012). These brain regions are hypothesized to experience the largest proportion of stress, strain, and shearing forces in the majority of head injuries (Ropper & Gorson, 2007).

2.1.6 Neuroimaging of concussion/mTBI

Concussion and mTBI have been examined extensively across many modalities including traditional neuroimaging tests such as computed tomography (CT) and standard magnetic resonance imaging (MRI), as well as more sophisticated imaging methods such as functional MRI (fMRI), magnetic resonance spectroscopy (MRS), and diffusion tensor imaging (DTI).

Computed tomography (CT) and magnetic resonance imaging (MRI):

While CT and MRI were formerly standard practice for any head injury, the consistently negative findings in individuals with concussion/mTBI (but not more severe head injuries) have resulted in their use to rule out more severe injuries rather than a diagnostic test of mTBI *per se* (Aubry et al., 2001; McCrory et al., 2012). More recent studies have noted that while the MRI of an acute concussion patient will most likely appear normal, abnormalities presumably related to the mTBI may become visible several days later.

Yuh et al (2010) assessed 135 mTBI patients who presented to ER and had initially normal CT and MRI scans; when the same individuals were reassessed approximately 2 weeks later, 25% had abnormal CTs (including contusion, hemorrhage, or edema) and over 40% had abnormal MRIs (contusions, hemorrhagic axonal injury). Each indication of abnormality on MRI was associated with an increased risk of poorer outcome, indicating that the persistent problems observed in a consistent minority of mTBI patients may have an underlying neurobiological substrate. Bigler et al (2013) found that MRI evidence

of hemosiderin deposits (indicating the presence of blood in neuronal tissue) can be present in as many as 29% of children with mTBI while no orthopedic-injury controls show such deposits. Additionally, white matter hyperintensities are associated more frequently with mTBI versus other injuries (Marquez de la Plata et al., 2007).

Electrophysiological studies: Electroencephalography (EEG), event-related potentials (ERP) and visual evoked potential (VEP)

EEG changes in acute concussion have been observed in subsets of patients with mTBI. Quantitative changes can include diffuse slow wave activity (McLelland et al., 1994), focal abnormalities (Geets & Louette, 1985), and lower power of alpha and beta frequencies (Tebano et al., 1988). When a single quantitative EEG (qEEG) measure is calculated from these and other aspects of EEG such as coherence, power asymmetries, and mean frequency, researchers can compute an index score of overall EEG abnormalities which can reliably differentiate concussed athletes from nonconcussed athletes (Barr et al., 2012; McCrea et al., 2010). Further, this qEEG measure normalizes by 45 days postinjury in accordance with the resolution of clinical symptoms (Barr et al., 2012).

Abnormal EEG findings have also been reported in athletes with a remote history of concussion (average of 3.4 years), where attenuated amplitude was observed using an event-related potential (ERP) oddball paradigm (Broglio et al., 2009). Individuals who sustain a second concussion exhibit exacerbated

attenuation of ERP signals and a delayed rate of recovery compared to those who sustain a single concussion (Slobounov, Cao, & Sebastianelli, 2009). Athletes with a history of multiple concussions have been reported to display persistent attenuation of ERP amplitude despite being clinically asymptomatic (Theriault et al., 2009).

The visual-evoked potential (VEP) records the electrical signal from the visual cortex in response to a switching checkerboard pattern and was among the first waveforms studied in TBI. While some found abnormalities among head-injured patients (Feinsod et al., 1976; Gaetz & Weinberg, 2000; Moore et al., 2014; Papathanasopoulos et al., 1994), differences in methodology have obscured its utility. Our own investigation has revealed that the P100 waveform is sensitive to concussion and PCS, and normalizes in conjunction with the resolution of clinical symptoms (McCrady et al., 2014).

Functional magnetic resonance imaging (fMRI)

fMRI has been utilized extensively to examine head injury as it putatively detects alterations in neuronal activity as a function of local blood flow (Ogawa et al., 1990). Task-related fMRI studies, in particular, show potential for illuminating differences in how the concussed brain processes complex information in comparison to the nonconcussed state. Together, fMRI studies indicate that those with concussion have more widespread and nonspecific activation of cortical areas during performance of various cognitive tasks compared with nonconcussed individuals (McAllister et al., 1999, 2001). The increased activation is presumed to

indicate ‘neural inefficiency,’ whereby the brain engages in more widespread recruitment of brain regions to assist in task performance without altering neural architecture (McAllister et al., 1999, 2001; Maruishi et al., 2007; Turner & Levine, 2008; Scheibel et al., 2009).

A noteworthy fMRI study of mTBI is Chen et al’s (2004) work detailing a reduction of blood-oxygen-level dependent (BOLD) signalling in the dorsolateral prefrontal cortex (DLPFC) of concussed athletes. These athletes appeared to show recruitment of additional brain regions that were not recruited in those of controls subjects (Chen et al., 2007), and these observations were more pronounced in concussed athletes with depression symptoms (Chen et al., 2008). While Chen et al’s athletes showed no actual deficits in their performance on the task, Mayer (2011) observed that abnormal connectivity within the default mode network (a number of highly interconnected pathways that mediate passive mental activities) predicted the presence of cognitive complaints with a month of the injury. There is substantial variability among fMRI studies regarding scanning time, region of interest versus whole brain analysis, as well as the lack of controlling for concussion history, multiple concussions, and time since concussion.

Magnetic resonance spectroscopy (MRS)

MRS has emerged as a promising method for detecting acute abnormalities following concussion as well as persistent metabolic changes associated with prolonged symptoms (Gardner, Iverson, & Stanwell, 2014). Most commonly, studies report reductions in N-acetyl aspartate (NAA; a marker of

neuronal viability), often with corresponding elevations in choline (Cho; component of cell membranes) and/or creatine (Cr; metabolic marker) (Govind et al., 2010; Vagnozzi et al., 2008, 2010). These findings are believed to indicate reduced neuronal integrity in conjunction with increased metabolic function as the brain attempts to resume normal functioning (Vagnozzi et al., 2008). A non-linear normalization of NAA levels has been observed, where NAA slowly increases in the first 2 weeks followed by a sharp increase around 3 weeks (Vagnozzi et al., 2008). These alterations have also been reported up to 3 weeks following a concussive injury in athletes (Johnson et al., 2012). Importantly, white matter NAA levels may be able to distinguish between symptomatic and asymptomatic individuals who sustained a concussion within 2 months (Kirov et al., 2013b) or even after several months of symptoms (Dean et al., 2013). However, it is important to note that similar NAA changes have been reported in many other neurological disorders, and thus far no study has compared mTBI to other injured groups or to those with neuropsychiatric conditions. Therefore, the specificity of these changes to mTBI is currently unknown.

Diffusion tensor imaging (DTI)

DTI, a magnetic resonance method for quantifying white matter integrity by assessing water movement through brain tissue, is highly accurate at differentiating individuals with TBI of all severities, including SRC (Hellyer et al., 2013; Hulkower et al., 2013; Wilde et al., 2008). DTI may also help to predict outcome from mTBI; Rao et al (2012) found that DTI findings of frontotemporal

white matter disruption within 1 month of mTBI were related to the presence of depression symptoms by 1 year. Several studies have also demonstrated that persistent axonal disruption is associated with continued neurobehavioural and neurocognitive sequelae (Ling et al., 2012; Mayer et al., 2011; 2012a, b; Messe et al., 2011; 2012).

A substantial caveat to the above literature is the neglect of a non-athlete control group. Recent studies suggest that participation in contact sport alone can alter the brain (Bazarian et al., 2014; Koerte et al., 2012; Mayinger et al., 2017; McAllister et al., 2014), and, thus far, neuroimaging studies of concussed athletes have only made comparisons using nonconcussed athletes who were still active in sports at the time of the study. It would perhaps be more illuminating to compare contact sport athletes to non-contact sport athletes or physically active non-athlete controls to attempt to understand the way that concussion and contact sports in isolation affect brain measures. Additionally, the use of a separate control group would allow us to determine whether the neurobiological substrates investigated with neuroimaging techniques are specific to concussion/mTBI *per se*, or whether they are indicative of any injury — a problem that has been a significant hurdle thus far to uncovering a biomarker specific to concussion (Bigler, 2013).

2.2 POTENTIAL IMPLICATIONS OF MTBI/CONCUSSION EFFECTS ON HIPPOCAMPAL NEUROGENESIS

2.2.1 Introduction

The hippocampus plays an invaluable role in spatial and episodic memory. The classic case of hippocampal dysfunction is the story of H.M., a 27-year old man who underwent bilateral resection of the medial temporal lobes including the hippocampal formation, to control his seizures (Corkin, 2013; Milner, Corkin, & Teuber, 1968). As a result, he was unable to learn any new information and could recall only remote memories of his childhood. The case highlighted the importance of the hippocampus for autobiographical memory storage and access, and for acquisition of new semantic information. Impairments to the dentate gyrus, and of neurogenesis in particular, have unique consequences to memory acquisition. These impairments affect a function known computationally as ‘pattern separation,’ but is also recognized as ‘memory resolution’ or ‘memory interference.’

It has long been recognized that the hippocampus may be uniquely vulnerable to mTBI (Lowenstein et al., 1992). Reports of postinjury disruptions to the hippocampus include electrophysiological abnormalities (Eakin & Miller, 2012; Fedor et al., 2010; Wolf et al., 2017), disrupted GABAergic transmission (Lowenstein et al., 1992; Schneider et al., 2016; Zanier et al., 2003), impaired long-term potentiation (White et al., 2017), decreased expression of hippocampal BDNF (Griesbach et al., 2007), and decreased dendritic and synaptic density in

the DG (Chohan et al., 2015; Eakin & Miller, 2012). These effects may be more pronounced in younger individuals (Yu & Morrison, 2010), and after repeated mTBI (Acabchuk et al., 2016). In humans, volumetric loss of the hippocampus has also been reported in those with a history of childhood/adolescent TBI (all severities; Beauchamp et al., 2011; Wilde et al., 2007). Reduced functional connectivity to the hippocampus and its efferents have also been reported as far as 6 months following mTBI (Johnson et al., 2012; Marquez de la Plata et al., 2011). Together, the converging evidence from both human and animal literature supports the notion that the hippocampus is highly vulnerable following mTBI.

2.2.2 Neuroanatomy of the hippocampus

Organization and structure

The hippocampus lies within the medial temporal lobe, directly adjacent and superior to the temporal horn of the lateral ventricle (Figure 1). The hippocampus itself is composed of three sections: the dentate gyrus (DG) and hippocampus proper (or Ammon's horn [*cornu ammonis*; CA]) are thin sheets of neurons folded over each other in a spiral form, as well as the subiculum, which is a transition zone for the 3-layer composition of the hippocampus to the 6-layer composition of the neocortex. Leading outward from the hippocampus are the entorhinal, perirhinal, and parahippocampal cortices. Output fibres consist of white matter tracts running medially through the structure, which gather into the fimbria and eventually form the fornix, which carries output from CA1 and CA3.

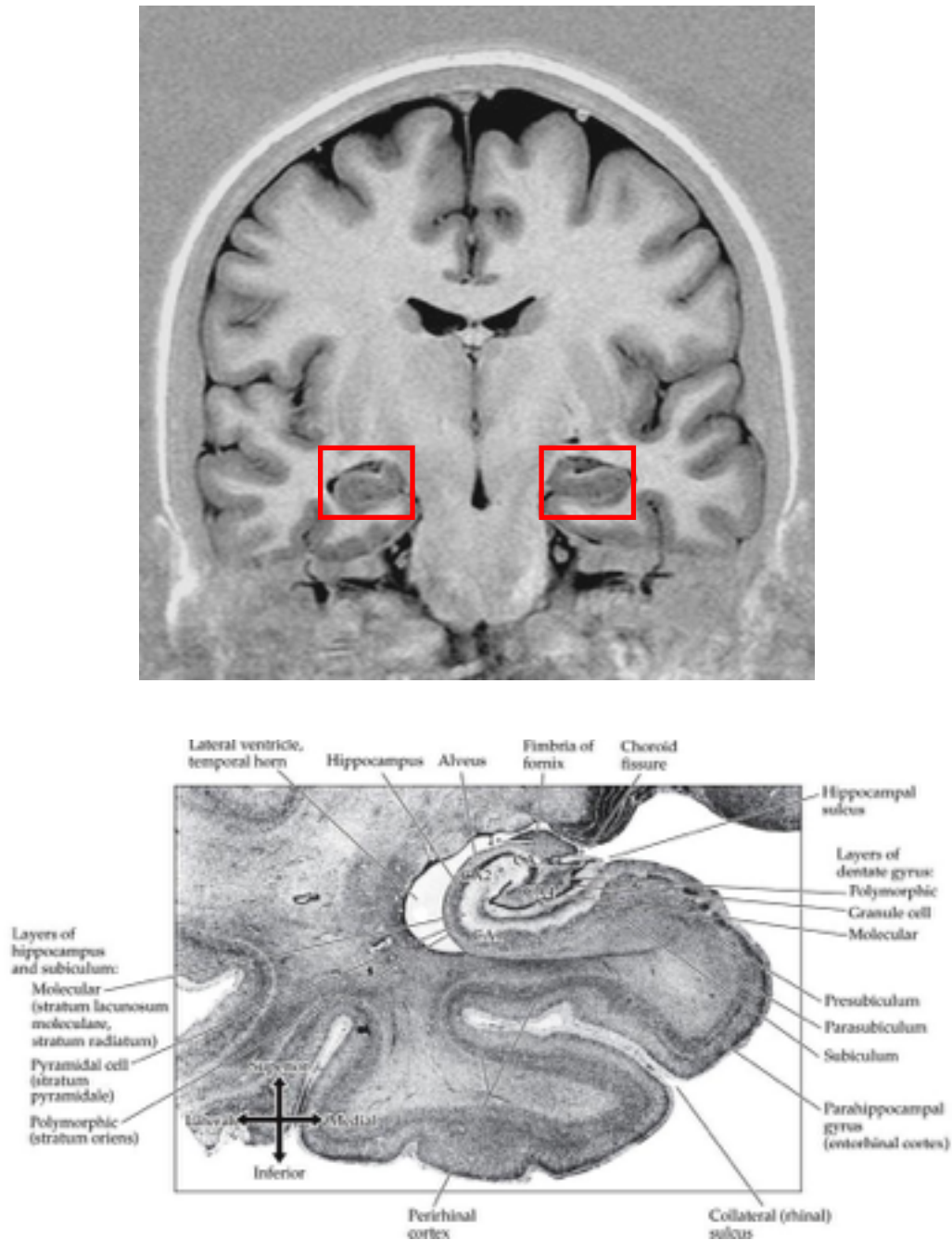


Figure 1: Anatomical location of the hippocampus within the medial temporal lobe; close-up of hippocampus and related structures (Blumenfeld, 2010)

The fornix and the subiculum, which receives input from the CA1, are the main efferent pathways.

The cornu ammonis is comprised of regions CA1 to CA4 (the latter residing in the innermost section of the spiral structure). The hippocampus has three layers: both the DG and CA regions have a superficial molecular layer and deep polymorphic layer (referred to as the ‘hilus’ in the DG); the DG has an intermediate granule cell layer while the cornu ammonis has a pyramidal layer. In the DG, the polymorphic layer contains numerous interneurons, as well as DG axons projecting to CA3. The granule cell layer (GCL) contains granule cells, while the superficial molecular layer carries perforant path fibres which synapse onto granule cells. The CA’s pyramidal layer contains the pyramidal neurons which project to other hippocampal regions. The molecular layers of the DG and CA3 face each other and form the hippocampal sulcus.

The perforant, or ‘tri-synaptic’ pathway (Figure 2) consists of input from the entorhinal cortex which synapses onto granule cells of the DG; these cells sparsely project onto CA3 pyramidal cells; efferent CA3 pyramidal cells project via Schaffer collaterals which synapse onto CA1 pyramidal cells — these cells project back to the subiculum. Pyramidal cells of the subiculum project to the fornix and the deep layers of the entorhinal cortex. In addition to the perforant path, projections from CA1 direct to CA3 compose the alvear pathway. See Figure 2 for perforant path hippocampal circuitry.

Neurotransmitters

Inputs to the hippocampus are primarily excitatory neurotransmitters, with glutamate as the main transmitter of the perforant pathway. Cholinergic neurons

arising from the septohippocampal axis (originating in the medial septum) also carry input largely to pyramidal neurons but also to interneurons. Hippocampal interneurons are GABAergic and reside in the polymorphic layer. GABA is also carried by afferent and efferent pathways, such as from the septum and the contralateral hippocampus. NMDA receptors are located throughout the hippocampus and are crucial to memory formation and long-term potentiation. The locus coeruleus (LC) carries noradrenergic inputs to all layers of the hippocampus, particularly in the DG hilar and CA3 regions. Serotonin inputs arise from the dorsal and median raphe nuclei of the brainstem and terminate mostly on the GABAergic interneurons.

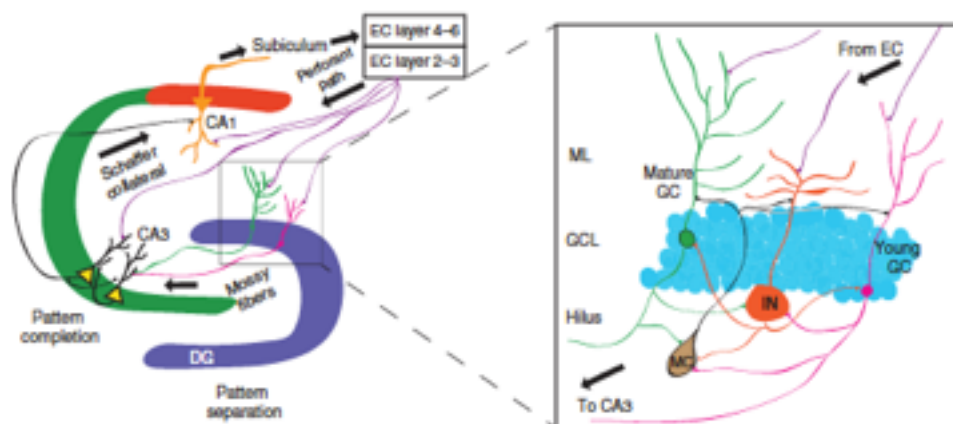


Figure 2: Perforant pathway of the hippocampus (Kheirbek et al., 2012a).

Vascular innervation

Blood supply to the hippocampus is provided by branches of the posterior cerebral artery, which gives rise to the anterior, middle, and posterior hippocampal arteries.

2.2.3 Hippocampal neurogenesis

The discovery that the mammalian brain could generate newborn neurons was arguably among the most profound observations known to neuroscience, marking a paradigm shift in our previously held view of the brain as an unchanging, predetermined organ. Though there is limited evidence that other areas of the brain may be neurogenic as well (for review, see Gould, 2007), the hippocampus is the only confirmed area in the human brain that generates neurons which mature to receive synaptic input, generate action potentials, and project to target regions.

Hippocampal neurogenesis is the process of the production and functional integration of adult-born neurons into existing hippocampal circuitry (Figure 3). Neural stem cells (NSC) are produced throughout life at a relatively constant rate within the subgranular zone (SGZ) of the DG of the hippocampus (Dravansky et al., 2011), creating a pool of neural or glial progenitors whose lineage, proliferation, and development are dictated by environmental, genetic, and pharmacologic factors (Ming & Song 2011). Over a period of 2 weeks, neural progenitors migrate as neuroblasts to the molecular layer of the DG to receive input from surrounding cells — a critical period at which point 50% will die off (Vivar & van Praag, 2013). Initially, these immature neurons are tonically activated by local GABA, released from local interneurons; as synapses form they respond to GABAergic and later glutamatergic inputs (Ge et al., 2006). Immature

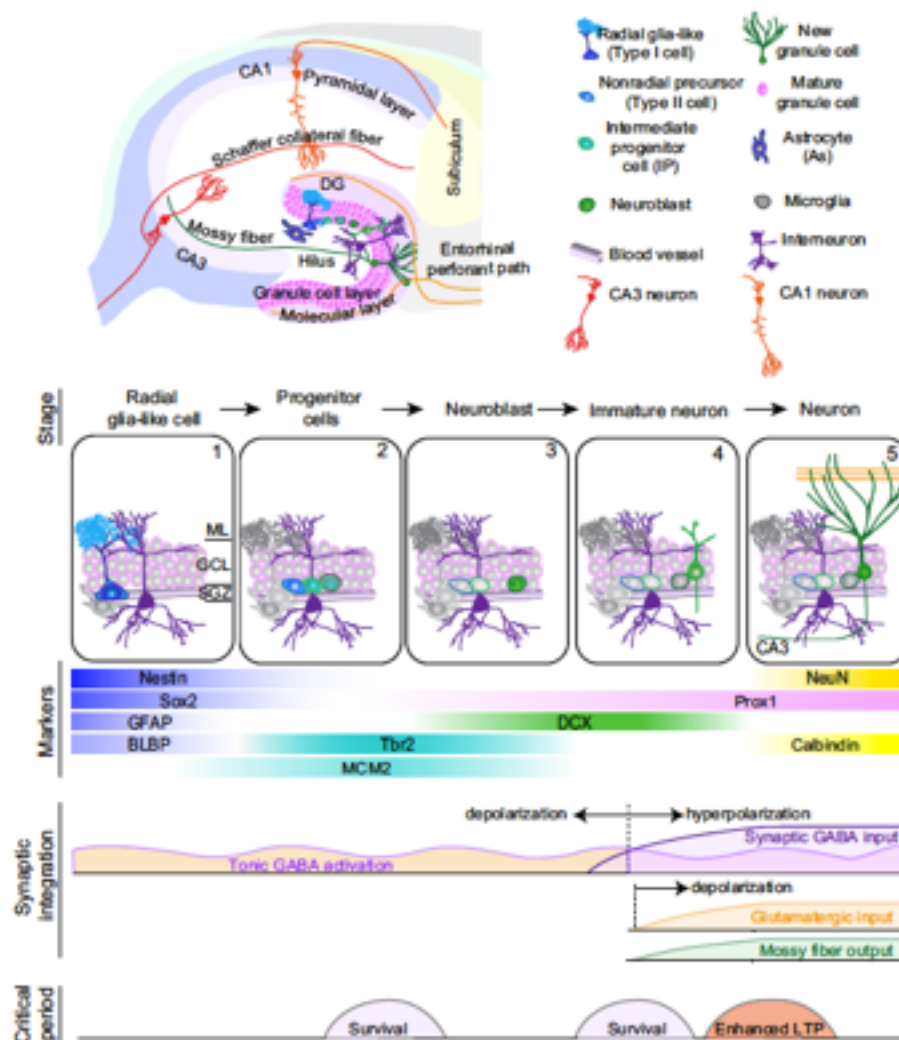


Figure 3: Adult hippocampal neurogenesis in the dentate gyrus: circuitry, stages, immunohistochemical markers, synaptic integration, and critical periods (Ming & Song, 2011).

granule cells are hyperexcitable and have an enhanced propensity for synaptic plasticity (Ge et al., 2008), which contributes to their role in learning and memory.

By 3-4 weeks, these immature granule cells begin to take on features of mature granule cells, extending their dendrites through the molecular layer while their axons transverse the hilus to terminate in the CA3 region. The outputs become integrated into the mossy fiber collateral pathway, a component of the tri-

synaptic pathway (Faulkner et al., 2008). This stage comprises a second critical period, where, without experience-dependent activation, the immature neurons will fail to integrate and will die off (Tashiro et al., 2006)

A variety of conditions have been shown to affect neurogenesis in different ways. Environmental enrichment (Kempermann et al., 1997) and learning (Gould et al., 1999) appear to increase the number of neural precursors available while running (van Praag, Kempermann, & Gage, 1999) increases the survival and integration of adult-born neurons (Olsen et al., 2006). Some dietary supplements which can influence inflammation and anti-oxidation processes may also enhance neurogenesis in some animal models (Beltz et al., 2007; Dylla et al., 2010). To the contrary, chronic stress is well-recognized to impair neurogenesis (Gould et al., 1998; Malberg & Durman 2003). Advancing age has also been associated with a downregulation of neurogenesis via a decrease in the pool of neural progenitors (Kuhn, Dickinson-Anson, & Gage, 1996), an effect which may be buffered with the addition of exercise (Siette et al., 2013). Impaired neurogenesis has also been implicated in certain psychiatric disorders (discussed below), based on the evidence that antidepressant interventions such as certain antidepressant drugs (Kodama et al., 2004; Malberg et al., 2000; Santarelli et al., 2003) and anticonvulsant therapy (Madsen et al., 2000; Scott, Wojtowicz, & Burnham, 2000) require neurogenesis for their efficacy. It is worth noting, however, that there may be differences between animal models, behavioural tests, and testing paradigms.

2.2.4 Functional implications of newborn neurons

Impairments to neurogenesis can result from a smaller pool of neural precursors or the failure of adult-born neurons to integrate into hippocampal circuitry. Though there are some conflicting reports concerning individual tasks and methods of neurogenesis ablation, in general, studies support a role for adult-born neurons in tasks involving a component of high interference, meaning overlapping contextual details or spatial similarity (Becker, 2016). Ablating neurogenesis in animal models impairs contextual fear conditioning (Pan et al., 2012; Park et al., 2015; Saxe et al., 2006; Winocur et al., 2006), delayed non-match to sample task (Winocur et al., 2006), discrimination tasks involving spatial locations and objects (Clelland et al., 2009) or contextual information (Kheirbek et al., 2012a; Nakashiba et al., 2012; Niihori et al., 2012), interference with previously learned information (Luu et al., 2012; Winocur et al., 2012), and extinction (Deng et al., 2009; Noonan et al., 2010).

Complementary to the above studies, enrichment and exercise — which are known promoters of neurogenesis — are associated with improved contextual discrimination on a fear conditioning test (Wojtowicz et al., 2008), and contextual discrimination of visual cues (Sahay, Wilson, & Hen, 2011a; Saxe et al., 2006) and of spatial locations (Creer et al., 2010). Additionally, enrichment and exercise have been shown to buffer the impairments to cognition as a result of normal ageing (van Praag et al., 2005), chronic stress (Hutton et al., 2015; Veena et al., 2009), and binge alcohol consumption (Leasure & Nixon, 2010).

These ‘high interference’ tasks have been presumed to reflect the function of ‘pattern separation’ — a computational term which refers to sparse neuronal coding that generates orthogonalized memory traces. But while some evidence supports the notion of pattern separation, contradictory information requires that we consider carefully the semantic implications of employing a term which specifically refers to an underlying neural code to refer to an observed behaviour (Becker, 2016). Further, though pattern separation may well be a function of the DG, the actual contribution of adult-born neurons is less well established.

The pattern separation hypothesis

The term ‘pattern separation’ refers to a computational theory describing sparse neural coding for overlapping inputs and the generation of orthogonalized memory traces from this information (Treves & Rolls, 1987). Its complement is pattern completion — the process of retrieving a previously encoded memory — which is a function believed to be performed primarily by the CA3 region (Rolls 2013).

Leutgeb et al (2007) recorded from DG and CA3 cells in response to a gradually changing environment (from a circle to a square shape), and found that while CA3 cells only responded to a drastic change, DG cells responded strongly to each incremental change in the environment’s shape. Human fMRI studies have revealed that during performance of a high interference memory task, the signal in the DG/CA3 was strongest when identifying an image whose highly

similar pair had been previously learned (Bakker et al., 2008), and that the DG actually responded identically to similar and new stimuli (Lacy et al., 2011).

The contribution of the DG to contextual discrimination has been well-documented in animal models (Gilbert, Kesner, & Lee, 2001; Hunsaker, Rosenberg, & Kesner, 2008; Kim & Lee, 2011). Ablation of neurogenesis by various means has been shown to impair learning in contextual fear discrimination tasks (see Figure 4; Nakashiba et al., 2012; Sahay et al., 2011; Sahay, Wilson, & Hen, 2011a; Tronel et al., 2012), as well as spatial discrimination when distances are small (Clelland et al., 2009; Creer et al., 2010). It has also been shown that increasing the pool of neural precursors is sufficient to augment performance on contextual discrimination tasks (Sahay, et al., 2011). The contributions of newborn neurons are likely reliant on their enhanced ability for synaptic plasticity (Kheirbek, Tannenholz, & Hen, 2012).

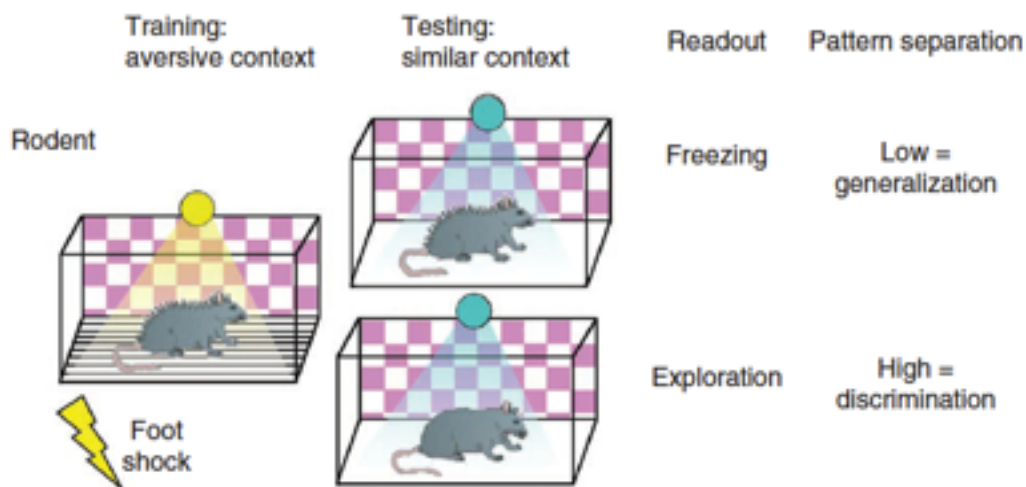


Figure 4: Depiction of contextual fear discrimination task in rodents (Kheirbek et al., 2012a).

Although DG signalling appears to be strongly associated with high memory interference, a large subset of granule cells can be recruited for similar contexts (Schmidt, Marone, & Markus, 2012), which seems counterintuitive to the notion of pattern separation. Further to this point, immature granule cells are hyperactive rather than firing sparsely, so how might they be responsible for generating sparse neural codes? One suggestion is that they are indirectly responsible for sparse coding by influencing greater feedback inhibition on mature granule cells (Ikrar et al., 2013; Kheirbek et al., 2012b; McAvoy et al., 2015; Sahay, Wilson, & Hen, 2011b). In this regard, increasing the population of immature granule cells provides more extensive synapsing onto hilar interneurons, which causes a greater net increase on the overall inhibition of the DG (McAvoy, Besnard, & Sahay, 2015). The stage of maturation of immature/mature granule cells also greatly affects how they contribute to the overall tone of the DG; between 4 and 8 weeks immature granule cells contribute with increasing strength to the overall inhibition of granule cells in the GCL (Temprana et al., 2015).

The memory interference/memory resolution theory

The memory interference/memory resolution theory incorporates the pattern separation computation performed by the DG with the specific and opposing characteristics of newborn and mature granule cells. Aimone et al (2011) suggest that newborn neurons may initially be coarsely tuned (low resolution) to a wide variety of inputs, while mature GCs fire more sparsely (high resolution) and commensurate with experience in responding to a particular stimulus (Aimone et

al., 2011; Tashiro et al., 2007). The newborn neurons initially show high sensitivity to minute contextual changes, and over time their prolific firing rate is tuned in an experience-dependent fashion (Tronel et al., 2015). This experience-dependent tuning also could help explain the need for sufficient neurogenesis for memory retention and recall across long time delays (Aimone, Wiles, & Gage, 2006; Pan et al., 2012) and their preferential firing to contexts that differ by time (Rangel et al., 2014). These considerations in addition to the notion of increasing overall feedback inhibition together provide a plausible explanation for how neurogenesis and the functions of the newborn neuron population may overcome memory interference, while also contributing to the pattern separation function of the DG.

2.2.5 Implications of neurogenesis in psychiatric disorders

Hippocampal neurogenesis has been found to have important implications in mental health. Evidence continues to accumulate in animal studies showing that effective psychiatric treatments such as environmental enrichment (Kempermann et al., 1997), voluntary exercise (van Praag et al. 1999), acute sleep deprivation (Grassi Zucconi et al., 2006), electroconvulsive shock treatment (Scott, Wojtowicz, & Burnham, 2000), and the administration of several antidepressants (Malberg et al., 2000; Tanti et al., 2013) increase neural progenitor populations. In addition, significant precursors to the development of psychiatric illness such as chronic stress or corticosterone treatment are known to impair hippocampal neurogenesis

(Gould & Cameron 1996, Malberg & Duman 2003, Yau et al., 2014). Volumetric reductions of the hippocampus have been found previously among people with major depressive disorder and trauma (McKinnon et al., 2009), and it is possible that these reductions reflect lower numbers of adult-born neuron in the hippocampus (Boldrini et al., 2013; Meyer et al., 2012). These findings together have implicated impaired neurogenesis in the aetiology of many psychiatric disorders (Anacker & Hen, 2017; Besnard & Sahay, 2016; Jacobs, van Praag, & Gage, 2000; Kempermann & Kronenberg 2003; Kheirbek et al., 2012).

Due to the complexity of investigating neurogenesis *in vivo*, no study as of yet has directly measured neurogenesis in psychiatric patients. In a postmortem study, Boldrini et al (2013) reported a smaller neural progenitor population in the brains of untreated patients with major depressive disorder compared with non-psychiatric age-matched controls. Reif et al (2006) were unable to detect such an association with postmortem histological studies of individuals with major depressive disorder, but they did find smaller pools of progenitors in schizophrenia patients. Contrary to Boldrini (2013), Reif's (2006) sample included treated depression patients, and thus the neurogenic effects of some antidepressant drugs may have contributed to their results. As previously mentioned, the consistently low volumes of hippocampi among psychiatric patients may be evidence for a decreased propensity for neurogenesis (Boldrini et al., 2013). In support of this theory, antidepressant studies in rodents have implicated increased neurogenesis specifically in the efficacy of such drugs at reducing certain depressive- and

anxiety-like behaviours (Santarelli et al., 2003; David et al., 2009). Though exculpatory evidence indicates that neurogenesis-dependent drug responses may be dependent upon mouse strain (Holick et al., 2008), the type of antidepressant (Surget et al., 2008), and the behavioural paradigm utilized (David et al., 2009), the evidence remains that, at the very least, neurogenesis is a significant piece of the puzzle.

The mechanism by which impaired neurogenesis is associated with psychiatric disorders was initially described as impaired pattern separation, resulting from the loss of the adult-born neuronal population (Kheirbek et al., 2012). The loss of sparse neural coding may result in a phenomenon called ‘generalization,’ whereby environmental cues signalling danger are generalized to contexts which share only vague similarities with the initial danger cue. Due to the overlapping in signals within the DG/CA3 circuit, a similar cue can trigger a memory that results in the expression of fear (see Figures 5 and 6). Though many maintain that ablation of neurogenesis *per se* is insufficient to produce anxiety- or depression-like behaviours *de novo*, some animal studies have demonstrated that enhanced anxiety-like behaviours such as decreased novelty exploration after ablation of neurogenesis (Denny et al., 2012; Jessberger et al., 2009). One possibility is that the overall mood state may affect the processing of information carried out by immature neurons (Becker & Wojtowicz, 2007).

Neuroimaging studies of people with anxiety disorders largely support the notion of fear generalization, and classical conditioning paradigms have been

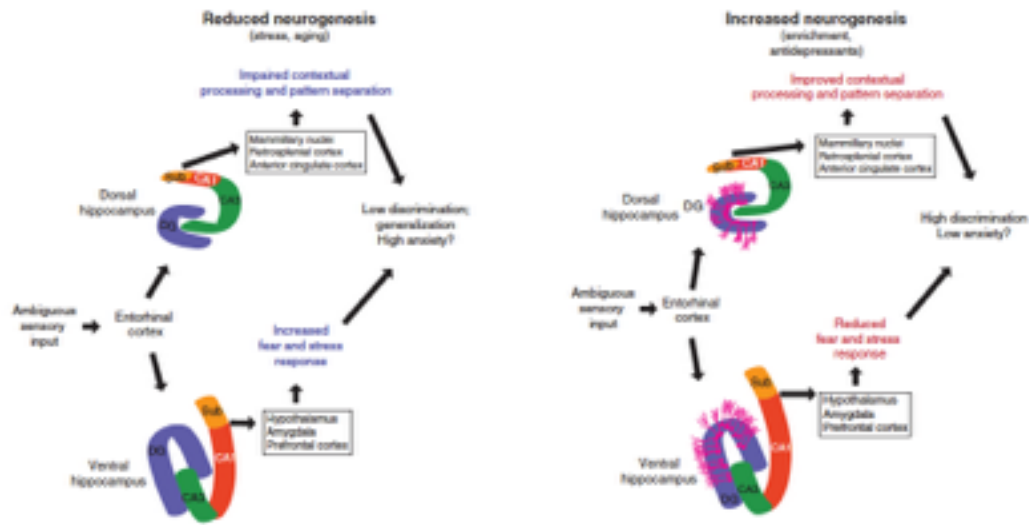


Figure 5: Depiction of hippocampal connectivity under conditions of reduced and increased neurogenesis (Kheirbek et al., 2012a).

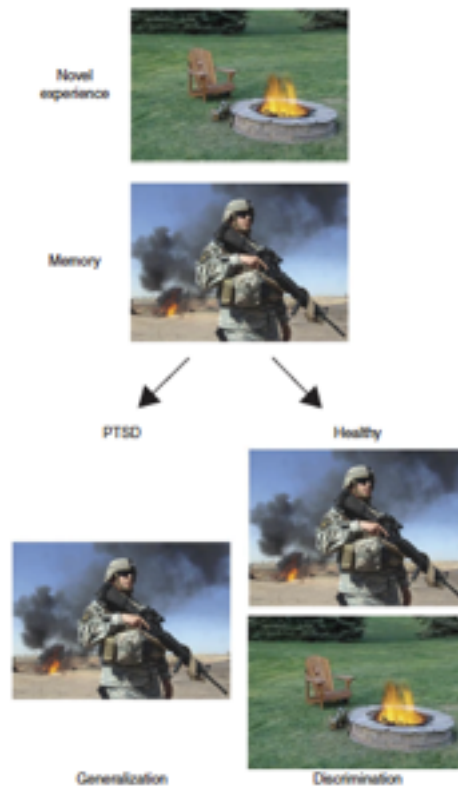


Figure 6: Implication of generalization of memory representation in posttraumatic stress disorder (Kheirbek et al., 2012a).

helpful in this regard. Behavioural indicators of generalization such as increased startle response, heightened responsiveness to danger cues, and the presence of anxiety to neutral stimuli have been noted in psychiatric disorders such as Posttraumatic Stress Disorder, Panic Disorder and Social Anxiety Disorder (Bouton & Moody 2004; Hayes et al., 2011; Lissek et al. 2008, 2010; Mineka & Zinbarg 2006).

2.2.6 High memory interference in humans: tests of Mnemonic Similarity

Given our inability to measure neurogenesis *in vivo*, there has been great interest in a neuropsychological test that is putatively linked with neurogenesis. Kirwan and Stark (2007) developed what was initially referred to as a ‘behavioural pattern separation test’ (in the interest of recent evidence as discussed above, ‘mnemonic similarity test’ [MST] will be used to refer to this test for the remainder of this thesis) to assess participants’ ability to discriminate between highly similar stimuli. After an initial non-encoding phase where non-repeating images are presented one after the other, a test phase begins which involves the presentation of one third brand new images, one third the identical image as one previously presented (‘old’), and one third a highly similar ‘lure’ stimulus. The lure stimuli consist of highly similar images designed to maximize contextual similarity (see example images in Figure 7). Participants indicate whether each item is ‘new,’ ‘old,’ or ‘similar’ to a previous image from the presentation phase.

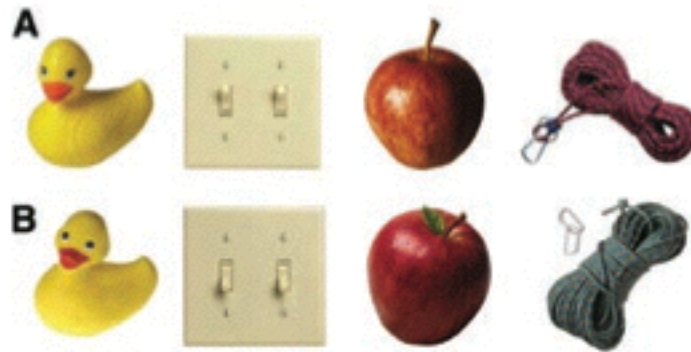


Figure 7: Example stimuli from Kirwan and Stark's (2007) Mnemonic Similarity Test. A) Image examples presented in the initial phase and B) their highly similar lures presented in the test phase.

Bakker et al (2008) demonstrated that participants' accurate identification of similar stimuli was associated with a strong signal in the DG/CA3 region on fMRI analysis, while old stimuli elicited a response from the CA1 and other medial temporal areas. Improving the spatial resolution of fMRI allowed Lacy et al (2010) to extend these findings to show the specificity of firing patterns of the DG by showing that, contrary to the CA3 region, the DG responded the same after presentation of a very similar lure stimulus as it did to a first presentation, potentially indicating recognition of novelty. The extent of DG activity was highly correlated with successful identification of lure stimuli, indicating perhaps the successful orthogonalized encoding of memory representations.

Clinical samples of individuals with neurogenesis-linked conditions provide convergent validity for the test's promising ability to indirectly assess neurogenesis *in vivo*. Studies have demonstrated a negative relationship between similar stimulus identification accuracy and the severity of self-reported symptoms of depression (Dery et al., 2013, 2015; Shelton et al., 2013). High stress levels have also been

been correlated with poorer identification of similar stimuli (Dery et al., 2015; Shelton et al., 2013), as have binge alcohol consumption behaviours (Goldstein et al., 2016). Non-demented older adults with mild cognitive impairments have also shown specific deficits at identifying lure stimuli but not old or new stimuli as compared with older, unimpaired adults and young participants (Holden et al., 2013; Toner et al., 2009). In all the above-mentioned studies, participants with conditions linked to impaired neurogenesis err on the side of generalization; rather than indicate a stimulus is ‘similar,’ they indicate they believe it is ‘old.’ Notably, none of the aforementioned studies have detected differences in accuracy with respect to either old or new stimuli.

One study assessed whether the implementation of an exercise program could improve performance on the MST. Dery et al (2013) took previously inactive undergraduate students and gave them a supervised aerobic exercise program to follow for 6 weeks. Responsiveness to exercise was determined by VO_2 max score (an indicator of fitness level), by which individuals on the program were divided into responders (fitness improved) and non-responders (no change in fitness level). Responders on average showed an 11% increase in accuracy at correct identification of a lure, while non-responders showed no change (0%). Again, there was no difference in accuracy at identifying repeat or foil stimuli, which speaks to the specificity of exercise’s effects on the identification of highly similar stimuli. This study has recently been replicated successfully (Heisz et al., 2017), and responders to the exercise program not only showed more accurate

identification of similar stimuli but also increased levels of serum neurotrophic factors such as brain-derived neurotrophic factor and insulin-like growth factor-1.

2.2.7 Animal models of mTBI: evidence for an impairment of neurogenesis

Direct investigations of postinjury neurogenesis have presented conflicting reports of the effects of TBI due to the limitations of bromo-deoxyuridine (BrdU) staining. BrdU specifically labels cells undergoing mitosis or DNA fragmentation; as such, BrdU labels dividing NSCs whose lineage has not yet been determined. Numerous reports noted extensive BrdU labeling after TBI, indicating that NSC proliferation that peaks at around 48 hours post-injury, which initially led to the conclusion that TBI stimulates neurogenesis (Dash et al., 2001; Kernie, Erwin, & Parada, 2001; Rice et al., 2003; Sun et al., 2005, 2007; Urrea et al., 2007). However, when others cross-labeled BrdU+ cells with neural and glial markers, it becomes apparent that TBI reduces the proportion of NSCs that become neurons (Gao, & Chen, 2013; Rice et al., 2003; Rola et al., 2006; Sun et al., 2007). NSC proliferation also occurs in the subventricular zone of the olfactory bulb (another neurogenic area in rodents) after TBI (Ramswamy et al., 2005), which may indicate that the brain increases pools of NSCs after injury, perhaps as an endogenous repair mechanism.

Evidence suggests that the increase in NSCs following TBI is directed to a glial fate. Gliogenesis is known to occur following TBI as an endogenous repair

mechanism (Hellewell & Morganti-Kossmann 2012). Rola et al (2006) noted that hippocampal astrocyte and monocyte markers were increased by 200-500% after injury, while markers of immature neurons declined over 7 days, and failed to increase to levels comparable to those of control animals by 2 weeks. This change was accompanied by a dramatic increase in BrdU + TUNEL staining between 6-24 hours following injury, indicating that many of the NSCs died off. Gao et al (2013) conducted a highly detailed examination of cell types following brain injury (Figure 8). Although TBI induced a twofold increase in BrdU+ cells in the SGZ at 48 hours post-injury, the number of new neurons generated by 5 weeks was lower than in the controls. The overwhelming majority of surviving cells were cross-labeled with astrocytic or microglial markers, and were located in the non-neurogenic areas, in a uniform distribution across the hippocampus. Taken together, the evidence indicates that while TBI does appear to induce a transient proliferation of NSCs in the dentate gyrus, neuronal differentiation is reduced in favour of glial lineage, thus reflecting an overall inhibitory effect on neurogenesis.

The impairment of neurogenesis following TBI in animals has important implications for postinjury memory disturbances, a known consequence of mTBI in humans. Animal mTBI models have indicated impairments to tasks that involve components of high memory interference such as contextual fear conditioning (Davies et al., 2016) and spatial learning (Ogier et al., 2017), which may be a reflection of impaired neurogenesis. These effects may be dependent on the type of mTBI model utilized (Mychasiuk et al., 2016). Neurogenic interventions such as

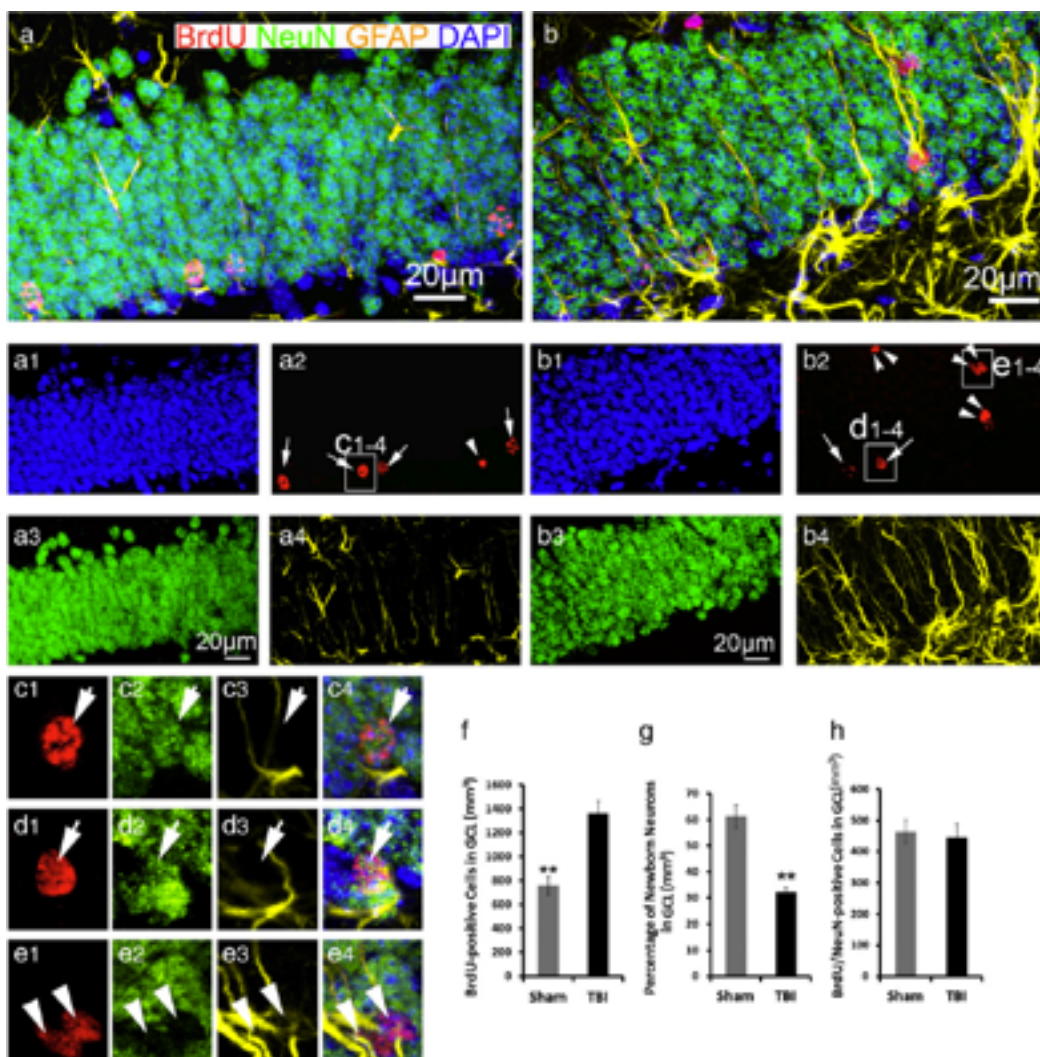


Figure 8: Neurogenesis and gliogenesis in the DG at 5 weeks following TBI or sham surgery (Gao et al., 2013). (a, b) GCL of (a) sham and (b) TBI mice. (a1-a4) depict individual channels of (a); (b1-b4) depict individual channels of (b). Nuclei with white arrows are >10mm in diameter, while arrowheads indicate nuclei <10mm (c1-c4). (d1-d4) BrdU and NeuN co-labeling newborn neurons in the GCL of sham mice. (d1-d4) BrdU and GFAP indicating newborn astrocytes. (f, g, h) surviving cell types in groups of mice.

peptide-6 administration (Chohan et al., 2015), and environmental enrichment (Briones, Woods, & Rogozinska, 2013; Chen et al., 2005; Gaulke et al., 2005; Giza et al., 2005; Kline et al., 2007; Will et al., 2004) have been shown to improve

cognition and recovery following TBI. While these studies have demonstrated an *a priori* effect for enrichment, it is important to note that the exercise component may only confer a benefit to recovery if an appropriate latency period is observed following the injury, which is time-dependent on the severity of the injury (Griesbach et al., 2007). Additionally, these results may speak to the recent evidence that exercise is beneficial to concussion recovery (Baker et al., 2012; Thomas et al., 2015), with some suggesting that return to normal exercise be used as an indicator of physiological recovery (Leddy et al., 2016).

2.2.8 Effects of mTBI on fear learning and anxiety: evidence for overgeneralization?

Anxiety can present in approximately 23% of mTBI patients within the first year following the concussion (Moore, Terryberry-Spohr, & Hope, 2006). In animal models, mTBI is known to induce anxiety-like behaviours (Davies et al., 2016; Fox et al., 2016; Meyer et al., 2012; Mychasiuk et al., 2016; Singh et al., 2016). These studies consistently report an increase in generalized anxiety behaviour such as decreased exploration of open spaces, decreased entries into the elevated plus maze (EPM), and greater freezing with extinction sessions compared with sham surgery controls. Pre-exposure to stress appears to exaggerate these anxiety-like behaviours (Davies et al., 2016; Ogier et al., 2017) which may be attenuated by blocking glucocorticoid receptors in the hippocampus, indicating that glucocorticoids such as corticosterone (cortisol, in humans) may be implicated

in post-TBI anxiety (Fox et al., 2016). While some have reported that environmental enrichment attenuates anxiety-like behaviours following TBI others report no protective effect (Johnson et al., 2013; Kovesdi et al., 2011). Johnson et al (2013) observed enriched and non-enriched head-injured mice and found an *increase* in behaviours related to a lack of anxiety, such as time spent and head dipping in the open arm of the EPM. Possibly, the injury protocol of controlled cortical impact to the frontal region resulted in increased risk-taking behaviours (Bechara et al., 1994; Floden et al., 2008), which would isolate its effects from a TBI-induced increase in overall anxiety (Pandey et al., 2009). Kovesdi et al's (2011) results demonstrated a mild but nonsignificant effect of enrichment on anxiety; however, this group used the blast injury model of concussion, which may be more similar to a severe traumatic brain injury due to the accumulation of neurodegenerative markers (Kovesdi et al., 2011; Xiong et al., 2013), and thus an insufficient recovery time for these animals before testing may have contributed to the conflicting results.

A study from Reger et al (2012) may shed light on the differential effects on anxiety behaviours following mTBI, and support the hypothesis that mTBI impairs neurogenesis which results in increased anxiety. They employed fear conditioning training over multiple sessions and reported that mTBI resulted in an increase in both cued and context-specific fear responses. It is well known that stress can impair neurogenesis and is highly related to the development of mood disorders in humans (Jacobs, van Praag, & Gage, 2000). One possibility is that the

increase in training sessions resulted in an overall increase in stress levels, which may perpetuate the detrimental effects on neurogenesis and exacerbate generalization to fear cues.

It is important to note that the substantial differences between human and rodents brains make it difficult to directly extrapolate insights gleaned from rodent research to their equivalent application to human mTBI victims (Spain et al., 2010). Furthermore, it has been noted that even between rodent brains show considerable pathological heterogeneity following identical brain injury protocols (Tutzo et al., 2012). These challenges firmly support the notion that an investigation which can generate conclusions about putative links to neurogenesis in humans is paramount in understanding post-mTBI sequelae such as impaired cognition and anxiety disorders. Thus far, *in vivo* exploration of neurogenesis-related markers in the human brain has been marred with complications, obstacles, and lack of reproducibility (for review, see Ho et al., 2013). The ability of a putative neurogenesis-dependent task that can be utilized in humans would have the utmost value in demonstrating the link between mTBI and impaired neurogenesis, and consequences to cognition and anxiety.

**CHAPTER 3: THE PSYCHIATRIC SEQUELAE OF MILD TRAUMATIC
BRAIN INJURY: A CRITICAL REVIEW OF THE LITERATURE AND
THE PRESENTATION OF TWO CLINICAL PROFILES OF
PSYCHIATRIC SEQUELAE**

McCradden MD¹, Rosebush PI², Mazurek MF³

Departments of Neuroscience (MiNDS)¹, Psychiatry and Behavioural
Neurosciences², and Medicine³ (Neurology), McMaster University Medical
Centre, 1200 Main Street W, Hamilton Ontario, L8N3Z5

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ABSTRACT

Mild traumatic brain injury (mTBI) is now recognized to carry the risk of developing a postinjury psychiatric problem, with depression and anxiety reported most frequently. While much literature exists on the topic, there are many questions left unanswered while methodological problems have limited our understanding of the precise etiological link between mTBI and psychiatric sequelae. The present paper provides a thorough review of studies investigating any psychiatric conditions that developed following mTBI in both adult and youth populations, and comments on the strengths and limitations of this literature. We identify key issues that have been thus far been left unaddressed which can aid our understanding of how to best to identify and treat these patients.

We also present results from a retrospective chart review study of a sample of 245 youth patients (less than 25 years of age) presenting to a neurology clinic with mTBI symptoms and fully recovered while under our care. Of these, 77 patients (30% of the overall sample) who had no pre-existing lifetime psychiatric problems experienced significant psychiatric symptoms during their recovery. Significant life stressors surrounding the time of the concussion was present for 20 individuals who were excluded from analysis, resulting in the inclusion of data from 57 individuals. Two clinical profiles were uncovered: 1) new psychiatric problems (n=43, 75%) which presented immediately following mTBI in the absence of any identifiable stressors; and 2) new psychiatric problems that developed secondary to persistent postconcussion symptoms (n=14, 25%) among

individuals who had concussion symptoms for several months. For 65% of these patients their psychiatric symptoms persisted past the point where their mTBI symptoms had resolved (e.g., headache, balance problems, etc.), with anxiety disorders being the most common persistent diagnoses.

In light of previous literature and our own results, it is evident that post-mTBI psychiatric problems are present in a subset of patients with no pre-existing psychiatric problems, pertinent stressors, or identifiable risk factors, and that clinical heterogeneity exists in the presentation and course of these symptoms. Those charged with the treating youth concussion should be attuned to the possibility of psychiatric sequelae that can develop directly from, surrounding, or in the aftermath of mTBI.

INTRODUCTION

Mild traumatic brain injury (mTBI) as a field of study has experienced a surge in interest over the past two decades. This newfound attention has largely been driven by high-profile athletes who sustained concussions like Sydney Crosby, as well as retired athletes like Eric Lindros, who has particularly drawn attention to the long-term neuropsychiatric problems following multiple concussions. A committee panel conducting the largest systematic review of published, peer-reviewed literature to date concluded that significant evidence exists to support an association between mTBI and the 6-month or more development of mood disorders, with possible links to post-traumatic stress disorder, suicide, psychosis, and drug/alcohol abuse (Hesdorffer, Rauch, Tamminga 2009).

The present paper will review and critique the literature regarding the psychiatric sequelae following mTBI in adult and youth populations. The full range of psychiatric diagnoses and symptoms is presented as they are denoted by the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (*DSM-V*; American Psychiatric Association, 2013). Youth psychiatric sequelae (including studies involving all individuals under the age of 18) are described as psychiatric/neurodevelopmental problems and psychobehavioural problems to reflect the main areas of inquiry within the literature. A summary discussion will follow to identify the limitations and outstanding issues within the literature as a whole. We also present the data from a sample of patients presenting with new onset psychiatric disorders following mTBI. Two clinical profiles were identified and are

described, as are the persistent psychiatric problems experienced by this sample. We conclude with future directions for the elucidation of the link between mTBI and psychiatric problems.

METHODOLOGY

A literature search was conducted using the following terms: *concussion*, *mTBI*, *head injury*, and *brain injury* in conjunction with *psychiatric*, *psychological*, *anxiety*, *depression*, *suicide*, *substance use/abuse*, *neurodevelopmental*, *attention deficit*, and *psychobehavioral*. Duplicates were removed, as were all reviews and non-English language articles, and relevant papers were identified by perusal of the abstract. Papers were included if they were primary articles assessing patients who were formally diagnosed with concussion/mTBI and subsequently developed psychiatric or psychological problems. Samples assessing military personnel (exclusively or by majority) were excluded. Iterative searches were then conducted of the reference sections of each of these papers.

Though definitions of “mild” TBI vary somewhat between studies (variations on the following diagnosis will be noted as necessary), generally these include individuals experiencing a biomechanical force to the head, resulting in *any* of the following: loss of consciousness (LOC) <30 minutes; posttraumatic amnesia (PTA) lasting no more than a 24-hour period; focal neurological deficits; altered mental status; Glasgow Coma Scale (GCS) of 13-15 (generally

describes a patient who, at worst, may have briefly lost consciousness, not fully oriented, localizes to painful stimuli).

Psychiatric diagnoses were collected in a wide variety of settings, with different individuals of various qualifications making the diagnoses, and utilizing a multitude of tools (i.e., structured clinical interview, clinical rating scale, open-ended interview, self-report, etc.). It is important to note that this heterogeneity of diagnostic protocols has likely contributed to the range of prevalence reports for psychiatric conditions following mTBI. Additionally, an important diagnostic consideration is that all studies disregarded the criterion of time in making diagnoses. For example, a diagnosis of generalized anxiety disorder (GAD) requires symptoms to be present for a 6 month period; this time requirement is disregarded, and the diagnosis relies solely on the reported symptoms. For this reason, adjustment disorder (which describes individuals with less than a 2-week symptom period) is not often reported as an outcome within the literature. An additional diagnosis that is not generally made is “mood disorder due to general medical condition” (in this case, the mTBI), due to the lack of certainty regarding mTBI as a purely causative factor of post-injury psychiatric problems.

ADULT PSYCHIATRIC SEQUELAE

Depression

Depression and depressive symptoms have been the most widely studied psychiatric phenomena following head injury. A major depressive episode (MDE)

constitutes a 2 week period of depressed mood or the loss of interest or pleasure in usual things, accompanied by symptoms such as significant weight change, change in sleep (hyper- or hyposomnia), psychomotor agitation or retardation, fatigue, feelings of worthlessness, excessive or inappropriate guilt, concentration difficulties, or suicidality. Dysthymia involves a chronic, unremitting mood state requiring fewer depressive symptoms to merit a formal diagnosis. In general, these and other depressive disorders are combined under the term “depression,” unless specified individually. While depression can be captured and supported by clinical rating scales (e.g., Beck Depression Inventory [BDI] score of >15 , Hamilton Depression Rating Scale [HAM-D] score of >20), one must note that depression is *clinical* diagnosis, thus necessitating patient contact by an individual trained in psychiatric diagnostics.

Epidemiological reports note that depression is present among the general North American population in approximately 7.4% of adults under 40, and 9.8% among older adults (40-59), with a slightly higher prevalence observed among females of all ages (Pratt & Brody, 2014). It is also well known that patients with a chronic medical illness are at a 2- to 3-fold increased risk of having a comorbid depression (reviewed in Katon, 2011).

Depression is a well-recognized potential consequence of mTBI among persons admitted to emergency centres, with 1-year prevalence rates reported from 8% to 50% (Bombardier et al., 2010; Bryant et al., 2010; Mayou et al., 2001; O'Donnell et al., 2004; Rapoport et al., 2003a,b). Elevated depression symptoms

detected on the Beck Depression Inventory-II (BDI-II) may be present in as many as 59% of TBI outpatients (Glenn et al., 2001), and can be elevated in athletes with concussion (Kontos et al., 2012). Post-mTBI depression is also frequently comorbid with anxiety (Jorge et al., 2004; Mayou et al., 2001; O'Donnell et al., 2004), and is associated with worse postinjury psychosocial functioning and more psychological distress and postconcussion symptoms (Rapoport et al., 2003a). While some have reported lower rates of depression among older (age 60+ years) versus younger mTBI patients (Rapoport et al., 2003b), others have noted that the risk of MDE following mTBI tends to increase after age 18 throughout adulthood (Levin et al., 2005).

Bryant and colleagues (2010) investigated new onset psychiatric disorders using DSM-IV criteria for 437 consecutive patients presenting to hospital with mTBI, who were not currently psychotic or suicidal, and found that 11.6% of the sample was diagnosed with a new depressive disorder by 12 months. The majority of these diagnoses were detected by 3 months, lending support to the notion that post-TBI depression is at least not solely the result of long-term coping with the symptoms. Bombardier (2010) assessed 559 head injury admissions to a level 1 trauma centre with a GCS of >13 and found that 50% of the mTBI patients reported new depressive symptoms significant enough to warrant treatment at at least one follow-up in the first postinjury year. This high rate may be explained by that fact that though they attempted to exclude individuals with preinjury depression, after conducting psychiatric interviews assessing the lifetime history of

depression, suicidality, or antidepressant use, they noted that 26% of the sample was determined to have experienced a prior depressive episode, and 15.7% were currently depressed at the time of the injury. Of note in both studies, mTBIs were largely sustained in MVAs (76%) and concurrent injuries were not mentioned. Bryant's (2010) random recruitment procedure utilized a balanced inclusion of short, medium, and long-stay patients — but patients with mTBI had higher injury severity scores than their non-TBI comparison group, despite no group differences in length of hospital stay (mean = 12.78 days for non-TBI, 11.79 days for mTBI). Despite meeting the criteria for mTBI, a stay in the hospital of this length suggests other injuries or medical conditions were present, and it is difficult to determine what influence these may have had on the development of depression following mTBI.

Importantly, one must consider the holistic view of the individuals involved in these studies to understand the link between mTBI and depression. The majority of population samples included in mTBI studies consist of individuals involved in motor vehicle accidents (MVAs). Inherent in these samples are complicating factors such as: legal issues (litigation as either victim or perpetrator), which are well recognized to be related to depression (Bay & Donders, 2008); substance and alcohol use, particularly at the time of hospital admission and its contribution to the injury; whether other injuries were sustained in the accident; and consequences due to the MVA, such as whether the mTBI patient injured others in the accident, and to what severity, or whether loved ones were injured as

well. These important psychological dimensions may well influence the onset and duration of depression following mTBI, and provide important context for understanding how mTBI itself may be implicated in depression.

At risk for developing depression after mild TBI are those with postinjury stress such as financial difficulties, abuse, death or the chronic illness of a family member (Bay & Donders, 2008; Bay et al., 2002, 2004 2012), lifetime childhood adversity (Bay et al., 2004), postinjury involvement in litigation (Bay et al., 2008), and substantial somatic symptoms (Bay et al., 2008; Kerr et al., 2012). Fear of employment complications after head injury may contribute to stress which can then influence the development of depression, or these experiences may be the result of a postinjury depression (Gomez-Hernandez et al., 1997).

A further consideration is the link between contact sport participation and the development of chronic traumatic encephalopathy (CTE). Though our understanding of the precise links between contact sport play, concussions, postconcussion syndrome, and long-term risk of psychiatric disorders is still in its infancy, the possibility exists that, given the age range of the majority of mTBI studies, some individuals who present with depression may be in the early stages of CTE. For an excellent review of the current state of the evidence on CTE, the reader is referred to Meehan et al (2015).

Attempts to isolate the effects of mTBI alone on the development of depression have utilized carefully selected comparison groups using individuals admitted to hospital for single or multiple orthopedic injuries not involving the

head. Compared with orthopaedic patients, mTBI patients report more severe depression symptoms up to 6 weeks after hospitalization (Ma et al., 2014), though others have failed to detect significant differences between similar patient groups (Malec et al., 2007). However, Malec et al's (2007) patients were assessed upon hospital release — within a few days for mTBI patients, while for the orthopaedic injury group the average date of discharge was 47 days. The orthopaedic group had therefore been in the hospital while the mTBI patients were home, which makes a true comparison difficult without considering important environmental factors which could contribute to the development of depression. Losoi et al (2016) carefully selected 74 adults — 40 with ankle injuries and no head injury, 34 with mTBI alone — who were assessed prospectively for 1 year on measures of post-concussion symptoms, cognition, depression, traumatic stress, quality of life, life satisfaction, resilience, and return to work. A subgroup of both sets of patients reported ongoing postconcussion or postconcussion-like symptoms (such as fatigue, headache, insomnia) at 1 year, of which a large percentage had reported depression, traumatic stress, and/or low resilience at 1 month postinjury. The authors note that all of the control patients with persistent symptoms had a concurrent mental health problem (such as depression or traumatic stress). Malec's (2007) finding that perception of injury-related impairment is the single most important contributor to the development of depression. The possibility exists that individuals prone to depression — which has long been linked with susceptibility

to negative interpretations (Beck, 1967) — are more likely to overestimate their injury severity, which in turns exacerbates depression symptoms.

Some have investigated whether antidepressant treatments might improve post-TBI vocational efficacy as well as mood. Ashman et al (2009) enrolled acute mTBI patients diagnosed with a new major depressive disorder diagnosis and a score of 18+ on the Hamilton Depression Scale (HAM-D) and gave 41 either sertraline (mean initial HAM-D of 27.5 for the group) or placebo (mean initial HAM-D of 25.2 for the group) to over 10 weeks. They saw a clinically significant recovery, defined as 50% or more reduction in the HAM-D score, in 59% of the sertraline group (mean HAM-D at end of treatment = 13.7) versus 32% of the placebo group (mean HAM-D = 16.2). When analyzing the specific effects of time, group and clinical measurements, time was the only significant predictor of improvement of depression symptoms. Similar negative findings have been reported with the use of amitriptyline, a tricyclic antidepressant (Dinan & Mobayed, 1992), though this study compared treatment response of 13 mTBI patients with 13 matched depressed patients without head injury without a placebo control group. On the other hand, Fann et al (2000) also administered sertraline to 15 depressed mTBI patients (sustained between 3 and 24 months prior) and found that the overwhelming majority of patients showed an improvement over time in measures of mood, physical, emotional, and social role functioning, as well as an improvement in multiple PCS symptoms and

neurocognitive testing. They did not, however, utilize a placebo comparison group which would have allowed for the discrimination of the effect of time since injury.

It is widely believed that the difference in response between antidepressant drugs and placebo has been overestimated, leading to the belief that antidepressants are more effective than the data conclusively demonstrate (Ioannidis, 2008). While some question this notion (see for example, Naudet et al., 2013), the fact remains that we are currently uncertain of the true influence of antidepressant drugs on symptoms of depression. Furthermore, recent evidence indicates that while depression is a single diagnosis, considerable heterogeneity exists in clinical profiles and perhaps even in neurological ‘biotypes’ — and these biotypes may dictate susceptibility to treatment response (Drysdale et al., 2017). Further, a meta-analysis of antidepressant use among mild- to moderate-TBI patients concluded that pharmacological intervention shows no significant beneficial effect on depression symptoms (Barker-Collo, Starkey, & Theadom, 2013).

A few studies have attempted to utilize neuroimaging to delineate mTBI with and without comorbid depression. In a sport-related concussion (SRC) sample, Chen et al (2008) compared 40 symptomatic concussed male athletes with and without newly presenting depressive symptoms between 4-7 months postinjury, and compared them to 16 controls without concussion. Using a sophisticated working memory task combined with fMRI, they demonstrated that task-related BOLD activity was significantly attenuated among concussed athletes

with depression symptoms in the dorsolateral prefrontal cortex (DLPFC), rostral anterior cingulate cortex (rACC), medial orbitofrontal cortex (OFC), and parahippocampal gyrus (PHG). When age and PCS symptoms were controlled for, severity of depression predicted grey matter density in the rACC, and the extent of task-related activity in the rACC and mOFC. The researchers noted that high levels of concussion symptoms were usually correlated with depression levels, but a subset of athletes with high symptom scores did not have any depression symptoms. When comparing these two groups, a significant difference emerged in the rACC and mOFC: high PCS athletes without depression showed similar activation patterns to the control group, while those with high PCS and depression symptoms showed significantly attenuated activation in these regions. Hypofrontality, particularly in the DLPFC, is commonly reported among depressed patients without head injury, in addition to increased activity in limbic areas such as the amygdala and insular cortex (Dunlop & Mayberg, 2014). Chen's (2008) results indicate that concussed athletes with depression symptoms show similar brain activity patterns to those without concussion; however, it is interesting that differences emerged between depressed and non depressed groups who both had high levels of symptoms. This finding suggests that there may be a neurobiological substrate underlying post-injury depression that is independent of the severity of postconcussion symptoms.

A recent study (Alhilali et al., 2015) involved 45 mTBI subjects with depression (n=38), anxiety (n=32), or irritability (n=18) compared to a control

group of 29 mTBI patients without neuropsychiatric problems, matching for demographics and performance on neurocognitive tests. The researchers utilized diffusion tensor imaging (DTI) to assess regional fractional anisotropy (FA; a measure of axonal integrity). MTBI patients with depression had significantly lower FA in the right nucleus accumbens, anterior limb of the internal capsule, and superior longitudinal fasciculus, while anxious mTBI patients had lower FA in the cerebellar vermis (associated with primitive fear conditioning responses). The authors note that nowhere in the brain were FA levels lower in the control group compared with the depressed or anxious groups, and irritable mTBI patients presented similar FA to control subjects. While the authors note that areas affected by post-mTBI depression overlap with findings in nontraumatic depression, the largest study to date using vigorous statistical methods demonstrate that there are likely no substantial differences among unmedicated depressed patients and healthy controls (Choi et al., 2014). White matter changes on DTI are reported to be common, but vary in location and severity after mTBI (the reader is referred to Asken et al., 2017 for a thorough review of DTI findings after civilian, military, and SRC mTBI populations). Alhalali's (2015) study represents the first attempt to describe differing white matter changes across post-mTBI psychiatric symptoms, which suggests that different injury patterns affecting white matter may be associated with different postinjury psychiatric symptoms.

Previous assumptions in SRC literature were that any depressive symptoms in concussed athletes were related to their being removed from the team or the loss

of physical activity associated with athletic activities (Mainwaring et al., 2012). In contradiction of these beliefs, Mainwaring (2010) and Hutchison (2009) have demonstrated that postinjury mood symptoms present differently in athletes following musculoskeletal injuries (Hutchison 2009) and tears of the anterior cruciate ligament (ACL; Mainwaring et al., 2010) as compared with concussion in varsity athletes. Using the profile of mood states (POMS) questionnaire administered regularly following either head or non-head injury, both studies demonstrated that while physical injuries result in a large spike in anger that slowly subsides, concussion is associated with an overall mood disturbance that resolves around 2 weeks, in keeping with the average recovery time from concussion in this age group (McCrory et al., 2013). A similar pattern of depression symptoms was detected in high school and collegiate athletes using the BDI, which found elevated depression symptoms up to 2 weeks following concussion (Kontos et al., 2012). Roiger et al (2015) reported no significant differences between concussed and nonconcussed sport-matched athletes, but concussed athletes showed elevated depression levels compared with their own baseline up to one month following the injury. As the results from Chen et al (2008) indicate, there may well exist subsets of athletes who are at risk for clinical depression following SRC. If this is the case, group-wise comparisons may mask significant changes to depression levels among subsets of athletes. Both of these studies carefully excluded individuals with pre-existing psychiatric issues, which, coupled with Mainwaring's (2010) and

Hutchison's (2009) results, speaks to concussion's potential effect on the development of mood disturbances during recovery.

Some have demonstrated that post-mTBI performance on neurocognitive testing can be negatively affected by the presence of depression symptoms (Chamelian et al., 2006; Hutchison et al., 2009; Kontos et al., 2012). In non-head-injured patients with depression, cognitive dysfunction is common enough to prompt the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-V) to include symptoms such as 'diminished ability to think or concentrate' and 'indecisiveness' in the symptom list, in recognition of the notion that cognitive dysfunction is a core feature of the disorder. It is well recognized that it is ineffective to test cognition while a person is depressed; however, this presents a significant problem for concussed athletes, since the decision to return an athlete to play is often determined by neurocognitive testing. As such, neglecting potential depression symptoms among concussed athletes could result in their being unduly removed from their sport — an action that could actually exacerbate their depression symptoms.

Kontos et al (2012) assessed 75 concussed high school and collegiate athletes on the BDI-II and the immediate postconcussion assessment and cognitive test (ImPACT; a computerized neurocognitive test widely utilized in concussed athletes) at baseline and in the 2 weeks following injury. They found that depression symptoms were significantly elevated at 2, 7, and 14 days postinjury, and that the severity of depression symptoms was correlated with poorer reaction

time and visual memory. While this result shows that postconcussion depression may be related to neurocognitive test performance, caution is warranted given that the study did not use a control group of athletes with and without depression symptoms, nor did they assess effects of depression alone on ImPACT performance. Supporting Kontos et al's (2012) findings are other reports demonstrating that the presence of major depression (Rapoport et al., 2003a) and untreated depression/anxiety (Yengo-Kahn & Solomon 2015) in mTBI is associated with poor neurocognitive performance overall, and particularly slower processing speed, memory, and higher symptom scores. One potential difficulty with making inferences from these findings is the lack of inclusion of information regarding current pharmacological medications or alcohol use (Kontos et al., 2012; Rapoport et al., 2003a), which can potentially affect neurocognitive test performance. While some composite and symptom measures have been shown to have a positive association with use, others such as psychostimulants may have a negative influence in athletic (Yengo-Kahn & Solomon 2015) and non-athletic psychiatric samples (Advokat 2010); still, quite little is known about the effects of such medications in baseline or postconcussion neurocognitive assessment, particularly in youth (Reddy et al., 2013). It is, however, fairly evident in psychiatric samples and healthy controls that antidepressant medications can have a positive effect on neurocognitive test performance (Advokat 2010), and thus must be considered as covariates in analysis. It is important to understand the precise relationship between postconcussion depression and neuropsychological

testing because these test results are often utilized to make return-to-play decisions. If false positives are the result of a mood condition and not postconcussion symptoms the athlete may be needlessly kept from an activity that has antidepressant effects.

Patients with depression also tend to report more PCS symptoms (Fann et al., 1995, 2000; Horner et al., 2008; Trahan et al., 2001), which has elicited criticism from those who note the significant overlap in symptoms between depression and PCS (Box 1), and prompting some to argue that almost anyone with PCS could also be diagnosed with depression (Iverson 2006). However, this argument is retained only if one disregards the core criteria for a depression

Box 1: Comparison of depression (DSM-V) and postconcussion symptoms (Postconcussion Symptom Scale)

Depression Symptoms	Postconcussion symptoms
Difficulty concentrating, making decisions, remembering	Difficulty concentrating, remembering
Fatigue, decreased energy	Fatigue, drowsiness
Insomnia or hypersomnia	Insomnia or hypersomnia
Irritability	Irritability
Aches and pains, headaches, cramps, digestive problems	Headaches, nausea
Loss of interest in pleasurable activities	Numbness
Depressed mood	Sadness
Psychomotor agitation or retardation	Dizziness, balance problems
Worry, anxiety, feeling tense	Nervousness
Feelings of guilt, worthlessness, helplessness, hopelessness, pessimism	More emotional
Significant weight change, change in appetite	Visual problems
Suicidality	Phono- and photophobia

diagnosis (a depressed mood or loss of interest/pleasure), and ignores the transient nature of PCS symptoms for the overwhelming majority of cases. Indeed there is considerable overlap in symptoms, and it has been observed that depressed outpatients without a head injury can score higher on PCS scales than non-depressed head injury patients (Lange et al., 2010). Importantly, one ought to be cautious in interpreting PCS symptoms under the umbrella of the depression diagnosis — while the overlap in symptoms does present a complication, treating the concussion symptoms could very well improve the depressive symptoms. Thus, focusing on the concussion symptoms first and foremost seems the most beneficent course of action for the patient, and once dealt with one can concern oneself with any residual depression.

A noteworthy consideration (for post-mTBI depression and all psychiatric disorders) is that the mTBI may represent the first point of contact with the healthcare system, providing the opportunity for the detection of psychiatric problems. While many studies attempt to collect premorbid psychiatric history by structured interviews or medical records, the possibility remains that symptoms may have been present but unnoticed before the head injury provided an opportunity for them to be contextualized and diagnosed. Additionally, patients are not always aware of psychiatric symptoms and may not recognize whether a condition may have been present prior to the head injury. This, coupled with the fact that many psychiatric history interviews are conducted in the acute

concussion stage, leads to the possibility that premorbid rates of psychiatric history are underestimated.

Taken together, the evidence suggests that mTBI may influence the development of depression, which is related to perceptions of symptom severity and injury-related impairment. Postinjury depression symptoms may well have an underlying neurobiological substrate that may be the direct consequence of the mTBI itself, given the proximity of symptom presentation to the injury and the independence of these changes from symptom levels. However, little is known about the heterogeneity of depression after injury; what is the difference between a concussed person who presents with depression symptoms in the days following the injury and someone who develops depression after several months? Further research is needed to describe the presentation and course of depression, as well as the relevant psychosocial and circumstantial factors surrounding and following the mTBI.

Anxiety

Anxiety disorders involve the anticipation of perceived threats, and are differentiated by the specific type of threat with which the individual is preoccupied. The anxiety tends to involve an overestimation of risk/danger, and is typically accompanied by symptoms such as impaired concentration, edginess/restlessness, irritability, or initial insomnia. Within the mTBI literature, “anxiety disorder” typically encompasses all or some of: generalized anxiety disorder

(GAD), social anxiety disorder, phobic disorders, and panic disorder.. Posttraumatic stress disorder (PTSD) is also often added under this heading; however the literature on PTSD and mTBI is substantial, and will be discussed in its own section.

Generalized anxiety disorder (GAD) and other anxiety disorders

Bryant (2010) studied a mild TBI sample (described above) and reported rates of new onset GAD at 9.5%, agoraphobia 6.5%, social anxiety disorder 5%, and panic disorder 3.5%, all of which were nearly twice as likely to occur among mTBI survivors than non-head injured ED outpatients. Anxiety is the most frequently observed postinjury psychiatric comorbidity, present in association largely with major depressive disorder (Fann et al., 1995; Jorge et al., 2002). In one large-scale study of older 1560 mTBI survivors (ages 45-64 years; Horner et al., 2008), anxiety was included in the assessment of mood and affective symptoms and it was reported that as many as 40% of those who presented to hospital with mTBI showed significant mood/anxiety symptoms within one year. Using a multivariate odds ratio the authors demonstrated that mood/anxiety problems were most common among those with a preinjury history of psychiatric or mood disorders, poor postinjury physical functioning and social support, and postinjury unemployment. Further, having a previous mTBI was associated with a 2.1X higher risk (95% CI, 1.4-3.1) of reporting postinjury mood/anxiety problems; a

finding which has been echoed among studies of retired professional athletes (Guskiewicz et al., 2007; Kerr et al., 2012).

Similar to depression, others have observed a higher prevalence of anxiety symptoms and diagnoses among mTBI patients compared with patients who sustained non-head injuries (Bryant et al., 2010; Ma et al., 2014; Schochuber et al., 1988) and compared with rates for the general population (Ashman et al., 2004). Covassin (2014), on the other hand, examined a sample of 136 concussed and orthopedically-injured athletes matched for sex, sport, and time lost to injury and found no significant difference in the prevalence of anxiety symptoms measured by the State Anxiety Inventory (SAI) between the groups. However, the concussed athletes felt they had significantly less social support in dealing with their injury, which was associated with their high anxiety levels at the time they returned to their sport. Quite possibly these results are reflective of athletes' attitudes toward concussion. Generally, athletes tend to underestimate the severity of concussion and are therefore less nervous as they expect a full and rapid recovery (Anderson et al., 2016), believing that other injuries (such as ligament or muscle tears) carry worse implications. Additionally, the SAI is a measure of state anxiety, which may be less likely to be subject to short-term situational changes. To the contrary, Meier (2015, 2016) utilized the Hamilton Anxiety rating scale (HAM-A) and found that concussed athletes had significantly higher levels of anxiety at 1 day, 1-2 weeks, and 1 month as compared with their uninjured teammates. The authors also found that cerebral blood flow (CBF) in some

cortical areas was inversely proportional to the magnitude of slow-to-recover athletes' initial psychiatric symptoms (Meier et al., 2015).. Though the sample size in the study was quite small (n=44 total, with n=17 undergoing all imaging timepoints), the results are consistent with other studies which have raised the possibility that some underlying brain dysfunction might contribute to postinjury psychiatric symptomatology (Chen et al., 2008; Jorge et al., 2007).

The anxiety response is the result of a coordinated effort by multiple, evolutionarily beneficial neurobiological loops (reviewed in Calhoon & Tye, 2015). In its pathological state, dysfunction may result from any one or more disruptions along these loops. Generally, the amygdala is first to respond to a potential threat detected by the sensory systems and thalamus. The basolateral nucleus of the amygdala (BLA) directs its fear response to the bed nucleus of the stria terminalis (BNST), which contains dense reciprocal connections with the ventral hippocampus (vHC). The vHC is a critical mediator of the anxiety response, and does so by accessing memories, resolving ambiguity, and integrating contextual cues to appraise the incident threat with input from the medial prefrontal cortex. Feed-forward cues are sent to the hypothalamus and brainstem nuclei to elicit autonomic responses to drive the fear response. It has recently been suggested that hippocampal neurogenesis (the process of the growth, maturation, and integration of adult-born neurons; Ming & Song, 2011) is implicated in anxiety responses (Besnard & Hen, 2016; Kheirbek et al., 2012). Under this hypothesis, impaired neurogenesis resulting in fewer adult-born neurons reduces discrimination of

similar contextual cues, creating a generalized fear response to a wider range of stimuli. The potential link between neurogenesis and post-mTBI anxiety will be discussed in more detail in the discussion section.

Posttraumatic stress disorder

Posttraumatic stress disorder (PTSD) has received a great deal of attention in the military due to the traumatic nature of the war environment as well as the high occurrence of blast-induced TBIs and the psychiatric sequelae of such injuries (Hoge et al., 2008; Bell et al., 2009; McKee and Robinson 2014). The present discussion will focus mainly on non-military samples, as blast-induced TBIs may have their own distinct pathology (Kaur et al., 1995; Duckworth 2013) and the aetiology of PTSD is a complex and poorly understood phenomenon (Elder et al., 2010; McKee and Robinson 2014).

PTSD was long believed to be the most common post-TBI psychiatric diagnosis among the general population (North et al., 1999; O'Donnell et al., 2004). Bryant et al (2010) reports that in a prospectively assessed population made up predominantly of motor vehicle collision survivors, the 1-year prevalence of new-onset PTSD was only 7%, with all cases being detected by 3 months postinjury. In sport-related concussion PTSD is typically not present, likely due to the nature of the injury mechanism. Additionally, sport-related concussion is not typically associated with initiation of litigation whereas work-related injuries and vehicular accidents can often result in the mTBI victim pursuing compensation.

Involvement in litigation relating to a head injury is strongly associated with prolonged neuropsychological dysfunction (Belanger et al., 2005; Bryant et al., 2010). As a significant proportion of MVAs involve litigation, and the majority of studies of mTBI involve those who were in MVAs, the understanding of the development of PTSD can become complicated by factors other than the brain injury.

Psychotic disorders

Certain reports have suggested that a history of moderate-severe head injury may be associated with increased risk of psychosis (Fann et al., 2004; Sachdev, Smith, & Cathcart, 1994; Wilcox & Nasrallah, 1987). These studies are supported by a recent meta-analysis which found evidence for this increase in risk, though a dose-response relationship with severity of TBI was not found (Molley et al., 2011). As the present discussion is focused specifically on mTBI, the discussion is limited to the few studies which have only examined mild head injury psychosis which presented *after* the mTBI.

Fann et al (2004) conducted a review of HMO records for all TBIs presenting to ERs, hospital, or outpatient clinics and divided their analysis by mild versus moderate-severe TBI (n=803 mTBI). They found that the only timepoint in which there was an increased risk of receiving a diagnosis of psychosis was at 13-24 months postinjury, *if* the patient had received a prior psychiatric diagnosis (odd ratio 2.1 [CI 1.0-4.3]). It bears mention that the presence of a “prior

psychiatric diagnosis” was confined to the one year prior to the mTBI, thus it is likely that the rate of premorbid psychiatric problems was severely underestimated in this sample. In addition, the authors present no indication of what these prior diagnoses were; therefore, it is possible that these individuals had prior psychotic episodes, which is the strongest risk factor for future psychotic episodes (Fujii et al., 2002).

Two studies involving pure mTBI samples have investigated patients with diagnoses of psychotic illnesses which were given *after* one or more mTBIs. AbdelMalik and colleagues (2003) examined 67 patients with schizophrenia or schizoaffective disorder from 23 families, including 102 unaffected siblings. Patients were asked about their history of head injury associated with a loss of consciousness, with circumstances of the injury and any sequelae recorded. Independent raters blinded to psychiatric diagnosis rated the severity of each head injury; all head injuries included for analysis involved at least a period of being dazed/confused, and at most LOC of under 1 hour. The researchers found that 23.9% of those with a schizophrenia diagnosis had sustained one or more childhood head injuries before age 10, compared with 11.8% of their unaffected siblings. History of mTBI corresponded to a 2.35X higher odds (CI 1.03-5.36, $p = .04$) of receiving a schizophrenia diagnosis when at least 1 childhood head injury was present, which remained significant after adjusting for family membership. Head injuries sustained during adolescence (11-17 years of age) were not significant ($p = .07$). Childhood head injury prior to age 10 was also associated

with a younger age at the first psychotic episode (mean = 18.4, SD = 4.0; no head injury, mean = 24.7, SD = 7.7; $p = .003$).

While AbdelMalik's (2003) study hints at a possible relationship between childhood head injury and psychosis, one must consider the effects of a possible attribution bias. Families with individuals who develop major psychiatric illnesses are very likely to adopt a constructive narrative with which to explain the development of this illness — head injury may thereby provide a plausible 'trigger' in this narrative. As such, for individuals affected by psychosis, parents and family members may be more likely to remember their previous head injuries as compared with unaffected siblings. This could lead to an underestimate of head injuries among unaffected children. One must also consider that schizophrenia is now regarded as a neurodevelopmental problem (Insel, 2010), and so those who will ultimately be diagnosed with schizophrenia may have shown abnormal behaviours during childhood. These behaviours can put one at an increased risk for situations that can be associated with head injuries such as bullying, self-injurious behaviour, or a lack of motor coordination and control. All of these factors can potentially explain a link between psychosis and mTBI, though this does not exclude the notion that head injury may still increase the risk of developing psychosis.

Deighton et al (2016) interviewed 747 participants considered to be at 'clinical high risk' (CHR) for psychosis (average age 18.5 years) and compared them with 278 healthy age-matched controls. All participants completed a

questionnaire pertaining to their history of head injury, which was rated by an observer blinded to psychiatric diagnosis. Participant exclusion criteria were: moderate-severe head injury (>30 minutes of LOC), 3 or more mTBIs, or any mTBI for which symptoms persisted over 2 months. Participant groups (mTBI vs no mTBI) differed significantly by IQ, with healthy controls displaying higher IQs than CHRs, regardless of mTBI history in both groups. 747 CHR participants were included; of the 85 who transitioned to psychosis 24 (28%) had a history of head injury, compared with 207 (32%) of the 654 non-transitioning patients. The overall CHR sample reported significantly more previous mTBIs as compared with healthy controls, which may indicate a propensity to head injury among individuals prone to psychosis, or, as previously stated, an increased likelihood of head injury recall in this group. Of the CHRs who transitioned to psychosis ($n=85$ with head injury; $n=207$ without head injury), those with previous mTBIs were significantly younger at the age of the first and the most recent mTBI ($p=.04$), with no overall differences in the total number of mTBIs or the severity. Both CHR groups (with and without mTBI) reported more experiences with bullying compared with controls, and CHRs with mTBI history reported the highest levels of bullying. Increased bullying has also been reported among mTBI-affected young adolescents without psychiatric illness as compared to those without a history of mTBI (Ilie et al., 2014).

As has been suggested (AbdelMalik et al., 2003), individuals from families prone to psychotic illness may be more likely to be ‘weird,’ which can make them

targets for bullying. This can lead to a double-hit of increased risk for psychiatric illness by increasing the likelihood that they will sustain a head injury, and by creating a psychological predisposition through increased stress or decreased social support. A recent meta-analysis supports this hypothesis, indicating that the risk of psychosis following TBI is highest among individuals prone to psychosis (Molley et al., 2011). Prospective, longitudinal studies would be required to discern the direction of the relationship between mTBI and psychosis.

Suicidality

A systematic review on the subject of post-TBI suicidality concluded that moderate-severe head injuries carry a 3-4 times increased risk of death by suicide than the general population, but that mTBI carries a similar risk to the general population (Simpson & Tate, 2007). In one of the seminal studies examining a range of head injury severities, Teasdale and colleagues (2001) determined that any head injury carried a 2-5X higher risk of dying by suicide from 1 month to 4 years postinjury. Two studies have specifically examined mild TBI and the risk of suicide (Bethune et al., 2016; Fralick et al., 2016).

Bethune et al (2016) assessed a consecutive sample of 871 patients who presented to the ER with mTBI. Patients were identified by abstraction of medical records and contacted for follow-up interviews at 3 (n=871) and 6 months (n=500). 6.3% and 8.2% of the sample reported suicidal ideation at the 3 and 6 month follow-up periods respectively, which was noted to be higher than the 3%

reported in the general population (Kessler et al., 2005). Social isolation was determined to be an important factor in the likelihood of reporting suicidality, particularly affecting divorced or widowed mTBI patients. The authors report a marked elevation in suicidal ideation among patients who were ‘victims’ (e.g., mTBI sustained as a passenger in MVA, or as a pedestrian hit by a car), and hypothesized that a loss of control may be related to likelihood of suicidality. This interpretation is consistent with the ‘learned helplessness’ model of depression (Maier, 1984); hopelessness has been shown to be a highly significant factor in association with depression and suicidality (Zhang & Li, 2013). The authors are the first to consider blood alcohol levels at the time of the injury, and they found a significant association between being above the legal limit for alcohol consumption and suicidality at both assessments. While this study highlights some important factors for suicidality in a community sample with mTBI, statistical methods were somewhat unclear and it is difficult to determine how premorbid and injury factors were controlled for in their determination of the associations with suicidality.

Fralick and colleagues (2016) conducted a 20-year study of concussion and suicide risk by extracting data from the medical records of Ontario residents and reporting the frequency of completed suicides as well as factors surrounding these deaths. The authors segregated concussion by whether it was sustained on a weekend or weekday. This distinction captured what was believed to reflect a difference in injury mechanism — while a concussion suffered on a weekday is

most likely due to a work-related injury, weekend concussions are more likely incurred in the process of recreational activities (note: no data was presented to ascertain this difference). Of the 235 110 patients who had sustained a concussion, postmortem coroner reports identified 667 completed suicides within the study period. This corresponded to a rate of 31 suicides per 100,000 persons — the rate of suicide among the general population at this time was 9 suicides per 100,000. The study identified a 3X higher absolute risk of committing suicide among those sustaining weekday concussion (29 per 100,000), while a 4X higher risk was found for those sustaining weekend concussions (39 per 100,000). After controlling for prior suicide attempts, pre-existing psychiatric conditions, male sex, low socioeconomic status, and substance abuse, there remained a 1.27 increased risk (CI 1.06-1.53) of suicide after a weekend concussion. With weekday concussion as a referent, an increased risk of suicide was most strongly predicted by a previous suicide attempt (multivariate adjusted risk ratio of 5.65 (3.26-9.81). Each subsequent concussion was associated with a 1.30 (1.12-1.63) increased risk of suicide.

While certainly compelling in their demonstration of an association between mild head injury and suicide, the authors had limited personal data for these patients — in particular, the presence of alcohol and other drugs, the mechanism of head injury, and medicolegal status of the patients, which would serve to illuminate the clinical picture of patients at risk for suicide following head injury. Though they attempted to exclude patients with more severe injuries,

between 1-18% of patients had positive findings on x-ray, CT, or MRI which may indicate that some injuries ought to have been considered ‘moderate’ rather than ‘mild.’ Additionally, though there may indeed be an association, considering the 5+ year latency (average of 5.7 years) between injury and suicide, the question remains as to whether there is a direct link between the two or whether peripheral factors may speak more to the risk of suicide in the mTBI population. The authors may also have underestimated previous psychiatric history by confining their analysis to include only diagnoses made in the one year prior to the incident concussion.

Aside from psychiatric diagnoses, drug problems, and socioeconomic status, personality factors may also predispose individuals to suicide following mTBI. One study examined the prevalence of head injury among individuals referred for depression in an outpatient care centre (Oquendo et al., 2004). Forty-four percent of the sample reported a history of mTBI, and the first suicide attempt followed the mTBI for 80% of cases. Using a backward stepwise regression model the researchers found that lifetime aggression and hostility were most predictive of a post-TBI suicide attempt, though these factors were equally predictive of suicide attempts in non-TBI samples as well. They also found that hostility and aggression were predictive of TBI itself, suggesting that both these personality traits may underlie the risk of sustaining a TBI and of demonstrating postinjury suicidal behaviour.

As has been touched on elsewhere, chronic traumatic encephalopathy (CTE), a dementing disorder associated with repeated head trauma such as in contact sports and military deployment, has also been associated with suicidality (McKee & Robinson 2014). Though a full discussion of CTE is beyond the scope of this review, it bears mention that a potential complication of the aforementioned studies is whether the study participants were in actuality suffering from CTE, and not a postconcussion psychiatric disorder. The age of onset of confirmed CTE cases has ranged from 17 to 64 years of age, and there appears to be a time lag between the cessation of participation in contact sports or the military and the onset of neuropsychiatric symptoms (McKee et al., 2009, 2013). The evidence for an association between mTBI and suicide is complicated by a plethora of non-injury factors, and it is difficult to know at this point whether mTBI itself can influence suicidality in the absence of other risk factors.

Personality disorders

While some have investigated the development of personality disorders following moderate and severe TBI (Hibbard et al., 2000; van Reekum et al, 1996), no studies have investigated or quantified new onset personality disorders following mTBI.

Substance Abuse

Substance use disorders can be both precedent and antecedent to head injury. People who drink are more likely to fall, get in fights, etc. and thus increase their risk for sustaining a head injury (Oquendo et al., 2004). Subsequently, postinjury situational factors may potentially increase one's likelihood to drink as a response to factors such as social isolation, stress, and job-related concerns. Certain studies have noted that substance abuse can actually *decline* in the year after head injury, which is potentially a reflection of physician advice to avoid drinking, or as a result of dealing with persistent postconcussion symptoms (Ashman et al., 2004). Similarly, Bryant (2010) found only a 2.5% incidence of new substance abuse after mTBI, which was noted to be below the population norm. Preinjury alcohol use may be associated with the development of psychiatric illness after TBI, which may be an indicator that a person is susceptible to psychiatric problems (Deb et al., 1999). Importantly, substance abuse may be most susceptible to memory bias if collected retrospectively, and, unlike psychiatric diagnoses or medications, may not be coded on many patients' medical charts.

YOUTH PSYCHIATRIC SEQUELAE

Only in recent years has more attention been directed to youth mTBI psychiatric sequelae. Early studies focused mainly on behavioural outcomes, while later studies began to look at the full range psychiatric sequelae. This section is divided as follows: 1) psychiatric and neurodevelopmental sequelae, which correspond to diagnoses made with the DSM; and 2) psychological and

psychobehavioural outcomes, which examine a range of psychological symptoms, behavioural and personality changes; and 3) family factors which may be associated with increased likelihood of reporting psychiatric/psychological symptoms following mTBI.

Psychiatric and neurodevelopmental disorders

Attention deficit with hyperactivity disorder (ADHD)

Until quite recently the consensus was that the most likely post-TBI diagnosis among children was ADHD (Bijur et al., 1990; Massagli et al., 2004; McKinlay et al., 2009). However, a significant limitation of these studies is the lack of consideration of the high rate of pre-injury hyperactivity, number of hospitalizations, and aggressiveness reported among children who sustain a head injury (Bijur et al., 1990). Additionally, it has been well documented that youth who have attention problems are more likely to sustain injuries in general, and ADHD appears to be equally prevalent among mTBI and orthopedic injury groups (Basson et al., 1991; Max et al., 2004).

McKinlay (2009) utilized a birth cohort of 1265 New Zealand-born children who were studied at birth, 4 months of age, and yearly until 16 years of age and found that by 14-16 years of age, a mTBI (involving LOC <20 minutes, GCS 13+, and no skull fracture) sustained between 0-5 years old increased the likelihood of ADHD, and conduct disorder/oppositional defiant disorder (CD/ODD, and substance abuse issues). MTBI patients were divided into hospital

inpatients (n=19, hospital stay <2 days, no other injuries) and outpatients (n=57, no hospital stay or were seen by a general practitioner), and 839 individuals without head injury used for a reference group. Among those admitted to hospital there was an increased risk of postinjury mood problems, but not among hospital outpatients. While the study has a large age range and admirable follow-up length, the authors somewhat vaguely describe that "measures were chosen to provide sufficient information for a *Diagnostics and Statistical Manual of Mental Disorders* (Third Edition, Revised) (*DSM-II-R*)," and no single standardized interview was conducted. Without any data regarding postconcussion symptoms and limited knowledge regarding what constitutes a 'concussion' in this very young age range (from 0-5 years), one is left to wonder about whether a concussion was actually sustained which could potentially impact the development of these children. In addition, the study reports a curiously high rate (43%) of psychiatric disordered behaviour (diagnosis of anxiety, mood, substance abuse, CD/ODD, or ADHD) among the reference group. Indeed, others report psychiatric issues occurring in 16-20% of children who report to hospital or outpatient clinics for non-head injuries (Luis et al., 2002; Massagli et al., 2002). To improve upon these results would require a consistent definition of psychiatric disordered behaviour among children, and a direct comparison to a control group of the development of individual diagnoses following injury, as compared with the standard rate of development of psychiatric conditions in non-injured youth.

Schachar (2004) retrospectively assessed head injury history (abstracted from the medical record and divided by mild [GCS 13-15], moderate [GCS 9-12], or severe [GCS 3-8]) of at least 2 years prior to the study in children 5-17 years old. By parental interview, they excluded those with pre-head injury diagnoses of ADHD or learning disabilities. The presence of any head injury resulted in an increased likelihood of meeting criteria for ADHD, regardless of injury severity. Anxiety did not differ between head injured subjects and controls, though greater head injury severity was associated with greater levels of anxiety. The subjects were assessed between 2.1 and 15 years following the last head injury. Given this time, as well as the lack of awareness of psychiatric problems following youth head injury and the fact that all ratings were done by parents and teachers rather than the child him/herself, it is possible that psychiatric symptoms may have gone undetected.

One must consider that ADHD may be less of a consequence to mTBI and more of a concussion phenotype. Indeed, concentration problems and memory difficulties are detected in at least one third of youth mTBI patients (Barlow, 2016), and while it was previously believed that they, like adults, recover within a 1-2 weeks it has been recently been recognized that young patients (children and adolescents) can take several weeks to 3 months to recover (Purcell, 2014). Another noteworthy aspect to the complexity of post-TBI incidence of ADHD is the tendency for children with behavioural problems to sustain head

injuries at a higher rate than neurotypical children (Gerring et al., 1988; Light et al., 1998, Ponsford et al., 1999).

Mood, anxiety, and other psychiatric symptoms and disorders

Massagli (2004) conducted a large study including 1960 HMO patients, with 490 mTBI patients (excluded those with LOC of >1 hour or had intracranial lesions) matched 3:1 to a random but sex- and age-matched group of non-injured controls. Psychiatric diagnoses were indicated by the medical record, by filling a prescription for psychiatric medication, or utilization of psychiatric services. They found that 26% of mTBI cases reported a psychiatric diagnosis within 3 years of a head injury compared with 16% of non-head injured controls. An increased risk of developing a new psychiatric disorder was significant for mTBI subjects without a psychiatric history in the first postinjury year. When stratified by the type of psychiatric problem, only ‘other or unspecified mental disorder’ and hyperactivity carried a significantly elevated risk. The lack of detailed clinical information makes it difficult to interpret these results. With ‘unspecified mental disorder’ as the most common diagnosis and a lack of mTBI symptom measures, it is difficult to determine whether these subjects were simply presenting with postconcussion sequelae rather than a significant mental illness.

Studies which utilize more sophisticated methodology have begun to undermine the notion that mTBI carries no increased risk for the development of mood and anxiety disorders. Luis et al (2002) documented consecutive hospital admissions for youth aged 5-15 years and compared mTBI (n=45, 44% from

recreation, falls, or sport-related) to moderate/severe TBI (n=19) as well as to an orthopaedic injury control group (n=35) at 6 months following presentation to hospital. The groups did not differ in preexisting ADHD, head trauma, psychiatric disturbance, or postinjury litigation status. Using a structured clinical interview at 6 months postinjury, they found that new anxiety problems were detected in 35.7% of the mTBI group compared with 11.4% of the orthopaedic control group, and new mood problems were found in 21.4% of mTBIs, versus 2.8% of the orthopedic controls. The authors also found that psychosocial stress predicted the development of psychiatric problems, which is notable given that subjects who experienced abuse or neglect at any point prior to or during the study were excluded. In a similar study by Hawley (2003), who found that by one year, significantly anxiety (Hospital Anxiety and Depression Scale score 8-21) was present significantly more often in 42% of mTBI patients compared with 7% of controls (children of the same age, sex, and social background and in the same school class as mTBI patients). Significant depressive symptoms were detected in 11% of mTBI patients compared with 7% of controls, which did not reach statistical significance in a groupwise comparison.

Ellis and colleagues (2015) utilized the Pan Am program for surveillance of sport-related concussions to retrospectively investigate the records of 172 youth (<19 years of age) concussion patients, and the 20 of these (11%) who developed postinjury psychiatric outcomes. Among those with who developed a *new* psychiatric condition (n=19), 52.6% suffered a depressive disorder, 21.1% anxiety,

and 5.3% had mixed anxiety/depression. One additional case (5.3%) developed bipolar disorder, and one asymptomatic patient committed suicide. Upon presentation to a physician immediately following the concussion, all patients completed the postconcussion symptoms scale (PCSS). Patients who developed new psychiatric disorders (NPDs) scored higher on levels of sadness, nervousness, and emotional lability while reporting no differences in levels of irritability, suggesting that patients who may be at risk of developing NPDs can be identified upon first medical contact following concussion. There were no significant differences in the frequency of personal or familial psychiatric history between the NPD group versus the main sample. Notably 50% of the overall sample was presenting with their first concussion, while 75% of those who developed NPDs had reported 1 or more previous concussions. This finding is consistent with other studies noting an association between multiple mTBIs and increased mood symptoms in children (Liu & Li, 2013) and among former athletes (Guskiewicz et al., 2007; Kerr et al., 2012). Ninety percent of patients with NPDs also met criteria for PCS, which underlines the need for treating these patients for both a psychiatric condition and a persistent postconcussion syndrome. The authors note that for the vast majority these NPDs resolved, though no data are given to document how or when these conditions resolved, or their relation to any persistent concussion symptoms.

PTSD, though well studied in adults, is more scarce in the youth literature. Hajek et al (2010) reported that parent-rated PTSD symptoms among children

and adolescents did not differ from orthopaedic controls in the first year following mTBI. The sample largely consisted of recreation or sport-related injuries (57% of the sample), so perhaps this result is not unexpected. In contrast, O'Connor et al (2012) reported higher PTSD symptoms among mTBI-injured youth compared with orthopedically-injured youth, but their definition of 'mild' TBI is somewhat unclear, and may pre-select for more serious injuries.

Bloom (2001) found that depressive disorders were common new psychiatric diagnoses among children in the year following a mTBI, and noted that parents were more likely to be concerned with externalizing disorders (disruptive, oppositional, defiant, conduct behaviours) rather than internalizing disorders (anxiety and depression). This finding highlights the need for more attention to be paid to children following head injury to ensure that emerging psychiatric symptoms are detected and that appropriate help is given. Without disruptive, readily observed behavioural issues, internalizing problems in particular may go undetected, leaving such children vulnerable to long-term problems.

Perhaps the most notable objection to this literature is that with the exception of Luis (2002) and McKinlay (2009), all previous studies rely on medical records for their information regarding psychiatric complaints. Physicians in general are more hesitant about prescribing and diagnosing psychiatric conditions in children and adolescents, and thus information on the medical charts may insufficiently describe the child's state of mind. Additionally many youth with

psychiatric or psychological complaints may seek out help from a variety of sources such as counsellors, psychotherapists, and social workers whose input may not be included in a medical chart.

Psychological and psychobehavioural problems

Some studies avoided the categorization and diagnosis of the psychiatric sequelae of head injury and instead focused on psychological outcomes after mTBI. Basson and colleagues (1991) conducted a well-designed cross-sectional study of trauma and non-trauma hospital admissions to examine such outcomes as a function of head injury. Two hundred and sixty-four children under 18 years of age were grouped by trauma with head injury (GCS >13, negative CT scan), trauma without head injury, and emergency appendectomy, with their siblings (n=64) used as a control group. Individuals with pre-existing psychiatric or delinquency were excluded in order to specifically isolate new postinjury psychobehavioural issues, and groups were matched for age, race, parental insurance, and demographic neighbourhood (note: more boys presented in both trauma groups). A phone interview using the Achenbach's Child Behaviour Checklist was conducted by a social worker with the child's parent between 2 months to 5 years following the incident, and a substantial psychobehavioural change was defined as 4 or more new disruptive behaviours that followed the incident. All trauma cases reported an increase in hyperactivity, scholastic difficulties, rage attacks, and emotional changes; however, 48% of the head injury

group had significant psychobehavioural changes postinjury as compared with 30% of the non-head injured trauma controls, and 0% of the appendectomy patients. The authors note that among head-injured children, psychological problems were not concentrated in any specific area; rather, they demonstrated a range of disturbances, which for nearly all (96%) surfaced in the first month following injury.

Hawley (2003, 2004) conducted a similar study involving 419 mTBIs assessed between 6 months and 5 years postinjury who had been admitted to a hospital between 5-15 years of age, and were matched them by age and sex with non-head injured controls. Twenty-one percent of the mTBI patients were noted to have persistent personality changes (Hawley 2004), a finding that has been echoed among other studies documenting personality changes after youth concussion (Bloom et al., 2001; Liu & Li, 2013). MTBI youth were at particular risk of developing emotional problems (73.5%), temper control problems (59%), and mood fluctuations (61%) (Hawley 2003).

It is important to note that while Hawley (2003, 2004) and Basson et al (1991) were effective in collecting large samples with multiple comparison groups, the substantial range from the time of the injury to the time of the study interview makes it difficult to determine what role the head injury had in the development of these problems. Hawley (2003) reports that only 11.7% of mTBI subjects were assessed within 1 year of the injury, and 34.7% (mTBI) were still affected by postinjury problems, though they report that these were often from other injuries

sustained in the event. Further, there is no indication that they considered behaviours which pre-dated the head injury. While Basson (1991) did exclude those with pre-existing psychiatric problems, considering the follow-up range it is difficult to tell whether a potential memory bias might affect their results. The further from the head injury, the more difficult it would be to remember the following events, and parents with children who have a significant behavioural problem might be more likely to attribute these problems to the head injury. Additionally, we are given little information as to the relationship between postinjury psychobehavioural disturbances and postconcussion symptoms. Basson (1991) reports that 67% of psychobehavioural issues resolved, but again given the discrepancy in follow-up length it is difficult to determine how these issues were related to postconcussion sequelae.

In a recent and remarkably broad study, Ilie and colleagues (2014) administered an Ontario-wide health survey to grade 7-12 students, comprising 93% of the province's adolescent population. To assess history of concussion, participants were asked if they had ever been 'knocked out' for at least 5 minutes, or had to stay in the hospital at least 1 night because of a head injury. Twenty percent of the students had at least one lifetime TBI, which were observed more frequently in males and with no difference between the grades. The overall findings reflected a disturbing observation of elevated psychological distress, increased risk of being bullied, and increased engagement in bullying as a perpetrator among those with a history of TBI. Those with TBIs were more likely

to have been treated pharmacologically for anxiety and/or depression (5.9%, no TBI 2.7%; OR 2.45, CI 1.08-5.56). Especially concerning was the risk of suicidality: 15.2% of students with TBI history reported suicidal ideation representing a 1.52 increased risk (no TBI 9.2%; CI 1.19-1.94), and 5.9% reported at least one suicide attempt (no TBI 2%; OR 3.39, CI 2.15-5.35). Students with TBIs also reported being bullied more frequently than students without TBI at school and via the internet, or being threatened or injured with a weapon. In a perhaps paradoxical finding, TBI students were also more likely to be bullies themselves, experience threats or direct harm to others, carrying weapons, and getting into fights. Delinquent behaviours were also more common such as joyriding, drug use and distribution, theft, and breaking and entering.

Several aspects of Ilie's (2014) study are noteworthy. The study is quite likely an understatement of the association of these behaviours among individuals having suffered TBI due to the criterion of loss of consciousness, as it is well documented that at least half if not most concussions do not involve any LOC (Guskiewicz et al., 2000; McCrea et al., 2003). These students may, however, represent the more severe end of head injuries given that injury characteristics are not described or controlled for in terms of severity. The study's strength lies in the substantial numbers involved — a full 882 TBI cases compared with 3803 non-TBIs — and the scope of population studied, though institutionalized adolescents were not included which can again underestimate the risk. It also is one of the few studies that has relied on the mTBI subjects themselves reporting on their own

behaviour, while most previous studies rely on parent and teacher ratings or medical chart information.

Considering the nature of the study it is difficult to know whether youth who sustain mTBI are more likely to exhibit these behaviours *prior to* the head injury, or whether these behaviours are part of post-mTBI sequelae. Nonetheless, it does demonstrate that those who sustain mTBI are more likely to have multiple psychiatric and behavioural issues than those who do not sustain mTBI. Regarding the prevalence of bullying, the dichotomy of victimization versus perpetration is a complex one; are these the same individuals reacting to their own victimization, or are they different groups reacting in opposite fashion following a head injury? Limited evidence suggests that more severe TBIs are associated with greater peer victimization compared with orthopedic injuries, but this appears to be unrelated to injury-related deficits (Hung et al., 2017). It would also helpful to note the family situation, as others have noted that family functioning may have an impact on the trajectory of psychiatric changes following a TBI (Max et al., 1997, 1998).

Parent/Family factors in relation to postconcussion symptoms

Some notable research into the association between personal and family factors and the presence of postconcussion symptoms may shed some light on the likelihood of developing post-mTBI psychiatric sequelae. Yeates et al (2012) found that premorbid symptoms and behavioural problems were associated with

increased reporting of postinjury symptoms among both mTBI- and orthopedically-injured groups. This finding may indicate: that 1) those with premorbid psychobehavioural problems may experience worse postconcussion sequelae than neurotypical children; that 2) parents may be more likely to be attentive to postinjury symptoms if their child has had behavioural issues in the past; that 3) parents with children with psychobehavioural issues may be more sensitive to changes in functioning following an injury.

The presence and persistence of post-mTBI symptoms may be related to parental factors. In one intriguing finding, Yeates et al (2012) revealed that higher parent-rated somatic symptom scores were significantly related to higher family functioning and resources, particularly for those with mTBI and LOC. This modifying effect of family functioning was not significant for children's self-rated symptoms. The authors comment that this finding was counterintuitive, and suggests that perhaps family adversity may make it less likely that parents are attentive to mTBI symptoms, or that the lifestyle of higher-functioning families is more amenable to the detection of mTBI sequelae (i.e., higher demands in classes and activities, more supervision). We also suggest that higher functioning families may be more prone to somatization, particularly considering the media attention that has surrounded concussion in the past decade. These families may be more anxious about the impact of mTBI on their child, and be more likely to over-attend to the child's symptoms. This notion is supported by research demonstrating that over time, noninjury factors become more predictive of

parent- but not child-rated PCS symptoms, and that parental adjustment in particular predicts parent-rated PCS symptoms at 1 year (McNally et al., 2013; Olsson et al., 2013). Evidence from families where a child has a significant medical illness have likewise indicated that parental anxiety may be related to the child's anxiety (Koplewicz et al., 2002), though not all studies agree (Landolt et al., 2003).

A noteworthy difficulty of interpreting the literature is the lack of quantification and consideration of premorbid psychiatric or behavioural issues. In prospective studies, the propensity of those with behavioural problems to sustain mTBI could likely result in a very small sample size. An additional concern is that the averaging of group data concerning psychiatric symptoms could camouflage a subset of patients who have clinically significant elevations in these symptoms. Another concern, similar to the adult literature, is that the mTBI could present an opportunity for the patient's first intersection with the healthcare system — this could result in an over-estimate of postinjury behavioural problems, when in fact postinjury problems were present prior to the head injury. This is particularly true of studies in which the first follow-up is remote from the initial injury. To the contrary, underestimates of psychiatric symptoms are also possible; we have consistently observed that parents of adolescents are often more likely to attribute any mood-related symptoms to 'typical teen' behaviour, particularly in female adolescents. It is thus highly important to utilize both parent- and self-rated measures when evaluating post-mTBI sequelae.

DISCUSSION

The literature review presented in this paper considers the full range of potential psychiatric sequelae following concussion/mTBI. While it is now largely believed that mTBI can result in psychiatric problems at a rate higher than would be expected compared with other injuries, debate rages on as to the causality. The prevalent models within the literature are predominantly biopsychosocial models that consider pre- and postinjury factors (for an excellent review, see Brother, De Marco, & Freeman, 2015). While these factors are undoubtedly relevant to the problem, the underlying assumption appears to be that they wholly account for the presence of a new psychiatric problem. Indeed, the lack of consideration in all studies to date concerning postconcussion symptoms implies that we can distinctly observe two groups: mTBI subjects with concussion symptoms, and mTBI subjects with psychiatric symptoms. This differentiation promotes the view that one is either treated for concussion or for a psychiatric problem; a dichotomy that, in our experience, leaves many patients only half-treated. For improved knowledge about post-mTBI psychiatric problems, we must overcome these presumptions with better methodological designs.

Selecting appropriate comparison groups is essential to establishing effects specific to mTBI. Among children, adolescents, and young adults, appropriate non-injured comparison groups allow for the estimation of the normal rate of the development of psychiatric disorders compared with rates observed among head-injured individuals. While comparisons to non-head injured peers can

demonstrate how the type of injury might differentially be related to the development of psychiatric conditions, the additional comparison to a non-hospitalized, uninjured group would demonstrate the base rate of new onset psychiatric problems by which to compare the injured and head-injured rates.

Most studies neglect consideration of any current or prior medications that may influence postinjury behaviours. While some have studied whether pharmacological interventions can improve mood after mTBI (Ashman et al., 2009; Fann, Uomoto, & Katon, 2000), few studies have actually included medication data in both prospective and retrospective examinations of psychiatric diagnoses. It is therefore unclear how many mTBI patients might have been treated for a psychiatric condition and no longer meet diagnostic criteria, or how such medications might influence postconcussion symptoms, or how many patients are prescribed medication for postinjury psychiatric problems.

One must also strongly consider how most studies conceptualize "new psychiatric disorders" (NPDs; Max, 2014; Max et al., 1997): a psychiatric diagnosis received after mTBI would count as a NPD if that specific diagnosis was not present prior to the injury. In this case, a patient with a preinjury depression diagnosis counts as having a NPD if they develop a postinjury anxiety disorder. This classification scheme neglects the likely possibility that if an individual had a previous psychiatric condition, they may have an underlying vulnerability to future development of psychiatric issues. This method therefore may be overestimating the number of individuals with new psychiatric problems after mTBI. In addition,

among those who quantify pre-existing psychiatric disorders, the large majority of studies have included these diagnoses in only the year prior to the head injury, rather than assessing the lifetime history. One must wonder if this method for assessment of premorbid injury history holds any construct validity. If we are to say that an individual is vulnerable to psychiatric problems as a result of some underlying brain dysfunction, then it holds that we ought to assess lifetime history of psychiatric problems since this would best indicate such a vulnerability. To the contrary, if we instead assume that an individual who has recently suffered or is currently suffering from a psychiatric condition has a psychological vulnerability due to the difficulties inherent to such conditions, then recent psychiatric history may be sufficient.

A further consideration is that when pre-existing psychiatric conditions are prospectively quantified, it is usually done at the initial point of contact with study participants. This time would be very shortly after the mTBI event, at which point the person is very likely to still be experiencing symptoms. As structured clinical interviews can take as much as hour, plus the addition of other tests and questionnaires participants are expected to complete, this process may risk overtaxing the concussed brain and end up being less accurate. To the contrary, performing an assessment too far from the injury in someone who is still affected by mTBI-related sequelae can result in the 'good ol' days' bias which has been shown to likely result in overestimation of one's pre-injury functioning and underestimation of preinjury symptoms (Iverson et al., 2010).

Despite sport-related concussion being the most well-known and prevalent type of mTBI, relatively little evidence exists to describe the potential psychiatric sequelae. A 2016 review on the topic found only seven publications, most of which pointed to an increased prevalence of anxiety and depression in athletes with concussion (Finkbeiner et al., 2016). These publications consisted of: retrospective studies of former NFL players (Guskiewicz et al., 2007; Kerr et al., 2012), a survey of 5 National Hockey League (NHL) players (Caron et al., 2013), a dissertation about long-term anxiety and depression in former athletes (Marchese, 2005), and conference abstracts without a follow-up publication (Hong et al., 2013; Stern et al., 2011). A recent study (Topolovec-Vranic et al., 2015) involving a nation-wide survey given to youth athletes, coaches, parents, and medical professionals who were asked to identify mental health consequences of sport-related concussion indicated that only 53.5% of all respondents were able to identify these sequelae. To the contrary, 91.2% identified the cognitive sequelae and 84.2% identified the physical sequelae. Medical professionals fared best, identifying 70.3% of mental health sequelae, and females overall identified more mental health symptoms than males. This survey indicates that despite the increase in awareness surrounding concussion, mental health outcomes are less well recognized.

To address some of the methodological concerns presented in this paper, we describe here a group of patients with mTBI who presented to our neurology clinic with postconcussion symptoms and developed new onset psychiatric problems. We identified 245 young patients (<age 25) who presented to our clinic

with concussion symptoms and fully recovered under our care, from which we identified 77 cases (31% of the sample, 32M:45F) of new onset psychiatric problems. These cases were carefully screened for any potential pre-existing psychiatric problems, and we further excluded any of those for whom it became clear during a follow-up appointment that they may have had a psychiatric problem prior to the mTBI. A ‘significant psychiatric problem’ was determined by whether the psychiatric symptom(s) was more severe or different from the common postconcussion symptoms such as irritability, mood lability, and sadness. These patients were not on medications prior to the injury, and were not involved in litigation at any point during the follow-up. Injuries were sustained from either sport-related activities (90%) or a fall/accident (10%). From the 77 patients, we identified n=20 patients who had a significant stressor around the time of the head injury, such as family dysfunction, the death of a family member or friend, or severe academic/athletic/financial pressure. These factors were judged to be relevant to the development of psychiatric problems, and they were therefore excluded from this analysis so as to isolate patients who had no identifiable confounding factors,. Our 57 included patients were found to fit two into clinical profiles: 1) immediate psychiatric problem; 2) psychiatric problem secondary to postconcussion syndrome (results presented in Table A).

1. Immediate psychiatric problem: (n=43, 22M:21F, 75% of psychiatric cases) these patients presented with a new psychiatric problem overwhelmingly within the first week following the mTBI, and at most up to 1 month. No

significant stressors were identified prior to or within the immediate postconcussion period that were clearly linked to the development of the new psychiatric problem. These psychiatric problems were largely anxiety (44%) or mood (35%), with some suffering from both (16%) and a minority demonstrating behavioural or conduct issues (9%).

2. Psychiatric problems secondary to postconcussion syndrome: (n=14, 8M:6F, 25%) these patients were almost all university students (1 patient was in high school) who developed a new psychiatric problem after months of continued postconcussion symptoms. These PCS symptoms were judged to be relevant to the development of the psychiatric problem. Patients typically reported symptoms interfering with at least one domain of their lives (academic, athletic, vocational, interpersonal), with some individuals dealing with the loss of an athletic career, ongoing problems with academics, career transitions, or a suddenly sedentary lifestyle. These psychiatric problems were characterized almost entirely by anxiety (43%), mood (36%) or both (21%), with few demonstrating conduct/behavioural issues (7%).

These clinical profiles demonstrate that the majority of postconcussion psychiatric problems are not the result of coping with a brain injury, and that nearly one third of young adults may present with new psychiatric symptoms very shortly after the mTBI. The immediacy of the presentation of these symptoms in a substantial majority of psychiatric cases is in accordance with previous findings (Bryant et al., 2010; Ellis et al., 2015; Meier et al., 2015, 2016), and raises the

Table A: Clinical profiles of psychiatric postconcussion patients		
	Immediate Psychiatric Problem	Psychiatric secondary to persistent PCS
N (%)	N = 43 (75%)	N = 14 (25%)
Psychiatric symptom onset	< 1 month	> 5 months
Median age	16 years	21 years
Pertinent stressors preceding concussion	None identified	None identified
Stressors present during concussion recovery	None identified	Persistent PCS symptoms affecting work of interpersonal life, dealing with changes to or loss of athletic career, academic challenges as a consequence of PCS symptoms, sedentary lifestyle
Type of psychiatric problem	Anxiety 44% Mood 35% Mixed 16% Conduct/Behavioural 9%	Anxiety 43% Mood 36% Mixed 21% Conduct/Behavioural 7%
Psychiatric conditions persisting past the resolution of concussion symptoms	N = 27 (63%)	N = 10 (71%)
	Anxiety disorder (n = 16), depression (n = 5), mixed anxiety/depression (n = 3), adjustment disorder w/mood and conduct features (n = 1), FNSD (n = 1), mood disorder NOS (n = 1)	Anxiety disorder (n = 4), depression (n = 3), mixed anxiety/depression (n = 3), adjustment disorder w/mood features (n = 1)
<i>Functional neurological symptom disorder (conversion disorder; FNSD); not otherwise specified (NOS); postconcussion syndrome (PCS)</i>		

possibility that the head injury itself induces a dysfunction that can elicit psychiatric symptoms.

For 65% of the sample, psychiatric symptoms persisted past the point by which all other mTBI symptoms had resolved, resulting in the formal diagnosis of their ongoing psychiatric problem (full results presented in Table B). Anxiety was the most common diagnosis, with depression and mixed anxiety and depression also being fairly common.

These data indicate that psychiatric symptoms can outlast mTBI symptoms in the majority of patients who develop postinjury psychiatric sequelae. There are a number of reasons this might be the case: 1) psychiatric postconcussion symptoms may take longer to resolve from the mTBI-induced pathophysiological changes to the brain as compared with physical symptoms (i.e., headache, balance problems); 2) mTBI may elicit changes to neurobiological systems that contribute to the maintenance of psychiatric systems; 3) mTBI may

Table B: Prevalence of persistent psychiatric disorders among youth who recovered from mTBI

	N	% of psychiatric sample N=57	% of whole sample N=245
Anxiety disorder	20	35%	8%
Depression	8	14%	3%
Mixed anxiety/depression	6	11%	2%
Adjustment disorder	2	4%	<1%
Functional Neurological Symptom Disorder	1	2%	<1%
Mood disorder (not otherwise specified)	1	2%	<1%

reduce the brain's usual coping methods for handling stress or psychosocial adjustments following an injury. Note that these possibilities are not mutually exclusive; indeed, further research is necessary to understand how patients with postconcussion psychiatric differ from non-psychiatric cases, and what brain changes contribute to the persistence of psychiatric symptoms. To date, and to the best of our knowledge, none have directly compared mTBI patients with and without psychiatric symptoms to healthy controls with and without psychiatric symptoms. Such comparisons would be ideal in differentiating how mTBI-related neuropathology might appear similar or different to those with pure psychiatric problems.

Sporadic evidence comparing individuals with PCS alone compared with PCS and a psychiatric problem has indicated that underlying neurobiological substrates may be associated with certain psychiatric symptoms. Reduced hippocampal volume has been associated with the presence of a post-TBI depression and a reduced probability of returning to productive activity by 1 year postinjury, compared with TBI sufferers without depression and after controlling for pre-injury depression (Jorge et al., 2007). Decreased regional cerebral blood flow may be more profound in concussed athletes with elevated depression and anxiety symptoms and relate to poorer outcome by 1 month (Meier et al., 2015). Concussed athletes with elevated depression levels show more profound attenuation of prefrontal activity during a working memory task as compared to concussed athletes without depression symptoms (Chen et al., 2008). Fronto-

temporal white matter abnormalities 1 month post-mTBI significantly predict the presence of depression at 1 year postinjury (Rao et al., 2012). Retired contact athletes with depression show greater white matter abnormalities as compared with their non-depressed peers and an age- and education-matched healthy aging sample (Hart et al., 2013). While these studies illuminate potential differences between the brains of mTBI patients with and without psychiatric symptoms, it would be useful to compare these patients with individuals with the same psychiatric problem but without head injury, in order to attempt to differentiate neurobiological substrates of psychiatric comorbidities following mTBI.

One possibility for consideration is that mTBI impairs hippocampal neurogenesis. It has been suggested that hippocampal neurogenesis may be linked to depression (Anacker & Sahay, 2016; Kemperman & Kronenberg, 2003; Jacobs 2000) and anxiety (Besnard & Hen, 2017; Kheirbek 2012) — the two most common problems people report following mTBI. Evidence from animal models of TBI indicate that following head injuries, a shift from neurogenesis to gliogenesis impairs the birth and maturation of adult-born neurons until after a period of recovery in proportion to injury severity (Gao & Chen, 2013). Neurogenic interventions such as environmental enrichment (Briones, Woods, & Rogozinska, 2013; Chen et al., 2005; Gaulke et al., 2005; Giza et al., 2005; Kline et al., 2007; Will et al., 2004) and peptide-6 administration (Chohan et al., 2016) are able to attenuate some post-injury cognitive and behavioural deficits. Consistent with this hypothesis, individuals who are already at risk for depression

or anxiety (i.e., potentially with lower preinjury levels of neurogenesis) are most likely to experience worsening of psychiatric problems following mTBI. It may also explain the new problems that individuals without a pre-existing psychiatric history experience following mTBI.

Though it is generally acknowledged that an impairment to neurogenesis *per se* is insufficient to produce anxiety- and depression-like behaviours in animal models (Anacker & Hen, 2016), some have suggested that impaired neurogenesis may interact with an underlying mood state to produce anxiety/depression *de novo* (Becker & Wojtowicz, 2007). As mTBI is well known to elicit a disturbed mood state (Mainwaring et al., 2010; Hutchison et al., 2009; 2017), perhaps this disturbance interacts with impaired neurogenesis to produce anxiety and depression in the near 1/3 of individuals observed in prospective studies who develop these problems. Further, it may explain why the initiation of exercise early in the recovery phase is showing such promise for enhancing recovery in both acute and prolonged cases of concussion (Leddy et al., 2010; Majerske et al., 2008), and has been included in recent concussion in sport guidelines (McCrory et al., 2017).

CONCLUSION

Psychiatric sequelae of concussion/mTBI is an important target for research to allow us to better assist those with persistent problems following the injury. Reducing stigma associated with such sequelae could reduce bullying,

increase support for students, and improve return-to-play conditions for athletes. Further research might potentially identify biomarkers for the development of psychiatric sequelae, and provide an opportunity for early intervention. The literature must move forward with the careful consideration of the multitude of factors which can affect the development of psychiatric problems, and, while not specifically addressed in our study, also address how premorbid psychiatric disorders can influence postconcussion symptoms and coping with a brain injury. As knowledge of CTE improves, a critical goal for research will be delineating post-mTBI psychiatric sequelae from CTE-related prodromal psychiatric symptoms.

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**CHAPTER 4: CONTACT SPORT PARTICIPATION AND CONCUSSION
EFFECTS ON A HIGH MEMORY INTERFERENCE TASK**

McCradden MD¹, Becker S², Rosebush PI³, Mazurek MF⁴.

Departments of Neuroscience (MiNDS)¹, Psychology, Neuroscience, and
Behaviour², Psychiatry and Behavioural Neurosciences³, and Medicine⁴
(Neurology), McMaster University Medical Centre, 1200 Main Street W,
Hamilton Ontario, L8N3Z5

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ABSTRACT

Sport-related concussion is one of the most impactful injuries sustained by youth and varsity athletes. Recent attention has also been paid to the effects of contact sport participation in the absence of concussion, and the potential cognitive effects of repeated ‘subconcussive’ head injuries.

The hippocampus is known to be vulnerable to head injury. A test involving a high memory interference component, known as the mnemonic similarity test (MST), may be able to detect deficits of hippocampal neurogenesis. The goal of this project was to utilize the MST to investigate cognitive changes in: 1) concussed athletes and 2) contact athletes sustaining subconcussive impacts over a single rugby season.

A total of 160 McMaster athletes participated between September 2014-January 2016. During the preseason, all individuals completed sport psychology questionnaires and a semi-structured psychiatric interview. We then administered the MST, which tests recognition of images that are new, old, or very similar to previously presented images. Two subgroups were studied: 1) Concussion: 11 athletes in the original cohort supplemented by 6 others referred to our neurology clinic were matched using a 1:2 ratio with athlete controls and were tested while symptomatic (~2-4 weeks postinjury) and again upon recovery; 2) Contact athletes: in addition to the preseason assessment, 13 rugby players also completed midseason and postseason testing.

In the concussion subgroup, we found impaired identification of similar stimuli during the symptomatic phase, which had significantly improved upon full concussion recovery. The identification of old stimuli was also mildly impaired while symptomatic, and also improved. Regression analysis revealed that concussion was significantly predictive of the degree of impairment in the identification of similar stimuli. In the contact athlete subgroup, we found a significant impairment of their ability to identify similar stimuli during the midseason, but in the postseason this resolved and surpassed preseason performance. We compared an orthopedic injury group to matched concussion and uninjured groups and found that only the concussion group showed impaired performance on the MST.

This study is the first to utilize the MST in concussion and contact sport samples. We found that the ability to discriminate between highly similar stimuli is impaired following concussion, and with contact sport participation - in both subgroups, test performance improved after a reprieve from sport participation. This study contributes to the growing body of evidence indicating subconcussive head impacts may affect cognition in the absence of an overt concussion, particularly on a highly sensitive, high interference memory test. These results may reflect a head-injury-induced impairment of hippocampal neurogenesis.

INTRODUCTION

Concussion, a form of mild traumatic brain injury (mTBI), is the result of biomechanical forces to the head that cause physical symptoms such as headache, dizziness, and balance impairments, while also affecting mood and cognition. Sport-related concussions (SRCs) represent 3-8% of all athletic injuries for which children and adolescents present to the ER (Kelly et al., 2001), and among varsity athletes SRC impacts an estimated 300,000 athletes annually (Marar et al., 2012). Despite the surge of research interest and media coverage of concussion, a lack of knowledge about concussion remains a significant obstacle to individuals seeking appropriate treatment and following proper return-to-play procedures (Karlin, 2011; Kaut et al., 2003; McCrea et al., 2004; Williamson & Goodman, 2006). Despite this attention, attitudes to SRC are still rather cavalier, with continued resistance to concussion education reported among parents, coaches, and administrators (Echlin, 2010; Echlin et al., 2010; Chrisman, Quitquit, & Rivara, 2013).

Concussion is associated with cognitive impairments (McCrea et al., 2003, 2005), mood dysfunction (Hutchison et al., 2009; Mainwaring et al., 2010), and anxiety (Meier et al., 2015, 2016). In addition, the question of whether ‘subconcussion’ — repetitive head impacts that do not result in a concussion diagnosis — may induce similar changes has seen a surge of recent investigations. Alterations in axonal integrity have been reported during a single season of participation in a contact sport, which may be associated with impaired cognitive

testing (Bazarian et al., 2014; McAllister et al., 2012). The potential link between contact sports and chronic traumatic encephalopathy (CTE), a dementing disorder well documented among former contact sport athletes, has raised the question of whether athletes are at significant risk independent of a known concussion history (Jordan et al., 2013; McKee et al., 2014), especially considering emerging evidence that neuropsychiatric problems occur in retired athletes at a higher rate than the normal ageing population and in proportion to the number of self-reported concussions (Didehbani et al., 2013; Guskiewicz et al., 2007; Hart et al., 2013).

One potential mechanism by which concussion induces cognitive and mood-related dysfunction is by suppression of hippocampal neurogenesis, the process of adult-born neurons proliferating and integrating into hippocampal circuitry. The level of neurogenesis (proliferation and/or survival) has been linked to performance on cognitive tasks that have a high interference component, including contextual fear conditioning (Nakashiba et al., 2012; Sahay et al., 2011; Sahay, Wilson, & Hen, 2011; Tronel et al., 2012), delayed non-match to sample (Winocur et al., 2006), discrimination tasks involving similar spatial locations and objects (Clelland et al., 2009) or contextual information (Kheirbek et al., 2012; Nakashiba et al., 2012; Niibori et al., 2012), interference with previously learned information (Luu et al., 2012; Winocur et al., 2012), and extinction (Deng et al., 2009; Noonan et al., 2010). It has also been shown that increasing the pool of

neural precursors is sufficient to augment performance on contextual discrimination tasks (Sahay, et al., 2011).

Adult-born neurons may also have implications for anxiety- and mood-related processing. Anxiety in particular has been linked to impaired neurogenesis by way of producing ‘overgeneralization’ — a reduced ability to discriminate between similar fearful contexts (Kheirbek et al., 2012; Besnard & Sahay, 2016). Under this model, anxiety occurs as a result of a reduced ability to discriminate ambiguous cues that may signal danger, resulting in an over-responsiveness to any potential danger cues. Neuroimaging studies have noted the presence of heightened responsiveness to danger cues, increased startle response, and anxiety to neutral stimuli in many studies of humans with anxiety disorders (Bouton & Moody 2004; Hayes et al., 2011; Lissek et al. 2008, 2010; Mineka & Zinbarg 2006).

Animal models have indicated that while a transient increase in neural stem cells is observed following experimental mTBI, these cells overwhelmingly become glia and not neurons, reflecting an overall impairment to neurogenesis (Gao & Chen, 2013; Rola et al., 2006). Pro-neurogenic interventions such as environmental enrichment and pharmacological interventions have been shown to attenuate TBI-related cognitive deficits (Briones, Woods, & Rogozinska, 2013; Chen et al., 2005; Chohan et al., 2015; Gaulke et al., 2005; Giza et al., 2005; Kline et al., 2007; Will et al., 2004), and may also prevent the development of post-TBI anxiety-like behaviours (Johnson et al., 2013).

Increased anxiety has been found in several animal models of TBI (Davies et al., 2016; Fox et al., 2016; Johnson et al., 2013; Kovesdi et al., 2011; Meyer et al., 2012; Mychasiuk et al., 2016; Reger et al., 2012; Singh et al., 2016). Anxiety disorders have been reported in up to 23% of mild traumatic brain injury (mTBI) survivors (Moore et al., 2006). Prospective studies note a higher post-mTBI prevalence of anxiety compared with the general population (Bryant et al., 2010; Ellis et al., 2015) and with orthopedic controls (Luis et al., 2002). Athletes with concussion have also been observed to exhibit increased anxiety compared with their uninjured teammates (Meier et al., 2015, 2016), and larger overall mood disturbances (Hutchison et al., 2009, 2017; Mainwaring et al., 2010).

Though at present we are unable to measure neurogenesis non-invasively *in vivo* (for a review of potential biomarkers, see Ho et al., 2013), a test of contextual discrimination might show promise for detecting putatively neurogenesis-linked changes in performance. Kirwan and Stark (2007) developed a test of mnemonic similarity (MST), and performance on the test has been shown to be negatively affected by depression (Dery et al., 2013, 2015; Shelton et al., 2013), binge alcohol consumption (Goldstein et al., 2016), and age-related cognitive impairments (Holden et al., 2013; Toner et al., 2009). In addition, responsiveness to an aerobic fitness regime is associated with improvements to performance on the MST (Dery et al., 2013; Heisz et al., 2017).

The present study assessed whether concussed athletes would be impaired on the MST, and whether contact sport participation alone might be associated

with changes in MST performance. We hypothesized that concussed athletes would show impairments at identifying highly similar stimuli, which would recover following their recommencement of exercise as part of their return-to-play protocol. We also believed that nonconcussed athletes would show similar impairments during the competitive sport season, and that this performance would normalize following a break from competition and training.

METHODS

Participants

Members of the McMaster University varsity men's rugby, soccer, and football teams, and the women's flag football team were recruited through their coaches for participation in the study. We further recruited individual athletes from the swimming, volleyball, and baseball teams. The study was approved by the Hamilton Health Sciences Research Ethics Board. All athletes were included initially, and were divided into groups based on responses to the psychological tests and whether or not they sustained a concussion during the year. Exclusion criteria for all participants were: 1) having sustained a moderate or severe head injury any time during the season; 2) had taken illicit drugs at the time of the injury, 3) having consumed alcohol heavily within the past 24 hours. Control participants consisted of relatively physically active members of the McMaster community, as well as individuals from a chiropractic college.

Psychometric Scales

Structured Clinical Interview for the DSM-IV (SCID) and Open Interview: The SCID was utilized to screen for current and past psychiatric disorders. A modified version of the SCID screener was used, focusing on mood, anxiety, and substance-related issues which allowed us to minimize the time commitment for the athletes while also obtaining the most pertinent and most likely psychiatric issues in this population.

Sport Competition Anxiety Test (SCAT): The SCAT (Martens *et al.*, 1990) is a test of trait anxiety which measures 15 items, 10 of which are features associated with anxiety. The 5 unscored items are spaced evenly to reduce the likelihood of an internal response-set bias. Athletes are asked how they “usually” feel before a game, and rank each item on a scale of 1 - 3 (1 = rarely, 2 = sometimes, 3 = often). The SCAT is frequently employed in both clinical sport psychology settings and in research, and has evidence of high internal consistency (KK-20 values: .95 - .97), and high test-retest reliability (.77) (Martens *et al.*, 1990).

Competitive Sport Anxiety Inventory-2 (CSAI-2): The CSAI-2 is a 27-item inventory of state anxiety in terms of cognitive and somatic anxiety, as well as measuring self-confidence. Evidence indicates that the CSAI-2 is reliable, with internal reliability coefficients (Cronbach alpha coefficient) of .81 (cognitive anxiety), .82-.83 (somatic anxiety), and .88-.91 (self-confidence) (Cox *et al.*, 2003; Martens *et al.*, 1990). The test has been shown to have predictive validity with regard to athletic performance (Burton *et al.*, 1988; Craft *et al.*, 2003), in accordance with certain models of athletic performance anxiety (Hanin, 1995).

Hamilton Anxiety Rating Scale (HAM-A): To assess anxiety in non-athletes we used the HAM-A (Hamilton 1959), which has been shown to have high reliability and concurrent validity, though with limitations as to the differentiation of anxiety- versus depression-related symptoms (Maier *et al.*, 1988). The HAM-A is a 14-item researcher-rated inventory of both psychic and somatic anxiety complaints. The scores for each symptom range from 0 (not present) to 7 (severe).

The total score range from 0-56, where <17 indicates low anxiety, 18-24 mild to moderate anxiety, and >24 indicates moderate to severe anxiety.

Cognitive testing in non-athletes: To control for broader effects of executive functioning, we also administered two cognitively demanding control tasks: 1) Trail Making Test (Reitan, 1958) - two parts, requiring spatial scanning, speed, and cognitive flexibility skills, scored on total time to completion of each part; and 2) Digit span backwards (Standardized Assessment of Concussion; McCrea *et al.*, 1997) - athletes were asked to recite 3 to 7 digits in reverse order, scored by total number of errors.

Cognitive testing in athletes: All varsity level athletes are required to undergo the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) test as part of a standard preseason assessment battery. ImPACT is a well-validated and prolific tool for concussion management (Schatz et al., 2006). The test assesses attention span, working memory, sustained and selective attention, non-verbal problem-solving, and reaction time, and these are further divided into composite scores speed and accuracy scores: verbal memory, visual memory, visual motor speed, reaction time, and impulse control. The test automatically flags invalid results from poor effort, guessing, and responses made too quickly. We excluded all test results flagged as invalid by ImPACT, which resulted in the data from 2 participants being discarded.

Mnemonic Similarity Test: The mnemonic similarity test (MST; formerly, “visual pattern separation” test) was originally developed by Kirwan and Stark (2007) and

has been well-validated in terms of its ability to evoke differential responses in the dentate gyrus to highly similar stimuli (Bakker *et al.*, 2008). The test consists of two parts: the first presents non-repeating images (“encoding phase”), and the second tests the participant’s memory of the previously presented images (“retrieval phase”). Stimuli in the retrieval phase are categorized as follows: new (not presented in encoding phase), old (same image presented as in the encoding phase), and similar (the lure is highly similar to an item presented in the encoding phase). Task stimuli consisted of 384 images of everyday namable objects. The test was carried out using the SuperLab 5.0 software (BioPac Systems, Canada). In the encoding phase, participants saw 128 non-repeating images presented sequentially for 1.5 seconds each, and were asked to determine whether each object was an ‘indoor’ or ‘outdoor’ item. Presentation was followed by a 500msec ‘mask’ where no image was visible. Under the same timing schema, in the retrieval phase half of these images were presented again exactly as they were in the encoding phase (“old” images), while the other half were lures (“similar” images) that were highly similar to previously studied items, designed to generate memory interference. An additional 64 images were presented which had not been shown previously in the test (“new” images). Image presentations were randomized in order to minimize practice effects. Responses were collected using the Cedrus RB-530 response pad (BioPac Systems, Canada). Four versions of the test were created to minimize practice effects, and participants who completed multiple

testing sessions did not complete the exact same version of the test more than once.

Percent correct scores were calculated based on participant responses in the retrieval phase. The percentages of new images that elicited a response of “new” and old images that elicited a response of “old” were calculated as percent correct responses. Lure stimuli that elicited an incorrect response of “old” were scored as ‘false alarms’; whereas lures that elicited a response of “similar” were scored as ‘correct rejections.’ All responses (new/correct, old/correct, false alarm, and correct rejection) were calculated as percent correct based on the number of responses to each stimulus type and were tabulated by a rater blinded to clinical factors such as concussion status, timepoint, and anxiety.

Statistics

Results of the sport psychology tests were tabulated as continuous variables for the following values: SCAT total score, cognitive anxiety (CSAI-2), somatic anxiety (CSAI-2), and self-confidence (CSAI-2). ImPACT subscales were assessed by percentile rank for visual and verbal memory and visuospatial score, while simple reaction time and impulse control measures were computed as continuous variables. MST results were computed as the total accuracy for new, old, and lure stimuli. Group-wise comparisons were made using independent and paired samples t-tests, or one-way ANOVA. Levene’s test was conducted to ensure no violations of the assumptions of normality. Correlations were assessed using

Pearson's product-moment correlation. Post-hoc Tukey tests were conducted as indicated. All p values less than or equal to .05 were considered significant.

RESULTS

Variables related to MST performance

All participants who took the MST and who were not suffering from concussion symptoms, had no psychiatric disorder, had less than 5 previous concussions, and were assessed before the start of their competitive sport season were included for analysis (N=98, 77M:21F). The effect of gender was assessed with an independent samples t-test, which revealed no significant differences in accurate identification of lure stimuli ($t(96) = -.544, p = .588$ two-tailed), see Table A. Twenty-seven participants took the test a second time at an interval of 1 month separation to assess for a practice effect on the MST. A paired samples t-test revealed no significant difference from time 1 ($M = 55.22$) to time 2 ($M = 57.03$) ($t(26) = -1.039, p = .308$ two-tailed), see Table B. Pearson correlational analyses (results presented in Table C) revealed that lure identification was not significantly correlated with any of the following variables (all p values over .05): age, GPA, number of previous concussions, digit span backwards, Trails B. As we report in a second publication (McCradden et al., 2017; in press), Pearson correlational analysis showed that the SCAT total score, and CSAI2 cognitive and somatic scales were all negatively correlated with lure accuracy (SCAT: $r = -.326, p = .003$; CSAI2 cognitive subscale: $r = -.311, p = .006$; CSAI2 somatic subscale: $r = -.353, p = .002$) while the CSAI2 self-confidence subscale was positively correlated with lure accuracy ($r = .340, p = .002$). No significant correlations were found for any of the above measures and accuracy on old or new stimuli (all p values $> .05$).

The correlation between lure, new, and old stimuli identification and ImPACT test variables is presented in Table D. Only visual memory ($r = .263$, $p < .05$) and reaction time ($r = -.293$, $p < .05$) were significantly correlated with the correct identification of lure stimuli. No ImPACT subscales were correlated with correct identification of either new or old stimuli.

Participation in contact sports impairs MST performance

We assessed whether there was a difference in performance on the MST among athletes involved in different sports. Athletes with preseason data were divided into high-contact sport athletes (included men's rugby, football, wrestling, hockey, and women's football and soccer), low-contact athletes (included men's baseball, soccer, men's and women's swimming and running), and physically active controls (physically active people not involved in competitive sports). The determination of high-contact versus low-contact sport was based primarily on the observed concussion rates for each sport by gender (Zuckerman et al., 2015), and to ensure that a sufficient number of participants was included in each group. A one-way between groups ANOVA revealed no significant effect of group on identification of lure stimuli, ($F(2,123) = 1.368$, $p = .258$, two-tailed).

We then conducted a within-subjects assessment of MST scores of athletes who play rugby, a high intensity contact sport, over the course of an athletic season. We assessed 14 male rugby players from preseason to postseason at monthly intervals. One individual became concussed, resulting in 13 players' data

included for analysis. The preseason assessment ('preseason' time point) was conducted in early September, the midseason assessment ('midseason') was the average of the October and November scores, and the postseason assessment ('postseason') was completed in mid-January after at least 1 month has passed since their final rugby game. A one-way repeated measures ANOVA revealed significant differences across the three time points in correct identification of lure stimuli ($F(2,11) = 12.161$, $p < .005$, multivariate partial eta squared = .69, see Table E, Graph A). Post-hoc pairwise comparisons using Tukey's test indicated that the postseason lure identification score ($M = 55.38$) was significantly higher than the midseason score ($M = 65.60$; $p < .001$). No significant differences in correct identification of old stimuli ($F(2,11) = .202$, $p = .820$) or new stimuli ($F(2,11) = 1.805$, $p = .225$) across the playing season were detected.

Concussion impairs identification of lure stimuli

Between September 2014 and June 2015 we identified 19 athletes who suffered concussion and tested them on the MST while they were symptomatic ('acute' measurement) and after they had recovered from concussion ('recovery' measurement). One patient did not recover from concussion, and one patient was lost to follow-up, resulting in $n = 17$ patients included for analysis. These athletes included rugby players ($n = 10$), football players ($n = 4$), a figure skater ($n = 1$), an equestrian ($n = 1$), and a volleyball player ($n = 1$). These patients were initially identified by the coach or athletic trainer as having suffered a concussion, and

most saw a sport medicine physician at the McMaster Braley Sport Medicine Clinic. Each participant completed the acute measurement within 1 month of the concussion, while they were still suffering symptomatically. They were referred to our group (MFM) for further assessment and follow up based on concussion symptoms and were followed until they had recovered, at which point they were cleared for full participation in their sport. After recovery had been determined, we tested them on the MST to obtain their recovery scores.

For the 14 individuals who completed baseline testing, we conducted a one-way repeated measures ANOVA across time to assess differences in lure accuracy before, during (acute) and after concussion. The test revealed a significant effect of time, ($F(2, 12) = 22.072, p < .001$, multivariate partial eta squared = .786, see Graph B, Table F). Post-hoc Tukey tests indicated that the acute concussion score ($M = 44.29$) was significantly lower than both the preseason ($M = 61.00; p < .005$) and recovery score ($M = 72.71; p < .05$). The preseason timepoint showed a trend toward being lower than the recovery timepoint ($p = .099$). No significant differences were detected on the identification of old stimuli ($F(2,12) = .774, p = .520$) or new stimuli ($F(2,12) = .416, p = .681$).

To further explore the relationship between concussion and performance on the MST, we established a nonconcussed comparison group. As we report in another publication (McCradden et al., 2017; in press), anxiety is significantly associated with impaired identification of similar stimuli. Importantly, 9/17 of our concussed patients had significant anxiety problems, so in order to avoid

conflation of the results we paired each concussed patient with two nonconcussed patients matched as closely as possible for age, sex, sport, and anxiety level (SCAT total score). Independent samples t-test confirmed the groups were appropriately matched by SCAT score (concussed: $M = 20.5$; nonconcussed: $M = 19.8$; $t(1,51) = 21.642, p = .531$).

Independent samples t-test revealed significant differences between the concussed and nonconcussed groups on the identification of similar stimuli (concussed, $M = 40.81$; nonconcussed, $M = 53.55$; $t(1,50) = 3.610, p < .001$), and old stimuli (concussed, $M = 82.78$; nonconcussed, $M = 89.50$; $t(1,50) = 3.125, p < .005$), but not new stimuli (concussed, $M = 89.80$; nonconcussed, $M = 92.50$; $t(1,50) = .937, p = .158$, see Table F, Graph B).

A model including only the binary variable concussion status predicted 21% of the variance in lure identification scores (model $R^2 = .207, F(1, 53) = 13.032, p = .001; \beta = -12.521, p = .001$).

A second regression analysis including the trait anxiety score (SCAT total score) and concussion status was highly significant, with the two variables together predicting 37% of the variance in lure scores ($R^2 = .373, F(2, 52) = 13.961, p < .001$). Both trait anxiety ($\beta = -1.357, p < .005$) and concussion ($\beta = -13.010, p < .001$) were significant predictor variables.

We also wanted to assess whether the MST could be used as a diagnostic tool to potentially detect concussion. We therefore reversed our equation in a logistic regression model with concussion/no concussion as the variable to be

predicted and anxiety score and accuracy at identifying similar stimuli as the predictor variables. This model was significant ($\chi^2(2, N = 54) = 13.720, p < .005$), indicating that the model was able to distinguish between concussed and nonconcussed athletes at a level significantly greater than chance. The model as a whole explained between 24.0% (Cox & Snell R square) and 34.6% (Nagelkerke R square) of the variance in lure score, and correctly classified 78% of cases. The strongest predictor was lure score ($p < .005$) while SCAT did not reach significance as a predictor variable ($p = .3$).

Assessing the specificity of the MST to concussion compared with orthopedic injury group

As other neuropsychological tests that are highly utilized in concussion management have been shown to be affected by non-head injuries in addition to concussion (Bailey et al., 2010; Hutchison et al., 2010), we wanted to assess whether the MST would be specifically affected by concussion. We collected the MST data from all athletes who sustained an orthopedic injury not involving the head ($n=8$). Because this group had no individuals with significant anxiety problems, we matched them to the 8 concussed individuals and 8 control athletes, matched as closely as possible by anxiety score and age. We then conducted a series of one-way ANOVAs to assess group differences. There were no significant group differences in SCAT score ($F(2,23) = 2.093, p = .150$), or identification of new stimuli ($F(2,23) = .774, p = .476$). Significant group differences were detected in the identification of old stimuli ($F(2,23) = 3.866, p = .038$), with post-hoc

Tukey's test indicating that concussion group scores approached significance as compared with both the orthopedic injury group ($p = .086$) and the uninjured group ($p = .052$). We also found significant group differences in the identification of lure stimuli ($F(2,23) = 24.642, p < .001$), with post-hoc Tukey's test indicating that the concussion group scores were significantly lower than both the orthopedic injury ($p < .001$) and uninjured group scores ($p < .001$). Results are presented in Table G and Graph C.

Table A: T-test of MST performance in male and female athletes

	Males		Females		
	N	$M \pm \text{SEM}$	N	$M \pm \text{SEM}$	p value
Similar	77	53.48 ± 3	22	55.35 ± 4	0.588
Old	77	85.20 ± 2	22	88.93 ± 2	0.382
New	77	92.18 ± 1	22	93.11 ± 1	0.846

Table B: T-test assessing practice effects on the MST

	N	Time 1	Time 2	p value
		$M \pm \text{SEM}$	$M \pm \text{SEM}$	
Similar	27	55.22 ± 3	57.03 ± 3	0.308
Old	27	87.28 ± 2	90.32 ± 2	0.478
New	27	91.78 ± 1	89.21 ± 2	0.738

Table C: Pearson correlation of sport psychology tests with the correct identification of similar, old, and new stimuli on the MST

	N	Similar stimuli		Old stimuli		New stimuli	
		r	p value	r	p value	r	p value
SCAT total	82	-0.326**	<.005	0.087	0.462	-0.143	0.227
CSAI2 - Cognitive	78	-0.311*	<.05	0.226	0.101	-0.117	0.339
CSAI2 - Somatic	78	-0.353**	<.005	0.177	0.143	-0.013	0.915
CSAI2 - Self-confidence	78	0.340**	<.005	-0.087	0.473	-0.032	0.791

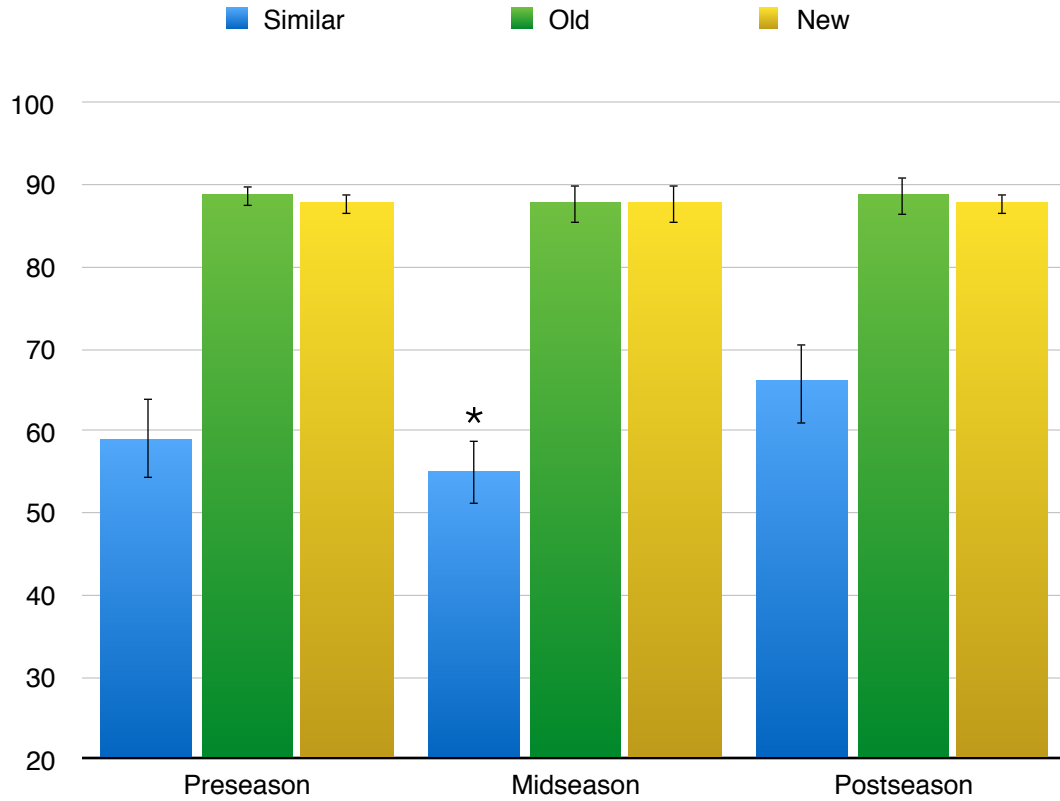
* $p < .05$ ** $p < .005$

Table D: Pearson correlation of ImPACT subscales with the correct identification of similar, old, and new stimuli on the MST

		Similar stimuli		Old stimuli		New stimuli	
N		<i>r</i>	<i>p</i> value	<i>r</i>	<i>p</i> value	<i>r</i>	<i>p</i> value
Visual memory	62	0.263*	< .05	0.161	0.224	0.155	0.236
Verbal memory	62	0.096	0.458	0.143	0.279	-0.039	0.766
Visuospatial	62	0.166	0.197	-0.075	0.57	-0.041	0.754
Reaction time	62	-0.293*	< .05	0.071	0.592	0.132	0.313
Impulse control	62	-0.020	0.875	-0.142	0.283	0.022	0.867

* $p < .05$

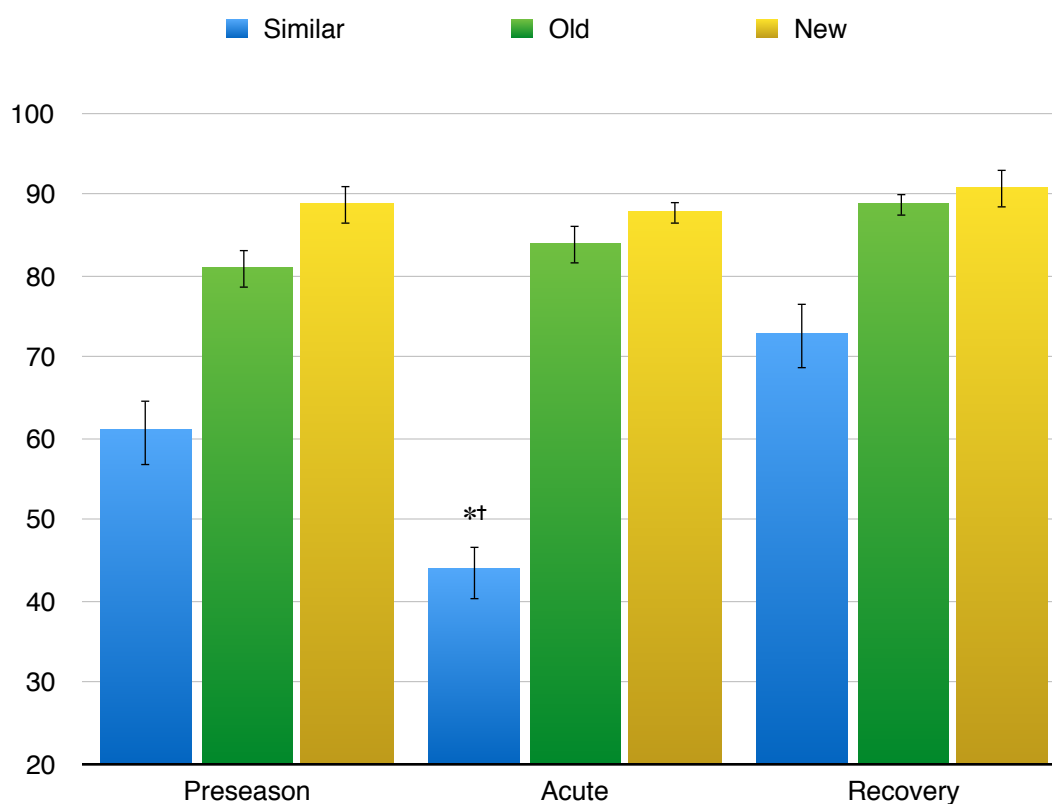
Graph A: MST performance by stimulus type across a single season of rugby in nonconcussed players



*One-way ANOVA detected a significant difference from postseason ‘similar’ value, $p < .001$.
Bars represent standard error of the mean.

Table E: One-way ANOVA assessing stimulus identification across a single season of rugby

		Preseason	Midseason	Postseason	<i>p</i> value
		<i>M</i> ± SEM	<i>M</i> ± SEM	<i>M</i> ± SEM	
	N				
Lure stimuli	13	59.41 ± 5	55.43 ± 4	65.61 ± 5	< .001*
Old stimuli	13	88.86 ± 1	87.53 ± 2	88.91 ± 2	0.890
New stimuli	13	87.74 ± 1	88.3 ± 2	88.40 ± 1	0.902

Graph B: MST performance by stimulus type in concussed athletes

One-way ANOVA

*significant difference from recovery 'similar' value, $p < .05$

†significant difference from preseason 'similar' value, $p < .05$

Bars represent standard error of the mean

Table F: One-way ANOVA assessing MST performance by stimulus type in concussed athletes

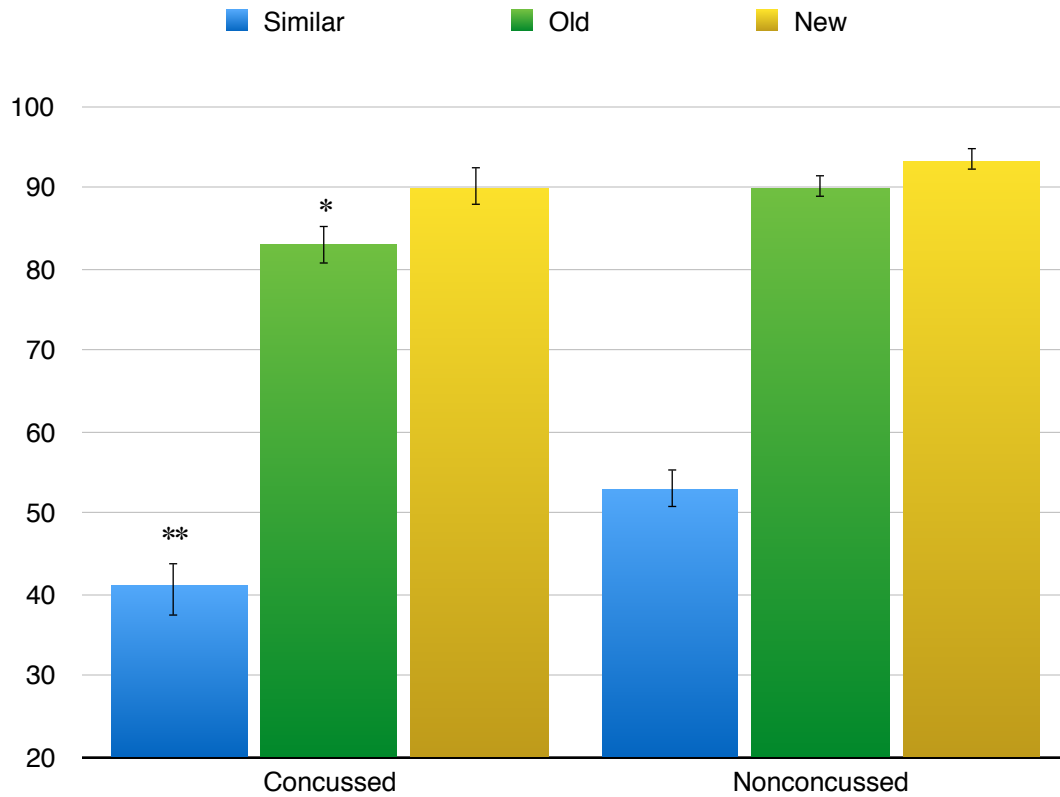
		Preseason	Acute	Recovery	
	N	$M \pm SEM$	$M \pm SEM$	$M \pm SEM$	p value
Similar	14	61.00 ± 4	$44.29^{*†} \pm 3$	72.71 ± 4	$< .001$
Old	14	81.17 ± 2	83.67 ± 2	88.83 ± 1	0.520
New	14	88.86 ± 2	88.43 ± 1	91.14 ± 2	0.681

Post-hoc Tukey comparisons:

*significant difference from recovery 'similar' value, $p < .05$

†significant difference from preseason 'similar' value, $p < .05$

Graph C: MST stimulus identification comparing concussed and nonconcussed groups



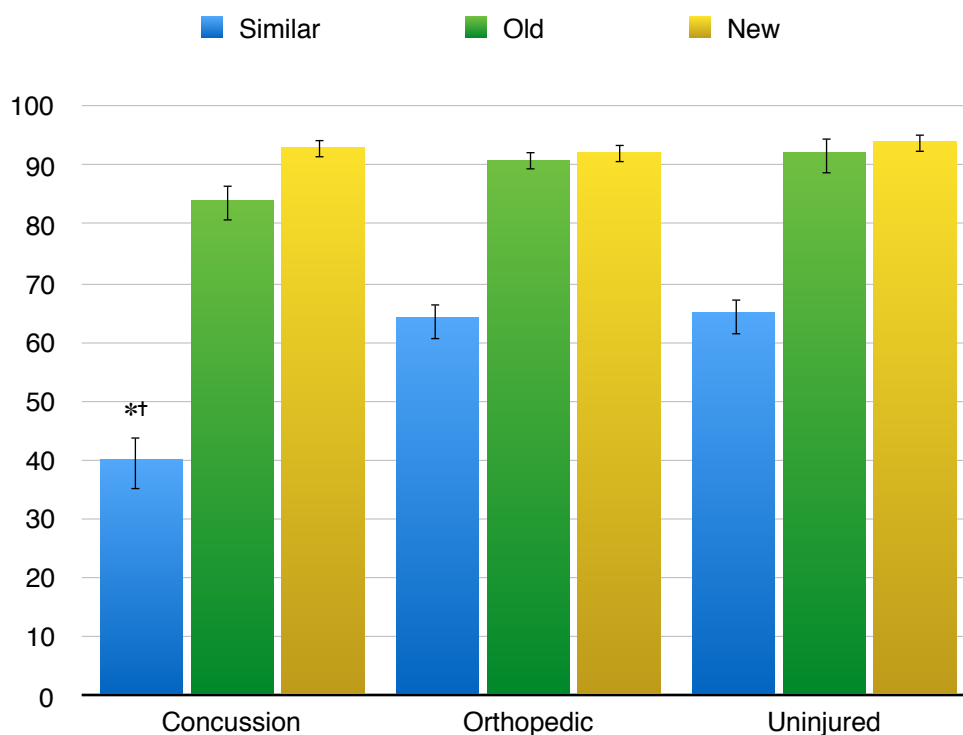
*Independent samples t-test, significant difference from nonconcussed, $p < .005$

**significant difference from nonconcussed, $p < .001$

Bars denote standard error of the mean

Table G: Independent samples t-test of MST performance among concussed and matched nonconcussed athletes

	Concussed N=17	Nonconcussed N=34	
	$M \pm \text{SEM}$	$M \pm \text{SEM}$	p value
Similar	40.80 $\pm$ 3	53.3 $\pm$ 2	< .001
Old	82.8 $\pm$ 2	89.5 $\pm$ 1	<.005
New	89.8 $\pm$ 2	92.5 $\pm$ 1	0.158

Graph D: MST results comparing concussion, orthopedic injury, and uninjured groups.

*One-way ANOVA, significant difference from orthopedic, $p < .05$

†One-way ANOVA, significant difference from uninjured, $p < .05$

Bars denote standard error of the mean

Table H: MST performance for concussion, orthopedic injury, and uninjured groups

		Concussion	Orthopedic	Uninjured	
	N	$M \pm SEM$	$M \pm SEM$	$M \pm SEM$	p value
Similar	8	40.00*† ± 4	64.13 ± 2	65.13 ± 3	< .001
Old	8	83.88 ± 3	91.43 ± 1	92.00 ± 2	0.038
New	8	93.29 ± 1	92.43 ± 1	94.29 ± 1	0.476

Post-hoc Tukey comparisons:

*significant difference from orthopedic, $p < .05$

†significant difference from uninjured, $p < .05$

DISCUSSION

The present study investigated the effects of concussion and contact sport participation on a test involving a component of high memory interference, the MST. We found that individuals with concussion are impaired at accurately discriminating highly similar images to previously studied items, and that their accuracy improves following a recovery period from concussion. This impairment was specific to concussion, and not seen with orthopedic injuries. Similarly we found that during the intensive competition season in a high contact sport, rugby players without concussion perform poorly at identifying highly similar images, which also improves following a reprieve from rugby. The specificity of impairment in both groups to the accurate identification of similar stimuli but not old stimuli suggests these results were not due to an overall effect of reduced attention span following concussion.

These results add to the growing notion that ‘subconcussion’ — cumulative head impacts that do not result in clinically diagnosed concussion (Bailes et al., 2013) — can result in changes in the brain. Investigations into the effects of subconcussion have indicated that one can observe reduced performance on neuropsychological tests (McAllister et al., 2012, 2014; Tsushima et al., 2016), and changes in white matter integrity which are associated with head acceleration metrics (Bazarian et al., 2014; McAllister et al., 2014). Given that white matter changes are commonly reported among concussed athletes (Ling et al., 2012; Mayer et al., 2011, 2012, Messe et al., 2011, 2012), and that it now appears that

subconcussive forces to the head are associated with white matter changes as well (Bazarian et al., 2014; Koerte et al., 2017; Mayinger et al., 2017; McAllister et al., 2014), it is possible that participation in contact sports can produce detrimental changes to brain function.

To the best of our knowledge these results are the first to document impaired neuropsychological test performance during a competitive season which improves upon reprieve from contact play. This is in contrast with some other studies which have not detected differences from the pre- to post-season (McAllister et al., 2012), even when neuroimaging evidence indicates reduced white matter integrity over this time period (McAllister et al., 2014). Others have compared contact versus non-contact athletes and have found group differences in performance on neuropsychological tests (Koerte et al., 2017; McAllister et al., 2012; Tsushima et al., 2016). Intra-sport differences in neuropsychological test performance have also been documented among high and low contact positions in youth football (Tsushima et al., 2017). Although helmet metrics have indicated that forces to the head during a competitive season may be correlated with white matter changes (Bazarian et al., 2014; Mayinger et al., 2017; McAllister et al., 2012, 2014), it is also known that there are substantial inter-individual differences in the forces a given athlete can withstand without exhibiting neurological dysfunction or sustaining a concussion (Guskiewicz et al., 2007, McCaffrey et al., 2007). One possibility is that there may be a subset of contact athletes who are more sensitive to subconcussive impacts (McAllister et al., 2012).

Concussion is well known to result in impaired performance on neuropsychological tests such as ImPACT, which tends to normalize in varsity athletes around 1 week following in the injury (McCrea et al., 2003, 2005). The utility of these tests in the management of concussion, and particularly multiple concussions, has been called into question (see for example Randolph, Lovell, & Laker, 2011). Few studies have directly compared concussed and nonconcussed athletes, and others have documented impaired performance on ImPACT following orthopedic injury (Hutchison et al., 2010) or in association with symptoms of psychological distress (Bailey et al., 2010). The MST has the potential to be utilized for the detection of concussion, given its fair ability to correctly categorize concussed/nonconcussed athletes. Notably, improvements upon the present study are required to assess the full potential of the test. Though we were able to match our concussed patients at a 2:1 ratio to nonconcussed athletes, anxiety was over-represented in this sample and female athletes under-represented. Further studies with larger samples including more female athletes could assist in elucidating whether the MST could serve as a diagnostic test for concussion.

Our finding that accuracy at identifying lure stimuli is correlated with athletes' baseline performance on the ImPACT visual memory subscale is may be reflective of the common component of high memory interference. Both the design memory and 'X's and O's' component which make up the visual memory composite involve contextually overlapping stimuli, both visual and spatial. Studies

which have successfully demonstrated group differences among contact and non-contact sport athletes have found these differences on subscales involving components of high memory interference (McAllister et al., 2012, 2014). However, it is important to note that other differences have been found as well, such as in processing speed and reaction time (Koerte et al., 2017; Tsushima et al., 2016).

We hypothesize that our results may reflect a concussion-induced reduction of hippocampal neurogenesis. Head injury has been shown to impair hippocampal neurogenesis in rodent models by shifting neural precursor lineage toward a glial rather than neuronal differentiation (Gao & Chen, 2013; Rola et al., 2006). Levels of neurogenesis are known to be related to the ability to discriminate between highly similar spatial representations (Clelland et al., 2009; Creer et al., 2010), and across similar visual contexts (Sahay et al., 2011). Reductions of neurogenesis result in deficits in contextual fear conditioning (Pan et al., 2012; Park et al., 2015; Saxe et al., 2006), which has also been observed following animal models of TBI (Davies et al., 2016; Reger et al., 2012). Known pro-neurogenic interventions such as environmental enrichment have been shown to improve post-TBI cognition (Briones, Woods, & Rogozinska, 2013; Chen et al., 2005; Gaulke et al., 2005; Giza et al., 2005; Kline et al., 2007; Will et al., 2004).

As we have yet to discover a biomarker of neurogenesis in human subjects, analogues of neurogenesis-dependent tasks used in rodents have been suggested for use with humans. As previously mentioned, the common component to

neurogenesis-dependent tasks appears to be the component of high memory interference (Becker, 2016), which is a function tested by the MST. Poor performance on the MST has been successfully linked with putatively neurogenesis-linked conditions such as depression (Dery et al., 2013, 2015; Shelton et al., 2013), high levels of stress (Dery et al., 2015; Shelton et al., 2013), mild cognitive impairment from normal ageing (Holden et al., 2013; Toner et al., 2009) and binge alcohol consumption (Goldstein et al., 2016). All of these conditions are associated with lower neurogenesis in rodents (Hutton et al., 2015; Kuhn, Dickinson-Anson, & Gage, 1996; Leasure & Nixon, 2010; Gould et al., 1998; Malberg & Durman 2003; van Praag et al., 2005; Veena et al., 2009). Further, exercise intervention is well known to augment neurogenesis in rodents (Kempermann et al., 1997; van Praag et al., 1999), and recent studies have demonstrated that an exercise intervention in humans is positively associated with increased accuracy at identifying similar stimuli on the MST (Dery et al., 2013; Heisz et al., 2017).

From this hypothesis, it follows that recovery from concussion and the resumption of exercise may underlie the improvements we see on the MST at the point when athletes have been cleared to return to play. Similarly, if subconcussion impairs neurogenesis, the improvements on the test may be due to the reprieve from repetitive head impacts. All the athletes in our study were physically active at the point when they were cleared to play again, but had not yet resumed participation in full-contact practices. They therefore were likely benefiting from

the resumption of exercise without the addition of head trauma, which may be related to their improvement in accuracy on the MST (Dery et al., 2013; Heisz et al., 2017).

An important question to consider is how concussion might affect neurogenesis. Decreased cerebral perfusion has been observed among athletes for up to one month following a concussion (Meier et al., 2015) which may potentially affect the precise coordination between angiogenesis and neurogenesis (Louissant et al., 2002). Palmer et al (2000) demonstrated that neural stem cells cluster in ‘neuroangiogenic foci,’ presumably due to a greater need for nutrients delivered from the blood to the growing cells. Concussion may disrupt these zones whether by decreased perfusion or by forces causing the miniscule capillaries to burst, and thereby damaging the surrounding tissue (Chatelin et al., 2011; Giza & Hovda, 2001).

The impairment to neurogenesis may help explain the apparent association between head injuries and smaller hippocampal volume (Beauchamp et al., 2011; Boldrini et al., 2013; Meyer et al., 2012; Wilde et al, 2007). It has been demonstrated that football players with a history of concussions have smaller hippocampal volumes than players without a history of concussion, and the full group of football players had smaller hippocampal volumes than healthy controls (Singh et al., 2014). Damage to the hippocampus as a result of head trauma may also contribute to the understanding of how contact sport participation has been associated with conditions such as CTE (McKee et al., 2009, 2013; Omalu et al.,

2005, 2006) and other dementing disorders (Lye & Shores, 2000; Jiang et al., 2013; Jellinger, 2004).

Some limitations in this study warrant discussion. One such limitation is the possible effect of nutrition. Athletes typically pay better attention to their food, and often supplement with vitamins or other substances — some potentially helpful (e.g., omega-3) and others potentially harmful (steroids, weight-loss supplements). Studying the effects of these compounds on neurogenesis is beyond the scope of this investigation. Additionally, though performance on the MST may be enhanced by participation in an aerobic exercise program (Dery et al., 2013; Heisz et al., 2017), it is thus far unknown what types of exercise can improve performance, by how much, and what length of exercise is sufficient to influence the test. We make no assumptions about these potential effects, and thus separated our control group based solely on whether the activities in which they partake on a regular basis were part of a competition season (e.g., a runner who may or may not run a marathon in the next year would be considered a non-athlete control participant).

Conclusions

The results of this study indicate that further research is necessary to understand the full effects of participation in contact sports, and whether the absence of an overt concussion may not indicate the absence of brain dysfunction. A growing body of evidence suggests that repetitive impacts to the head are not

benign, but further research is needed to understand how these impacts are relevant for cognition. We have implicated hippocampal neurogenesis as a potential product of concussion and subconcussion, but further research is warranted as the MST is, at best, a proxy measure of neurogenesis. An important question for future research will be to determine whether impairments to neuropsychological tests such as the MST can predict the development of postconcussion sequelae such as psychiatric problems, as well as perhaps identifying those at risk for CTE.

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**CHAPTER 5: ATHLETIC ANXIETY IMPAIRS PERFORMANCE ON A
TEST OF HIGH MEMORY INTERFERENCE**

McCradden MD¹, Becker S², Rosebush PI³, Mazurek MF⁴.

Departments of Neuroscience (MiNDS)¹, Psychology, Neuroscience, and
Behaviour², Psychiatry and Behavioural Neurosciences³, and Medicine⁴
(Neurology), McMaster University Medical Centre, 1200 Main Street W,
Hamilton Ontario, L8N3Z5

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ABSTRACT

Anxiety is a highly common mental illness affecting 2-7% of the North American population. Recent evidence has implicated impairments to hippocampal neurogenesis, the process of the growth, maturation, and integration of adult-born neurons, in the aetiology of anxiety disorders. Exercise is a known promoter of neurogenesis and has been shown to augment cognition in animal models. While a neurogenesis biomarker has yet to be discovered for *in vivo* use in humans, a test of high memory interference — the mnemonic similarity test (MST) — has shown significant associations with conditions known to affect neurogenesis in animal models. The present study attempts to link impaired performance on a test of high memory interference with anxiety in athletes.

A total of 160 McMaster athletes participated between September 2014-January 2016. During the preseason, all individuals completed sport psychology questionnaires and a semi-structured psychiatric interview. An additional cohort of 31 physically active controls was recruited from the university population. We then administered the MST, which tests recognition of images that are new, old, or very similar to previously presented images. Athletes were divided into two groups: 1) Anxious Athlete group (n=34) consisted of players who reported a diagnosed or treated anxiety disorder, as well as those with elevated scores on 2+ sport anxiety questionnaires; 2) Controls Athlete group (n=34) were matched by gender, age, and sport to the Anxious Athletes group.

One-way ANOVA revealed significant differences between the anxious athletes, control athletes, and healthy controls, with post-hoc Tukey's test indicating that anxious athletes were impaired at identifying similar stimuli, but not old or new stimuli. Each subscale of the sport psychology questionnaires (cognitive anxiety, somatic anxiety, and total trait anxiety) was negatively correlated with accuracy at identifying lures, while self-confidence demonstrated a positive correlation. Regression analysis revealed accurate identification of similar stimuli was significantly predicted by anxiety levels, and that when accounting for self-confidence this prediction ability was significantly improved.

The results indicate that anxiety is associated with impaired performance on a test of high memory interference, which is putatively linked with hippocampal neurogenesis. Self-confidence may mediate some of the effect of anxiety, indicating that athletes with high anxiety may be aided by efforts to improve their self-confidence.

INTRODUCTION

Anxiety is one of the most common mental health illnesses in North America, affecting approximately 2-7% of the population (Kessler et al., 2005). Anxiety disorders typically involve an overestimation of risk or danger, an anticipation of perceived threats, and are accompanied by symptoms such as impaired concentration, edginess, restlessness, irritability, or insomnia. The anxiety response is coordinated by multiple neurobiological loops involving the amygdala, bed nucleus of the stria terminalis (BNST), and ventral hippocampus (Calhoun & Tye, 2015).

Recently, it has been hypothesized that anxiety may be linked to an impairment of hippocampal neurogenesis (Besnard & Sahay, 2017; Kheirbek et al., 2012), the process by which adult-born neurons proliferate, integrate, and mature within the hippocampal circuitry. These newborn neurons have been shown to be integral to memory function by promoting the encoding of distinct memories in the presence of contextually-overlapping stimuli, or ‘memory interference’ (Aimone et al., 2011; Sahay et al., 2011). Impairment of neurogenesis may reduce memory ‘resolution,’ which could result in the behavioural effect of generalization, which presents as a heightened reactivity and anxiety to danger as well as neutral cues (Kheirbek et al., 2012; Lissek et al., 2008, 2010). Certain studies have observed increased anxiety-like behaviours among rodents with impaired neurogenesis (Deng et al., 2009; Denny et al., 2012; Jessberger et al., 2009), while others maintain that impaired neurogenesis is

insufficient to induce anxiety *de novo*. Reduced neurogenesis has also been shown to increase vulnerability to subsequent stress in rodent models (Snyder et al., 2009, 2011).

In the absence of an *in vivo* measure of neurogenesis in humans, researchers have sought analogues to the neurogenesis-sensitive tasks identified in non-human animals. One such analogue is the mnemonic similarity test (MST; Kirwan & Stark 2007) which has been putatively linked to neurogenesis-dependent variables. Impaired neurogenesis has been hypothesized to play a role in stress-induced depression (Jacobs, van Praag, & Gage, 2000), based on evidence that chronic stress suppresses neurogenesis (Gould et al., 1997, 1998), while antidepressant treatments including environment enrichment (Kempermann et al., 1997), voluntary exercise (van Praag et al., 1999), electroconvulsive shock treatment (Scott, Wojtowicz, & Burnham, 2000), and pharmacological antidepressants (Malberg et al., 2000; Tanti et al., 2013) are neurogenic. Moreover, blocking neurogenesis also blocks the behavioural efficacy of antidepressant drugs (Santarelli et al., 2003). Animals with suppressed neurogenesis also show impaired performance on recognition memory for highly similar stimuli (this includes both spatially and visually overlapping stimuli; Clelland et al., 2009; Creer et al., 2010). Thus the MST may be a strong behavioural indicator of neurogenesis levels in humans. Consistent with this hypothesis, individuals with high levels of depressive symptoms perform worse on the MST than do healthy controls (Dery et al., 2013, 2015; Shelton et al., 2013). Individuals with other

conditions linked to impaired neurogenesis, such as those who engage in binge alcohol consumption and cognitively impaired older adults also show poor performance on the MST (Goldstein et al., 2016; Holden et al., 2013; Toner et al., 2009). On the other hand, improvements in fitness due to increased exercise have been linked with an improvement in performance on the MST (Dery et al., 2013; Heisz et al., 2017).

To the best of our knowledge, no studies have yet assessed the potential effect of anxiety on the MST. The present study sought to investigate the link between performance on the MST and anxiety levels among varsity athletes. We chose the athlete group so as to standardize as best as possible the exercise levels among participants, in an attempt to isolate anxiety's contribution to performance on the test. We hypothesized that athletes with elevated levels of anxiety would perform poorly at identifying similar stimuli as compared to their non-anxious teammates and physically active controls.

METHODS

Participants

Members of the McMaster University varsity men's rugby, soccer, and football teams, and the women's flag football team were recruited through their coaches for participation in the study. We further recruited individual athletes from the swimming, volleyball, and baseball teams through their association with members of the aforementioned teams, personal contacts, and reaching out via social media. The study was approved by the Hamilton Health Sciences Research Ethics Board. Athletes were excluded if they were currently concussed, had consumed alcohol within the past 48 hours, or were under the influence of illegal drugs.

All participants were divided into groups as follows:

- 1) **Anxious Athletes** (AA; n=34): individuals who self-reported an anxiety disorder, current or past treatment for an anxiety disorder (pharmacological or therapeutic), or described having significant anxiety that impaired them in multiple aspects of life. We also included individuals who were identified as having high levels of anxiety by the Competitive State Anxiety Inventory-2 (CSAI-2; score of >22 on cognitive or somatic anxiety), and/or the Sport Competition Anxiety Test (SCAT; total score >22).
- 2) **Control athletes** (AT; n=34): these athletes were matched to the Anxious Athlete group by gender, age, GPA, sport, and concussion history to 34

athletes ('control athletes' group, AT) with normal sport psychology scores and no identified issues with anxiety or another psychiatric disturbance.

- 3) Healthy (non-athlete) controls** (HC; n=31): consisted of undergraduate and postgraduate students who engaged in moderate levels of physical activity (i.e., 3-4 times per week for at least 30 minutes at a time), and were without psychiatric disorders or high levels of anxiety.

Psychometric Scales

Structured Clinical Interview for the DSM-IV (SCID) and Open Interview: The SCID was utilized to screen for current and past psychiatric disorders. A modified version of the SCID screener was used, focusing on mood, anxiety, and substance-related issues which allowed us to minimize the time commitment for the athletes while also obtaining the most pertinent and prevalent psychiatric issues in this population.

Sport Competition Anxiety Test (SCAT): The SCAT (Martens *et al.*, 1990) is a test of trait anxiety which measures 15 items, 10 of which are features associated with anxiety. The 5 unscored items are spaced evenly to reduce the likelihood of an internal response-set bias. Athletes are asked how they “usually” feel before a game, and rank each item on a scale of 1 - 3 (1 = rarely, 2 = sometimes, 3 = often). The SCAT is frequently employed in both clinical sport psychology settings and in research, and has evidence of high internal consistency (KK-20 values: .95 - .97), and high test-retest reliability (.77) (Martens *et al.*, 1990).

Competitive Sport Anxiety Inventory-2 (CSAI-2): The CSAI-2 is a 27-item inventory of state anxiety in terms of cognitive and somatic anxiety, as well as measuring self-confidence. Evidence indicates that the CSAI-2 is reliable, with internal reliability coefficients (Cronbach alpha coefficient) of .81 (cognitive anxiety), .82-.83 (somatic anxiety), and .88-.91 (self-confidence) (Cox *et al.*, 2003; Martens *et al.*, 1990). The test has been shown to have predictive validity with regard to athletic performance (Burton *et al.*, 1988; Craft *et al.*, 2003), in accordance with certain models of athletic performance anxiety (Hanin, 1995).

Hamilton Anxiety Rating Scale (HAM-A): To assess anxiety in non-athletes we used the HAM-A (Hamilton 1959), which has been shown to have high reliability and concurrent validity, though with limitations as to the differentiation of anxiety- versus depression-related symptoms (Maier *et al.*, 1988). The HAM-A is a 14-item researcher-rated inventory of both psychic and somatic anxiety complaints. The scores for each symptom range from 0 (not present) to 7 (severe). The total score ranges from 0-56, where <17 indicates low anxiety, 18-24 mild to moderate anxiety, and >24 indicates moderate to severe anxiety.

Cognitive testing in non-athletes: To control for broader effects of executive functioning, we also administered two cognitively demanding control tasks: 1) Trail Making Test (Reitan, 1958) - two parts, requiring spatial scanning, speed, and cognitive flexibility skills, scored on total time to completion of each part; and 2) Digit span backwards (Standardized Assessment of Concussion; McCrea *et al.*,

1997) - athletes were asked to recite 3 to 7 digits in reverse order, scored by total number of errors.

Cognitive testing in athletes: All varsity level athletes are required to undergo the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT), a well-validated tool for concussion management (Schatz et al., 2006), assessment as part of a standard preseason assessment battery. The test assesses attention span, working memory, sustained and selective attention, non-verbal problem-solving, and reaction time divided into composite scores based on speed and accuracy: verbal memory, visual memory, visual motor speed, reaction time, and impulse control. The test automatically flags invalid results from poor effort, guessing, and responses made too quickly. We excluded all test results flagged as invalid by ImPACT, which resulted in the data from 2 participants being discarded.

Mnemonic Similarity Test: The mnemonic similarity test (MST; formerly, “visual pattern separation” test) was originally developed by Kirwan and Stark (2007) and has been well-validated in terms of its ability to evoke differential responses in the dentate gyrus to highly similar stimuli (Bakker *et al.*, 2008). The test consists of two parts: the first presents non-repeating images (“encoding phase”), and the second tests the participant’s memory of the previously presented images (“retrieval phase”). Stimuli in the retrieval phase are categorized as follows: new (not presented in encoding phase), old (same image presented as in the encoding phase), and similar (the lure is highly similar to an item presented in the encoding phase). Task stimuli consisted of 384 images of everyday namable objects. The

test was carried out using the SuperLab 5.0 software (BioPac Systems, Canada). In the encoding phase, participants saw 128 non-repeating images presented individually for 1.5 seconds each, and were asked to determine whether each object was an ‘indoor’ or ‘outdoor’ item. Presentation was followed by a 500msec ‘mask’ where no image was visible. Under the same timing schema, in the retrieval phase half of these images were presented again exactly as they were in the encoding phase (“old” images), while the other half were lures (“similar” images) that were highly similar to previously studied items, designed to generate memory interference. An additional 64 images were presented which had not been shown previously in the test (“new” images). Image presentations were randomized in order to minimize practice effects. Responses were collected using the Cedrus RB-530 response pad (BioPac Systems, Canada). Four versions of the test were created to minimize practice effects, and participants who completed multiple testing sessions did not complete the exact same version of the test more than once.

Percent correct scores were calculated based on the participant response in the retrieval phase. The percentages of new images that elicited a response of “new” and old images that elicited a response of “old” were calculated as percent correct responses. Lure stimuli that elicited an incorrect response of “old” were scored as ‘false alarms’; whereas lures that elicited a response of “similar” were scored as ‘correct rejections.’ All responses (new/correct, old/correct, false alarm, and correct rejection) were calculated as percent correct based on the number of

responses to each stimulus type and were tabulated by a rater blinded to clinical factors such as concussion status, timepoint, and anxiety.

Statistics

Results of the sport psychology tests were tabulated as continuous variables for the following values: SCAT total score, cognitive anxiety (CSAI-2), somatic anxiety (CSAI-2), and self-confidence (CSAI-2). ImPACT subscales were assessed by percentile rank for visual and verbal memory and visuospatial score, while simple reaction time and impulse control measures were computed as continuous variables. MST results were computed as the total accuracy for new, old, and lure stimuli. Group-wise comparisons were made using independent and paired samples t-tests, or one-way ANOVA. Levene's test was conducted to ensure no violations of the assumptions of normality. Correlations were assessed using Pearson's product-moment correlation. Post-hoc Tukey tests were conducted as indicated. All p values less than or equal to .05 were considered significant.

RESULTS

Group-wise comparisons of anxious vs non-anxious athletes on sport psychology tests

To verify quantitative differences between our AT and AA groups, we conducted a series of independent samples t-tests to compare the AT and AA groups on the SCAT and each subscale of the CSAI-2 (results presented in Table A). We found a significant difference in SCAT total scores, indicating that the control athletes ($M = 16.0$) had a lower SCAT total score than the anxious athletes group, ($M = 21.2$; $t(63) = -6.200$, $p < .001$ two-tailed). Each of the cognitive anxiety and self-confidence subscales also were significantly different between AT and AA groups, with anxious athletes reporting higher levels of cognitive anxiety ($M = 20.1$) and somatic anxiety ($M = 15.2$) compared to control athletes (cognitive anxiety, $M = 14.9$; $t(61) = -5.147$, $p < .001$ two-tailed; somatic anxiety, $M = 11.0$; $t(61) = -4.799$, $p < .001$ two-tailed) and lower self-confidence ($M = 23.0$) compared with control athletes ($M = 29.4$; $t(63) = 5.503$, $p < .001$ two-tailed).

Group-wise comparisons of anxious athletes, non-anxious athletes, and controls on the MST

A one-way between groups ANOVA indicated that there were no significant differences between the AT, AA, and HC groups in the correct identification of new ($p = .576$) or old ($p = .209$) stimuli. However, a significant difference was identified between the groups on their accuracy at identifying lure stimuli ($F(2, 95) = 22.544$, $p < .001$). Post-hoc Tukey tests revealed that the AA

group ($M = 43.8$) performed significantly worse than both the AT ($M = 61.2$) and HC ($M = 58.9$) groups, as can be seen in Table C and Graph A.

In another publication we reported that performance on the visual memory subscale of the ImPACT test is significantly correlated with accuracy at identifying lure stimuli on the MST (McCradden et al., 2017, in press). Considering this relationship, we conducted an additional test comparing MST scores of the two athlete groups while controlling for ImPACT scores (controls do not take the ImPACT as this is part of varsity sport preseason testing protocol) to control for any potential influence of this component. A one-way between groups analysis of covariance was conducted, and a preliminary check assured no violations of normality, linearity, homogeneity of variances, homogeneity of regression slopes, and reliable measurement of the covariate. After accounting for ImPACT visual memory scores, there remained a significant difference between AA and AT groups in the accuracy at identifying lure stimuli ($F(1,50) = 21.322, p < .001$, partial eta squared = .329). The contribution of the covariate was negligible ($p = .857$, partial eta squared = .001).

Regression analyses to predict performance on the MST

To further explore the relationship between current anxiety and lure identification, we removed the individuals with previously diagnosed anxiety disorders from the sample and conducted the following analyses on the remaining athletes. We first investigated whether anxiety scores on the SCAT or CSAI-2 were

significantly related to lure accuracy. Pearson correlational analyses revealed that the SCAT total score, and the CSAI2 cognitive, and somatic scales were negatively correlated with lure accuracy (SCAT: $r = -.326$, $p = .003$; CSAI2 cognitive subscale: $r = -.311$, $p = .006$; CSAI2 somatic subscale: $r = -.353$, $p = .002$) while CSAI2 self-confidence subscale was positively correlated with lure accuracy ($r = .340$, $p = .002$). There was no significant correlation between any of these measures and accuracy on either old or new stimuli (all p values $> .05$; see Table C).

To further evaluate the relationship between lure identification and anxiety measures on the SCAT and CSAI-2, we conducted a series of regression analyses to assess which test contributed mostly strongly to identification of similar stimuli. The following regression models were significant with respect to variance in similar stimulus identification: self-confidence alone accounted for 11.8% of the variance ($R^2 = .118$, $F(1, 77) = 10.198$, $p = .002$); trait anxiety alone accounted for 11.3% of the variance ($R^2 = .113$, $F(1, 80) = 10.238$, $p = .002$); and somatic anxiety alone accounted for 12.8% of the variance ($R^2 = .128$, $F(1, 77) = 11.117$, $p = .001$). Accounting for cognitive anxiety alone approached significance, accounting for 9.5% of the variance in scores ($R^2 = .095$, $F(1, 77) = 7.988$, $p = .006$).

Given the relatively low predictive ability of each variable, we reconsidered the relationship between anxiety and lure accuracy. As it is well-documented that chronic stress impairs neurogenesis in rodents (Gould &

Cameron 1996, Malberg & Duman 2003, Yau et al., 2014), we hypothesized that athletes would become stressed if their anxiety levels were out of proportion to their coping resources. This hypothesis is in accordance with the biopsychosocial model (BPSM) of athletic performance, which argues that performance suffers when the perceived demand of a competitive environment exceeds the athlete's perceived coping resources (Blascovich & Tomaka, 1996). We used the self-confidence measure as a proxy for 'coping resources' and competitive trait anxiety as a measure of 'perceived demand.' We then coded each athlete as follows:

If anxiety > self-confidence = **threat**

If anxiety < self-confidence = **challenge**

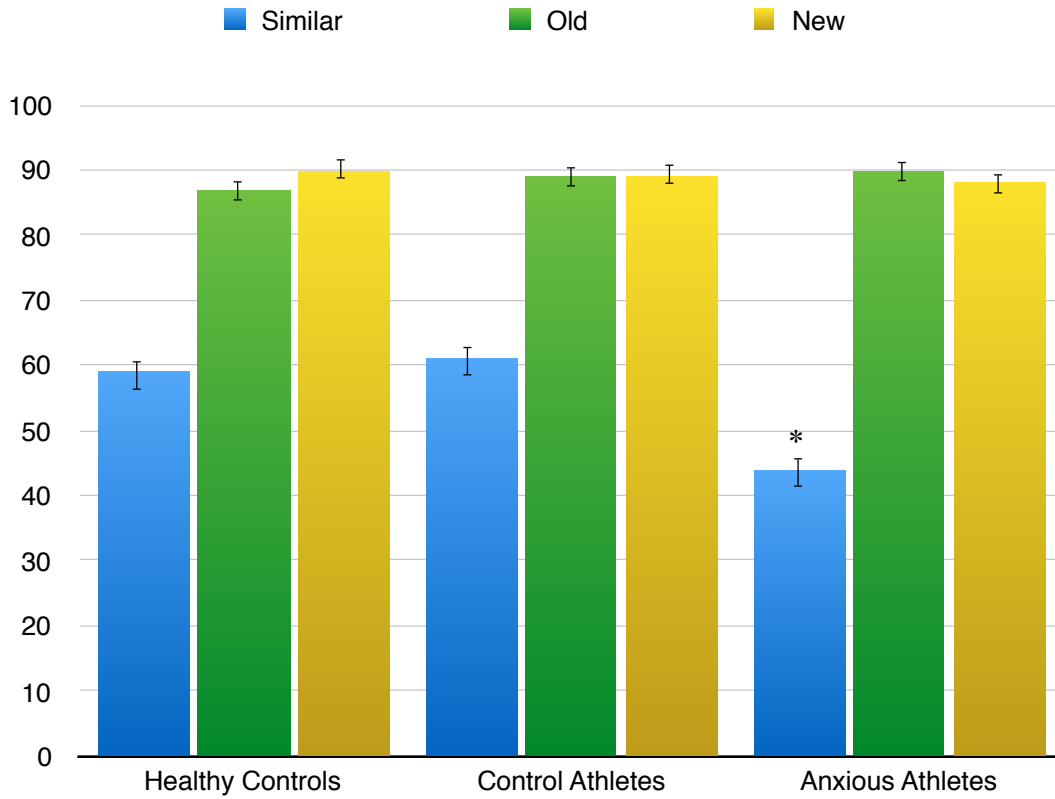
In order to avoid artificial conflation from anxiety alone, we included only the individuals who had anxiety scores within 1 standard deviation of the mean (18, SD = 4). An independent samples t-test verified that the threat and challenge groups did not differ significant in anxiety levels ($p = .412$).

An independent samples t-test revealed that the threat and challenge groups' MST scores differed significantly, with challenged athletes ($M = 58.58$) performing better than threatened athletes ($M = 47.32$; $t(56) = -3.475$, $p < .001$). We next considered whether this new variable would predict lure performance better than the anxiety scores alone. With challenge/threat as a categorical predictor, the model was significant and accounted for 17.7% of the variance in lure accuracy score ($R^2 = .177$, $F(1, 56) = 12.077$, $p < .001$).

Table A: Sport psychology test scores and independent t-test results comparing athletes with and without anxiety

		Athlete Controls	Anxious Athletes	
SCAT		Mean $\pm$ SEM	Mean $\pm$ SEM	<i>p</i> value
	Total score	16.0 $\pm$ 1	21.2 $\pm$ 1	< .001
CSAI-2				
	Cognitive anxiety	15.0 $\pm$ 1	20.1 $\pm$ 1	< .001
	Somatic anxiety	11.0 $\pm$ 0	15.2 $\pm$ 1	< .001
	Self-confidence	29.4 $\pm$ 1	23.0 $\pm$ 1	< .001

Graph A: MST performance by stimulus type and group



*Indicates significance $p < .001$, anxious athletes (AA) differed from control athletes (AT) and healthy controls (HC)
Vertical bars represent standard error of the mean (SEM)

Table B: One-way ANOVA testing MST performance between groups

	HC		AT		AA		<i>p</i> value
	N	<i>M</i> ± SEM	N	<i>M</i> ± SEM	N	<i>M</i> ± SEM	
Similar	31	58.9 ± 2	34	61.2 ± 2	34	43.8 ± 2	<.001*
Old	31	87.1 ± 1	34	89.0 ± 1	34	90.1 ± 1	0.209
New	31	90.3 ± 1	34	89.0 ± 1	34	88.4 ± 1	0.576

*Post-hoc Tukey's test, significant difference from AT and HC groups, $p < .001$

Table C: Pearson correlation between sport psychology test scores and the correct identification of similar, new, and old stimuli

	N	Similar stimuli		New stimuli		Old stimuli	
		r	p value	r	p value	r	p value
SCAT total	82	-.326**	<.005	-0.143	0.227	0.087	0.462
CSAI2 - Cognitive	78	-.311*	<.05	-0.117	0.339	0.226	0.101
CSAI2 - Somatic	78	-0.353**	<.005	-0.013	0.915	0.177	0.143
CSAI2 - Self-confidence	78	.340**	<.005	-0.032	0.791	-0.087	0.473

DISCUSSION

In this paper we present evidence that athletic anxiety impairs discrimination of visual images of objects that are highly similar to previously studied items (lure identification accuracy). This deficit is putatively related to impaired neurogenesis, given that rodents with reduced neurogenesis exhibit impairments on a wide range of high interference memory tests (Clelland et al., 2009; Deng et al., 2009; Kheirbek et al., 2012; Luu et al., 2012; Nakashiba et al., 2012; Nölbori et al., 2012; Noonan et al., 2010; Pan et al., 2012; Park et al., 2015; Saxe et al., 2006; Winocur et al., 2006, 2012). We found that competition anxiety levels as detected on sport psychology tests accounted for between 9 - 17% of the variance in lure scores. These results are consistent with findings in the literature that MST performance deteriorates with age and elevated stress, depression, and binge drinking levels, (Dery et al., 2013, 2015; Goldstein et al., 2014; Shelton et al., 2013), all of which are associated with lower neurogenesis in rodents (Hutton et al., 2015; Kuhn, Dickinson-Anson, & Gage, 1996; Gould et al., 1998; Leasure & Nixon, 2010; Malberg & Durman 2003; van Praag et al., 2005; Veena et al., 2009).

Anxiety is hypothesized to be related to reduced neurogenesis, which impairs discrimination of overlapping contexts (Nakashiba et al., 2012; Sahay et al., 2011; Sahay, Wilson, & Hen, 2011; Tronel et al., 2012) thereby causing over-generalization of fear (Anacker & Hen, 2017; Besnard & Sahay, 2016; Kheirbek et al., 2012). While suppressing neurogenesis alone is likely insufficient to produce

anxiety-like behaviours *de novo*, it can result in decreased novelty exploration (Denny et al., 2012; Jessberger et al., 2009; Revest et al., 2009), and novelty suppressed feeding (Bessa et al., 2009). It is hypothesized that impairments to neurogenesis results in a smaller population of adult-born neurons, which impairs the ability to create non-overlapping memory representations for similar events, resulting in behavioural over-generalization (Anacker & Hen, 2017; Besnard & Sahay, 2016; Kheirbek et al., 2012). An impaired ability to discriminate similar visual cues has also been observed in individuals with panic disorder (Lissek et al., 2008, 2010). The evidence presented in this study indicates that even athletes, who presumably have higher levels of neurogenesis due to regular exercise (van Praag et al., 1999), are prone to over-generalization on a visual memory test.

While anxiety relates to the identification of similar stimuli on the MST, it was not a strong predictor of performance. We hypothesized that this might be because athletes react to anxiety in different ways; some can interpret anxiety as a positive influence on performance, and find it helpful to even *increase* their own anxiety levels to elicit better performance (Lane et al., 2011). The biopsychosocial model (BPS) by Blascovich and colleagues (1996) has been able to successfully predict that cardiovascular indices of stress are correlated with a perceived inability to meet the demand of a given athletic task (Blascovich et al., 2004). Self-esteem has been shown have predictive value as to whether an athlete feels they can meet a demand (Seery et al., 2004). The BPS model also has predictive value among healthy adolescents in a social stress task (Yeager, Lee, & Jamieson, 2016).

In the current study, we hypothesized that athletes with high anxiety and low confidence would consistently experience stress, more than their peers with higher self-confidence who also have elevated anxiety levels. This stressed/unstressed division was a strong predictor of accurate identification of lure stimuli, indicating that stress may interact with anxiety to produce deficits on the test, potentially as a result of impaired neurogenesis. This evidence is consistent with other studies using the MST in healthy adults that have documented that accuracy at lure identification is negatively affected by stress levels (Dery et al., 2015; Shelton et al., 2013).

The current study has several limitations that should be noted. Our sample of athletes involved rugby players, who sustain a very high level of contact on a regular basis throughout their season. Contact sports have been shown to affect performance on other neuropsychological tests (McAllister et al., 2012) and our own evidence indicates lure identification accuracy is negatively affected by intensity of contact sport participation (McCradden et al., 2017, in press). The data collected in this study were from a baseline preseason measure, but we cannot ascertain whether the athletes were participating in contact-heavy practices or in recreational contact sports prior to their participation in this test.

Another potential contributor is the possible effect of nutrition. Athletes typically pay better attention to their food intake, and often supplement with vitamins or other substances — some potentially helpful (e.g., omega-3) and others potentially harmful (steroids, weight-loss supplements). Studying the effects of

these compounds on neurogenesis is beyond the scope of this investigation. Additionally, although the MST is enhanced by participation in a high intensity aerobic exercise program (Dery et al., 2013), it is thus far unknown what types of exercise can improve performance, by how much, and what length of exercise is sufficient to improve performance. We make no assumptions about these potential factors, and thus separated our control group based solely on whether or not their regular activities were part of a competition season (e.g., a runner who may or may not run a marathon in the next year would be considered a non-athlete control participant).

Conclusions

The results of this study support the notion that anxiety may be associated with a reduced ability to discriminate between highly similar stimuli, which is potentially related to a reduction of neurogenesis. Further research is needed to determine how well the MST might reflect *in vivo* levels of neurogenesis, and potential biomarkers for neuroimaging would be helpful in this regard. Given that the relationship between anxiety levels and test performance was strengthened when considering self-confidence, and important area for sport psychology (and non-sport psychology) may be to employ skills that serve to enhance self-confidence in anxious athletes.

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CHAPTER 6: DISCUSSION

Concussion has become a major public health crisis, particularly affecting the youth population and athletes involved in contact sports. Though the large majority of individuals recover quickly and without long-term problems, a subset will experience significant and potentially persistent neuropsychiatric sequelae. The hippocampus is well-recognized for its role in cognition and memory, and is known to be vulnerable to head injury (Beauchamp et al., 2011; Johnson et al., 2012; Lowenstein et al., 1992; Marquez de la Plata et al., 2011; Wilde et al., 2007). Animal models indicate that hippocampal neurogenesis — the process of the growth, maturation, and integration of adultborn neurons — is impaired following experimental head injury (Gao et al., 2013; Rola et al., 2006). Reductions of hippocampal neurogenesis have recently been linked to mood and anxiety (Anacker & Hen, 2017; Besnard & Sahay, 2016; Kheirbek et al., 2012), which are frequently observed following mTBI (Bryant et al., 2010; Luis et al., 2002; Ellis et al., 2015). The central aim of this thesis was to explore the neuropsychiatric sequelae of concussion and contact sport participation in youth and university-age subjects.

This thesis documents for the first time, that (1) psychiatric symptoms in concussed youth can present immediately after concussion in the absence of identifiable risk factors; that (2) anxiety is the most common and persistent psychiatric symptom in youth with concussion; that (3) concussion impairs performance on a test involving high memory interference, the mnemonic similarity test (MST); that (4) participation in contact sports also impairs performance on the MST; and that (5) performance on the MST is related to anxiety levels in athletes.

In Chapter 3, I presented the literature to date which has examined the psychiatric sequelae of mTBI, and identified several areas where our knowledge of the link between mTBI and psychiatric conditions may be significantly limited due to methodological problems and design flaws. I then presented a clinical sample of youth and young adults with concussion who developed significant psychiatric symptoms during the course of their recovery. These subjects had no known risk factors for the development of psychiatric problems, such as litigation or stressful life events. Two clinical patterns were identified: for 75% of the sample, psychiatric problems presented immediately, while for the other 25% persistent postconcussion symptoms were judged to be relevant to the development of a new psychiatric problem. Both groups reported anxiety symptoms most frequently, with mood problems almost as prevalent and a minority reporting conduct or behavioural issues. For over 2/3 of the sample, these psychiatric symptoms persisted past the resolution of physical concussion symptoms (e.g., headache, exercise intolerance) and resulted in formal diagnoses of psychiatric disorders. These results are consistent with others reporting postconcussion psychiatric disorders occurring in the youth population (Ellis et al., 2015). While a sample bias may be present given that these individuals were referred to a neurology clinic, others have also noted increased anxiety and mood disturbances in athletes immediately following concussion (Hutchison et al., 2009, 2017; Mainwaring et al., 2010; Meier et al., 2015, 2016). With the immediacy of psychiatric symptom onset in the absence of risk factors, our data suggest that concussion itself may induce a disruption of brain function that can result in psychiatric symptoms.

In Chapter 4, I explored the effects of concussion and contact sport participation (rugby) on a high memory interference task, the mnemonic similarity test (MST), which

shows putative links with neurogenesis-dependent conditions in humans (Dery et al., 2013, 2015; Goldstein et al., 2016; Holden et al., 2013; Shelton et al., 2013; Toner et al., 2009). Specifically, I found that after sustaining a concussion, athletes were impaired at identifying highly similar stimuli to previously presented images while their accuracy at identifying old and new images was unchanged. After recovering from concussion and at the point of returning to play, their performance improved and surpassed baseline levels. A similar pattern for identification of similar images was observed during the season of nonconcussed rugby players: their accuracy during the season was below their preseason scores, but after one month off from rugby their performance improved. Performance on this test was not affected by musculoskeletal injury, nor were practice effects evident. These results add to the accumulating evidence that participation in contact sports, independent of diagnosed concussion, may be associated with cognitive impairments (Koerte et al., 2017; McAllister et al., 2012a, 2014; Tsushima et al., 2016). The MST's association with neurogenesis-linked conditions such as depressed mood (Dery et al., 2013, 2015; Shelton et al., 2013), binge alcohol consumption (Goldstein et al., 2016), stress (Dery et al., 2015; Shelton et al., 2013), and exercise (Dery et al., 2013; Heisz et al., 2017) has indicated its promise as a proxy measurement of neurogenesis *in vivo*. We have hypothesized that concussion impairs hippocampal neurogenesis, which may underlie the performance deficits we observed in concussed athletes on this test.

In Chapter 5, we asked whether anxiety levels affect performance on the MST. From our larger athlete group we identified a cohort of athletes who had significant anxiety problems, and matched them by age, gender, and sport to non-anxious athletes. Both groups were also compared to a non-athlete control group with moderate levels of physical activity. Anxious athletes were impaired at identifying similar stimuli by

groupwise comparison, and anxiety levels were predictive of accurate identification of similar stimuli. These results support previous hypotheses of anxiety being related to a generalization of memory representations which may be related to an impairment of hippocampal neurogenesis (Besnard & Sahay, 2016; Kheirbek et al., 2012a).

Taken together, the evidence presented in this thesis provides initial support to the notion that concussion, subconcussive head impacts, and anxiety may be associated with reductions to hippocampal neurogenesis. We posit that, if true, hippocampal neurogenesis may underlie the common postconcussion complaints of impaired cognition and mood and anxiety problems. We further hypothesize that impaired neurogenesis may be a contributing factor to the presentation of some psychiatric symptoms, such as anxiety and mood disturbances, following concussion.

The work in this thesis provides a clear direction for future research. Most importantly, the MST is only, at best, a proxy measure of neurogenesis in humans and further research is required to determine the extent to which it reflects the process of neurogenesis. While previous studies have reported success in doing so (Manganas et al., 2007; Pereira et al., 2007), these have not yet been replicated. Caution is thus warranted in over-interpreting the relationship between the test and levels of neurogenesis in humans. Our sample of concussed athletes involved a large number of anxious athletes, and few female athletes — larger sample sizes will be required to ascertain the strength of association between concussion and the MST, in the absence of anxiety. A highly promising direction may be in using the test to potentially identify those who are at risk of developing psychiatric problems after a concussion. If baseline performance on the MST is lower than the norm, it could potentially indicate that an individual may be more likely to develop anxiety and mood problems after concussion. Another use for the test may be

for assessing the effects of postconcussion exercise protocols. It has recently been acknowledged that early exercise (after an appropriate time delay) after sustaining a concussion may be a useful strategy to reduce the likelihood of persistent postconcussion symptoms and enable earlier return-to-play and return-to-learn (McCrory et al., 2017). Improvements on the MST have been linked with responsiveness to aerobic exercise interventions (Dery et al., 2013; Heisz et al., 2017) and the presence of pro-neurogenic factors such as brain-derived neurotrophic factor (BDNF; Heisz et al., 2017). The MST may prove useful in evaluating the efficacy of exercise interventions following concussion, and may help identify the ideal timing for such interventions during recovery.

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