Part 1: LITERATURE REVIEW

A literature review of DTI findings in contact team sports-related concussions.

Part 2: EMPIRICAL PAPER

Multiple sports concussion in male rugby players: a neurocognitive and neuroimaging study

Submitted by Katherine Woollett, to the University of Exeter

as a thesis for the degree of Doctor of Clinical Psychology, May 2017

Table of Contents

List of Tables

Literature review

Empirical paper

List of Figures

Literature review

SCHOOL OF PSYCHOLOGY

DOCTORATE IN CLINICAL PSYCHOLOGY

LITERATURE REVIEW

A literature review of DTI findings in contact team sports-related concussions from 2012 to 2016.

Trainee Name:	Katherine Woollett
Primary Research Supervisor:	**Professor Huw Williams** Consultant Clinical Psychologist, Mood Disorders Centre
Secondary Research Supervisor:	**Professor Phil Yates** **Course Convenor** School of Psychology, University of Exeter **Consultant Clinical Neuropsychologist** Royal Devon and Exeter Hospital
Target Journal:	Journal of Sports Medicine
Word Count:	4,912 words (excluding abstract, table of contents, list of figures, tables, references, footnotes, appendices)

Submitted in partial fulfilment of requirements for the Doctorate Degree in Clinical Psychology, University of Exeter

Abstract

Background: Sport related concussions (SRC) are a known risk in contact sports. Some of the highest reported incidence rates are in contact team sports. Yet, the characterisation of the diffuse axonal damage after a SRC to date is imprecise, partly due to the heterogeneous nature of SRCs but also due to variability of findings using sophisticated imaging technology such as diffusion tensor imaging (DTI). Emerging evidence suggests that DTI has the diagnostic sensitivity to detect axonal injury associated with SRCs in athletes.

Objectives: The aim of this review is to evaluate the evidence for the utility of DTI to characterise SRC in team contact sports. Specifically, the review will examine if DTI metrics in athletes post- SRCs differ from those observed in control athletes at the acute, sub-acute and chronic stages. In addition, the results of the literature review will be used to evaluate if the empirical evidence supports the current return to play/retire from play rules in contact team sports.

Method: Articles on sports related concussion and diffusion tensor imaging were selected from online databases published between January 2012 and December 2016. The search yielded 4920 articles, with 2501 non-duplicated results. A total of 24 full-text articles were assessed for eligibility, which led to eight eligible articles included in this review.

Results: Regardless of the timeframe post- injury, the results suggest that DTI is sensitive to detect changes to the white matter (WM) of the brain in contact team sport athletes post- SRC. However, the findings are inconsistent in terms of the directionality of the DTI metrics and the WM regions affected. A

number of studies found increases in fractional anisotropy (FA) whilst other showed decreases in FA. There was also variability in terms of the white matter regions affected, one study reported differences across the whole white matter skeleton whilst others found these were limited to smaller areas of WM.

Conclusion: Results confirmed that DTI has diagnostic sensitivity to identify axonal injury due to sports related concussion in contact team athletes. Further longitudinal studies and improved methodology are required to elucidate its utility in injury diagnosis, management and prognostic capability.

Keywords: *sport related concussion, diffusion tensor imaging, contact sport, return to play.*

Introduction

Sport-related concussion (SRC) is a traumatic brain injury (TBI) that falls at the mild end of the spectrum of TBI (mTBI) and has historically been associated with symptoms as opposed to structural brain injury. A unified definition of SRC/concussion is lacking (see Sharp & Jenkins, 2015). A SRC either results from direct contact of an object striking the head or from rapid acceleration/deceleration forces in which the brain moves around in the skull producing shear and compression of white matter (WM) tracts leading to diffuse axonal and vascular injury. The symptoms of SRC include headache, blurred vision, dizziness, sleep disturbance, memory problems and other cognitive disturbances e.g. poor concentration and changes in emotion regulation (McCrea, 2008; Bigler, 2008). SRCs are estimated to resolve 7-10 days post-injury in approximately 80-90% of cases. In approximately 15% of cases individuals may experience chronic symptoms, a syndrome known as post-concussion syndrome (PCS; McCrea, 2003). The most common persistent symptoms are memory difficulties, impaired attention and executive function, fatigue, sleep problems, headache, irritability, anxiety or depression, and emotion regulation difficulties (McCrea, 2003). Many of these symptoms are present in a multitude of other medical and psychiatric diagnosis which makes the diagnosis of PCS complex.

The characterisation of the diffuse axonal damage after a SRC (and other mTBI) to date is imprecise, partly due to the heterogeneous nature of SRCs but also due to normal findings on conventional neuroimaging (computed tomography and structural magnetic resonance imaging (MRI)), coupled with variability of findings using more sophisticated imaging technology such as

diffusion tensor imaging (DTI) (Aoki, Inokuchi, Gunshin, Yahagi, & Suwa, 2012; Gardner et al., 2012; Hulkower, Poliak, Rosenbaum, Zimmerman, & Lipton, 2013). SRCs are a known risk in contact sports (Marar, McIlvain, Fields, & Comstock, 2012). The highest SRC rates are reported for team contact sports, particularly American football, men's ice hockey and female football (Wasserman, Kerr, Zuckerman, & Covassin, 2016). The true incidence of SRCs is not known, however, the incidence of SRCs seen in emergency departments increased 60.5% over a 9 year period in a sample ≥15 year olds in Australia, with the largest increases seen in sports such as rugby, football, roller sports and cycling (Finch, Clapperton, & McCrory, 2013). SRCs, like other mTBIs, are heterogeneous which makes diagnosis complex. There has been a growing interest in biomarkers of SRC (and other mTBI) that could improve diagnosis and management of the injury. Proteins such as S100B can be measured in serum levels and increased levels are proposed to indicate astrocytic damage after brain injury, however S100B does not offer good specificity in terms of severity of injury, particularly for mTBI, because the correlation between levels in cerebrospinal fluid and serum is low (Jeter et al., 2013). Proton magnetic resonance spectroscopy (MRS) detects levels of N-acetylaspartic acid (NAA), a marker of neuronal integrity. Decreased levels of NAA have been found in the whole brain in mTBI whether or not pathology was visible on neuroimaging (MRS; Jeter et al., 2013). DTI, a neuroimaging biomarker, has been shown to be sensitive to diagnose diffuse axonal injury in mTBI and SRC in both the acute and chronic phases post-injury (Gardner et al., 2012; Hulkower et al., 2013). DTI can also be used to examine the relationship between white matter (WM) injury and neurocognitive outcomes (Bigler, 2013a).

Diffusion Tensor Imaging

DTI is a neuroimaging technique used to characterise water diffusion in white matter tracts of the brain. DTI offers detailed information of the direction and the degree of water diffusion within individual voxels of a MRI image. There are four commonly used DTI metrics: fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) (Table 1). DTI can detect axonal injury in the acute, sub-acute and chronic phases of mTBI (Bigler, 2013). One review highlighted the importance of the post-injury phase when using DTI as the anisotropy may change over time as the microstructural changes evolve (Eierud et al., 2014). The review reported elevated levels of FA in the acute phase < 2 weeks and decreased levels of FA in the sub-acute phase > 2 weeks. High anisotropy values indicate that diffusion occurs only along one axis and is restricted in all other directions. The increased levels of anisotropy in acute stages are thought to reflect intracellular oedema because the water diffusion is inhibited, whereas decreases in FA are thought to reflect white matter degradation (extracellular water mixes and permeates the axon membrane) (Bigler, 2013a).

DTI methodology.

There are two methodologies commonly used in DTI: whole brain (WBA) and region of interest (ROI) analyses.

Table 1*. Diffusivity measures.*

Diffusivity measure	**Description**
Fractional anisotropy (FA)	A summary measure of microstructural integrity. High anisotropy values indicate that diffusion occurs only along one axis and is restricted in all other directions. It is sensitive to microstructural changes but less specific about the type of change.
Mean diffusivity (MD)	An inverse measure of membrane density. It is sensitive to cellularity, oedema and necrosis.
Axial diffusivity (AD)	AD is the apparent diffusivity measure parallel to the WM tracts. It decreases in axonal injury due to increased disruption to membrane barriers.
Radial diffusivity (RD)	RD is the apparent diffusivity measure perpendicular to the WM tracts and it increases with de- or dys- myelination. Changes in axonal diameters and density may also affect RD values.

Source: Alexander, Lee, Lazar & Field, 2007.

Whole brain analysis. The most commonly used WBA analysis is tract based statistics (TBSS) (Smith et al., 2006). TBSS aligns the FA images from each subject to a common space from which it creates a tract map, termed "mean FA skeleton" that includes only voxels that are central to the tracts common to all subjects in the group and excluding any areas of poor alignment. The FA skeleton data are analysed by computing statistics at each individual voxel and identifying areas where there are significant differences between groups.

ROI analyses. This approach requires a-priori identification of brain regions of interest and compares statistics in the voxels that are included in the pre-defined ROI. The ROI approach can identify small changes that may not be detected in WBA. However, it will not detect changes that were not hypothesised. There are a number of automated atlas-defined ROIs that can

be applied removing any subjectivity that may be introduced in hand-drawn approaches. A further advantage is that it can also reduce the severity of correction for multiple comparisons (Poldrack, 2007).

Diffusion Tensor Imaging and Sports Related Concussion

A systematic review by Gardner et al. (2012) suggested that DTI is a useful tool to detect axonal injury in SRC. However, there was variability in the brain regions where axonal injury was reported and the DTI metrics employed. Furthermore, the history of SRC was incomplete in the majority of studies (e.g. number of SRCs). The authors attributed some of the discrepancies between studies to methodological issues e.g. inappropriate control groups. Other research using DTI in conjunction with neurocognitive assessment has examined the relationship between WM injury and cognitive outcomes. DTI may have the potential to predict outcome 3-6 months post-injury in mTBI. Yuh et al. (2014) found that DTI changes identified in the sub-acute stage (mean 11 days) predicted poorer outcome at 6 months which was related to increased neurocognitive impairment (executive function) and post-concussive symptoms. Similarly, DTI changes in the acute and chronic phases have been shown to be negatively associated with outcome on neurocognitive tests of executive function, memory, language and attention (Hulkower et al., 2013). This suggests DTI is a useful method for detecting alterations to the integrity of WM tracts at different phases, and may be able to predict outcome post-injury.

Contact Team Sports and Sport Related Concussion

The 4th International Conference on Concussion in Sport (2012) published a consensus statement which sets out guidelines to follow for diagnosis, monitoring and management of SRC. The guidelines recommend side-line assessment of acute concussion by a physician. Following the assessment the athlete should be closely monitored for deterioration and if diagnosed with a SRC should not return to play (RTP) on the same day. The guidelines do not recommend neuroimaging unless severe injury is suspected. Neuropsychological assessment is recommended only when considered necessary by the physician and may be used to assist RTP decisions.

Despite the publication of the aforementioned guidelines, there is a lack of consistency in SRC management and treatment across sports. The majority of national contact sport teams, such as rugby, ice-hockey, and American football follow the guidelines (World Rugby, 2016). However, lower level clubs (e.g. community) may not be able to implement the guidelines. For example, depending on the level play (e.g. professional or community) the diagnosis may be performed by a medic, a physiotherapist or a coach who may not have the necessary medical knowledge to do so.

Return to Play

The guidelines issued by 4th International Conference on Concussion in Sport (2012) recommend a minimum period of 24 hours rest, followed by a RTP approach that should include a comprehensive assessment, physical and cognitive rest followed by a graded and progressive RTP protocol. Once

neurocognitive testing returns to baseline (if measured) and symptoms resolve, a specific post-concussion RTP exercise procedure that consists of six stepwise (incremental) stages of physical exercises is followed, until the athlete is fit to return to play. The guidelines do not set out clearly how cognitive rest should be fulfilled. Cognitive processes such as slowed processing and reaction times, that may be present during cognitive recovery, can contribute to re-injury (Sabini & Nutini, 2011). The RTP protocol is recommended for use age ≥13. There are no specific variations to the protocol for different genders or repeat SRCs.

The guidelines are a useful for those involved in the clinical management of athletes however they focus primarily on symptoms not what happens at a brain structure level. One study found that 90% of a sample of 141 footballers RTP without missing a game, on average 6-9 days post injury (Cancelliere et al., 2014). The presence of more than four symptoms was associated with longer periods of time before RTP (Cancelliere et al., 2014). Athletes' knowledge of RTP rules and SRC management remain poor and underreporting of symptoms is common particularly in male athletes, thus athletes may RTP before full recovery (Covassin, 2012).

Furthermore, sustaining a SRC may confer a greater chance of repeated injury occurring, and the risk seems to increase with each SRC (Guskiewicz et al., 2003). Conversely, other studies have not found increased risk for a second SRC (Guskiewicz, Marshall, Broglio, Cantu, & Kirkendall, 2002; MCcrea et al. 2009). The risk of sustaining a concussion may be mediated by the risk-taking style of players, as no greater risk was conferred post-injury (Burman, Lysholm, Shahim, Malm & Tegner, 2016).

If there is a repeat injury whilst the first SRC is still resolving it can set off a neurometabolic cascade that results in cellular inflammation which, in rare cases, can have catastrophic results, known as second impact syndrome (SIS) (Thomas et al., 2011). The period of vulnerability where another impact can worsen ongoing pathology is not well defined and has important implications for RTP.

Long-Term Outcome

There is ongoing debate regarding the link between SRC and long-term outcomes. Athletes may be affected many years later by mild cognitive impairment, depression and chronic traumatic encephalopathy (CTE; known as dementia pugilistica), a form of neurodegeneration that is proposed to be due to cumulative SRCs (Mckee, Stein, Kiernan, & Alvarez, 2016). CTE is characterised by tau-positive neurofibrillary tangles and is accompanied by cognitive decline, poor impulse control and mood changes (Mckee et al., 2016). However, the aetiology is uncertain with the majority of the studies being single case or cross-sectional designs that rely on self-report measures (Maroon et al., 2015).

In conclusion, issues of how structural brain injury presents post-injury and how they resolve or evolve in the short and long term remain unresolved. Understanding the brain pathology in SRC is important to improve management post-injury, contribute to our understanding of recovery and inform RTP. Thus, a new review of DTI studies of SRCs in contact team sports (highest incidence) is warranted to explore if any of the issues identified by Gardner et al. (2012) have been clarified.

Objectives

The current review will explore the existing empirical literature of DTI in athletes that participate in team contact sports and have sustained SRCs. In particular, the review will consider the following question:

Do athletes with SRCs show changes on DTI metrics, indicating possible axonal injury, at different post injury stages (i.e. acute, sub-acute and chronic stages)?

In addition, the results of the literature review will be used to evaluate if the empirical evidence supports the current return to play/retire from play rules in contact team sports.

Method

Search Strategy

Five electronic databases were searched: PubMed, Web of Science, PsycINFO, EMBASE and SPORTDiscuss. The search terms entered are shown in Table 2. The search terms were selected in consultation with senior researchers Grant Iverson, Derek Jones and Andrew Gardner (who have published reviews of DTI and cumulative SRCs in leading journals). Section one includes possible variations of SRC terminology that would identify any studies of SRC, and section two covers variations of DTI terminology that would identify any studies that used DTI. The studies identified through this combination addressed the main aim of the review. The studies were also to be used to elucidate if DTI findings support the current RTP rules. The terms were combined using the Boolean operator ‘OR’ to combine terms within each section. The Boolean operator ‘AND’ was used to combine terms in section one

and terms in sections two. Wildcards (e.g. neurocog*) and truncation were adjusted to each database. In addition, reference lists of all included studies were scanned for other articles not yielded in the database searches.

Table 2. *Search terms*

Concussion*, sport*, sport related concuss*, mild traumatic brain injur*, mildTBI*, head injury, mild head injur*, athelet*	Diffusion tensor imaging, diffusion magnetic resonance imaging, diffusion weighted MRI, diffusion*, Tractography, fractional anisotropy*

Data Extraction

The author screened the search results by first checking the titles, followed by abstracts and full contents against the inclusion and exclusion criteria (Table 3). Studies that did not meet the criteria were excluded at each stage. The remaining studies were quality assessed by the author.

For the purpose of this review contact team sports was defined as team sports in which there is frequent body contact or ball contact, and a high incidence of SRC (Clay et al., 2013; Pfister et al., 2015). SRC was operationalised by adopting a conservative set of diagnostic criteria namely the guidelines of the 4th International conference on Concussion in Sports, American Academy of Neurology or an indication in the article that a physician made the diagnosis.

Table 3. *Inclusion and exclusion criteria for literature review*

Inclusion criteria	Exclusion criteria
• Primary research • Available in English • Published in a peer review journal between January 2012 and December 2016. • Observational. Cohort, correlational, cross-sectional and longitudinal studies • Male and female participants over 18 years old • Participants play a contact team sport • Concussion as a result of playing the sport being considered	• Book reviews, expert opinions, conference abstracts, letters or commentaries • Not available in English • Non-peer reviewed journals • Systematic review • Participants are aged under 18 • Participants have developmental cognitive impairments • Participants have degenerative disorders e.g. Alzheimer's disease • Participants have an acquired brain injury as a result of stroke, brain tumours, road traffic accidents, falls, or other neurological conditions e.g. epilepsy

Quality Assurance

The studies included were quality assessed using the Effective Public Health Practice Project's (EPHPP; 1998) Quality Assessment Tool for Quantitative Studies. This tool is designed primarily to assess quantitative intervention studies. This tool evaluates studies on eight dimensions: selection bias, study design, confounders, blinding, data collection methodology, and withdrawals and dropouts (Appendix A). To adapt the tool for the current review question G was excluded as it pertains to intervention studies. In addition, only Q1 and Q4 of question B, Q1 of question D and Q3 of question H were considered (see Table 4). Each component was rated on a three-grade scale: strong, moderate or weak.

Table 4 – *Adaptation of the EPHPP rating tool*

Question A **Selection bias**	Q1. Are the subjects included in the study athletes engaged in contact team sports? Q2. What percentage of the selected sample agreed to participate?
Question B **Study design**	Q1. State the type of study design that was employed? Q2. Was this appropriate for the study?
Question C **Confounders**	Q1. Were there important differences between the groups prior to the study? Q2. If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis)?
Question D **Blinding**	Q2. Were the participants aware of the research question?
Question E **Data collection methods**	Q1. Were data collection tools valid? Q2. Were data collection tools reliable?
Question F **Withdrawals and dropouts**	Q1. Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group? Q2. Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).
Question H **Analysis**	Q3. Are the analysis methods appropriate for the study design?

Results

Search Results

The searches were conducted between the 19th December 2016 and 4th January 2017. Inclusion criteria were applied to 4920 articles. 2501 non-duplicated articles remained. A total of 24 full-text articles were assessed for eligibility, of which eight met full criteria for inclusion. A summary of the search can be found in Figure 1.

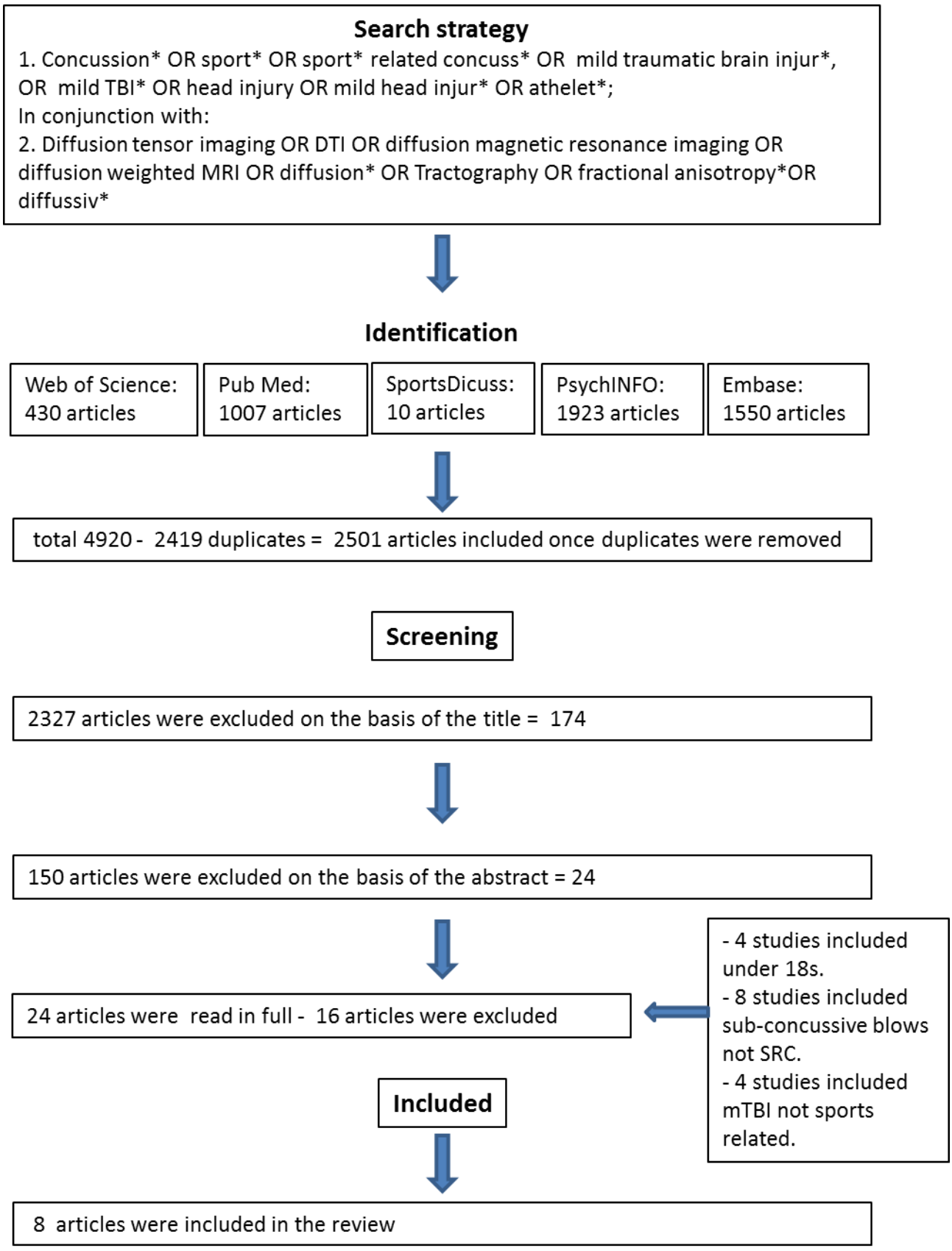


Figure 1. Search Strategy.

Study Characteristics

The review found eight studies published from January 2012 to December 2016 that included athlete samples aged >18 and employed DTI. A total of 305 athletes were included of which 144 were control athletes, 217 were male and 88 female. Three of the eight studies included only male participants, one study included only females and the remaining four included mixed samples. Study 7 included a 50:50 male/female ratio that was balanced across groups, and study 5 matched the number of females in both groups. The contact sports included are in Table 4. Four studies included non-contact and contact sport athletes in the control group, and three studies did not specify which sports the control group engaged in. The age ranged from 18 to 26 years old. Sample sizes ranged from 19 to 86. All SRCs were sports related with the exception of two injuries in study 5. A summary of the studies reviewed can be found in Table 4.

All studies used at 3T scanner. There was variability in the MR imaging parameters applied. For example, the voxel size ranged from 1.88 mm^3 to 2.7 mm^3 (Table 5). One study used a ROI approach, four a WBA approach and three employed both ROI and WBA. The most frequently examined ROI was the corpus callosum (CC) however there was not a consistent approach to how this was divided in the studies. Study 2 parcelated the CC into five vertical sub-divisions and study 7 into: genu, body and splenium (Table 5).

Table 5 – *Study characteristics and main findings*

	Study	Sample	Study design	Main findings	Study strengths/weakness	Other measurements	Summary and comments	QA
1.	Koerte et al., 2012	25 university male ice hockey players. 14 had at least 1 reported concussion before the season and 5 experienced a SRC during the season. 6 excluded from analyses. Data for a total of 17 subjects included in analyses. Age: 22.24 ± 1.59	Pre-(baseline) and post-season longitudinal design	Significantly higher trace, AD (mean percentage change 5.2%, range -1.96 to 12.07%), RD mean percentage change 7.8%, range -4.75 to 18.09%) values were found in the right precentral region, the right corona radiata, and the anterior and posterior limb of the internal capsule at the post-season compared to pre-season time point. No significant differences in FA. Changes in RD were more pronounced in the SRC players concussed in season compared to other players.	Strengths: - Longitudinal design. Weaknesses: - Cohort includes athletes with in season SRC which are not differentiated from those without in-season SRC in the analysis. - Demographic information not reported	- Neuropsychology - MRS - Concussion incidence	All additional measures are reported in separate research papers and not combined with the DTI data. Mean percentage changes in diffusivity measures included but reporting of results is not clear. It is difficult to interpret the significance of the findings without the statistics and/or effect sizes. The time between last SRC and DTI scans is not reported. Demographic information is reported in a separate article. However, it is unclear which of the subjects are included in both studies.	Moderate This study had a week rating for Question 3 – Confounders: some players have a history of SRC and others do not but are included in same group.
2.	Chamard et al., 2016	20 Female athletes: 10 with a history of concussion/10 with no history of concussion.	Cross-sectional: chronic stage of SRC	• No significant differences in FA between groups. • Significantly higher MD values were found in the SRC group in the left forceps minor, the left inferior fronto-	Strengths: - Groups matched for age and education.	-MR spectroscopy - PCSS[1]	The athletes in SRC group are engaged in sports but does not specify which sport.	Moderate This study had a weak rating Question 3 – Confounders.

[1] Post-Concussion Symptom Scale

		Age: SRC group = 21.7 ± 2.06 Control group = 21 ± 1.33		occipital fasciculus, the left cingulum, the left uncinated fasciculus, the left longitudinal fasciculus and the anterior thalamic radiations bilaterally, the superior longitudinal fasciculus bilaterally and the corticospinal tract bilaterally. • ROI showed significantly lower FA for the SRC group in sub-division 3 of the CC. • The effect sizes ranged from Cohen's *d* =1.22 [CI: 0.28-1.42]; -2.36 [CI 1.42 – 3.30] (not included in study but calculated for the literature review).	- Asymptomatic athletes only - Chronic stage SRC only. - Time since last SRC reported mean = 19.5 (15) months. - Frequency of SRC reported mean = 2.6 (2.3). Weaknesses: - The control group is made up of athletes who are also engaged in contact-sports. There may be effects of sub-concussive blows and/or un-recognised SRCs.			It does not state the sports played by control group.
3.	Murugavel et al., 2014	37 male varsity-level athletes: 21 contact-sport	Longitudinal design across 3	Within SRC group findings:	Strengths:	- T1 weighted MRI - SCAT2[2]	Cognitive, SCAT2 and mood data not reported in detail.	Moderate

[2] Sport Concussion Assessment Tool – 2nd Edition.

		athletes with a recent SRC/16 non-contact varsity sport athletes. Age: SRC group = 20.19 ± 1.03 Control group = 19.9 ± 1.67	time points: acute (2 days), sub-acute (2 weeks) and chronic phases (30 days).	RD values significantly higher at 2 days vs. 2 weeks FA significantly lower at 2 days vs. 2 weeks Significant overlap between RD and FA clusters. Between group findings: RD values significantly higher in SRC group at 2 days post injury compared to controls. No RD differences at 2 weeks. A trend for changes in RD at 2 months. FA is significantly lower for SRC group at 2 days post injury. No significant FA differences at 2 weeks. There were significant FA differences at 2 months. The significant cluster includes parts of the posterior limb, the retrolenticular part of the IC, the inferior fronto-occipital fasciculus, inferior longitudinal fasciculus and the anterior thalamic radiation.	- Longitudinal study with 3 time points. - Groups matched for age and education. - Most recent SRC diagnosed by a team physician. - Most recent SRC did not include LOC. - Control group includes only non-contact sport athletes. Weaknesses: - Data missing or excluded for athletes across time points. A total of 7 athletes scanned at 3	- ImPACT[3] - PHQ-9[4] - GAD-7[5] - RTP time for most recent SRC recorded	Associations between DTI findings and above mentioned measures is not explored/reported in the study. SRC group includes athletes with varying frequency of SRC (range 0-3) and this is not considered in the analysis. RTP time not considered either. Effect sizes not reported. Insufficient statistical data available to calculate the effect sizes.	Data collection is weak. Different participants are compared at different time points. Only 7 individuals were tested at the 3 time points.

[3] Immediate Post-Concussion Assessment and Cognitive Test.
[4] Patient Health Questionnaire – 9 Item Scale.
[5] Generalised Anxiety Disorder – 7 Item Scale.

					times points, 5 athletes at 2 days and 2 weeks, 4 athletes at 2 weeks and 2 months, 2 athletes at 2 days and 2 months and 3 only scanned at one time point.			
4.	Sasaki et al., 2014	34 Ice hockey players: 16 players with previous SRCs (8 suffered a SRC during the season) (10 male/6 female)/18 players had no history of SRC (8 male/10 female). Age: SRC group= 21.7 ± 1.5 Controls=21.3 ± 1.8	Cross sectional design - Chronic stage	Within SRC group: athletes who suffered a SRC during the season showed no significant differences on DT metrics, cognitive scores or post-concussion symptoms. Between group: The SRC group show significantly higher FA values in the bilateral corona radiate, bilateral posterior limb of the internal capsule, bilateral superior frontal white matter. B) significantly higher AD values in the left corona radiate, and c) significantly lower RD values in the genu of the corpus callosum, bilateral corona radiata, bilateral posterior limb of the internal capsule, right anterior limb of the internal capsule, right cerebral	Strengths: - Cognitive assessment - Post-concussion symptoms SCAT2 - Minimum 42 days/maximum 161 since last SRC Weaknesses: - Females and males included in same group analyses.	- Cognitive assessment - Post-concussion symptoms of the SCAT2	Control group are also ice-hockey players. It is difficult to interpret the significance of the findings without the statistics and/or effect sizes.	Moderate This study has a weak rating on Question 3 – Confounders: The groups included heterogeneous samples.

				peduncle, bilateral superior frontal and orbito frontal WM, right superior and inferior temporal WM, and right external capsule. DTI metrics did not correlate with cognitive or post-concussive measures.	- Gender was not balanced across groups. - The control group athletes may have been exposed to sub-concussive blows			
5.	List et al., 2015	20 athletes (2 female) with mTBIs and a control group of 20 athletes (2 female) without TBIs. Age: SRC group = 25.7 ± 5.5 Control group = 25.5 ± 5.3	Cross-sectional: chronic stage of SRC	No significant differences between the two groups on DTI measures: FA and MD A higher number of SRCs correlated with lower cortical thickness in the left insula (r=-0.49) and right superior temporal cortex (r=0.51). Significant differences between groups were found on verbal fluency tests.	Strengths: - Inclusion criteria included: minimum 6 months since last mTBI Weaknesses: - Females and males included in same group analyses. - SRC group includes athletes from various sports. - The last reported injury in 2 cases is not a SRC. - Post-concussive symptoms	- Cortical thickness - Neuropsychological testing	The study compared athletes with multiple SRCs to athletes without SRCs on three measures: DTI, cortical thickness and neuropsychological testing. No significant differences between the two groups on two DTI measures: FA and MD. Significant differences between groups were found on verbal fluency tests. Comments: Control group includes athletes but the sport they play is not specified.	Moderate This study has a weak rating on Question 3 – Confounders: The groups included heterogeneous samples.

					assessed but not reported.			
6.	Zhu et al., 2015	8 male football players with in-season SRC (no prior SRCs (1 case but excluded)/11 male control athletes (not football but sport not specified) Age: SRC group = 20 ±1.3 Controls 20.5 ± 1.8	Longitudinal design with three time points: day 1, 7 and 30	DTI significant changes FA values across WM skeleton in SRC group between day 1 and 30 (2% change effect size 0.67 [CI: 0.27-1.61]) and 7 and 30 (1.7%change; effect size 0.63[CI: 0.31-1.57]) at both time points FA values were lower. No significant changes were found in any of the 48 anatomical sub-regions included in the WM skeleton. No significant differences in MD, RD and AD. No correlations performed between Impact scores and DTI	Strengths: - Longitudinal study with three time points: acute, sub-acute and chronic stages. Weaknesses: - Control group are not football players but sport not specified.	ImPACT rs-fMRI	In addition to DTI, the Impact battery was administered at pre-season as baseline, day 1 and every 2-3 days until return to baseline around day 7. Neuropsychology worse on visual memory, processing speed, RT on day 1 but returned to baseline or improved from baseline on day 6 +/- 2.4 days Rs-functional connectivity: significant differences between SRC and non-SRC groups reported. DMN functional connectivity increased on day 1, significantly dropped on day 7 and recovered on day 30.	Strong This study has no weak ratings.
7.	Churchill et al., 2016	43 athletes: 21 (11 female) with history of concussion/22 (11 female) with no documented history of concussion. Age: SRC group = 21 ± 1.7 Control group = 19.5 ± 1.5	Cross sectional study - Chronic stage.	Athletes with a history of concussion showed significant changes in DTI measurements. SRC group showed: a) increased FA in the corona radiata (anterior and posterior) and the genu of the corpus callosum; and b) decrease MD in the posterior corona radiate and corpus callosum. The higher the number of concussions the more FA values increased and MD values decreased. FA and MD values showed minimal	Strengths: - Minimum 9 months since last mTBI. - Matched for age and education. Weaknesses: - Females and males included in same group analyses. Although	- Grey matter volume. - Cerebral blood flow. - Post-concussion symptoms assessed using the SCAT3[6]	It is difficult to interpret the significance of the findings without the statistics and/or effect sizes.	Moderate The study has a weak rating on Question 3 – Confounders: the groups included heterogeneous samples.

				correlation with clinical symptoms. The concussion group showed decreases in frontal brain volume and CBF compared to controls. Increased recovery time from the most recent SRC was associated with reduced fronto-temporal volume.	gender is balanced across groups the effect of gender is not explored in the analyses. - The control group includes athletes that are engaged in contact sports (volleyball, basketball and women's hockey).			
8.	Meier et al., 2016	86 collegiate athletes: 40 SRC group (10 females) recruited within a day of SRC/46 control group (16 females) of which 15 had a previous SRC. Age: SRC group = 20.12 (1.4) Control group = 20.31 (1.5)	Longitudinal: 3 time points = acute (T1), sub-acute (T2) and chronic (T3) phases	Between group: ROI analyses: SRC group significantly higher FA in the SLF compared to controls at T1, T2 and T3. Voxel-wise analyses: the SRC group compared to control group showed significantly higher FA at T1 in the right sagittal stratum, the bilateral superior CP, the right retro lenticular IC, the left and right SLF, the right forceps minor and inferior fronto-occipital fasciculus, and left posterior corona radiate. FA remained significantly higher is these clusters at T2 and T3.	Strengths: - Longitudinal design 3 time points. - Matched for age and education Weaknesses: - Participants in control group played soccer and American football, 33% had a history of concussion.	-Plasma Tau levels -ANAM[7] -	SRC group includes 3 athletes that were not engaged in contact sports.	Moderate This study scored weak on Question 3 – Confounders: The groups included heterogeneous samples. The control group included

				T1 effect sizes range d=0.60-1.05 T2 effect sizes range d=0.66-1.21 T3 effect sizes range d=0.75-1.17 Number of days before RTP positively correlated with FA in the left SLF ROI at T1 (r_s =0.44) and T3 (r_s=0.52) No within subjects analyses were reported.				participants with historical SRCs

Table 6. *Summary of DTI methodologies and statistical analysis used in the studies reviewed*

	Study	MRI hardware specifications	MR imaging parameters	No of ROIs/ anatomical structures examined	DTI pre-processing and statistical analyses methodology
1.	Koerte et al., 2012	3T Achieva, Philips system – 8 channel head coil	DTI sequence with two averages and the following parameters: 60 non-colinear diffusion directions, TR=7015msec, TE=60msec, b-value=0 and 700 sec/mm2, and 70 slices. Matrix size 100x100, voxel size 2.2x2.2x2.2mm.	Whole brain analysis using Tract-Based Spatial Statistics (TBSS) part of FSL.	Voxel wise statistics applied to skeletonized FA, RD, AD and trace data using FSL. Paired group statistics were used to compare pre- and post- season scans<0.05 corrected for multiple comparisons.
2.	Chamard et al., 2013	3T Siemens Trio system	Diffusion weighted parameters: diffusion weighted gradients applied in 64 directions, b-values=0 and 700sec/mm2 and four averages in each direction, TR=800ms, TE=101ms FOV 256x256mm2, acquisition matrix 128x128, slice thickness 2mm, 75 slices	Whole brain analysis ROI approach analysis for the corpus callosum parcelated into five vertical sub-divisions following the classification proposed by Hofer and Frahm, 2006.	FA images from all subjects were coregistered into a template and then linearly aligned to MIN space. All Fa images were averaged to generate a group mean FA image. The mean FA image was thinned to create a mean FA skeleton. Each participants FA data were then projected onto the skeleton to create a skeletonised FA map. For the whole brain analysis T-tests were used with a significance threshold of p<0.05 family –wise error corrected (FWE) using TBSS package. For the ROI analysis t-tests were performed for each of the five sub-divisions of the corpus collusum.
3.	Murugavel et al., 2014	3T Siemens Skyra system – 16 channel, phase array coil	Diffusion weighted parameters: diffusion weighted gradients applied in 64 gradient directions, b-values=0 and 1000sec/mm2 and four averages in each direction, TR=12,100ms, TE=96ms, FOV 256mm2, voxel size 1.88x1.88mm2, slice thickness 1.9mm, 70 axial slices	Whole brain analysis using TBSS.	The mean FA skeleton based on the included participants FA volumes was thresholded to include voxels with FA >0.25 to restrict analyses to the core WM tracts.

4.	Sasaki et al., 2014	3T Achieve, Philips Medical system – 8 channel head coil array	Diffusion tensor imaging sequence with two averages and following parameters: 60 non-colinear diffusion directions, TR=7015msec, TE=60msec, b-value=0 and 700 sec/mm2, and 70 slices. 2.2mm isotropic voxel size and 100 x100 matrix reconstructed into a 112x112 matrix with a resolution of 2x2x2.2mm3.	A whole brain statistical group analysis was employed (TBSS).	FA images from all subjects were coregistered into a template and then linearly aligned to MNI space. All FA images were averaged to generate a group mean FA image. The mean FA image was thinned to create a mean FA skeleton. Each participants FA data were then projected onto the skeleton to create a skeletonised FA map. Group comparisons for each voxel of the skeleton were conducted using FSL software with a corrected significance levels for multiple comparisons of $p<0.05$. Comparisons were adjusted for age, handedness, sex and motion.
5.	List et al.,2015	3T Siemens TRIO MR system – 12 channel head coil	Diffusion weighted images (TR = 7500ms, TE= 86ms, 61 axial slices, voxel size of 2.3 x 2.3 x 2.3 mm^3; 64 directions with a b-value of 1000 s/mm^2 and 10 b0) and high resolution T1 weighted MPRAGE images (TR = 1900ms, TE= 2.52 ms, 192 sagittal slices, voxel sixe 1 x 1 x 1 mm^3, flip angle 9^o).	One fronto-temporal ROI comprising: rostral and caudal anterior cingulated, entorhinal area, insula, superior frontal area, caudal middle frontal area, pans opercularis, inferior temporal area, lateral orbitofrontal area, medial orbitofrontal area, middle temporal area, pars orbitalis, pars triangularis, rostral middles frontal area, superior temporal area, frontal pole, and temporal pole, fusiform, parahippocampal, transverse temporal for each hemisphere.	FSL – FA and MD maps of the ROI were extracted for each subject using Freesurfer software. A voxel based analyses was conducted on the bilateral ROI to establish any group differences in FA and MD. If significant group differences were established the number of mTBIs was used as a factor corrected for multiple comparisons at $p<0.01$.
6.	Zhu et al., 2015	GE 3T Sigma scanner – 8 channel head coil.	Diffusion tensor imaging sequence with following parameters: TR=13.7s, TE=77.5ms, acquisition matrix 128 x 128, FOV=22cm x 22cm, 48 contiguous 2.4mm axial slices.	A whole brain statistical group analysis was employed (TBSS).	FA images from all subjects were coregistered into a template and then linearly aligned to the ICBM-DTI-81 white matter atlas. The mean FA image was thinned to create a mean FA skeleton. The skeleton mask was divided into 48 anatomical

					regions based on the ICBM-DTI-81 white matte atlas. Repeated measures ANOVAs on FA, MD, RD and AD were used with 2 tailed paired t-tests for post-hoc analysis of time points. Significance level corrected for multiple comparison was set at p <0.001 for each of the 48 regions.
7.	Churchill et al., 2016	3T Achieva Phillips system – 8 channel head coil array	Diffusion weighted echo planar imaging with 30 gradient orientations at b=700 sec/mm2, FOV=24x24cm, 120x120 acquisition matrix, 66 axial slices, 2mm isotropic voxels, bandwidth=1736Hz/pixel, TE/TR=90/12300ms. T1 weighted grey matter images also acquired.	Whole brain analysis.	FA and MD maps were obtained and co-registered to the FMRIB58 template. A 6mm FMHW Smoothing kernel was applied. The whole brain and ROI data analyses used between groups T-tests with a significance threshold of P<0.05 family-wise corrected.
8.	Meier et al., 2016	3T General Electric Healthcare Discovery MR750 system – 32 channel, phase array coil	Diffusion weighted parameters: 30 non-collinear directions, b-value= 1000sec/mm2, TR=8,800ms, TE= average 78.5ms, range 76.8-84.9ms, FOV 256mm2, voxel size 2.7x2.7x2mm, slice thickness 2mm, 69 slices	ROI analysis: the genu, body and splenium of the CC, the left and right uncinated fasciculus, superior longitudinal fasciculus, anterior corona radiate, superior corona radiata, combined anterior and posterior internal capsule and the cerebellar peduncles. Whole brain voxel-wise analyses.	ROI analysis was performed with time, ROI and interaction between time and ROI as fixed effects. Minimum cluster volume = 160ul was employed to reduce false positives. A family-wise error correction was applied at p<0.05 to both analyses. ROI analyses. First the mean and SD of FA at each voxel was calculated across the control group using FA images that were normalised to the FMRIB58_FAtemplate. Clusters with increased/decreased FA were calculated for each subject at T1, T2 and T3. WBA each participants FA image was aligned to standard template space FMRIB58.

Critical Summary

Diffusion Tensor Imaging Differences in Athletes

Only one study did not find any significant differences on DTI measures between team athletes with a history of SRC and athletes without a history of SRC (study 5). The findings across the remaining seven studies varied substantially. Studies 4, 7, 6 and 8 found increased FA values in SRC groups compared to control groups in a number of different WM regions. Of these, one study reported differences across the FA skeleton (study 6), one study reported these differences in the genu of the CC and the corona radiata (study 7), and another across many different regions (study 8 - Table 5). Finally one study reported increases in FA in the internal capsule, bilateral superior frontal WM and right superior temporal WM (study 4). Two studies reported lower FA values in the SRC group compared to controls. Study 2 found lower FA values in part of the CC, whilst study three reported lower FA at two days and two months post injury in many different regions e.g. posterior limb, and anterior thalamic radiation. In study 1 no significant differences pre- and post- season in terms of FA measures were found. Studies 1 and 4 included overlapping participants. Similarly, there were no consistent findings on other DTI measures e.g. MD (see Table 5 for full details).

Diffusion Tensor Imaging Across Stages of Sport Related Concussion

The findings of three studies which employed a longitudinal design that included the acute, sub-acute and chronic stages (studies 3, 6 and 8) suggest that DTI is sensitive to detect changes in diffusivity measures in the three

phases of injury, in line with previous DTI findings in mTBI (Aoki, Inokuchi, Gunshin, Yahagi, & Suwa, 2012).

Acute and sub-acute stages. In the acute stage two studies found differences within subjects compared to the chronic stage. Study 3 reported increases in FA in the acute but not the sub-acute phase in a large cluster (Table 5). Study 6 found increases in FA values over the full white matter skeleton in the acute stage and sub-acute stages compared to measurements at 30 days post-injury. There were no significant findings for other DTI metrics.

Chronic stage. Four studies employed a cross-sectional design of DTI measures in the chronic stage of SRC. One study did not find any differences between groups on DTI measures (study 5). The findings of the remaining studies suggest that DTI is sensitive to detect changes in the chronic stage. Studies 4 and 7 found increased FA values in athletes with a history of SRC in the corona radiata, CC and superior frontal WM. Study 2 found lower FA values using a ROI approach for the CC and higher MD values in a large number of WM areas in athletes with SRC (Table 5).

Study 1 employed a pre- and post- season longitudinal design. The study reported significant differences in RD and AD DTI measures in the post season compared to pre-season. However, the sample ranged from players without SRCs, some with SRCs and three that sustained a SRC in season.

In sum, the findings suggest that there are significant variations in DTI measures across all stages of SRC within and between groups post-SRC but the findings are not homogeneous or consistent.

Diffusion Tensor Imaging and Return to Play

The time elapsed before RTP was only considered by study 8. They found a positive correlation between days before RTP and FA values in the left SLF. Players who were off play for longer due to their symptoms, had higher FA values in the acute phase (one day post-SRC) and the chronic stage (one month post-SRC). There were no statistically significant correlations between FA values and behavioural testing. The relationship between FA values, symptom severity and mood measures was not reported.

The findings of study 6 suggest that there are ongoing structural brain changes beyond acute and sub-acute stages. The study reported a return to baseline levels of performance on neuropsychological tests by day. However, the changes on DTI metrics and rs-fMRI connectivity levels persisted beyond this period (30 days). This suggests that mechanisms such as cognitive reserve, where there is more flexibility in the neural networks selected to perform tasks, and/or neural compensation, whereby additional networks are used to perform the task, may be at play in order for individuals to maintain optimal levels of performance whilst the brain is recovering from injury, a process that continues in the chronic stage (Barulli & Stern, 2013; Turner & Levine, 2008).

In sum, the variability of findings and the lack of direct investigation of the relationship between RTP and DTI metrics reviewed in the studies make it difficult to evaluate whether current RTP guidelines are adequate. Future research that employs DTI metrics in conjunction with RTP, injury frequency and severity, cognitive and physical and psychological symptoms is needed to explore this hypothesis in more detail.

Discussion

The review showed that SRCs are related to changes in DTI metrics across all phases post-injury. However, no conclusive findings were found for any of the four commonly employed DTI metrics (Table 5). Similarly, no conclusive findings were found for common brain regions in which DTI metric differences were observed. In addition, there was a lack of detail in the majority of the studies in terms of the SRCs e.g. severity and frequency, presenting symptoms and time off before allowed to RTP.

The articles included in the current review include heterogeneous participants and in some cases non-optimal control groups. This type of participant selection introduces confounding factors such as sub-concussive blows in control subjects, differences between male and female athletes, and differences in the rate of exposure to concussive or sub-concussive blows between contact sports. The demographic differences between the groups may contribute to the DTI inconsistencies and reduce the internal validity on the control comparisons. The lack of a second rater may have also introduced bias in terms of the studies selected and the ratings assigned to them.

The review by Gardner et al. (2012) reported variability in the findings pertaining to FA and MD metrics which was also observed in the current review. Gardner et al. (2012) also reported variability in terms of the neuroanatomical brain regions where changes were found. Neuroanatomical variability was also present in the current review. The review highlighted the lack of details provided in terms of SRC history and characterisation. There is minimal improvement of these issues as some studies reported frequency of SRCs but information regarding severity is still lacking. Another area of improvement is the inclusion

of time frames between the last SRC and DTI data acquisition in most studies. However, other areas still need to be improved e.g. control groups include athletes that also play contact sports where they are exposed to sub-concussive blows. Gardner (2012) also reported variability in terms of DTI metrics by post-injury stage in three longitudinal studies. However, this included a paediatric study, a study of boxers over > 30 years old (no SRC history or control group) and a study of age and gender matched university football players. The results were not comparable given the heterogeneity of the samples. The current review included three longitudinal studies with age and gender matched participants across groups, and information regarding the number of SRCs, yet it also found variability in terms of DTI metrics. Importantly participants in the control group of one of these included athletes with historical SRCs which may have influenced the findings. In summary, the majority of the methodological issues identified by Gardner (2012) have not been resolved.

This review highlights the importance of considering DTI findings in conjunction with other important factors such as presence of symptoms, the frequency of SRCs, adequate control groups and further exploration of effects of gender and age. It was striking to note that none of the studies included symptomatic athletes. Critically, it is possible that athletes that retire from play show more severe symptomology and that this is associated with more severe or more extensive structural brain alterations post-injury.

Limitations

A number of limitations need to be considered when interpreting the findings of the studies in this review.

The control groups in three studies include athletes that were engaged in contact sports (studies 3, 4, and 7). One study included athletes with a previous SRC in the control group (study 8). Three studies did not specify which sport athletes in the control played (2, 5 and 6). Hence, the control groups may include athletes that have been exposed to multiple sub-concussive blows. Sub-concussive blows have been reported to be associated with changes in neurocognitive functioning and DTI in athletes (Bazarian et al., 2014) which may be a source of bias that contributes to the inconsistent findings between studies.

Four studies included male and female athletes but did not explore gender differences in the analyses. Gender differences are reported in terms of risk of incurring a SRC, cognitive performance, reporting symptoms and intensity of symptoms reported post-SRC (Covassin, Elbin, Crutcher, & Burkhart, 2013).

The inconsistency of findings across studies may be due to the heterogeneous nature of SRCs, the number of concussions, the severity of the injury, the mechanism of the injury and lack of clinical details (e.g. presence of pre- post- amnesia). Three studies included individual information of number of SRCs (studies 2 and 5), only one investigated the relationship between this variable and DTI (study 7). This makes it difficult to differentiate between long-standing diffuse axonal injury associated with previous SRCs or whether the DTI findings relate to the most recent SRC or both. This is compounded by lack of information regarding potential sub-concussive blows in control groups where DTI changes have also been reported in athletes post season (Mcallister, Maerlender, Beckwith, & Crisco, 2012).

The standardised effect sizes (ES) were reported by studies 6 and 8, and calculated for study 2. The ES ranged from medium (d=0.60) to large effects

(*d*=2.36). Insufficient information was provided by studies 3, 4 and 7 to calculate ES. Study 1 reported mean percentage changes. This suggests that studies found medium to large effects. However, the confidence intervals are also large, thus the true size of the effect is uncertain. Furthermore, the clinical significance is not known given the variability of the DTI findings and other methodological issues mentioned above.

All studies employed 3T magnet strength. The head coils and DTI scanning parameters varied. Understanding how the methodological issues may impact on the DTI data is extremely complex and beyond the scope of this review, nevertheless it is important to consider these issues, for example differences in scan resolution derived from the scanning parameters may account for some of the variance in the reported findings. Differences in analyses methodology may explain variation in terms of the results.

The eligibility screens applied to the searches only yielded a small number of studies to be included in this review. The lack of a second rater may have introduced bias in terms of how articles were screened e.g. relevant articles may have been missed. The quality rating questionnaire employed was adapted for use in the current study which in turn may have also affected the quality ratings of the studies e.g. a more favourable rating may have been given.

Clinical Implications

SRCs can be associated with long-term axonal injury, cognitive, behavioural and psychological effects. DTI research suggests it may be an

effective tool for early diagnosis and management of WM injury. More clarity of DTI metrics and how they relate to injury at all stages post-SRC is needed. It remains unclear if the frequency of SRCs and other injury characteristics such as length of LOC are associated with poorer outcomes. Therefore detailed, routine and repeated neuropsychological assessment is required to establish any individual changes in cognition and psychological functioning is beneficial. This would be important for athletes who are at the 'high' end of cognitive functioning, e.g. university students, as the neuropsychological measures may not be sensitive to subtle cognitive changes. Closer monitoring of neuropsychological aspects of SRC may also be informative for RTP protocols. DTI used in conjunction with neuropsychological assessment and other biomarkers may improve the characterisation of long-term outcomes (Bigler, 2013) and better inform RTP protocols.

Future Directions

Future research needs to include prospective longitudinal studies and larger sample sizes. Gender, age, education, and the effects of sub-concussive blows must be considered when selecting study and control groups. Standardisation with regard to reporting and measuring the SRC characteristics, in terms of the severity and frequency of injury, the time before return to play post-SRC, and the frequency and severity of symptoms present post-SRC is needed to make full use of the diagnostic potential of DTI.

The majority of athletes start playing sports at a young age when the brain is developing rapidly but the impact of axonal injury associated with SRCs on brain development is largely unknown. Longitudinal studies that address the

effects of frequency, severity and age at which each SRC was acquired will help determine the long-term effects of axonal injury on cognitive functioning and development of PCS.

Lastly, further research with athletes who are symptomatic and/or retire from play to be able to identify and characterise which factors may contribute to the development of PCS, cognitive and psychological difficulties, and delay recovery.

Conclusions

The current review suggests that DTI is a useful tool to employ for the detection of SRC related WM abnormalities at different stages post-injury. However, there is variability in the anatomical locations where WM changes are reported and the relationship between WM changes and outcome needs further investigation. Overall there needs to improved methodology and agreed ways to measure outcome.

References

Alexander, A.L., Lee, J.E., Lazar, M., & Field, A.S. (2007) Diffusion tensor imaging of the brain. *Neurotherapeutics, 4*, 316-329.

Aoki, Y., Inokuchi, R., Gunshin, M., Yahagi, N., & Suwa, H. (2012). Diffusion tensor imaging studies of mild traumatic brain injury: a meta-analysis. *Journal of Neurology, Neurosurgery & Psychiatry*, *83*(9), 870–876.

Barulli, D., & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. *Trends in Cognitive Science, 17*, 502-509

Bazarian, J. J., Zhu, T., Zhong, J., Janigro, D., Rozen, E., Roberts, A., … Blackman, E. G. (2014). Persistent, long-term cerebral white matter changes after sports-related repetitive head impacts. *PLoS ONE, 9,* e94734.

Bigler, E. D. (2013). Neuroimaging biomarkers in mild traumatic brain injury (mTBI). *Neuropsychology Review*, *23*, 169–209.

Burman, E., Lysholm, J., Shahim, P., Malm, C., & Tegner, Y. (2016). Concussed athletes are more prone to injury both before and after their index concussion: a data base analysis of 699 concussed contact sports athletes. *BMJ Open Sport & Exercise Medicine*, *2*, e000092.

Cancelliere, C., Hincapié, C. A., Keightley, M., Godbolt, A. K., Côté, P., Kristman, V. L., … Cassidy, J. D. (2014). Systematic review of prognosis and return to play after sport concussion: Results of the international collaboration on mild traumatic brain injury prognosis. *Archives of Physical*

Medicine and Rehabilitation, *95,* S210-S229.

Chamard, E., Lassonde, M., Henry, L., Tremblay, J., Boulanger, Y., De Beaumont, L., & Théoret, H. (2013). Neurometabolic and microstructural alterations following a sports-related concussion in female athletes. *Brain Injury*, *27*, 1362–301.

Churchill, N., Hutchison, M., Richards, D., Leung, G., Graham, S., & Schweizer, T. A. (2016). Brain Structure and Function Associated with a History of Sport Concussion: A Multi-Modal Magnetic Resonance Imaging Study. Journal of *Neurotrauma, 33*, 1-7

Covassin, T., Elbin, R. J., Crutcher, B., & Burkhart, S. (2013). The Management of Sport-Related Concussion: Considerations for Male and Female Athletes. *Translational Stroke Research 4,* 420-424.

Eierud, C., Craddock, R. C., Fletcher, S., Aulakh, M., King-Casas, B., Kuehl, D., & Laconte, S. M. (2014). Neuroimaging after mild traumatic brain injury: Review and meta-analysis. *NeuroImage*, *4*, 283–294.

Finch, C. F., Clapperton, A. J., & McCrory, P. (2013). Increasing incidence of hospitalisation for sport-related concussion in Victoria, Australia. *Medical Journal of Australia*, *198*, 427–430.

Gardner, A., Kay-Lambkin, F., Stanwell, P., Donnelly, J., Williams, W. H., Hiles, A., … Jones, D. K. (2012). A systematic review of diffusion tensor imaging findings in sports-related concussion. *Journal of Neurotrauma*, *29*, 2521–38.

Guskiewicz, K. M., Marshall, S. W., Broglio, S. P., Cantu, R. C., & Kirkendall, D. T. (2002). No evidence of impaired neurocognitive performance in

collegiate soccer players. *The American Journal of Sports Medicine*, *30*, 157–162.

Guskiewicz, K. M., Mccrea, M., Marshall, S. W., Cantu, R. C., Randolph, C., Barr, W., … Kelly, J. P. (2003). Cumulative Effects Associated With Recurrent Concussion in Collegiate Football Players The NCAA Concussion Study. *Journal of the American Medical Association, 290*, 2549-2555.

Hulkower, M. B., Poliak, D. B., Rosenbaum, S. B., Zimmerman, M. E., & Lipton, M. L. (2013). A decade of DTI in traumatic brain injury: 10 years and 100 articles later. *American Journal of Neuroradiology, 34,* 2064-2074.

Jeter, C. B., Hergenroeder, G. W., Hylin, M. J., Redell, J. B., Moore, A. N., & Dash, P. K. (2013). Biomarkers for the Diagnosis and Prognosis of Mild Traumatic Brain Injury/Concussion. *Journal of Neurotrauma*, *30*, 657–670.

Koerte, I. K., Kaufmann, D., Hartl, E., Bouix, S., Pasternak, O., Kubicki, M., … Shenton, M. E. (2012). A prospective study of physician-observed concussion during a varsity university hockey season: white matter integrity in ice hockey players. Part 3 of 4. *Neurosurgery Focus, 33,* E3.

List, J., Ott, S., Bukowski, M., Lindenberg, R., & Flöel, A. (2015). Cognitive function and brain structure after recurrent mild traumatic brain injuries in young-to-middle-aged adults. *Frontiers in Human Neuroscience, 9*, 1–9.

Marar, M., McIlvain, N. M., Fields, S. K., & Comstock, R. D. (2012). Epidemiology of Concussions Among United States High School Athletes in 20 Sports. *The American Journal of Sports Medicine*, *40*, 747–755.

Maroon, J. C., Winkelman, R., Bost, J., Amos, A., Mathyssek, C., & Miele, V.

(2015). Chronic traumatic encephalopathy in contact sports: A systematic review of all reported pathological cases. *PLoS ONE*, *10*, 1–16.

Mcallister, T. W., Maerlender, a, Beckwith, J. G., & Crisco, J. J. (2012). Cognitive effects of one season of head impacts in a cohort of collegiate contact sport athletes. *Neurology*, *79*, 393–393.

McCrea, M.A. (2008). *Mild traumatic brain injury and postconcussion syndrome*. New York: Oxford University Press.

McCrea, M.A., Hill, C., Carolina, N., Randolph, C., … Kelly, J. P. (2009). Effects of symptom-free waiting period on clinical outcome and risk of reinjury after sport-related concussion. *Neurosurgery, 65*, 876–882.

McCrory, P., Meeuwisse, W. H., Aubry, M., Cantu, B., Dvorak, J., Echemendia, R., … Turner, M. (2013). Consensus Statement on Concussion in Sport: The 4th International Conference on Concussion in Sport Held in Zurick, November 2012. *British Journal of Sports Medicine, 16,* 178-179.

Mckee, A. C., Stein, T. D., Kiernan, P. T., & Alvarez, V. E. (2016). The neuropathologyof chornic traumatic encephalopathy. *Brain Pathology*, *25*, 350–364.

Meier, T. B., Bergamino, M., Bellgowan, P. S. F., Teague, T. K., Ling, J. M., Jeromin, A., & Mayer, A. R. (2016). Longitudinal assessment of white matter abnormalities following sports-related concussion. *Human Brain Mapping, 37*, 833-845.

Murugavel, M., Cubon, V., Putukian, M., Echemendia, R., Cabrera, J., Osherson, D., & Dettwiler, A. (n.d.). A Longitudinal Diffusion Tensor Imaging Study Assessing White Matter Fiber Tracts after Sports-Related

Concussion. *Journal of Neurotrauma, 31*, 1860-1871.

Poldrack, R. A. (2007). Region of interest analysis for fMRI. *Scan, 2,* 67-70.

Sabini, R. C., & Nutini, D. N. (2011). Return-to-play guidelines in concussion: a closer look at the literature. *The Physician and Sportsmedicine*, *39*(3), 23–30.

Sasaki, T., Pasternak, O., Mayinger, M., Muehlmann, M., Savadjiev, P., Bouix, S., … Koerte, I. K. (2014). Changes in white matter microstructure in ice hockey players with a history of concussion: a diffussion tensor imaging study. *Journal of Neurosurgery*, *120*, 882–890.

Sharp, D. J., & Jenkins, P. O. (2015). Concussion is confusing us all. *Practical Neurology*, *15*, 172–186.

Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Saheer Cader, M., & Matthews, P.M. (2006). Tract-based spatial statistics: volxelwise analyses of multi-subject diffusion data. *Neuroimage, 31*, 1487-1505

Thomas, M., Haas, T. S., Doerer, J. J., Hodges, J. S., Aicher, B. O., Garberich, R. F., … Maron, B. J. (2011). Epidemiology of sudden death in young, competitive athletes due to blunt trauma. *Pediatrics*, *128*, e1–e8.

Turner, G. R., & Levine, B. (2008). Augmented neural activity during executive control processing following diffuse axonal injury. *Neurology*, *71*, 812–818.

Wasserman, E. B., Kerr, Z. Y., Zuckerman, S. L., & Covassin, T. (2016). Epidemiology of Sports-Related Concussions in National Collegiate Athletic Association Athletes From 2009-2010 to 2013-2014: Symptom Prevalence, Symptom Resolution Time, and Return-to-Play Time. *The American*

Journal of Sports Medicine, *44*), 226–33.

World Rugby. (2015). *Concussion guidelines*. [Brochure]. [Dublin, Ireland]: Author.

Yuh, E. L., Cooper, S. R., Mukherjee, P., Yue, J. K., Lingsma, H., Gordon, W., … Sinha, T. K. (2014). Diffusion Tensor Imaging for Outcome Prediction in Mild Traumatic Brain Injury: A TRACK-TBI Study. *Journal of Neurotrauma*, *1477*, 1–75.

Zhu, D. C., Covassin, T., Nogle, S., Doyle, S., Russell, D., Pearson, R. L., … Building, R. (n.d.). A Potential Biomarker in Sports-Related Concussion: Brain Functional Connectivity Alteration of the Default-Mode Network Measured with Longitudinal Resting-State fMRI over 30 Days. *Journal of Neurotrauma, 32*, 327-341.

Appendix A – Quality assessment tool

QUALITY ASSESSMENT TOOL FOR QUANTITATIVE STUDIES

EPHPP
Effective Public Health Practice Project

COMPONENT RATINGS

A) SELECTION BIAS

(Q1) Are the individuals selected to participate in the study likely to be representative of the target population?

1 Very likely
2 Somewhat likely
3 Not likely
4 Can't tell

(Q2) What percentage of selected individuals agreed to participate?

1 80 - 100% agreement
2 60 – 79% agreement
3 less than 60% agreement
4 Not applicable
5 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

B) STUDY DESIGN

Indicate the study design

1 Randomized controlled trial
2 Controlled clinical trial
3 Cohort analytic (two group pre + post)
4 Case-control
5 Cohort (one group pre + post (before and after))
6 Interrupted time series
7 Other specify _____
8 Can't tell

Was the study described as randomized? If NO, go to Component C.

No Yes

If Yes, was the method of randomization described? (See dictionary)

No Yes

If Yes, was the method appropriate? (See dictionary)

No Yes

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

C) CONFOUNDERS

(Q1) Were there important differences between groups prior to the intervention?

1 Yes
2 No
3 Can't tell

The following are examples of confounders:

1 Race
2 Sex
3 Marital status/family
4 Age
5 SES (income or class)
6 Education
7 Health status
8 Pre-intervention score on outcome measure

(Q2) If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis)?

1 80 – 100% (most)
2 60 – 79% (some)
3 Less than 60% (few or none)
4 Can't Tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

D) BLINDING

(Q1) Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants?

1 Yes
2 No
3 Can't tell

(Q2) Were the study participants aware of the research question?

1 Yes
2 No
3 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

E) DATA COLLECTION METHODS

(Q1) Were data collection tools shown to be valid?

1 Yes
2 No
3 Can't tell

(Q2) Were data collection tools shown to be reliable?

1 Yes
2 No
3 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

F) WITHDRAWALS AND DROP-OUTS

(Q1) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?

1 Yes
2 No
3 Can't tell
4 Not Applicable (i.e. one time surveys or interviews)

(Q2) Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).

1 80 -100%
2 60 - 79%
3 less than 60%
4 Can't tell
5 Not Applicable (i.e. Retrospective case-control)

RATE THIS SECTION	STRONG	MODERATE	WEAK	
See dictionary	1	2	3	Not Applicable

G) INTERVENTION INTEGRITY

(Q1) What percentage of participants received the allocated intervention or exposure of interest?

1 80 -100%
2 60 - 79%
3 less than 60%
4 Can't tell

(Q2) Was the consistency of the intervention measured?

1 Yes
2 No
3 Can't tell

(Q3) Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?

4 Yes
5 No
6 Can't tell

H) ANALYSES

(Q1) Indicate the unit of allocation (circle one)

community organization/institution practice/office individual

(Q2) Indicate the unit of analysis (circle one)

community organization/institution practice/office individual

(Q3) Are the statistical methods appropriate for the study design?

1 Yes
2 No
3 Can't tell

(Q4) Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?

1 Yes
2 No
3 Can't tell

GLOBAL RATING

COMPONENT RATINGS

Please transcribe the information from the gray boxes on pages 1-4 onto this page. See dictionary on how to rate this section.

A	**SELECTION BIAS**	**STRONG**	**MODERATE**	**WEAK**	
		1	2	3	
B	**STUDY DESIGN**	**STRONG**	**MODERATE**	**WEAK**	
		1	2	3	
C	**CONFOUNDERS**	**STRONG**	**MODERATE**	**WEAK**	
		1	2	3	
D	**BLINDING**	**STRONG**	**MODERATE**	**WEAK**	
		1	2	3	
E	**DATA COLLECTION METHOD**	**STRONG**	**MODERATE**	**WEAK**	
		1	2	3	
F	**WITHDRAWALS AND DROPOUTS**	**STRONG**	**MODERATE**	**WEAK**	
		1	2	3	Not Applicable

GLOBAL RATING FOR THIS PAPER (circle one):

1	STRONG	(no WEAK ratings)
2	MODERATE	(one WEAK rating)
3	WEAK	(two or more WEAK ratings)

With both reviewers discussing the ratings:

Is there a discrepancy between the two reviewers with respect to the component (A-F) ratings?

No Yes

If yes, indicate the reason for the discrepancy

1	Oversight
2	Differences in interpretation of criteria
3	Differences in interpretation of study

Final decision of both reviewers (circle one):

1	**STRONG**
2	**MODERATE**
3	**WEAK**

Appendix B

Instructions for manuscript submission – Journal of Sports Medicine

Author Guidelines

Language editing

Hindawi has partnered with Editage to provide an English-language editing service to authors prior to submission. Authors that wish to use this service will receive a 10% discount on all editing services provided by Editage. To find out more information or get a quote, please click here.

Submission

Manuscripts should be submitted by one of the authors of the manuscript through the online Manuscript Tracking System. Regardless of the source of the word-processing tool, only electronic PDF (.pdf) or Word (.doc, .docx, .rtf) files can be submitted through the MTS. There is no page limit. Only online submissions are accepted to facilitate rapid publication and minimize administrative costs. Submissions by anyone other than one of the authors will not be accepted. The submitting author takes responsibility for the paper during submission and peer review. If for some technical reason submission through the MTS is not possible, the author can contact jsm@hindawi.com for support.

Terms of Submission

Papers must be submitted on the understanding that they have not been published elsewhere and are not currently under consideration by another journal published by Hindawi or any other publisher. The submitting author is responsible for ensuring that the article's publication has been approved by all

the other coauthors. It is also the authors' responsibility to ensure that the articles emanating from a particular institution are submitted with the approval of the necessary institution. Only an acknowledgment from the editorial office officially establishes the date of receipt. Further correspondence and proofs will be sent to the author(s) before publication unless otherwise indicated. It is a condition of submission of a paper that the authors permit editing of the paper for readability. All inquiries concerning the publication of accepted papers should be addressed to jsm@hindawi.com.

Peer Review

All manuscripts are subject to peer review and are expected to meet standards of academic excellence. If approved by the editor, submissions will be considered by peer-reviewers, whose identities will remain anonymous to the authors.

Concurrent Submissions

In order to ensure sufficient diversity within the authorship of the journal, authors will be limited to having two manuscripts under review at any point in time. If an author already has two manuscripts under review in the journal, he or she will need to wait until the review process of at least one of these manuscripts is complete before submitting another manuscript for consideration. This policy does not apply to Editorials or other non-peer reviewed manuscript types.

Article Processing Charges

Journal of Sports Medicine is an open access journal. Open access charges allow publishers to make the published material available for free to all interested online visitors. For more details about the article processing charges of Journal of Sports Medicine, please visit the Article Processing Charges information page.

Units of Measurement

Units of measurement should be presented simply and concisely using System International (SI) units.

Title and Authorship Information

The following information should be included

- Paper title
- Full author names
- Full institutional mailing addresses
- Email addresses

Abstract

The manuscript should contain an abstract. The abstract should be self-contained and citation-free and should not exceed 200 words.

Introduction

This section should be succinct, with no subheadings.

Materials and Methods

This part should contain sufficient detail so that all procedures can be repeated. It can be divided into subsections if several methods are described.

Results and Discussion

This section may each be divided by subheadings or may be combined.

Conclusions

This should clearly explain the main conclusions of the work highlighting its importance and relevance.

Acknowledgments

All acknowledgments (if any) should be included at the very end of the paper before the references and may include supporting grants, presentations, and so forth.

References

Authors are responsible for ensuring that the information in each reference is complete and accurate. All references must be numbered consecutively and citations of references in text should be identified using numbers in square brackets (e.g., “as discussed by Smith [9]”; “as discussed elsewhere [9, 10]”). All references should be cited within the text; otherwise, these references will be automatically removed.

Preparation of Figures

Upon submission of an article, authors are supposed to include all figures and tables in the PDF file of the manuscript. Figures and tables should not be submitted in separate files. If the article is accepted, authors will be asked to provide the source files of the figures. Each figure should be supplied in a separate electronic file. All figures should be cited in the paper in a consecutive order. Figures should be supplied in either vector art formats (Illustrator, EPS, WMF, FreeHand, CorelDraw, PowerPoint, Excel, etc.) or bitmap formats (Photoshop, TIFF, GIF, JPEG, etc.). Bitmap images should be of 300 dpi resolution at least unless the resolution is intentionally set to a lower level for scientific reasons. If a bitmap image has labels, the image and labels should be embedded in separate layers.

Preparation of Tables

Tables should be cited consecutively in the text. Every table must have a descriptive title and if numerical measurements are given, the units should be included in the column heading. Vertical rules should not be used.

Proofs

Corrected proofs must be returned to the publisher within 2-3 days of receipt. The publisher will do everything possible to ensure prompt publication. It will therefore be appreciated if the manuscripts and figures conform from the outset to the style of the journal.

Copyright

Conflicts of Interest

Conflicts of interest (COIs, also known as ‘competing interests’) occur when issues outside research could be reasonably perceived to affect the neutrality or objectivity of the work or its assessment. For more information, see our publication ethics policy. Authors must declare all potential interests – whether or not they actually had an influence – in a ‘Conflicts of Interest’ section, which should explain why the interest may be a conflict. If there are none, the authors should state “The author(s) declare(s) that there is no conflict of interest regarding the publication of this article.” Submitting authors are responsible for co-authors declaring their interests. Declared conflicts of interest will be considered by the editor and reviewers and included in the published article.

Authors must declare current or recent funding (including for article processing charges) and other payments, goods or services that might influence the work. All funding, whether a conflict or not, must be declared in the ‘Acknowledgments’. The involvement of anyone other than the authors who 1) has an interest in the outcome of the work; 2) is affiliated to an organization with such an interest; or 3) was employed or paid by a funder, in the commissioning, conception, planning, design, conduct, or analysis of the work, the preparation or editing of the manuscript, or the decision to publish must be declared.

Clinical Study

When publishing clinical studies, Hindawi aims to comply with the recommendations of the International Committee of Medical Journal Editors (ICMJE) on trials registration. Therefore, authors are requested to register the clinical trial presented in the manuscript in a public trials registry and include the trial registration number at the end of the abstract. Trials initiated after July 1, 2005 must be registered prospectively before patient recruitment has begun. For trials initiated before July 1, 2005, the trial must be registered before submission.

Ethical Guidelines

In any studies that involve experiments on human or animal subjects, the following ethical guidelines must be observed. For any experiments on humans, all work must be conducted in accordance with the Declaration of Helsinki (1964). Papers describing experimental work which carries a risk of harm to human subjects must include a statement that the experiment was conducted with the human subjects’ understanding and consent, as well as a statement

that the responsible Ethical Committee has approved the experiments. In the case of any animal experiments, the authors must provide a full description of any anesthetic or surgical procedure used, as well as evidence that all possible steps were taken to avoid animal suffering at each stage of the experiment.

SCHOOL OF PSYCHOLOGY

DOCTORATE IN CLINICAL PSYCHOLOGY

EMPIRICAL PAPER

Multiple sports concussion in male rugby players: a neurocognitive and neuroimaging study

Trainee Name: Katherine Woollett

Primary Research Supervisor: **Professor Huw Williams**

School of Psychology, University of Exeter

Secondary Research Supervisor: **Dr Phil Yates**

Course Convenor

School of Psychology, University of Exeter

Consultant Clinical Neuropsychologist
Royal Devon and Exeter Hospital

Field Collaborators: **Dr Milton Fraser and Jonathan Fulford**

School of Psychology, University of Exeter

University of Exeter Medical School

Target Journal: Journal of the International Neuropsychological Society

Word Count: 8,780 words (excluding abstract, table of contents, list of figures, references, footnotes, appendices)

Submitted in partial fulfilment of requirements for the Doctorate Degree in Clinical Psychology, University of Exeter

Acknowledgements

The neuroimaging data processing and analyses were overseen by Jonathan Fulford (University of Exeter) with advice from Fraser Milton (University of Exeter) and Derek Jones (University of Cardiff).

Abstract

***Objective**:* Following a sport related concussion (SRC) visible symptoms generally dissipate in 7-10 days post-injury. However, little is known about the cumulative effects of SRCs both in terms of structural damage to the white matter of the brain and neurocognitive performance. To address this issue, the relationship between the number of SRCs (frequency), axonal white matter (WM) damage and neurocognitive performance was examined. There were three predictions. First, increases in SRC frequency will be associated with decreases in performance on neurocognitive tests. Second, the frequency of SRC will be associated with axonal injury measured three WM tracts: the corpus callosum, the fronto-occipital fasciculus and the inferior longitudinal fasciculus. Third, less accurate and slower performance on a response inhibition task (STOP-IT) will be associated with greater axonal injury.

***Methods**:* A cross-sectional correlational design was utilised. Participants were rugby players with a history of SRC, rugby players with no history of SRC and control athletes (N=40) who completed a neurocognitive test battery and had a DTI brain scan. The neurocognitive battery consisted of the following standardised tests: Speed and Capacity of Language Processing Test, CogState Electronic Battery, Stroop Colour and Word Test, Controlled Oral Word Association Test, the Trail Making Test and the experimental test STOP-IT Electronic Test. White matter axonal injury was measured by DTI using fractional anisotropy (FA) and mean diffusivity (MD) metrics. The DTI data was processed using FSL to extract FA and MD DTI metrics in three a-priori regions of interest.

***Results**:* Spearman's correlation analyses did not find significant associations between SRC frequency and neurocognitive performance on the

FAS (r_s=0.053, 95% CI [-0.27, 0.36]), TMT-A (r_s=0.058, 95% CI [-0.26, 0.37]), TMT-B (r_s= -0.046, 95% CI [-0.27, 0.36]) and the Stroop Interference (r_s= -0.25, 95% CI [-0.07, 0.52]). Similarly, no significant Spearman's correlations were found between SRC frequency and the computerised neurocognitive tests STOP-IT-SSRT (r_s= -0.04, 95% CI [-0.28, 0.35])), STOP-IT–Accuracy (r_s= -0.05, 95% CI [-0.27, 0.36]), CogState Detection subtest (r_s= -0.15, 95% CI [-0.17, 0.44]), CogState Identification subtest (r_s= -0.065, 95% CI [-0.26, 0.37]), CogState One card learning subtest (r_s= 0.24, 95% CI [-0.08, 0.52]) or the CogState One back task subtest (r_s= 0.06, 95% CI [-0.26, 0.37]).

In terms of the DTI data there were no significant associations between SRC frequency and axonal injury measured by FA values in the CC (r_s= 0.005, 95% CI [-0.31, 0.32]), ILF (r_s= 0.028, 95% CI [-0.29, 0.34]) or FOF (r_s= -0.022, 95% CI [-0.30, 0.33]). The same was pattern was found for MD values in the CC (r_s= 0.081, 95% CI [-0.24, 0.39]), ILF (r_s= -0.16, 95% CI [-0.16, 0.45]) or FOF (r_s= -0.15, 95% CI [-0.17, 0.44])

Finally, there were no significant Spearman's correlations between axonal injury FA values and the STOP-IT SSRT in any of the ROIs: CC (r_s= 0.005, 95% CI [-0.31, 0.32]), ILF (r_s= 0.028, 95% CI [-0.29, 0.34]) or FOF (r_s= -0.022, 95% CI [-0.30, 0.33]). Equally, there were no significant correlations between MD values STOP-IT SSRT in the CC (r_s= -0.028, 95% CI [-0.29, 0.34]), ILF (r_s= -0.16, 95% CI [-0.16, 0.45]) or FOF (r_s= -0.15, 95% CI [-0.17, 0.44]).

Likewise, there were no significant Spearman's correlations between accuracy on the STOP-IT and FA values and in any of the ROIs: CC (r_s= 0.19, 95% CI [-0.13, 0.48]), ILF (r_s= -0.045, 95% CI [-0.27, 0.35]) and FOF (r_s= -0.032, 95% CI [-0.29, 0.34]), or MD values in the CC (r_s= -0.11, 95% CI [-0.21,

0.41]), ILF (r_s= 0.017, 95% CI [-0.30, 0.33]) or FOF (r_s= 0.082, 95% CI [-0.24, 0.39]).

This study did not find support for the hypothesis that cumulative SRCs are associated with poorer performance on neurocognitive tests or with axonal injury as measured by FA and MD DTI metrics.

Conclusion*:* The null findings suggest that there are no cumulative effects of SRCs. The current findings are inconsistent with previous cross-sectional research that indicates that there are long-term changes to diffusivity measures present after single SRCs as well as cumulative effects in contact sport athletes. Likewise they are at odds with evidence suggesting that after three SRCs neurocognitive performance can be affected. The study needs to be extended to include a larger sample to ensure the results are not due to low statistical power.

Keywords: *sport-related concussion, mild TBI, rugby, contact sports, diffusion tensor imaging, neurocognitive performance.*

Introduction

Approximately 10 million people worldwide sustain a traumatic brain injury (TBI) each year, with an incidence rate of approximately 235 per 100,000 in Europe (Moretti et al., 2012; Tagliaferri, Compagnone, Korsic, Servadei, & Kraus, 2006). Mild traumatic brain injuries (mTBI) account for the majority of TBIs (approximately 80%), and approximately 85% of patients report full recovery from both neurological and neuropsychological symptoms. In a subset of approximately 15% of cases patients can develop long-term cognitive (e.g. poor concentration; memory difficulties), physical (e.g. headache; fatigue) and emotional (e.g. anxiety; depression) sequelae which can persist for weeks or years, this is known as post-concussive syndrome (PCS; Bigler, 2008). The diagnosis of PCS is complex. Many of the symptoms may be present in other physical and mental health conditions, an issue that is compounded by the lack of a unified definition. The Diagnostic and Statistical Manual of Mental Disorders (DSM-V) and the International Classification of Diseases (ICD-10) criteria for diagnosis of PCS are not equivalent. In the DSM-V PCS has been replaced by ‘Major or Mild neurocognitive disorder due to traumatic brain injury’. It defines ‘neurocognitive disorder’ as neurocognitive deficits that present immediately after a TBI or recovery of consciousness, persist beyond three months, and cannot be explained by other mental disorders. The ICD-10 requires loss of consciousness, and intolerance to stress, emotion or alcohol, which are not included in the DSM-V. The lack of agreement between definitions of PCS means that there is variability in the symptoms that are assessed and how they are classified, making it difficult to build a clear picture of the sequelae SRCs (Williams et al., 2010; see Bigler, 2008 for a full

discussion).

Collision sports such as ice hockey, American football, rugby, boxing and horse riding expose athletes to high risks of experiencing a TBI that typically lies at the very mild end of the spectrum (mild to severe), known as sports related concussion (SRC), with an annual incidence rate estimated at 170 per 100,000 (Theadom et al., 2014).

There is general agreement in the field that mTBIs, including SRC's, can have negative long-term effects on cognition, such as executive function (Bigler, 2008; Wall et al., 2006). Response inhibition (to deliberately withhold a response) is a measure of executive function frequently used in clinical and research settings to measure flexibility of cognitive functions. Stop-signal tasks are widely used to for this purpose. In such tasks participants are required to change from an automatic response when a stop-signal is presented unpredictably, to a controlled response inhibition (Verbruggen & Logan, 2008a). Stop-signal tasks involve brain activations within the frontal lobe bilaterally, with communication via white matter (WM) tracts between and across brain regions being important to achieve this task (Menon, Adleman, White, Glover, & Reiss, 2001). Impairments in response inhibition are often reported following brain injuries, particularly to the frontal lobes, that usually involve grey matter and WM injury (Burgess & Shallice, 1996; Newcombe et al., 2011). Performance on response inhibition tasks has been associated with brain network activity. A study comparing TBI patients (severity unclassified in this study) to controls on a stop-signal task, found that patients were impaired. Patients showed damage to a WM tract in the salience network (SN)[1] that responds to salient stimuli and

[1] The SN includes the dorsal anterior cingulate cortex, anterior insula, and inferior frontal gyri.

is important for the initiation of cognitive control by regulating dynamic changes in the brain's default mode network (DMN)[2]. The DMN is active during wakeful rest or task negative processes such as introspection and daydreaming (Buckner, Andrews-Hanna, & Schacter, 2008). The patients also showed less deactivation in parts of the DMN. The findings suggest that axonal damage in one brain region may impact upon functioning across intrinsic connectivity networks (Bonnelle et al., 2011). Other studies have also shown connectivity aberrations between and within brain networks during resting state functional magnetic resonance imaging (fMRI) following TBI (Sharp, Scott, & Leech, 2014) and mTBIs (Mayer, Mannell, Ling, Gasparovic, & Yeo, 2011; Stevens et al., 2012). This suggests that deficits of 'higher-level' cognitive functions, which require integration of information processing across the intrinsic connectivity networks, can be affected (Greicius, Supekar, Menon, & Dougherty, 2009; Sharp et al., 2011; Stevens et al., 2012). Quantifying structural damage and its impact on functional connectivity are key factors to gain better understanding of cognitive outcome post-injury.

SRCs are frequent in contact sports, rates of more than 50% of rugby players with multiple SRCs have been reported (Savage, Hooke, Orchard, & Parkinson, 2013). The period required for recovery may increase by up to three times that required for a single concussion (Eisenberg, Matthew A. Andrea, Meehan, & Mannix, 2013). The increased recovery period would expose athletes to a heightened risk of further concussion before the brain has recovered. In rare cases this may lead to second impact syndrome (SIS), which involves rapid brain swelling, increased metabolic changes within brain cells

[2] The DMN includes the ventromedial prefrontal cortex, dorsal medial prefrontal cortex, posterior cingulate cortex, inferior parietal lobule, lateral temporal cortex and hippocampus.

and in severe cases, death (Cantu & Gean, 2010). Although SRC is typically a very mild injury when there are repeated injuries, there may be a cumulative effect in terms of axonal WM damage (Henry et al., 2011) and cognitive symptoms (Gardner, Shores, & Batchelor, 2010). Investigating the cumulative effects of SRCs on intrinsic connectivity networks, needed for 'higher-level' cognitive functions, in contact sport athletes, is important to enable better management of injury. Moreover, the high prevalence of SRC in rugby, offers a valuable context to conduct research in an easily accessible sample.

Definition and Classification of Mild Traumatic Brain Injury and Concussion

Traumatic brain injury is defined as an alteration of brain function (AF), or evidence of brain pathology (BP) caused by external physical force (EPF) (Menon, Schwab, Wright & Mass, 2010). AF is defined as one of the following: Any loss (or decrease) of consciousness, any loss of memory for events immediately before or after the injury, neurologic deficit, and alteration of mental state (AMS) at time of the injury. Evidence of BP includes visual, neuroradiological or laboratory corroboration of brain damage. EPF includes the following events: head being struck, striking the head with an object, acceleration/deceleration movement without trauma to the head, forces generated by blast or explosion (Menon, Schwab, Wright & Mass, 2010).

TBIs are further defined and categorized on a continuum of injury (mild-severe), concussion is generally the mildest form. There is a lack of clear consensus regarding diagnostic definition and classification (Sharp & Jenkins, 2015). The term concussion usually refers to a sports related brain injury. The

diagnostic systems for mTBIs and concussion vary according to common key criteria and the duration of each of these: loss of consciousness (LOC), alteration of consciousness (AOC), post-traumatic amnesia (PTA), AMS, or focal neurologic deficit (Bigler, 2008; Bodin, Yeates & Klamar, 2012). In addition, the Glasgow Coma Scale (GCS) score is commonly used to aid diagnosis (Teasdale & Jennett, 1971) (see Tables 1 and 2).

Table 1. *Examples of TBI classification by severity System.*

System	**Mild**	**Moderate**	**Severe**
Veterans Health Administration and Department of Defense USA	LOC 0-30min AOC ⩽ 24hs PTA ⩽ 24hs GCS13-15	LOC >30min <24hs AOC >24hs PTA > 1 day and < 7 days GCS 9-12	LOC ⩾ 24hs AOC > 24hs PTA > 7 days GCS <9
Glasgow Coma Scale	GCS13-15	GCS 9-12	GCS 3-8

Table 2. *Examples of classification systems of concussion by severity.*

System	**Mild**	**Moderate**	**Severe**
American Academy of Neurology	Confusion No LOC Symptoms <15 minutes	Confusion No LOC Symptoms >15 minutes	LOC
Cantu	No LOC PTA < 30mins	LOC – 5 minutes PTA > 30mins <24hr	LOC – 5 minutes PTA > 24hr

Therefore the definition and classification of mTBI or concussion may vary depending of the system employed.

Diagnosis of Mild Traumatic Brain Injury

Diagnosis is obtained through a combination of neurological and neuropsychological investigations. This is not an easy task given the heterogeneous nature of mTBIs. Other variables such as age, education, pain, fatigue, mood and sleep disturbances, known to affect cognitive performance, are often present (Bigler, 2008). In mTBI (including SRCs), compared to more severe injuries with typically widespread microstructural axonal damage, there is an absence of contusions and haemorrhage. This microstructural neuronal damage is not identifiable through conventional neuroimaging methods, such as computed tomography (CT) which identifies intracranial haemorrhage; or MRI which can detect contusions, haemorrhage and WM damage at a macrostructural level (Shenton et al., 2012). Damage to the WM that is typically subtle in mTBIs may be detected with more sophisticated methods such as diffusion tensor imaging (DTI) that can be used in conjunction with other biomarkers, such as biofluid biomarkers that can be measured in serum e.g. S100B (Bigler, 2013a). Levels increase post-injury and are detected in serum if the blood brain barrier is disrupted (Papa, Ramia, Edwards, Johnson, & Slobounov, 2015).

Neuroimaging of Mild traumatic Brain Injury

Advances in neuroimaging methods now permit detection of neuropathology at millimetre and sub-millimetre level. The most sensitive and predictive method for mTBI is DTI, which permits evaluation of WM integrity in

the brain. DTI provides magnetic resonance (MR) metrics of water diffusion that can be used to assess axonal integrity. The most common indices to quantify diffusion are fractional anisotropy (FA) and mean diffusivity (MD). FA is an indication of the directionality (e.g. anterior to posterior) of water diffusion parallel to the WM tracts. A reduction in FA is generally thought to reflect loss of WM integrity that may indicate damage to myelin, fibre density or axon membranes diameter. MD is the average magnitude of water diffusion, regardless of direction. Differences in MD are thought to reflect overall restrictions to the movement of water diffusion. Myelination enforces directionality and thus increases FA. It also restricts overall water diffusion movement, thus lowering MD. DTI has been shown to be sensitive to neuropathological changes affecting the corpus callosum, superior longitudinal fasciculus, WM tracts within frontal and temporal lobes, in both the acute and chronic stages of mTBI, including SRCs (Aoki et al., 2012; Bigler, 2013a). It has been suggested that DTI used in combination with neurocognitive assessment could improve diagnosis of mTBI (Bigler, 2013a).

Neurocognitive Effects of Mild Traumatic Brain Injury

The pattern of neurocognitive changes post- mTBI remains unclear. Commonly reported cognitive effects are in the domains of memory, processing speed and executive function (McCrea, 2008). In particular, deficits in executive functions have been reported to persist after other symptoms may have resolved (see Williams et al., 2010). Although other studies have not found cognitive persistent effects (Broglio, Ferrara, Piland, Anderson, & Collie, 2006). Studies employing dual task paradigms (Sinopoli et al., 2014), and increased

load paradigms (Dean & Sterr, 2013) reported poorer performance on these tasks, suggesting that increasing task demands and/or employing tasks that require integration of processing across connected brain areas may reveal cognitive deficits. Brain connectivity can be divided into structural and functional connectivity (FC). The relationship between the two is complex and not fully understood. It is known that FC partly depends on structural connectivity (SC) but SC alone does not offer a complete description of connectivity as it can change over time (see Friston, 2011). Additionally, FC is found between brain regions where there are no direct structural connections. This suggests that brain regions that have either direct or indirect FC may be impacted if SC is disrupted (Friston, 2011).

SC can be affected by axonal injury arising from mTBI and it has been associated with performance on cognitive tests. A longitudinal study of 61 patients in the acute stage of mTBI. mTBI was defined by the presence of one or more of the following: confusion/disorientation, LOC <30 minutes, PTA <24hs, GCS of 13-15 and/or transient focal neurological signs (may include a mixture of complicated/uncomplicated mTBI patients). The authors found that patients performed poorly across neurocognitive domains (executive function, attention, language and memory) compared to nineteen aged-matched healthy controls. Performance was associated with diffuse axonal injury (measured by DTI). A set of 33 of these patients were evaluated 6 months post-injury. Three were excluded due to scan artifacts. The authors do not provide further information about other dropouts or withdrawals. Therefore, the sample may be biased and only include patients with persistent difficulties. The returning patients all showed persistent neurocognitive difficulties in the domains of executive function, attention, language and memory (Veeramuthu et al., 2015).

Thus, structural damage to WM tracts affects SC between brain regions and can have a detrimental impact on tasks in which information is processed and transported between structurally and functionally linked brain regions (Damoiseaux & Greicius, 2009; Menon & Uddin, 2010).

Functional MRI (fMRI) studies have shown patterns of altered brain activation in mTBI patients compared to controls. Alterations in the strength of FC in intrinsic connectivity networks including the DMN and pre-frontal cortex were reported in the sub-acute stage but were not present in the chronic stage. The connectivity measures were not associated with performance on tests of attention, memory, processing speed or executive function (Mayer et al., 2011). By contrast, student athletes (rugby, ice hockey and lacrosse) showed a reduction in magnitude of connectivity between brain regions as the number of SRC's increased (Johnson et al., 2012). No cognitive measures were reported thereby the consequences of the altered connectivity are unknown in this study. This suggests that processing across brain regions is impacted upon qualitatively because of the way in which axonal injury disconnects brain networks. These qualitative differences in brain activity may reflect differential use of similar neural resources (e.g. altered engagement) and the need to draw upon brain regions not used by controls (e.g. reorganization) in an attempt to maintain behavioural performance (Turner & Levine, 2008; McDonald, Saykin, & McAllister, 2012). The cognitive effects of altered structural and functional connectivity between and within brain regions, and the factors that may mediate these effects remain unclear.

Sports Related Concussion

The acute symptoms and short-term effects of sport concussions are well characterised, but as in other mTBIs, the long-term consequences, including PCS, are poorly understood and are a matter of controversy (Iverson, Brooks, Lovell, & Collins, 2006). Multiple SRCs may contribute to the development of PCS. Therefore athletes that engage in contact sports may be at increased risk.

In rugby union there are approximately 3.9 SRCs per 1000 player hours (one in every six games) (Brooks, Fuller, Kemp, & Reddin, 2005). Professional rugby has been reported to have the highest rate, approximately 9 concussions per 1000 player hours compared to rates of 6.5 in professional ice-hockey and 7.9 in amateur boxing per 1000 player hours. Furthermore approximately 50% of SRCs are not reported by players (McCrea, Hammeke, Olsen, Leo, & Guskiewicz, 2004).

Overall it is estimated that less than 40% of concussions are detected during play across sports, leaving players more susceptible to errors in judgment and decision making, and incurring a second concussion with potentially severe consequences (Cantu & Gean, 2010). Once an athlete has suffered a SRC it is estimated that there is at heightened risk of a future concussion for a 7-10 day period during which symptoms are resolving (Gardner, Shores, & Batchelor, 2010; Iverson, Echemendia, LaMarre, Brooks, & Gaetz, 2012). In athletes with multiple SRCs, the risk is further increased because the recovery period usually extends beyond the rest period before athletes return to play (Eisenberg, Andrea, Meehan & Mannix et al., 2013). If another SRC is sustained during the incomplete recovery period it can, in rare

cases, lead to SIS and potentially death (Cantu & Gean, 2010).

In addition, studies have reported that athletes with three or more SRCs had significantly higher FA values than controls across a larger number of brain regions (Henry, Tremblay, & De Beaumont, 2016). It is unclear why FA was higher in this group. The participants of this study and many other studies evaluating the effects of SRC are young adults in which the process of axonal myelination continues and may enhance WM repair (Orr et al., 2016). Alternatively, continued exposure to sub-concussive blows may influence the brains ability to repair itself post-injury. A longitudinal study of sub-concussive blows found elevated FA levels in American football players post-season compared to their pre-season scans. After a six month period off play, the FA values returned to baseline, suggesting that in active players WM changes may be ongoing (see Mayinger et al. 2017). In addition to the neuroimaging differences, changes in electrophysiology, the presence of more severe symptoms (e.g. LOC; amnesia) (Collins et al., 2003; McCrory et al., 2013), and poorer performance on tests of memory, processing speed, executive functions (e.g. response inhibition and verbal fluency), are also reported in athletes with three of more SRCs compared to athletes with no history of concussion (Gardner et al., 2010; Iverson et al., 2012).

One major shortcoming of these studies is that the comparisons are made between athletes that play the same contact sport. Thus subjects included in control groups may have a history of sub-concussive blows, i.e. brain trauma without signs of concussion. Repeated sub-concussive blows are reported to contribute to axonal injury and poorer cognitive performance (Bailes, Petraglia, Omalu, Nauman, & Talavage, 2013).

The neuropsychological sequelae of SRCs may be mild and of minimal concern during an athlete's early adulthood, however it can persist and accentuate over time, as the normal ageing process takes place (Tremblay et al., 2014). List et al. (2015) reported a dose-dependent cortical thinning in young to middle aged adults with multiple concussions (3-5), the higher the number of concussions the more cortical thinning was found in the right temporal lobe, right entorhinal area and bilateral insula. This suggests that there are persistent long-term alterations to brain structure. No differences were found on DTI metrics. If structural changes continue during the aging process it is possible that cognitive decline may become apparent or may present itself earlier than in aged matched controls.

In retired athletes there has been an increase in the prevalence of mild cognitive impairment that is thought to be linked to brain injuries acquired during their professional life (Guskiewicz et al., 2005). Furthermore, post-mortem studies have indicated that repeat concussions and sub-concussive blows may be linked to the development of chronic traumatic encephalopathy (CTE), a neurodegenerative disease of environmental aetiology (Iverson, Gardner, McCrory, Zafonte, & Castellani, 2015; Saulle & Greenwald, 2012). Gavett et al. (2010) suggest that CTE may develop following recurrent episodes of trauma induced axonal injury, which can result in overproduction and pathological aggregation of key proteins. This disease presents later in life after symptoms of the initial injury have ended. It is associated with cognitive difficulties of executive functioning and memory, mood changes, Parkinson's disease and dementia (Baugh et al., 2012; Yi et al., 2013). The incidence of CTE is currently unknown as it is only possible to diagnose post-mortem. Further research is needed to establish if there is a link between multiple SRCs and CTE as the

evidence to date is based on single cases. Other variables such as genetic risk factors may offer an alternative explanation for CTE (Maroon et al., 2015).

Neurocognitive Functioning and Brain Networks

To fully understand the neurocognitive sequelae of mTBI it is necessary to develop an understanding of the impact diffuse axonal injury exerts upon functional connectivity within and between brain networks in the long-term. Functional connectivity occurs between spatially remote brain regions and those that are in spatial proximity, reflecting the level of functional communication between brain regions (van den Heuvel & Hulshoff Pol, 2010). The WM tracts of the brain are the pathways that allow this information processing between brain regions to take place. Three brain networks have been identified as necessary for efficient cognitive control that enables us to select, attend and switch between salient events: the DMN, SN and central-executive network (CEN) (Menon, 2014; Chen et al., 2013; Goulden, et al., 2014). The CEN it is important for maintenance of information in working memory and decision making (Menon & Uddin, 2010). It is suggested that these networks interact to efficiently control higher-level cognitive process such as attention, memory and decision-making.

The SN is responsible for signaling when to switch between activity in the DMN and CEN in the presence of a task that requires attention (Goulden et al., 2014; Sidlauskaite et al., 2014; Sridharan, Levitin, & Menon, 2008). Activity in the CEN is negatively correlated with activity in the DMN and may have an inhibitory effect on DMN activation (Chen et al., 2013).

A study showed that structural damage to parts of the SN impacts on the coordinated activity between the SN and DMN. The study used a stop-signal

task that required participants to make fairly automatic motor responses to a visual cue, on occasion after a ‘stop’ cue they had to inhibit the response. The TBI patients (unclassified in this study) were impaired on the task. The TBI patients had damage to a particular SN tract that connects the right anterior insula to the pre-SMA (pre-supplementary motor area)-dACC (dorsal anterior cingulate cortex) which negatively impacted on the patients deactivation of the DMN and was associated with slower and less efficient inhibitory control (Bonnelle et al., 2012). The findings suggest that damage to WM tracts in intrinsic connectivity networks can impact negatively on their interaction and influence performance on higher-level cognitive tasks. Furthermore, coordinated activity between the SN, CEN and DMN appears to be important for efficient engagement of motor control, a pre-requisite for anyone engaged in sports to be able to play efficiently (Greicius et al., 2009; Sharp, 2014).

The Current Study

The main focus of this study was to investigate if frequency of SRC was associated with cognitive performance and axonal injury as measured by DTI. Evidence of axonal injury and worsened cognitive performance have been observed in athletes who suffered SRCs. However, most studies examining these issues have not combined neurocognitive and neuroimaging information. Furthermore, it is not possible to determine from the current evidence base if there is a cumulative effect of SRC, and if this is related to severity or frequency of injury as these aspects are often omitted by researchers. Moreover, heterogeneous groups and poor control groups are often employed in studies leading to potentially biased findings.

To contribute to a more complete understanding of the relationship between SRC and cognitive outcomes post-injury the project will employ a cohort of male university rugby players who have or do not have a history of SRCs, and male athletes not engaged in contact sports (no history of SRCs) as controls. It will explore whether rugby players with a higher frequency of SRC compared to rugby players with lower frequency of SRC and male non-contact sport athletes (SRC free), have enduring cognitive symptoms associated with underlying neurologic changes in the brain that may be indicative of the initial stages of PCS.

Research Aims and Hypotheses

The aims were to determine if multiple SRCs are linked to: i) lowered performance on neurocognitive tasks, ii) persisting structural changes measured by DTI, and iii) whether indicators of neurological injury are associated with decrements in neurocognitive performance on executive function tasks.

Three hypotheses were considered:

1. Performance on a battery of neurocognitive tests will be associated with frequency of SRC. It is predicted that as SRC frequency increases performance on the tests will decrease.
2. Frequency of SRC will be associated with:

   Axonal injury measured by i) decreased fractional anisotropy in three WM tracts: the corpus callosum (CC), the fronto-occipital fasciculus (FOF) and the inferior longitudinal fasciculus (ILF), and ii) increased mean diffusivity in three WM tracts: the corpus callosum, the fronto-occipital fasciculus and the inferior longitudinal fasciculus.

3. Less accurate and slower performance on a response inhibition task (STOP-IT) will be associated with greater axonal injury as measured in hypothesis 2 above.

The direction of the changes in FA and MD for this study was informed by the evidence base of DTI studies of mTBI. The majority of studies have found decreased values for FA across the spectrum of injury severity and time since injury (Hulkower et al. 2013). Although, some studies have reported the reversal of the expected DTI changes in athletes with multiple SRCs (Henry et al. 2016; Bazarian et al. 2014), there is insufficient evidence to validate these parameters given the heterogeneity of participants included in these studies (Gardner et al. 2012).

The three WM tracts to be examined are known to be vulnerable to the stretch and strain that occurs in mTBI and SRC. Furthermore, differences in DTI metrics have been consistently demonstrated between mTBI/SRC groups and control groups in these tracts (Aoki et al., 2012; Shenton et al., 2012; Cubon et al., 2011; Slobounov et al., 2012)

Method

This was a cross-sectional study. Neurocognitive and neuroimaging data was acquired for rugby players and a control group of athletes participating in non-contact sports.

Participants.

Members of the University of Exeter Men's Rugby team were invited to take part by e-mail (provided by the Director of Rugby). A total of 95 players were contacted. Two were studying abroad, ten were interested but could not

commit to take part, and twenty-eight volunteered to take participated in the study. Members of the University of Exeter Rowing team were recruited via an invitation circulated to male team members and via posters placed in the University of Exeter's sports centre. Members of the Sport and Health Sciences College (SHS) were recruited by attending undergraduate lectures and inviting students to take part. Posters were placed in the main SHS lecture theatres. Fifteen subjects contacted the research team. Two individuals did not meet the inclusion criteria (did not currently practice sport regularly). One control subject was claustrophobic and excluded from the study. A total of twelve male control subjects from the University of Exeter's Rowing team and SHS were included (Table 2- Appendix F).

Only male participants were recruited due to gender specific differences in SRC rates and outcome (Hootman, Dick, & Agel, 2007). All participants were fluent in English, did not have any contraindications for MRI, no significant medical or psychiatric comorbidity, or reported mental health difficulties. All rugby players had completed at least one season of play as part of the University of Exeter squad.

The inclusion criteria required participants to be enrolled at the University of Exeter and be ≥ 18 years of age. In addition, the control participants were required to have no history of head injury. There lower limit for the time elapsed since the last SRC for rugby players was ten weeks, there was no upper limit (Appendix F).

SRC dosage in the rugby players was categorised according to the frequency of injury (i.e. number of SRCs). This categorisation is based on previous studies that have used frequency of SRCs to group participants (Gardner et al., 2010). A SRC will be defined by the presence of a) being dazed

or confused, or b) loss of consciousness (LOC) that does not exceed 10 minutes. Injuries where LOC is >10 minutes are classified as complicated mTBI or moderate TBI (Table 1) and would not fulfil the inclusion criteria of this study.

Table 2*. Categorisation of loss of consciousness*

Loss of consciousness will be categorised as:
• none • dazed/confused • LOC < 1 minute • LOC 1-5 minutes • LOC 5-10 minutes • LOC >10minutes

All participants received £10 for their time and travel costs and entered into a prize draw. The prizes consisted of one £50 and two £30 high street vouchers.

Target sample size to be recruited.

Sample size considerations were informed by several sources of information. First, in the absence of previous studies in the topic research area, conservative power calculations for correlations based on medium effect sizes (ES) were performed. These revealed an unfeasible sample size (Appendix C). Second, other neurocognitive studies of multiple SRCs (Gardner et al., 2004; Gardner et al., 2010; Iverson et al., 2012), neuroimaging (DTI) studies of mTBI and SRCs (Zhang et al., 2010), and studies combining DTI metrics with neurocognitive variables (Veeramuthu et al., 2015) suggest that the ES may be higher than 0.5 (Appendix C). Therefore a sample size of approximately 60 participants may be appropriate. However, the ES reported in the aforementioned studies do not change the power calculations which indicate

that the study is underpowered. To account for this possibility, post-hoc sensitivity analyses that calculate the minimum ES that would have been detectable with power of .80 based on the recruited sample size, were employed.

Ethical Approval and Consent

The Exeter University Ethics Review Board approved the study (Appendix B). All participants were over 18 years old and able to consent. Information materials were sent out to participants at least one day before the appointment. On the day of the appointment, participants provided written consent (Appendix A). Participants were informed about the right to withdraw from the study at any time.

Measures

Demographic questionnaire. A short demographic questionnaire and screening questionnaire were used to assess suitability of all participants for the study by ensuring that they meet the inclusion/exclusion criteria (Appendix A).

To ensure participants did not have high levels of pain or sleep disturbances, known to have a negative impact on cognitive performance (Harrison & Home, 2000; Moriarty, Mcguire, & Finn, 2011). The following questionnaires were used:

McGill Pain questionnaire (Melzack, 1987)**:** A self-report questionnaire that consists of five main measures designed to as a multidimensional measure of pain was employed to measure any current orthopaedic pain associated with injuries. It will permit differentiation of non-concussive head pain and any headache pain associated with SRC's that will be measured by the SCAT3. Sections 1, 2 and 3 was employed. Section 1 – Pain location. Site of pain is drawn on the human body (anterior and posterior sides); Section 2 – Pain intensity: participants rate current pain by selecting one of the options: 0=none, 1=mild, 2=discomforting, 3=distressing, 4= horrible and 5=excruciating. Section 3 - Pain quality: has 20 descriptors which participants rate on a scale as: 0=none, 1=mild, 2=moderate, and 3=severe. Any participants with current pain that is described as distressing, horrible or excruciating (Section 2) will be excluded (Moriarty et al., 2011).

Sleep Scale from the Medical Outcomes Study (Allen, 2009)**:** A 12 item self-report questionnaire that assesses dimensions of sleep including: initiation, quantity, perceived adequacy and somnolence. Any participants that report sleeping less than an average 6 hours per night over the last four weeks which is perceived as inadequate and/or who experience somnolence will be excluded (Alhola & Polo-kantola, 2007).

Concussion history. Once suitability for participation has been established participants completed section three of the Sport Concussion Assessment Tool, 3rd Edition (SCAT3). This section assesses post-concussive symptom frequency and severity (Appendix A).

Neuropsychological tests[3]

Speed and Capacity of Language Processing Test (SCOLP)

(Baddeley, Emslie, & Nimmo-smith, 1993)***:*** To match individuals for cognitive ability the SCOLP was employed. This is a brief test that does not rely on pronunciation (often required by other tests). The SCOLP estimates pre-morbid cognitive ability employing two tasks: a lexical decision task and a speed of comprehension test. The former consists of sixty pairs of words comprising one real and one non-word. The words vary from very common to very unusual. The subject has to indicate which is the real word for each pair that is presented. The number of correct responses provides a measure of crystallised verbal intelligence. The speed of comprehension test estimates speed of verbal information processing. The subject is given two minutes to identify as many 'silly' or 'sensible' sentences as possible, by putting check marks against sensible sentences and crosses against silly sentences.

CogState Electronic Battery. This battery is currently the industry-standard concussion screen in rugby in the UK. It is a standardised, reliable, and widely used tool with published normative data employed to identify cognitive and psychological difficulties such as mild cognitive impairment, schizophrenia and mTBI (Maruff et al., 2013).

The battery sub-tests included are:

[3] Refer to Appendix F – Table 3 for validity and reliability of neuropsychological tests.

- Detection: A reaction-time test that measures psychomotor function and processing speed. Participants are instructed to press a button each time a playing card turns over (on a computer screen).
- Identification: A choice reaction time test that measures visual attention and decision-making. Participants are asked to state whether playing cards are red or black (on a computer screen) by pressing two buttons (one for Yes/one for No).
- One card learning: This test measures visual learning and memory. Participants are shown a sequence of playing cards on the screen, one at a time. Participants are asked to indicate whether they have seen each card earlier in the sequence or not.
- One back task: This is an n-back paradigm based task that measures visual learning and working memory. Participants are shown a series of playing cards, on at a time on a screen. Participants are required to indicate whether the card presented is the same or different to the preceding card.

STOP-IT electronic test. This is a stop-signal test that measures automatic and controlled response inhibition. Participants are instructed to make or withhold motor responses by pressing two separate buttons on a computer keyboard, one in response to a square and another in response to a circle, based on the presence or absence of an auditory stop signal. The program measures reaction time and error rates (Verbruggen, Logan, & Stevens, 2008b).

The Stroop colour and word test (Stroop). This test is a measure of inhibition of automatic and dominant responses. It has three conditions. In condition A the individual reads words printed in black ink that denote colours, in condition B the individual names the colour of the ink a row of Xs are printed in, for condition C the individual names the colour of the ink that words that denote colours are printed in (the word and colour of the ink are incongruent). The individual is given 45 seconds to complete each condition (Golden & Freshwater, 2002).

COWA test (FAS). The COWAT assess spontaneous production of words using designated letter: F, A or S. Individuals are asked to give as many words that start with the designated letter: F, A or S, as quickly as they can in a one minute period. They are instructed not to use proper nouns or to use the same word with different endings. One point is awarded for each correct word **(**Strauss, Sherman & Spreen, 2006**).**

Trail making test. This is a test of scanning and visuomotor tracking, and divided attention. It has two parts A and B. Part A assesses speed on a visual search by asking the individual to join up circles with numbers in them in ascending order. Part B requires the individual to join up circles with numbers or letters in them in ascending and alphabetical order in alternating fashion. Performance on Part B depends on working memory (Strauss, Sherman & Spreen, 2006).

Neuroimaging

The scans were acquired using a Philips Intera 1.5T scanner at the University of Exeter MRI centre. Scanning of both sequences was done using an

eight-element phased array coil. The total time for the scans was estimated to be 10 minutes.

Structural T1 weighted scan – a 3D echo planar imaging (EPI) sequence was employed. Relevant imaging parameters were TR/TE = 25 ms/4.6 ms, FOV 230 x 183 x 128mm, α = 30°. 160 sagittal partitions were acquired. The voxel size was 0.9mm x 0.9mm x 1.60mm. Fat saturation and fat selective excitation pulses were used to suppress the high signal from the scalp, reducing the motion sensitivity (Howarth et al., 2005).

DTI scan. Relevant imaging parameters were as follows: diffusion weighting gradients were applied in 32 directions with b-values 1000m/sec, TR/TE = 93ms/66 ms, FOV 224 x 224 x 183mm, α = 90°. 48 slices were acquired. The voxel size was 0.9mm x 0.9mm x 1.60mm.

The scans were processed using FSL part of the FMRIB Software Library (Smith et al., 2004) which included the following the steps: an Eddy current correction was applied to correct any motion and alignment issues, ii) the scans were skull-stripped, iii) FA and MD maps were created for each subject, and iv) the images were normalised into MNI space. Finally, three ROI masks were created using the ICBM-DTI-81 and JHU WM atlases and the FA and MD values for each individual for each of the ROIs were extracted.

Data analyses

Data were analysed using SPSS version 23.0 for Windows. Data were screened for outliers, homogeneity of variance and to ascertain if data were normally distributed.

To ensure that there were no pre-existing differences between rugby players and controls basic group comparisons were performed on the demographic variables: age, education and premorbid levels of functioning. Sleep and pain levels were also compared. T-tests or Mann-Whitney tests, if the data were not normally distributed, were used.

Region of interest data. For hypotheses 2 and 3 MD and FA values were extracted for each ROI (CC, ILF and FOF) using the DTI processing pipeline in FSL. The extracted values were then analysed using SPSS.

The target sample for this study was 60 athletes. The actual sample size achieved was 40 of which 28 were rugby players and twelve controls. Therefore, for the main analyses, a correlational approach using the whole sample was employed to establish if there is an association between SRC frequency as a continuum and the DTI/cognitive measures. This approach was chosen given the low number of control participants. This approach does not account for any pre-existing differences related to sub-concussive blows between rugby players with zero SRCs and controls. Therefore it may further reduce the power of the study by reducing the measurement reliability given the heterogeneous group employed (Kanyongo, Brook, Kyei-Blankson and Gocmen, 2007). If an association between SRC frequency and any of the DTI or cognitive measures was identified in the analysis this would need to be interpreted with caution and further examination of the data required. Spearman's rho correlations were employed. The significance threshold was set at P=0.005 corrected for ten comparisons (Hypothesis 1) and P=0.008 corrected for six comparisons (Hypotheses 2) and P=0.004 for twelve comparisons (Hypothesis 3).

Results

***Descriptive Statistics*.** A summary of the sample demographic statistics are shown in Table 2. There were no differences between rugby players and control athletes in terms of age (U(38)=129.0, Z=-1.187, p=0.26) or years of education (U(38)=119.5, Z=-1.57, p=0.15). The mean scaled score for speed of comprehension of the SCOLP did not differ rugby players and control athletes (U(38)=130.0, Z=1.13, p=0.27), the scores for the whole sample fell in the high average range (70-90th percentiles). The rugby players and control athletes reported sleeping between 7-8 hours on average per night (U(38)=120.0, Z=-1.50; p=0.13). Qualitative information of illegal drug and alcohol consumption showed that one rugby player reported historical (once) illegal drug use. None of the controls reported illegal drug use. All the rugby players reported alcohol consumption. Five indicated alcohol consumption once a month and 23 reported consumption two/three days a week. Ten controls reported alcohol consumption once a month and two reported consumption twice a week. Fourteen rugby players reported symptoms on the SCAT3 (score range 1-16). Two control participants reported symptoms (score range 2-5). Nine rugby players reported pain at the time of testing which did not exceed mild in any of the cases. None of the control participants reported pain. The median time since last SRC was 8.50 months, 25th percentile 3 months/75th percentile 14 months). A total of 60 SRCs were reported. Eleven rugby players did not report any SRCs. The SRC severity (LOC) for all of the reported SRCs was <1 minute. The RTP data (self-report) showed that on 24 occasions players had returned to play within the same game, there was no reported LOC in 17 of these cases and LOC <1 minute in the remaining 7 cases.

Table 3. *Background characteristics of the participants*

	Rugby players (N=28)	**Controls (n=12)**
Age (years)	20.0(19.0/20.0	20.50(18.25/24.00
Education (years)	14.00(13.00/14.00)	14.00(13.00/14.00)
Handedness	1 Left/27 Right	1 Left/11 Right
SCOLP – SoC[a] (Scaled score)	11.50(10.00/13.00)	14.00(10.25/15.00)
Average sleep (hours)	7.75(7.00/8.00)	7.00(7.00/7.87)
Pain present (cases)	9	0
SCAT3[b]	14	2
Time since last SRC (months)	8.50(3.00/14.00)	N/A

Measurements = medians (25th percentile/75th percentile)
[a] SoC = Speed of comprehension
[b] Number of players that reported symptoms

Main analysis

***Cognitive data*.** For the first hypothesis of this study, it was hypothesised that performance on the neurocognitive tests would decrease when the frequency of SRCs increased. The results showed that there were no significant Spearman's correlations between SRC frequency in the whole sample and the pen and paper neurocognitive tests, namely FAS (r_s=0.053, 95% CI [-0.27, 0.36]), TMT-A (r_s=0.058, 95% CI [-0.26, 0.37]), TMT-B (r_s= -0.046, 95% CI [-0.27, 0.36]) and the Stroop Interference (r_s= -0.25, 95% CI [-0.07, 0.52]) (see Table 4). Similarly, no significant correlations were found between SRC frequency and the computerised neurocognitive tests STOP-IT-SSRT (r_s= -0.04, 95% CI [-0.28, 0.35]), STOP-IT–Accuracy (r_s= -0.05, 95% CI [-0.27, 0.36]), CogState DET (r_s= -0.15, 95% CI [-0.17, 0.44]), CogState IDN (r_s= -0.065, 95% CI [-0.26, 0.37]), CogState OCL (r_s= 0.24, 95% CI [-0.08, 0.52]) or the CogState ONB (r_s= 0.06, 95% CI [-0.26, 0.37]) (see Table 4).

Table 4 - *Cognitive measures.*

Measure	Rugby players (n=28)	Controls (n=12)
FAS –Total	44.25 (9.82)	43.91 (5.94)
Trails Time A (secs)	22.83 (8.2)	22.41 (5.61)
Trails Time B (secs)	39.33 (8.45)	39.25 (10.41)
Stroop Interference (T-score)	57.57 (6.83)	63.08 (9.61)
STOP-IT – SSRT (msecs)	298.30 (144.22)	239.62 (48.47)
STOP-IT - Accuracy	0.85 (0.30)	0.89 (0.27)
CogState – DET[a] (RT)	2.45 (0.057)	2.46 (0.47)
CogState – IDN[b] (RT)	2.62 (0.031)	2.63 (0.48)
CogState – OCL[c] (Accuracy)	1.02 (0.47)	1.03 (0.80)
CogState – ONB[d] (RT)	1.39 (0.13)	1.34 (0.14)

Measurements = mean (SD).
[a] DET=Detection (score = speed of performance (log10 of reaction time (RT) of correct responses)
[b] IDN=Identification (score = speed of performance (log10 of RT of correct responses)
[c] OCL=One card learning (score = proportion of correct responses)
[d] ONB=One back task (score = speed of performance (log10 of RT of correct responses)

DTI data. Having established that there were no significant correlations between SRC frequency and cognitive performance, the second hypothesis was evaluated, namely to establish if there was an association between SRC frequency and axonal injury measured by FA and MD in the three a-priori ROIs. There were no significant Spearman's correlations between SRC frequency of the whole sample and FA in the CC (r_s= 0.005, 95% CI [-0.31, 0.32]), ILF (r_s= 0.028, 95% CI [-0.29, 0.34]) or FOF (r_s= -0.022, 95% CI [-0.30, 0.33]). The same was pattern was found for MD values in the CC (r_s= 0.081, 95% CI [-0.24, 0.39]), ILF (r_s= -0.16, 95% CI [-0.16, 0.45]) or FOF (r_s= -0.15, 95% CI [-0.17, 0.44]) (see Table 5).

Table 5 - *Mean diffusivity and fractional anisotropy values.*

ROI	Rugby players (N=28)	Controls (N=12)
CC – MD	0.000799 (0.000069)	0.000790 (0.000068)
ILF – MD	0.000801 (0.000027)	0.000795 (0.000042)
FOF – MD	0.000811 (0.000021)	0.000807 (0.000030)
CC – FA	0.3555 (0.0268)	0.3549 (0.0322)
ILF – FA	0.2938 (0.0226)	0.2841 (0.0194)
FOF – FA	0.2830 (0.0172)	0.2821 (0.0166)

Measurements = mean (SD)

DTI and STOP-IT task. Finally, the third hypothesis was investigated, namely to find out if there was an association between axonal injury and performance on the STOP-IT task. There were no significant Spearman's correlations between axonal injury FA values and the STOP-IT SSRT in any of the ROIs: CC (r_s= 0.005, 95% CI [-0.31, 0.32]), ILF (r_s= 0.028, 95% CI [-0.29, 0.34]) or FOF (r_s= -0.022, 95% CI [-0.30, 0.33]). Equally, there were no significant correlations between MD values STOP-IT SSRT in the CC (r_s= -0.028, 95% CI [-0.29, 0.34]), ILF (r_s= -0.16, 95% CI [-0.16, 0.45]) or FOF (r_s= -0.15, 95% CI [-0.17, 0.44]).

Likewise, there were no significant Spearman's correlations between accuracy on the STOP-IT and FA values and in any of the ROIs: CC (r_s= 0.19, 95% CI [-0.13, 0.48]), ILF (r_s= -0.045, 95% CI [-0.27, 0.35]) and FOF (r_s= -0.032, 95% CI [-0.29, 0.34]), or MD values in the CC (r_s= -0.11, 95% CI [-0.21, 0.41]), ILF (r_s= 0.017, 95% CI [-0.30, 0.33]) or FOF (r_s= 0.082, 95% CI [-0.24, 0.39]).

In sum, there were no significant associations between the number of SRCs and cognitive tests or DTI metrics. There were no significant associations between DTI metrics and performance on the response inhibition task.

Statistical power

Post-hoc sensitivity analyses revealed that there was insufficient power to detect a true correlation with a sample size of 40, critical r=+-0.41 (power = .80; alpha=.006, two tailed test). Accordingly, there is an increased risk of a Type II error, the null hypothesis is not rejected when it is false.

Discussion

The aim of this study was to investigate the relationship between SRC frequencies, cognitive performance and diffuse axonal injury in university rugby players. Contrary to the prediction that increases in frequency of SRC would be associated with poorer performance on cognitive tasks, the results suggest that there is no association between frequency of SRCs and cognitive functioning. This finding is consistent with studies that have not found associations between SRC and cognitive dysfunction (Iverson et al., 2006) but is inconsistent with studies that suggest there are cognitive consequences associated with multiple SRC's (Gardner et al., 2010b; Guskiewicz et al., 2003) and with sub-concussive blows (Marchi et al., 2013).

One explanation for this null finding could have been attributed to the format of neuropsychological tests. However, here we used a mixture of

computerised and traditional measures that have been widely validated to account for this possibility (Maruff et al., 2009; Strauss, Sherman & Spreen, 2006). Another factor that is important to consider, is that the rugby players all had chronic SRCs, thus their performance on cognitive tests may have returned to pre-injury levels after the acute phase, as reported in previous studies (Covassin, Elbin, Crutcher, & Burkhart, 2013). It is believed that the inflammatory processes associated with the pathology of acute mTBIs is transient and resolves within 7-10 days. However, there is variability in the time it may take for the pathophysiological processes arising from axonal injury to resolve (Giza & Hovda, 2001). Therefore a minimum period of ten weeks post-injury would allow for these processes to have resolved. Nevertheless, if any of the players had presented with persistent unreported symptoms within this time frame it would not be possible to elucidate if axonal injury is still resolving.

Alternatively, it may reflect compensatory mechanisms whereby increased connectivity between areas is needed to maintain similar levels of cognitive performance (Czerniak et al., 2015; Zhang et al., 2010). Linked to this idea is the specificity of the cohort employed to minimize the impact of confounding variables, all participants were from educational backgrounds where academic standards are high. It has been suggested that higher levels of education are associated with a ‘higher’ cognitive reserve and therefore this may be a protective factor that produces less pronounced effects of SRC (Barulli & Stern, 2013).

Similarly, there was no evidence to support that the frequency of SRCs is positively associated with axonal injury as measured by FA and MD. This finding is at odds with the majority of studies in the field. Although there is variability in terms of the neuroanatomical regions and the DTI metrics amongst

findings in the literature (perhaps reflecting the heterogeneity of SRCs), DTI is thought to have adequate sensitivity to detect SRCs. In particular in athletes with multiple SRCs (Henry et al., 2011) and with repetitive sub-concussive blows (Lipton et al., 2013). It is possible that methodological differences could account for the present finding. The current study employed a ROI approach that restricted DTI analyses to three WM tracts that are commonly reported to be affected in mTBI and SRC (Gardner, 2012; Bigler, 2013) but did not explore the WM tracts across the whole brain. Thus, the findings cannot rule out the possibility of axonal injury elsewhere in the brain. In addition, the scans were performed at 1.5T field strength which offers less spatial resolution compared to higher field strength utilised in the majority of previous studies. Stronger magnetic fields improve the signal-to-noise of the MRI signal. In a DTI image anisotropy is assessed by measuring the aggregate range of diffusivity across the tissues that make up the voxel. Therefore partial volume effects may affect the anisotropy values when larger voxels are employed (Hulkower, Poliak, Rosenbaum, Zimmerman, Lipton, 2013).

Finally, there were no associations between axonal injury and performance on the STOP-IT task. This finding is unsurprising given the lack of significant associations between SRC frequency, neurocognitive tasks and DTI metrics. One would expect a detectable decrease in performance and/or evidence of axonal injury for there to be an association between these variables.

Limitations

Whilst the findings suggest that there is no association between SRC frequency, axonal injury and cognitive performance, it is necessary to consider some additional issues:

The overall sample size is small. The post-hoc sensitivity analyses indicate that all the results are below the critical r values needed to achieve an 80% chance of finding a true effect. Thus, the study can be considered at high risk of a Type II error, failing to find differences where they do exist. In addition, only a small number of control non-contact sport athletes were included that may further contribute to the lack of power in the analyses. The two groups were combined for data analyses introducing uncontrolled confounding factors (e.g. sub-concussive blows in rugby players with zero SRCs). A larger sample size would permit analyses to be performed at group level.

The SRC data was self-reported and the details of the severity of the injury may be subjective as it relies on the individual's memory of the event. Nevertheless, the rugby players reported concussions were at the mildest end of the spectrum of SRC. No rugby players reported LOC over 1 minute nor severe post-SRC symptoms. Had there been individuals with SRCs with more severe LOC, presence of PTA or persisting symptoms in the sample there may have been neurocognitive effects or positive DTI findings.

The scanning parameters could have affected the quality of the images, in particular the spatial resolution, could introduce partial volume effects that may reduce the likelihood of detecting small changes in anisotropy (Hulkower et al., 2013).

Clinical Implications

A high rate of SRCs were reported by the rugby players in the study. In line with previous studies the current findings support the notion that in the majority of cases there are no long lasting effects of SRCs. All SRCs reported in this study were very mild which suggests that severity of injury is an important clinical factor to consider. Thus, reinforcing the need for better characterisation of SRCs and how cumulative injuries may change the severity of the injury i.e. is there a linear relationship between severity and LOC.

Nevertheless this should not lessen the importance of improving the early detection, classification and treatment of injury. This is particularly important because there is no agreement on increased risks of re-injury in the acute phase or if re-injury occurs in this phase if it can have more severe consequences. The results of the current study and evidence in the study area suggest that DTI cannot yet be used as a standalone technique for diagnosis and management of concussion. A transdiagnostic approach may benefit athletes. For example, the use of baseline and routine neuropsychology testing can provide pre- and post- measures that afford better characterisation of cognitive changes. Furthermore, repeated neurocognitive testing can provide information about changes in cognitive functioning during the recovery phase ensuring athletes do not RTP too early.

Future Directions

The study should be extended to include a larger overall sample, with equal group sizes to conduct between group comparisons. This type of

analyses would eliminate the confounding factor of exposure to sub-concussive blows between rugby players with zero SRCs and controls.

Further prospective longitudinal studies are required to establish within-subject differences post-SRCs and to examine if individuals with higher frequency of SRCs show differences in cognitive functioning and the way they recruit and use brain networks compared to controls. The University of Exeter's Rugby Team will be implementing baseline and repeated neurocognitive assessment for players that will contribute to understanding these issues. Likewise, longitudinal studies that follow-up contact sport athletes after retiring from sports to assess long-term outcomes are needed. Importantly, asymptomatic and symptomatic athletes should be included to gain a full understanding of the relationship between SRC frequencies, diffuse axonal injury, cognitive and psychological sequelae.

Conclusion

The results of the study contribute to a growing body of literature exploring the relationship between SRC, cognitive function and axonal injury. It did not find evidence for a relationship between SRC frequency and diffuse axonal brain injury or cognitive dysfunction. Further research should employ larger samples and could be extended to include measures of functional MRI.

References

Allen, R.P., Kosinski, M., Hill-Zabala, C.E., & Calloway, M.O. (2009). Psychometric evaluation and tests of validity of the Medical Outcomes Study 12-item Sleep Scale (MOS Sleep). *Sleep Medicine, 10*, 531-539.

Alhola, P., & Polo-kantola, P. (2007). Sleep deprivation: Impact on cognitive performance. *Neuropsychiatric Disease and Treatment*, *3*, 553–567.

Aoki, Y., Inokuchi, R., Gunshin, M., Yahagi, N., & Suwa, H. (2012). Diffusion tensor imaging studies of mild traumatic brain injury: a meta-analysis. *Journal of Neurology, Neurosurgery & Psychiatry*, *83*, 870–876.

Arciniegas, D. B., Anderson, C. a, Topkoff, J., & McAllister, T. W. (2005). Mild traumatic brain injury: a neuropsychiatric approach to diagnosis, evaluation, and treatment. *Neuropsychiatric Disease and Treatment*, *1*, 311–327.

Baddeley, A., Emslie, H., & Nimmo-smith, I. (1993). The Spot-the-Word test : A robust estimate of verbal intelligence based on lexical decision. *Bristish Journal of Clinical Psychology*, *32*, 55–65.

Bailes, J. E., Petraglia, A. L., Omalu, B. I., Nauman, E., & Talavage, T. (2013). Role of subconcussion in repetitive mild traumatic brain injury. *Journal of Neurosurgery*, *119*(5), 1235–45.

Barulli, D., & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: Emerging concepts in cognitive reserve. *Trends in Cognitive Sciences, 17*, 502-509.

Baugh, C. M., Stamm, J. M., Riley, D. O., Gavett, B. E., Shenton, M. E., Lin, A., … Stern, R. A. (2012). Chronic traumatic encephalopathy:

neurodegeneration following repetitive concussive and subconcussive brain trauma. *Brain Imaging and Behavior*, *6*, 244–254.

Bigler, E. D. (2008). Neuropsychology and clinical neuroscience of persistent post-concussive syndrome. *Journal of the International Neuropsychological Society* ,*14*, 1–22.

Bigler, E. D. (2013a). Neuroimaging biomarkers in mild traumatic brain injury (mTBI). *Neuropsychology Review*, *23*, 169–209.

Bigler, E. D. (2013b). Neuroinflammation and the dynamic lesion in traumatic brain injury. *Brain*, *136*, 9–11.

Bodin, D., Yeates, K.O., & Klamar, K. (2012). In Walter, K.D., & Apps, J.N. (Eds), *Pediatric and adolescent concussion. Diagnosis, management and outcomes* (pp. 9-19). New York: Springer.

Bonnelle, V., Ham, T., Leech, R., Kinnunen, K., Mehta, M., Greenwood, R., & Sharp, D. (2012). Salience network integrity predicts default mode network function after traumatic brain injury. *Proceedings of the National Academy of Sceinces*, *109*(12), 4690-4695.

Bonnelle, V., Leech, R., Kinnunen, K. M., Ham, T. E., Beckmann, C. F., De Boissezon, X., … Sharp, D. J. (2011). Default mode network connectivity predicts sustained attention deficits after traumatic brain injury. *The Journal of Neuroscience*, *31*, 13442–51.

Broglio, S. P., Ferrara, M. S., Piland, S. G., Anderson, R. B., & Collie, a. (2006). Concussion history is not a predictor of computerised neurocognitive performance. *British Journal of Sports Medicine*, *40*, 802–805.

Brooks, J. H. M., Fuller, C. W., Kemp, S. P. T., & Reddin, D. B. (2005). A prospective study of injuries and training amongst the England 2003 Rugby World Cup squad. *British Journal of Sports Medicine*, *39*, 288–293.

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The Brain's Default Network: Anatomy, Function, and Relevance to Disease. *Annals of the New York Academy of Sciences*, *1124*, 1–38.

Burgess, P. W., & Shallice, T. (1996). Response suppression , initiation and strategy use following frontal lobe lesions. *Neuropsychologia*, *34*, 263–273.

Cantu, R. C., & Gean, A. D. (2010). Second-Impact Syndrome and a Small Subdural Hematoma: An Uncommon Catastrophic Result of Repetitive Head Injury with a Characteristic Imaging Appearance. *Journal of Neurotrauma*, *27*, 1557–1564.

Chen, a. C., Oathes, D. J., Chang, C., Bradley, T., Zhou, Z.-W., Williams, L. M., … Etkin, a. (2013). Causal interactions between fronto-parietal central executive and default-mode networks in humans. *Proceedings of the National Academy of Sciences*, *110*, 19944–19949.

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

Covassin, T., Elbin, R. J., Crutcher, B., & Burkhart, S. (2013). The Management of Sport-Related Concussion: Considerations for Male and Female Athletes. *Translational Stroke Research, 4,* 420-424.

Czerniak, S. M., Sikoglu, E. M., Liso Navarro, A. A., McCafferty, J., Eisenstock,

J., Herbert Stevenson, J., … Stevenson, J. H. (2015). A resting state functional magnetic resonance imaging study of concussion in collegiate athletes. *Brain Imaging and Behavior*, *9*, 323–332.

Damoiseaux, J. S., & Greicius, Æ. M. D. (2009). Greater than the sum of its parts : a review of studies combining structural connectivity and resting-state functional connectivity. *Brain Structure and Function, 213*, 525–533.

Dean, P. J. A, & Sterr, A. (2013). Long-term effects of mild traumatic brain injury on cognitive performance. *Frontiers in Human Neuroscience*, *7*(30), 1-11.

Eierud, C., Craddock, R. C., Fletcher, S., Aulakh, M., King-Casas, B., Kuehl, D., & Laconte, S. M. (2014). Neuroimaging after mild traumatic brain injury: Review and meta-analysis. *NeuroImage: Clinical*, *4*, 283–294.

Eisenberg, Matthew A., Andrea, J., Meehan, W., & Mannix, R. (2013). Time Interval Between Concussions and Symptom Duration. *Pediatrics*, *132*, 8–17.

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioural and biomedical sciences. *Behaviour Research Methods, 39*, 175-191.

Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.P., Frith, C.D., and Frackowiak, R. S. J. (1995). Statistical Parametirc Maps in Functional ImagingL A General Linear Approach. *Human Brain Mapping*, *2*, 189–210.

Gardner, A. J., Iverson, G. L., Williams, W. H., Baker, S., & Stanwell, P. (2014). A Systematic Review and Meta-Analysis of Concussion in Rugby Union. *Sports Medicine, 44,* 1717–1731.

Gardner, A., Shores, E. A., & Batchelor, J. (2010). Reduced processing speed

in rugby union players reporting three or more previous concussions. *Archives of Clinical Neuropsychology*, *25*, 174–181.

Gavett, B.E., Stern, R.A., & McKee, M.D. (2011) Chronic traumatic encephalopathy: a potential late effect of sport-related concussive and subconcussive head trauma. Clinical Sports Medicine, 30, 179-188.

Giza, C.C., & Hovda, D.A. (2001). The neurometabolic cascade of concussion. *The Journal of Athletic Training, 36*, 228-235.

Goulden, N., Khusnulina, A., Davis, N. J., Bracewell, R. M., Bokde, A. L., McNulty, J. P., & Mullins, P. G. (2014). The salience network is responsible for switching between the default mode network and the central executive network: Replication from DCM. *NeuroImage*, *99*, 180–190.

Greicius, M. D., Supekar, K., Menon, V., & Dougherty, R. F. (2009). Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cerebral Cortex*, *19*, 72–78.

Guskiewicz, K. M., Mccrea, M., Marshall, S. W., Cantu, R. C., Randolph, C., Barr, W., … Kelly, J. P. (2003). Cumulative Effects Associated With Recurrent Concussion in Collegiate Football Players The NCAA Concussion Study. *Journal of the American Medical Association, 290*, 2549-2555.

Guskiewicz, K. M., Marshall, S. W., Bailes, J., McCrea, M., Cantu, R. C., Randolph, C., & Jordan, B. D. (2005). Association between recurrent concussion and late-life cognitive impairment in retired professional football players. *Neurosurgery*, *57*, 719–726.

Harrison, Y., & Home, J. A. (2000). The Impact of Sleep Deprivation on Decision Making : A Review. *Journal of Experimental Psychology: Applied,*

6, 236–249.

Henry, L. C., Tremblay, J., Tremblay, S., Lee, A., Brun, C., Lepore, N., … Lassonde, M. (2011). Acute and Chronic Changes in Diffusivity Measures after Sports Concussion. *Journal of Neurotrauma*, *28*, 1–12.

Henry, L. C., Tremblay, S., & De Beaumont, L. (2016). Long-Term effects of sports concussions: bridging the neurocognitve repercussions of the injury with the newest neuroimaging data. *The Neuroscientist*, *9*, 502-509.

Hootman, J. M., Dick, R., & Agel, J. (2007). Epidemiology of collegiate injuries for 15 sports: Summary and recommendations for injury prevention initiatives. *Journal of Athletic Training*, *42*, 311–319.

Hulkower, M. B., Poliak, D. B., Rosenbaum, S. B., Zimmerman, M. E., & Lipton, M. L. (2013). A decade of DTI in traumatic brain injury: 10 years and 100 articles later. *American Journal of Neuroradiology, 34,* 2064-2074.

Iverson, G. L., Echemendia, R. J., LaMarre, A. K., Brooks, B. L., & Gaetz, M. B. (2012). Possible Lingering Effects of Multiple Past Concussions. *Rehabilitation Research and Practice*, *2012*, 1–7.

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

Iverson, G. L., Brooks, B.L., Lovell, M. R., & Collins, M. W. (2006). No cumulative effects for one or two previous concussions. *British Journal of Sports Medicine*, *40*, 72-75.

Iverson, G. L., Gardner, A. J., McCrory, P., Zafonte, R., & Castellani, R. J. (2015). A critical review of chronic traumatic encephalopathy. *Neuroscience & Biobehavioral Reviews*, *56*, 276–293.

doi:10.1016/j.neubiorev.2015.05.008

Johnson, B., Zhang, K., Gay, M., Horovitz, S., Hallett, M., Sebastianelli, W., & Slobounov, S. (2012). Alteration of brain default network in subacute phase of injury in concussed individuals: Resting-state fMRI study. *NeuroImage*, *59*, 511–518.

Kanyongo, G.Y., Brook, G.P., Kyei-Blankson, L. & Gocmen, G. (2007) Reliability and statistical power: how measurement fallibility affects power and required sample sizes for several paramentric and non-parametric statistics. *Journal of Modern Applied Statistics Methods, 6(1)*, 81-90

Kinnunen, K. M., Greenwood, R., Powell, J. H., Leech, R., Hawkins, P. C., Bonnelle, V., … Sharp, D. J. (2011). White matter damage and cognitive impairment after traumatic brain injury. *Brain*, *134*, 449–463.

Lipton, M. L., Kim, N., Zimmerman, M. E., Kim, M., Stewart, W. F., Branch, C. A., & Lipton, R. B. (2013). Soccer heading is associated with white matter microstructural and cognitive abnormalities. *Radiology*, *268,* 850-857.

List, J., Ott, S., Bukowski, M., Lindenberg, R., & Flöel, A. (2015). Cognitive function and brain structure after recurrent mild traumatic brain injuries in young-to-middle-aged adults. *Frontiers in Human Neuroscience, 9*, 1–9.

Marchi, N., Bazarian, J. J., Puvenna, V., Janigro, M., Ghosh, C., Zhong, J., … Janigro, D. (2013). Consequences of Repeated Blood-Brain Barrier Disruption in Football Players. *PLoS ONE* 8 (E-resource): e56085.

Maroon, J. C., Winkelman, R., Bost, J., Amos, A., Mathyssek, C., & Miele, V. (2015). Chronic traumatic encephalopathy in contact sports: A systematic review of all reported pathological cases. *PLoS ONE*, *10*, 1–16.

Maruff, P., Thomas, E., Cysique, L., Brew, B., Collie, a., Snyder, P., & Pietrzak, R. H. (2009). Validity of the CogState Brief Battery: Relationship to Standardized Tests and Sensitivity to Cognitive Impairment in Mild Traumatic Brain Injury, Schizophrenia, and AIDS Dementia Complex. *Archives of Clinical Neuropsychology*, *24*, 165–178.

Maruff, P., Lim, Y., Darby, D., Ellis, K. a, Pietrzak, R. H., Snyder, P. J., … Masters, C. L. (2013). Clinical utility of the cogstate brief battery in identifying cognitive impairment in mild cognitive impairment and Alzheimer's disease. *Pharmachology and Toxicology*, *1*, 1-11.

Mayer, A. R., Mannell, M. V, Ling, J. M., Gasparovic, C. M., & Yeo, R. a. (2011). Functional connectivity in mild traumatic brain injury. *Human Brain Mapping*, *32*, 1825–35.

McCrea, M., Hammeke, T., Olsen, G., Leo, P., & Guskiewicz, K. (2004). Unreported Concussion in High School Football Players: Implications for Prevention. *Clinical Journal of Sport Medicine*, *14*, 13–17.

McCrory, P., Meeuwisse, W. H., Aubry, M., Cantu, R. C., Dvorák, J., Echemendia, R. J., … Turner, M. (2013). Consensus Statement on Concussion in Sport-The 4th International Conference on Concussion in Sport Held in Zurich, November 2012. *Clinical Journal of Sports Medicine*, *23*, 89-117.

McDonald, B.C., Saykin, A.J., & McAllister, T.W. (2012). Functional MRI of mild traumatic brain injury (mTBI): progress and perspectives from the first decade of studies. *Brain Imaging and Behaviour, 6*, 193-207.

Melzack, R. (1987). The short-form McGill Pain Questionnaire. *Pain*, *30*, 191–197.

Menon, V., Adleman, N. E., White, C. D., Glover, G. H., & Reiss, A. L. (2001). Error-Related Brain Activation during a Go / NoGo Response Inhibition Task. *Human Brain Mapping*, *143*, 131–143.

Menon, V., Schwab, K., Wright, D. W. & Mass A. I. (2010) Position statement: Definition of traumatic brain injury. *Archives of Physical Medicine and Rehabilitation, 91*, 1637-40.

Menon, V., & Uddin, l.Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure and Function, 214*, 655-667.

Moretti, L., Cristofori, I., Weaver, S. M., Chau, A., Portelli, J. N., & Grafman, J. (2012). Cognitive decline in older adults with a history of traumatic brain injury. *The Lancet Neurology*, *11*, 1103–1112.

Moriarty, O., Mcguire, B. E., & Finn, D. P. (2011). The effect of pain on cognitive function : A review of clinical and preclinical research. *Progress in Neurobiology*, *93*, 385–404.

Moser, R. S., Iverson, G. L., Echemendia, R. J., Lovell, M. R., Schatz, P., Webbe, F. M., … Barth, J. T. (2007). Neuropsychological evaluation in the diagnosis and management of sports-related concussion. *Archives of Clinical Neuropsychology*, *22*, 909–916.

Newcombe, V. F. J., Outtrim, J. G., Chatfield, D. a., Manktelow, A., Hutchinson, P. J., Coles, J. P., … Menon, D. K. (2011). Parcellating the neuroanatomical basis of impaired decision-making in traumatic brain injury. *Brain*, *134*, 759–768.

Noble, J. M., & Hesdorffer, D. C. (2013). Sport-Related Concussions: A Review

of Epidemiology, Challenges in Diagnosis, and Potential Risk Factors. *Neuropsychology Review*, *23*, 273–284.

Papa, L., Ramia, M. M., Edwards, D., Johnson, B. D., & Slobounov, S. M. (2015). Systematic Review of Clinical Studies Examining Biomarkers of Brain Injury in Athletes after Sports-Related Concussion. *Journal of Neurotrauma*, *32*, 661–673.

Santis, S. De, Drakesmith, M., Bells, S., Assaf, Y., & Jones, D. K. (2014). NeuroImage Why diffusion tensor MRI does well only some of the time : Variance and covariance of white matter tissue microstructure attributes in the living human brain. *NeuroImage*, *89*, 35–44.

Saulle, M., & Greenwald, B. D. (2012). Chronic Traumatic Encephalopathy: A Review. *Rehabilitation Research and Practice*, *2012*, 1–9.

Savage, J., Hooke, C., Orchard, J., & Parkinson, R. (2013). The Incidence of Concussion in a Professional Australian Rugby League Team, 1998–2012. *Journal of Sports Medicine*, *2013*, 1–7.

Sharp, D. J., Beckmann, C. F., Greenwood, R., Kinnunen, K. M., Bonnelle, V., De Boissezon, X., … Leech, R. (2011). Default mode network functional and structural connectivity after traumatic brain injury. *Brain*, *134*(8), 2233–2247.

Sharp, D. J., Scott, G., & Leech, R. (2014). Network dysfunction after traumatic brain injury. *Nature Reviews. Neurology*, *10*, 156–66.

Sharp, D. J., & Jenkins, P. O. (2015). Concussion is confusing us all. *Practical Neurology*, *15*(3), 172–186.

Shenton, M. E., Hamoda, H. M., Schneiderman, J. S., Boulx, S., Pasternak, O.,

Rathi, Y., ..., Zafonte, R. (2012). A Review of Magnetic Resonance Imaging and Diffusion Tensor Imaging Findings in Mild Traumatic Brain Injury. *Brain Imaging and Behavior*, *6*, 137–192.

Sidlauskaite, J., Wiersema, J. R., Roeyers, H., Krebs, R. M., Vassena, E., Fias, W., … Sonuga-Barke, E. (2014). Anticipatory processes in brain state switching — Evidence from a novel cued-switching task implicating default mode and salienceworks. *NeuroImage*, *98*, 359–365.

Sinopoli, K., Chen, J.-K., Wells, G., Fait, P., Ptito, A., Taha, T., & Keightley, M. (2014). Imaging “brain strain” in youth athletes with mild traumatic brain injury during dual-task performance. *Journal of Neurotrauma*, *31*, 1843–1859.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., … Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23*, S208–S219.

Stevens, M. C., Lovejoy, D., Kim, J., Oakes, H., Kureshi, I., & Witt, S. T. (2012). Multiple resting state network functional connectivity abnormalities in mild traumatic brain injury. *Brain Imaging and Behavior*, *6*, 293–318.

Strauss, E., Sherman, E.M.S., & Spreen, O. (2006). *A compendium of neuropsychological tests (3rd Ed.).* New York: Oxford University Press.

Szczepankiewicz, F., Lätt, J., Wirestam, R., Leemans, A., Sundgren, P., Westen, D. Van, … Nilsson, M. (2013). NeuroImage Variability in diffusion kurtosis imaging : Impact on study design , statistical power and interpretation. *NeuroImage*, *76*, 145–154.

Tagliaferri, F., Compagnone, C., Korsic, M., Servadei, F., & Kraus, J. (2006). A systematic review of brain injury epidemiology in Europe. *Acta Neurochirurgica*, *148*, 255–268.

Teasdale, G., & Jennett, B. (1971). Assessment of coma and impaired consciousness. A Practical Scale. *The Lancet*, *13*, 81–83.

Theadom, A., Starkey, N. J., Dowell, T., Hume, P. a., Kahan, M., McPherson, K., & Feigin, V. (2014). Sports-related brain injury in the general population: An epidemiological study. *Journal of Science and Medicine in Sport*, *17*, 591–596.

Tremblay, S., Henry, L. C., Bedetti, C., Larson-Dupuis, C., Gagnon, J.-F., Evans, a. C., … Beaumont, L. D. (2014). Diffuse white matter tract abnormalities in clinically normal ageing retired athletes with a history of sports-related concussions. *Brain*, *137*, 2997–3011

Turner, G. R., & Levine, B. (2008). Augmented neural activity during executive control processing following diffuse axonal injury. *Neurology*, *71*, 812–818.

van der Huevel, M. P., & Hulsoff Pol, H.E. (2010). Exploring the brain network: A review on resting state fMRI functional connectivity. *European Neuropsychopharmachology, 20*, 519-534.

Veeramuthu, V., Narayanan, V., Kuo, T. L., Delano-Wood, L., Chinna, K., Bondi, M. W., … Ramli, N. (2015). Diffusion tensor imaging parameters in mild traumatic brain injury and its correlation with early neuropsychological impairment: A longitudinal study. *Journal of Neurotrauma*, *32*, 1-13.

Verbruggen, F., & Logan, G. (2008a). Response inhibition in the stop-signal pardigm. *Trends in Cognitive Sciences*, *12*, 418–424.

Verbruggen, F., Logan, G. D., & Stevens, M. a. (2008b). STOP-IT: Windows executable software for the stop-signal paradigm. *Behavior Research Methods*, *40*, 479–483.

Wall, S. E., Williams, W. H., Cartwright-Hatton, S., Kelly, T. P., Murray, J., Murray, M., … Turner, M. (2006). Neuropsychological dysfunction following repeat concussions in jockeys. *Journal of Neurology, Neurosurgery, and Psychiatry*, *77*, 518–520.

Werner, C., & Engelhard, K. (2007). Pathophysiology of traumatic brain injury. *British Journal of Anaesthesia*, *99*, 4–9.

Williams, W.H., Potter, S., & Ryland, H. (2010). Mild traumatic brain injury and Postconcussion Syndrome: a neuropsychological perspective. *Journal of Neurology, Neurosurgery and Psychiatry*, *81*, 1–22.

Zhang, K., Johnson, B., Pennell, D., Ray, W., Sebastianelli, W., & Slobounov, S. (2010). Are functional deficits in concussed individuals consistent with white matter structural alterations: Combined FMRI & DTI study. *Experimental Brain Research, 204,* 57-70.

Appendix A

1. Information sheets

Multiple sports concussions in male university rugby players: a neurocognitive and neuroimaging study

PARTICIPANT INFORMATION SHEET - CONTROLS

Researcher: Dr Katya Woollett

Contact Details: kw360@exeter.ac.uk.

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

What is the purpose of this study?

The main purpose of this study is to investigate neurocognitive performance, brain structure and connectivity between brain regions following multiple sports concussions. We are focusing on executive function abilities (memory, attention, etc.), which can be affected following concussion.

Why have I been invited?

To understand the long-term effects multiple concussions may have on neurocognitive functioning, brain structure and connectivity between brain regions in those people who have a history of concussion, we need to establish the normal responses of healthy participants who have not suffered concussions.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

What is involved in the study?

What will I have to do if I take part?

We will use special brain scans (Magnetic Resonance Imaging - MRI) to study the structure and function of the brain when at rest (e.g. not performing a task). When you are in the scanner you will need to lie still. The scans take about twenty minutes. We will also ask you to do some neurocognitive tests that look at cognitive processes such as attention, inhibition, memory and processing speed. This will take approximately an hour allowing time for breaks whenever you need it. All scans will be reviewed by a neuroradiologist.

Will my taking part in this study be kept confidential?

We will collect basic data from you about your age, sex, and health. Audio recordings may also be made at some time points for research and/or teaching purposes, but only with your agreement. These data, along with the test results, will be safely stored on a University computer with all personal identifiers removed so that confidentiality is strictly maintained. All information regarding your participation will be treated as strictly confidential and will only be used for research purposes. Prof. Huw Williams will be responsible for security and access to these data. On completion of the study, the results will be published in scientific journals or presented in medical conferences, but identification of the participants will not be possible. We will inform you about these publications and how to access them.

Are there any risks or side-effects involved?

There are no known adverse effects involved in the neurocognitive tests.

What are the possible benefits of taking part?

This study will not help you but the information we get from this study will contribute to improve the treatment of people with difficulties after concussion.

What if there is a problem?

If you have a concern about any aspect of this study you should speak to the researchers who will do their best to answer your questions.

What will happen if I don't want to carry on with the study?

Your participation in the study is entirely voluntary. You are free to decline to enter or to withdraw from the study any time without having to give a reason. If you choose not to enter the study or to withdraw once entered, this will in no way affect you in any way.

Research Team: Prof. Huw Williams, Dr. Phil Yates, Dr. Katya Woollett.

This study has been reviewed and given a favourable opinion by the University of Exeter Research Ethics Committee.

Multiple sports concussions in male university rugby players: a neurocognitive and neuroimaging study

PARTICIPANT INFORMATION SHEET – RUGBY PLAYERS

Researcher: Dr Katya Woollett

Contact Details: E-mail: kw360@exeter.ac.uk.

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

What is the purpose of this study?

The main purpose of this study is to investigate neurocognitive performance, brain structure and connectivity between brain regions following multiple sports concussions. We are focusing on executive function abilities, which can be affected following concussion.

Why have I been invited?

To understand the long-term effects multiple concussions may have on neurocognitive functioning, brain structure and connectivity between brain regions, in those people who have a history of concussion, we need to establish the responses in a large number of people that have not sustained a concussion and those that have sustained one or more than one concussion.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

What is involved in the study?

<u>What will I have to do if I take part?</u>
We will use special brain scans (Magnetic Resonance Imaging - MRI) to study the structure and function of the brain when at rest (e.g. not performing a task). When you are in the scanner you will need to lie still. The scans take about twenty minutes. We will also ask you to do some neurocognitive tests that look at cognitive processes such as attention, inhibition, memory and

processing speed. This will take approximately an hour allowing time for breaks whenever you need. All scans will be reviewed by a neuroradiologist.

Will my taking part in this study be kept confidential?

We will collect basic data from you about your age, sex, and health. Audio recordings may also be made at some time points for research and/or teaching purposes, but only with your agreement. These data, along with the test results, will be safely stored on a University computer with all personal identifiers removed so that confidentiality is strictly maintained. All information regarding your participation will be treated as strictly confidential and will only be used for research purposes. Prof. Huw Williams will be responsible for security and access to these data. On completion of the study, the results will be published in scientific journals or presented in medical conferences, but identification of the participants will not be possible. We will inform you about these publications and how to access them.

Are there any risks or side-effects involved?

Because the brain scanner works by using magnetic fields, it cannot be performed on people who have implants such as cardiac pacemakers, aneurysm clips in their brain, ear implants, permanent eye lining, or have been exposed to metallic flakes or splinters travelling at high speed. Please inform the investigators if you might fall into any of these categories.

What are the possible benefits of taking part?

This study will not help you directly but the information we get from this study will contribute to improve the treatment of people that experience difficulties after concussion.

What if there is a problem?

If you have a concern about any aspect of this study you should speak to the researchers who will do their best to answer your questions.

What will happen if I don't want to carry on with the study?

Your participation in the study is entirely voluntary. You are free to decline to enter or to withdraw from the study any time without having to give a reason. If you choose not to enter the study or to withdraw once entered, this will in no way affect you in any way.

Research Team: Prof. Huw Williams, Dr. Phil Yates, Dr. Katya Woollett.

This study has been reviewed and given a favourable opinion by the University of Exeter Research Ethics Committee.

2. Consent forms

UNIVERSITY OF EXETER

DOCTORAL PROGRAMME IN CLINICAL PSYCHOLOGY

Participant informed consent form

Study investigating the neuropsychological and neuroanatomical effects of multiple sports concussions

Please initial all that apply:

I confirm that I have read and understood the information sheet provided and have had all my questions answered.	
I understand that my participation in this study is voluntary and that I can withdraw at any time without providing a reason.	
We do not share any information that you give us. All of your information is stored in a database. All of our databases are password-protected according to the Data Protection Act 1998 and are kept secure. Only anonymized, where all identifying information will be removed, data will be employed in statistical analysis and presentation of our findings.	
I agree to take part in this study	
I agree to complete the questionnaires and neuropsychological tests for this study	
I agree for pre-season baseline SCAT3 results collected by the club in the summer prior to the 2015/16 season may be shared with the researcher for analysis.	
I agree to complete the structural MRI scan	
I agree for you to contact my GP	
Please provide you GP details below:	

Participant name: _____

Signature: _____ Date: _____

Participant Safety Checklist

Name: **Date of Birth:**
Weight: **Name of Study/Volunteer Number:**

Please check the following list carefully, answering all appropriate questions. Please do not hesitate to ask staff, if you have any queries regarding these questions.

1. Do you have a pacemaker, artificial heart valve or coronary stent? Yes/No

2. Have you ever had major surgery? Yes/No
   If yes, please give brief details.

3. Do you have any aneurysm clips (clips put around blood vessels during surgery)? Yes/No

4. Do you have any implants in your body

   Yes ☐ No ☐ Joint replacements, pins or wires
   Yes ☐ No ☐ Implanted cardioverter defibrillator (ICD)
   Yes ☐ No ☐ Electronic implant or device
   Yes ☐ No ☐ Magnetically-activated implant or device
   Yes ☐ No ☐ Neurostimulation system
   Yes ☐ No ☐ Spinal cord stimulator
   Yes ☐ No ☐ Insulin or infusion pump
   Yes ☐ No ☐ Implanted drug infusion pump
   Yes ☐ No ☐ Internal electrodes or wires
   Yes ☐ No ☐ Bone growth/bone fusion stimulator
   Yes ☐ No ☐ Any type of prosthesis
   Yes ☐ No ☐ Heart valve prosthesis
   Yes ☐ No ☐ Eyelid spring or wire
   Yes ☐ No ☐ Metallic stent, filter or coil
   Yes ☐ No ☐ Shunt (spinal or intraventricular)
   Yes ☐ No ☐ Vascular access port and/or catheter
   Yes ☐ No ☐ Wire mesh implant
   Yes ☐ No ☐ Bone/joint pin, screw, nail, wire, plate etc.
   Yes ☐ No ☐ Other Implant_____

5. Do you have an artificial limb, calliper or surgical corset? Yes/No

6. Do you have any shrapnel or metal fragments, for example from working in a machine tool shop? Yes/No

7. Do you have a cochlear implant? Yes/No

8. Do you wear dentures, plate or a hearing aid? Yes/No

9. Are you wearing a skin patch (e.g. anti-smoking medication), have any tattoos, body piercing, permanent makeup or coloured contact lenses? Yes/No

10. Are you aware of any metal objects present within or about your body, other than those described above? Yes/No

11. Are you susceptible to claustrophobia? Yes/No

12. Do you suffer from blackout, diabetes, epilepsy or fits? Yes/No

For women:

13. Are you pregnant or experiencing a late menstrual period? Yes/No

14. Do you have an intra-uterine contraceptive device fitted? Yes/No

15. Are you taking any type of fertility medication or having fertility treatment? Yes/No

Important Instructions

Remove all metallic objects before entering the scanner room including hearing aids, mobile phones, keys, glasses, hair pins, jewellery, watches, safety pins, paperclips, credit cards, magnetic strip cards, coins, pens, pocket knives, nail clippers, steel-toed boots/shoes and all tools. Loose metallic objects are especially prohibited within the MR environment.
I have understood the above questions and have marked the answers correctly.

Signature (Participant/Parent/Guardian) Date

MR Centre Staff Signature

3. Participants Screening/Demographics Questionnaire

We are conducting a study of the experience and symptoms people may have after a head injury or concussion. Please answer the following questions in the space provided or marking/ticking your answers as indicated by the question.

Thank you for your cooperation

1. Participant number.

2. Age

3. Handedness?

Left Right Mixed

4. Highest level of Education?

5. Position of Play?

Forward Back
Specific

6. How many hours did you sleep last night?

7. Have you had any alcohol or drugs in the past 72 hours?

Yes No
Notes:

8. Have you eaten today?

Yes No Notes:

9. Do you need glasses?

Yes No
Notes:

10. Are you colour blind?

Yes No
Notes:

11. Do you have a hearing difficulty?

Yes No
Notes:

12. Do you have any problems with reading or writing?

Yes No
Notes:

13. Is English your first language?

Yes No
Notes:

If 'No', do you speak English fluently?

Yes ☐ No ☐

14. Have you used support services for any mental health issues?

Yes ☐ No ☐

15. Have you had any neurological illness or condition? E.g. stroke, encephalitis

Yes ☐ No ☐

If 'Yes' please specify

16. Have you ever had an injury to the head that caused you to be knocked out and/or dazed and confused for a period of time? E.g. from a sports injury, fall, blow to the head, road traffic.

Yes ☐ No ☐

If you answered 'Yes' to 16 continue completing the questions as listed, if 'No' skip to question 20.

17. How many times have you been knocked out and/or dazed and confused/ E.g. from a sports injury, fall, blow to the head, road traffic accident?

☐ Once ☐ Twice ☐ Three times ☐ Four times ☐ More than four

18. On the following pages, please tick the boxes that describe the times you have been injured, knocked out and/or dazed and confused, when, and if under influence of drug/alcohol.

Type of injury &date (m/year)	Dazed or confused	Unconscious for up to 1 minute	Unconscious for 1-5 minutes	Unconscious for 5-10 minutes	Unconscious for 10-30 minutes	Unconscious for over 30 minutes
1. _____ (_____/_____)						
Notes if Rugby: Taken off Pitch Yes No Return to play Yes No If 'No" when: _____ Good memory of match? Yes No If 'No" describe: _____ Any other comments: _____						
2. _____ (_____/_____)						

Notes if Rugby:

Taken off Pitch Yes No

Return to play Yes No If 'No" when: _____

Good memory of match? Yes No If 'No" describe: _____

Any other comments: _____

_____

3. _____ (_____/_____)						

Notes if Rugby:

Taken off Pitch Yes No

Return to play Yes No If 'No" when: _____

Good memory of match? Yes No If 'No" describe: _____

Any other comments: _____

Type of injury &date (m/year)	Dazed or confused	Unconscious for up to 1 minute	Unconscious for 1-5 minutes	Unconscious for 5-10 minutes	Unconscious for 10-30 minutes	Unconscious for over 30 minutes
4. _____ (_____/_____)						

Notes if Rugby:

Taken off Pitch Yes No

Return to play Yes No If 'No" when:
_____

Good memory of match? Yes No If 'No" describe:
_____

Any other comments:
_____

5. _____ (_____/_____)						

Notes if Rugby:

Taken off Pitch Yes No

Return to play Yes No If ‘No” when:
_____

Good memory of match? Yes No If ‘No” describe:
_____

Any other comments:
_____

6. _____ (_____/_____)						

Notes if Rugby:

Taken off Pitch Yes No

Return to play Yes No If ‘No” when:
_____

Good memory of match? Yes No If ‘No” describe:
_____

Any other comments:
_____

If “Other activity or “Unconscious for over 60 minutes” please specify the type of activity and how long for?”

19. Thank you for taking part in the study. Any information you have provided is confidential and will be used anonymously. If you have ever used illegal drugs, please indicate how frequently you used them during your most intense period of use

Never ☐ Once per year ☐ Once per month ☐ Most days ☐ Everyday ☐

20. If you drink alcohol please indicate how frequently on average

Never ☐ Once per year ☐ Once per month ☐ Most days ☐ Everyday ☐

Thank you for taking part in the study. Any information you have provided is confidential and will be used anonymously.

SCAT 3

SCAT3™

Sport Concussion Assessment Tool – 3rd Edition

For use by medical professionals only

Name | Date/Time of Injury: Date of Assessment: | Examiner:

What is the SCAT3?[1]

The SCAT3 is a standardized tool for evaluating injured athletes for concussion and can be used in athletes aged from 13 years and older. It supersedes the original SCAT and the SCAT2 published in 2005 and 2009, respectively[2]. For younger persons, ages 12 and under, please use the Child SCAT3. The SCAT3 is designed for use by medical professionals. If you are not qualified, please use the Sport Concussion Recognition Tool[1]. Preseason baseline testing with the SCAT3 can be helpful for interpreting post-injury test scores.

Specific instructions for use of the SCAT3 are provided on page 3. If you are not familiar with the SCAT3, please read through these instructions carefully. This tool may be freely copied in its current form for distribution to individuals, teams, groups and organizations. Any revision or any reproduction in a digital form requires approval by the Concussion in Sport Group.
NOTE: The diagnosis of a concussion is a clinical judgment, ideally made by a medical professional. The SCAT3 should not be used solely to make, or exclude, the diagnosis of concussion in the absence of clinical judgement. An athlete may have a concussion even if their SCAT3 is "normal".

What is a concussion?

A concussion is a disturbance in brain function caused by a direct or indirect force to the head. It results in a variety of non-specific signs and/or symptoms (some examples listed below) and most often does not involve loss of consciousness. Concussion should be suspected in the presence of **any one or more** of the following:

- Symptoms (e.g., headache), or
- Physical signs (e.g., unsteadiness), or
- Impaired brain function (e.g. confusion) or
- Abnormal behaviour (e.g., change in personality).

SIDELINE ASSESSMENT

Indications for Emergency Management

NOTE: A hit to the head can sometimes be associated with a more serious brain injury. Any of the following warrants consideration of activating emergency procedures and urgent transportation to the nearest hospital:

- Glasgow Coma score less than 15
- Deteriorating mental status
- Potential spinal injury
- Progressive, worsening symptoms or new neurologic signs

Potential signs of concussion?

If any of the following signs are observed after a direct or indirect blow to the head, the athlete should stop participation, be evaluated by a medical professional and **should not be permitted to return to sport the same day** if a concussion is suspected.

Any loss of consciousness?	Y N
"If so, how long?"	
Balance or motor incoordination (stumbles, slow/laboured movements, etc.)?	Y N
Disorientation or confusion (inability to respond appropriately to questions)?	Y N
Loss of memory:	Y N
"If so, how long?"	
"Before or after the injury?"	
Blank or vacant look:	Y N
Visible facial injury in combination with any of the above:	Y N

1 Glasgow coma scale (GCS)

Best eye response (E)	
No eye opening	1
Eye opening in response to pain	2
Eye opening to speech	3
Eyes opening spontaneously	4
Best verbal response (V)	
No verbal response	1
Incomprehensible sounds	2
Inappropriate words	3
Confused	4
Oriented	5
Best motor response (M)	
No motor response	1
Extension to pain	2
Abnormal flexion to pain	3
Flexion/Withdrawal to pain	4
Localizes to pain	5
Obeys commands	6
Glasgow Coma score (E + V + M)	of 15

GCS should be recorded for all athletes in case of subsequent deterioration.

2 Maddocks Score[3]

"I am going to ask you a few questions, please listen carefully and give your best effort."

Modified Maddocks questions (1 point for each correct answer)

What venue are we at today?	0	1
Which half is it now?	0	1
Who scored last in this match?	0	1
What team did you play last week/game?	0	1
Did your team win the last game?	0	1
Maddocks score		of 5

Maddocks score is validated for sideline diagnosis of concussion only and is not used for serial testing.

Notes: Mechanism of Injury ("tell me what happened"?):

Any athlete with a suspected concussion should be REMOVED FROM PLAY, medically assessed, monitored for deterioration (i.e., should not be left alone) and should not drive a motor vehicle until cleared to do so by a medical professional. No athlete diagnosed with concussion should be returned to sports participation on the day of Injury.

BACKGROUND

Name: _____ Date: _____

Examiner: _____

Sport/team/school: _____ Date/time of injury: _____

Age: _____ Gender: ☐ M ☐ F

Years of education completed: _____

Dominant hand: ☐ right ☐ left ☐ neither

How many concussions do you think you have had in the past? _____

When was the most recent concussion? _____

How long was your recovery from the most recent concussion? _____

Have you ever been hospitalized or had medical imaging done for a head injury? ☐ Y ☐ N

Have you ever been diagnosed with headaches or migraines? ☐ Y ☐ N

Do you have a learning disability, dyslexia, ADD/ADHD? ☐ Y ☐ N

Have you ever been diagnosed with depression, anxiety or other psychiatric disorder? ☐ Y ☐ N

Has anyone in your family ever been diagnosed with any of these problems? ☐ Y ☐ N

Are you on any medications? If yes, please list: ☐ Y ☐ N

_____

SCAT3 to be done in resting state. Best done 10 or more minutes post excercise.

SYMPTOM EVALUATION

3 How do you feel?

"You should score yourself on the following symptoms, based on how you feel now".

	none	mild		moderate		severe	
Headache	0	1	2	3	4	5	6
"Pressure in head"	0	1	2	3	4	5	6
Neck Pain	0	1	2	3	4	5	6
Nausea or vomiting	0	1	2	3	4	5	6
Dizziness	0	1	2	3	4	5	6
Blurred vision	0	1	2	3	4	5	6
Balance problems	0	1	2	3	4	5	6
Sensitivity to light	0	1	2	3	4	5	6
Sensitivity to noise	0	1	2	3	4	5	6
Feeling slowed down	0	1	2	3	4	5	6
Feeling like "in a fog"	0	1	2	3	4	5	6
"Don't feel right"	0	1	2	3	4	5	6
Difficulty concentrating	0	1	2	3	4	5	6
Difficulty remembering	0	1	2	3	4	5	6
Fatigue or low energy	0	1	2	3	4	5	6
Confusion	0	1	2	3	4	5	6
Drowsiness	0	1	2	3	4	5	6
Trouble falling asleep	0	1	2	3	4	5	6
More emotional	0	1	2	3	4	5	6
Irritability	0	1	2	3	4	5	6
Sadness	0	1	2	3	4	5	6
Nervous or Anxious	0	1	2	3	4	5	6

Total number of symptoms (Maximum possible 22) _____

Symptom severity score (Maximum possible 132) _____

Do the symptoms get worse with physical activity? ☐ Y ☐ N

Do the symptoms get worse with mental activity? ☐ Y ☐ N

☐ self rated ☐ self rated and clinician monitored

☐ clinician interview ☐ self rated with parent input

Overall rating: If you know the athlete well prior to the injury, how different is the athlete acting compared to his/her usual self?

Please circle one response:

no different | very different | unsure | N/A

Scoring on the SCAT3 should not be used as a stand-alone method to diagnose concussion, measure recovery or make decisions about an athlete's readiness to return to competition after concussion. Since signs and symptoms may evolve over time, it is important to consider repeat evaluation in the acute assessment of concussion.

COGNITIVE & PHYSICAL EVALUATION

4 Cognitive assessment

Standardized Assessment of Concussion (SAC)[4]

Orientation (1 point for each correct answer)

What month is it?	0	1
What is the date today?	0	1
What is the day of the week?	0	1
What year is it?	0	1
What time is it right now? (within 1 hour)	0	1
Orientation score		of 5

Immediate memory

List	Trial 1		Trial 2		Trial 3		Alternative word list		
elbow	0	1	0	1	0	1	candle	baby	finger
apple	0	1	0	1	0	1	paper	monkey	penny
carpet	0	1	0	1	0	1	sugar	perfume	blanket
saddle	0	1	0	1	0	1	sandwich	sunset	lemon
bubble	0	1	0	1	0	1	wagon	iron	insect
Total									

Immediate memory score total of 15

Concentration: Digits Backward

List	Trial 1		Alternative digit list		
4-9-3	0	1	6-2-9	5-2-6	4-1-5
3-8-1-4	0	1	3-2-7-9	1-7-9-5	4-9-6-8
6-2-9-7-1	0	1	1-5-2-8-6	3-8-5-2-7	6-1-8-4-3
7-1-8-4-6-2	0	1	5-3-9-1-4-8	8-3-1-9-6-4	7-2-4-8-5-6
Total of 4					

Concentration: Month in Reverse Order (1 pt. for entire sequence correct)

Dec-Nov-Oct-Sept-Aug-Jul-Jun-May-Apr-Mar-Feb-Jan	0	1
Concentration score		of 5

5 Neck Examination:

Range of motion Tenderness Upper and lower limb sensation & strength

Findings: _____

6 Balance examination

Do one or both of the following tests.

Footwear (shoes, barefoot, braces, tape, etc.) _____

Modified Balance Error Scoring System (BESS) testing[5]

Which foot was tested (i.e. which is the **non-dominant** foot) ☐ Left ☐ Right

Testing surface (hard floor, field, etc.) _____

Condition

Double leg stance:	Errors
Single leg stance (non-dominant foot):	Errors
Tandem stance (non-dominant foot at back):	Errors

And / Or

Tandem gait[6,7]

Time (best of 4 trials): _____ seconds

7 Coordination examination

Upper limb coordination

Which arm was tested: ☐ Left ☐ Right

Coordination score of 1

8 SAC Delayed Recall[4]

Delayed recall score of 5

INSTRUCTIONS

Words in *Italics* throughout the SCAT3 are the instructions given to the athlete by the tester.

Symptom Scale

"You should score yourself on the following symptoms, based on how you feel now".

To be completed by the athlete. In situations where the symptom scale is being completed after exercise, it should still be done in a resting state, at least 10 minutes post exercise.
For total number of symptoms, maximum possible is 22.
For Symptom severity score, add all scores in table, maximum possible is 22 x 6 = 132.

SAC[4]

Immediate Memory

"I am going to test your memory. I will read you a list of words and when I am done, repeat back as many words as you can remember, in any order."

Trials 2 & 3:

"I am going to repeat the same list again. Repeat back as many words as you can remember in any order, even if you said the word before."

Complete all 3 trials regardless of score on trial 1 & 2. Read the words at a rate of one per second. **Score 1 pt. for each correct response.** Total score equals sum across all 3 trials. Do not inform the athlete that delayed recall will be tested.

Concentration

Digits backward

"I am going to read you a string of numbers and when I am done, you repeat them back to me backwards, in reverse order of how I read them to you. For example, if I say 7-1-9, you would say 9-1-7."

If correct, go to next string length. If incorrect, read trial 2. **One point possible for each string length.** Stop after incorrect on both trials. The digits should be read at the rate of one per second.

Months in reverse order

"Now tell me the months of the year in reverse order. Start with the last month and go backward. So you'll say December, November … Go ahead"

1 pt. for entire sequence correct

Delayed Recall

The delayed recall should be performed after completion of the Balance and Coordination Examination.

"Do you remember that list of words I read a few times earlier? Tell me as many words from the list as you can remember in any order."

Score 1 pt. for each correct response

Balance Examination

Modified Balance Error Scoring System (BESS) testing[5]

This balance testing is based on a modified version of the Balance Error Scoring System (BESS)[5]. A stopwatch or watch with a second hand is required for this testing.

"I am now going to test your balance. Please take your shoes off, roll up your pant legs above ankle (if applicable), and remove any ankle taping (if applicable). This test will consist of three twenty second tests with different stances."

(a) Double leg stance:

"The first stance is standing with your feet together with your hands on your hips and with your eyes closed. You should try to maintain stability in that position for 20 seconds. I will be counting the number of times you move out of this position. I will start timing when you are set and have closed your eyes."

(b) Single leg stance:

"If you were to kick a ball, which foot would you use? [This will be the dominant foot] Now stand on your non-dominant foot. The dominant leg should be held in approximately 30 degrees of hip flexion and 45 degrees of knee flexion. Again, you should try to maintain stability for 20 seconds with your hands on your hips and your eyes closed. I will be counting the number of times you move out of this position. If you stumble out of this position, open your eyes and return to the start position and continue balancing. I will start timing when you are set and have closed your eyes."

(c) Tandem stance:

"Now stand heel-to-toe with your non-dominant foot in back. Your weight should be evenly distributed across both feet. Again, you should try to maintain stability for 20 seconds with your hands on your hips and your eyes closed. I will be counting the number of times you move out of this position. If you stumble out of this position, open your eyes and return to the start position and continue balancing. I will start timing when you are set and have closed your eyes."

Balance testing – types of errors

1. Hands lifted off iliac crest
2. Opening eyes
3. Step, stumble, or fall
4. Moving hip into > 30 degrees abduction
5. Lifting forefoot or heel
6. Remaining out of test position > 5 sec

Each of the 20-second trials is scored by counting the errors, or deviations from the proper stance, accumulated by the athlete. The examiner will begin counting errors only after the individual has assumed the proper start position. **The modified BESS is calculated by adding one error point for each error during the three 20-second tests. The maximum total number of errors for any single condition is 10.** If a athlete commits multiple errors simultaneously, only one error is recorded but the athlete should quickly return to the testing position, and counting should resume once subject is set. Subjects that are unable to maintain the testing procedure for a minimum of **five seconds** at the start are assigned the highest possible score, ten, for that testing condition.

OPTION: For further assessment, the same 3 stances can be performed on a surface of medium density foam (e.g., approximately 50 cm x 40 cm x 6 cm).

Tandem Gait[6,7]

Participants are instructed to stand with their feet together behind a starting line (the test is best done with footwear removed). Then, they walk in a forward direction as quickly and as accurately as possible along a 38mm wide (sports tape), 3 meter line with an alternate foot heel-to-toe gait ensuring that they approximate their heel and toe on each step. Once they cross the end of the 3m line, they turn 180 degrees and return to the starting point using the same gait. A total of 4 trials are done and the best time is retained. Athletes should complete the test in 14 seconds. Athletes fail the test if they step off the line, have a separation between their heel and toe, or if they touch or grab the examiner or an object. In this case, the time is not recorded and the trial repeated, if appropriate.

Coordination Examination

Upper limb coordination

Finger-to-nose (FTN) task:

"I am going to test your coordination now. Please sit comfortably on the chair with your eyes open and your arm (either right or left) outstretched (shoulder flexed to 90 degrees and elbow and fingers extended), pointing in front of you. When I give a start signal, I would like you to perform five successive finger to nose repetitions using your index finger to touch the tip of the nose, and then return to the starting position, as quickly and as accurately as possible."

Scoring: 5 correct repetitions in < 4 seconds = 1
Note for testers: Athletes fail the test if they do not touch their nose, do not fully extend their elbow or do not perform five repetitions. **Failure should be scored as 0.**

References & Footnotes

1. This tool has been developed by a group of international experts at the 4th International Consensus meeting on Concussion in Sport held in Zurich, Switzerland in November 2012. The full details of the conference outcomes and the authors of the tool are published in The BJSM Injury Prevention and Health Protection, 2013, Volume 47, Issue 5. The outcome paper will also be simultaneously co-published in other leading biomedical journals with the copyright held by the Concussion in Sport Group, to allow unrestricted distribution, providing no alterations are made.

2. McCrory P et al., Consensus Statement on Concussion in Sport – the 3rd International Conference on Concussion in Sport held in Zurich, November 2008. British Journal of Sports Medicine 2009; 43: i76-89.

3. Maddocks, DL; Dicker, GD; Saling, MM. The assessment of orientation following concussion in athletes. Clinical Journal of Sport Medicine. 1995; 5(1): 32–3.

4. McCrea M. Standardized mental status testing of acute concussion. Clinical Journal of Sport Medicine. 2001; 11: 176–181.

5. Guskiewicz KM. Assessment of postural stability following sport-related concussion. Current Sports Medicine Reports. 2003; 2: 24–30.

6. Schneiders, A.G., Sullivan, S.J., Gray, A., Hammond-Tooke, G. & McCrory, P. Normative values for 16-37 year old subjects for three clinical measures of motor performance used in the assessment of sports concussions. Journal of Science and Medicine in Sport. 2010; 13(2): 196–201.

7. Schneiders, A.G., Sullivan, S.J., Kvarnstrom. J.K., Olsson, M., Yden. T. & Marshall, S.W. The effect of footwear and sports-surface on dynamic neurological screening in sport-related concussion. Journal of Science and Medicine in Sport. 2010; 13(4): 382–386

ATHLETE INFORMATION

Any athlete suspected of having a concussion should be removed from play, and then seek medical evaluation.

Signs to watch for

Problems could arise over the first 24–48 hours. The athlete should not be left alone and must go to a hospital at once if they:

- Have a headache that gets worse
- Are very drowsy or can't be awakened
- Can't recognize people or places
- Have repeated vomiting
- Behave unusually or seem confused; are very irritable
- Have seizures (arms and legs jerk uncontrollably)
- Have weak or numb arms or legs
- Are unsteady on their feet; have slurred speech

Remember, it is better to be safe.

Consult your doctor after a suspected concussion.

Return to play

Athletes should not be returned to play the same day of injury.
When returning athletes to play, they should be **medically cleared and then follow a stepwise supervised program,** with stages of progression.

For example:

Rehabilitation stage	Functional exercise at each stage of rehabilitation	Objective of each stage
No activity	Physical and cognitive rest	Recovery
Light aerobic exercise	Walking, swimming or stationary cycling keeping intensity, 70% maximum predicted heart rate. No resistance training	Increase heart rate
Sport-specific exercise	Skating drills in ice hockey, running drills in soccer. No head impact activities	Add movement
Non-contact training drills	Progression to more complex training drills, eg passing drills in football and ice hockey. May start progressive resistance training	Exercise, coordination, and cognitive load
Full contact practice	Following medical clearance participate in normal training activities	Restore confidence and assess functional skills by coaching staff
Return to play	Normal game play	

There should be at least 24 hours (or longer) for each stage and if symptoms recur the athlete should rest until they resolve once again and then resume the program at the previous asymptomatic stage. Resistance training should only be added in the later stages.

If the athlete is symptomatic for more than 10 days, then consultation by a medical practitioner who is expert in the management of concussion, is recommended.

Medical clearance should be given before return to play.

Scoring Summary:

Test Domain	Score		
	Date:	Date:	Date:
Number of Symptoms of 22			
Symptom Severity Score of 132			
Orientation of 5			
Immediate Memory of 15			
Concentration of 5			
Delayed Recall of 5			
SAC Total			
BESS (total errors)			
Tandem Gait (seconds)			
Coordination of 1			

Notes:

CONCUSSION INJURY ADVICE

(To be given to the **person monitoring** the concussed athlete)

This patient has received an injury to the head. A careful medical examination has been carried out and no sign of any serious complications has been found. Recovery time is variable across individuals and the patient will need monitoring for a further period by a responsible adult. Your treating physician will provide guidance as to this timeframe.

If you notice any change in behaviour, vomiting, dizziness, worsening headache, double vision or excessive drowsiness, please contact your doctor or the nearest hospital emergency department immediately.

Other important points:

- Rest (physically and mentally), including training or playing sports until symptoms resolve and you are medically cleared
- No alcohol
- No prescription or non-prescription drugs without medical supervision. Specifically:
  - No sleeping tablets
  - Do not use aspirin, anti-inflammatory medication or sedating pain killers
- Do not drive until medically cleared
- Do not train or play sport until medically cleared

Clinic phone number

Patient's name

Date/time of injury

Date/time of medical review

Treating physician

Contact details or stamp

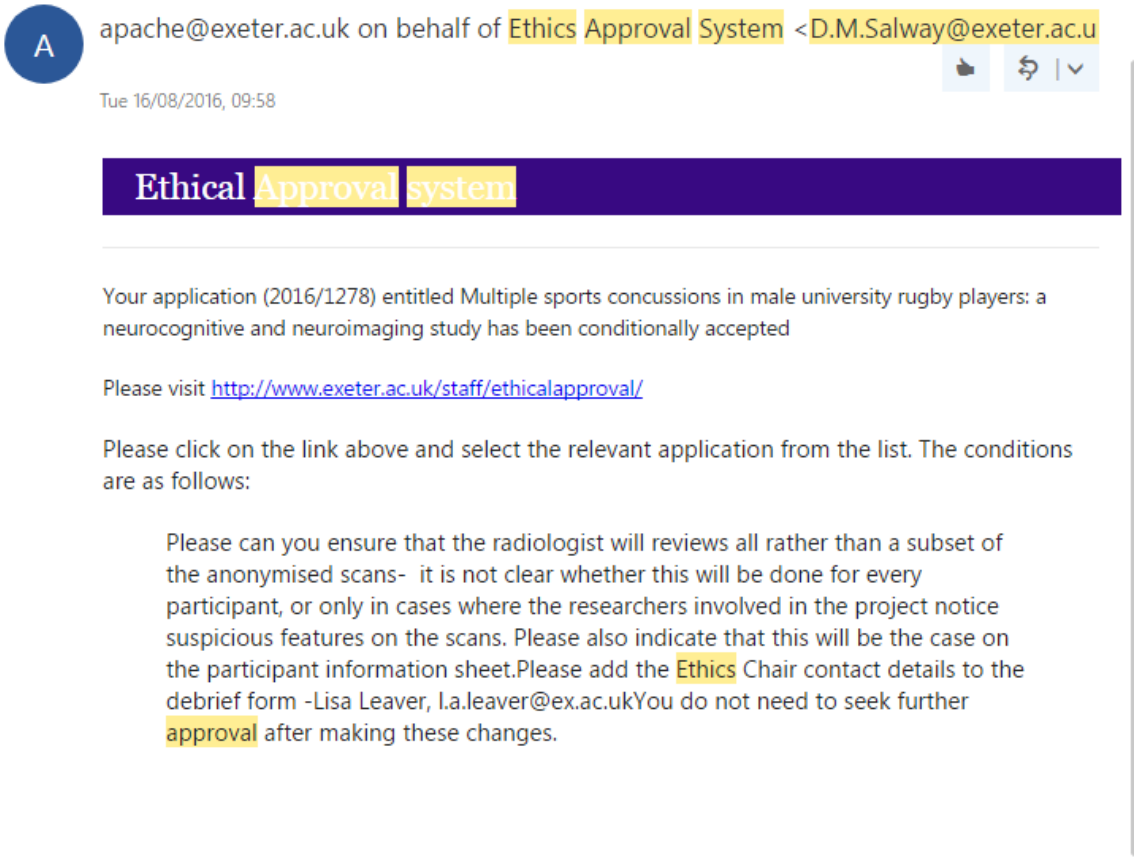
Study appointment.

Participants completed the background questionnaire, the McGill pain, MOS sleep, SCAT3 questionnaires and MRI safety checklist at the beginning of the session. Once these were checked by the researcher to ensure there were no contraindications to proceed with the study, the MRI scan and cognitive tests were explained in detail. All participants completed the cognitive tests and had the structural and DTI brain scans. For the cognitive tasks testing took place in a quiet well lit room. Participants were allowed to take breaks when they needed and the researcher ensured to check whether breaks were needed at least once during the session. During the MRI scans participants were checked for any metal objects, given ear protection, and foam padding to ensure they were comfortable. They were able to communicate with the MRI control room via an intercom system and were given a panic button should they want to stop the scan.

Participants were asked to stay at still as possible and were invited to relax or close their eyes for the scan (10 minutes). At the end of the study session participants were debriefed and offered the opportunity to ask any questions. They received £10 to cover their travel costs and entered into a prize draw for vouchers of an internet shopping site. Participants were sent their individual results and a picture of their brain scan approximately two weeks later.

Appendix B – Ethics Approval

1. Ethical approval



A

apache@exeter.ac.uk on behalf of Ethics Approval System <D.M.Salway@exeter.ac.u

Tue 16/08/2016, 09:58

Ethical Approval system

Your application (2016/1278) entitled Multiple sports concussions in male university rugby players: a neurocognitive and neuroimaging study has been conditionally accepted

Please visit http://www.exeter.ac.uk/staff/ethicalapproval/

Please click on the link above and select the relevant application from the list. The conditions are as follows:

Please can you ensure that the radiologist will reviews all rather than a subset of the anonymised scans- it is not clear whether this will be done for every participant, or only in cases where the researchers involved in the project notice suspicious features on the scans. Please also indicate that this will be the case on the participant information sheet.Please add the Ethics Chair contact details to the debrief form -Lisa Leaver, l.a.leaver@ex.ac.ukYou do not need to seek further approval after making these changes.

2. Debriefing form

Title: Multiple sports concussions in male university rugby players: a neurocognitive and neuroimaging study

Principal Researcher: Katya Woollett

Supervisors: Professor Huw Williams, Dr Phil Yates

Thank you for participating in this study – your time and effort is very much appreciated!

You have taken part in a study which investigates the long-term effects multiple concussions may have on neurocognitive functioning and brain structure.

"Neurocognitive functioning" involves domains such as memory, executive function (e.g. reasoning, controlling our attention, problem solving), and how quickly our brains process information (processing speed).

'Brain structure, connectivity between brain regions and MRI scans' The brain consists of grey and white matter. The grey matter is made up of the neurons (brain cells) bodies and the white matter is made up of neuron axons that connect different grey matter regions of the brain to each other. If external physical force is applied to the head, rapid acceleration/deceleration, or rotational forces in which the brain may collide with the skull, this can result in possible bruising of the brain, stretching and compression of nerve fibres (axons), and in some cases bleeding. MRI scans are able to detect if there are any changes to brain structure and connectivity between brain regions after concussions.

Purpose of the study:

To be able to process information and carry out tasks that require our attention and thinking abilities, our brain needs to pass information between different areas of the brain. This is done through fibres (white matter tracts) that can be stretched or compressed in the event of a concussion. In the majority of cases there are no long term sequelae to concussions, but there is emerging evidence to suggest that repeated concussions may have cumulative effects on the integrity of the white matter tracts of the brain that, in turn, may affect connectivity between brain region and neurocognitive functioning.

The current study aims to understand the long-term effects multiple concussions may have on neurocognitive functioning in those people who have a history of

concussion. To do so, we need to establish the responses in a large number of players that have sustained none, one, and more than one concussion. Investigating the cumulative effects of concussions on cognitive performance in participants of contact sport, such as rugby, that have high rates of concussions is important to enable better management of injury.

The current study will help better understand how concussions may lead to changes in neurocognitive performance by combining novel neuroimaging methods (brain scans) with neurocognitive testing. It will also offer novel information by comparing athletes with no history of concussion to athletes with varying frequency of concussions, which will contribute to how concussion is managed in sports. This is important because at present there isn't a clear and full understanding of the impact of concussions on neurocognitive functioning nor an agreed standard of how to manage concussions in sports.

If you feel worried or anxious about any aspects of this study:

All the procedures used in the study have been shown to be safe and are widely used in research studies to evaluate neurocognitive performance and brain structure (MRI scans). It is highly unlikely that any participants will have any brain abnormalities. However, in the unlikely event that this does happen, the scans will be reviewed by a neuroradiologist who will send the relevant information to your GP. If at any time you feel worried or anxious, please inform the principal researcher and/or contact the University of Exeter wellbeing service, your G.P., or one of the following helplines:

Samaritans: 116 123

MIND: 0300 123 3393

SANE: 0300 304 7000

University of Exeter Wellbeing Service: 01392 724381

Contact Details:

If you have any further questions, or you would like your data to be removed from the study, please do not hesitate to contact the Principal Researcher or ethics chair using the details below.

Principal Researcher:

Katya Woollett
Doctorate in Clinical Psychology programme
Washington Singer Laboratories
Perry Road

Exeter
EX4 4QG

Email: kw360@exeter.ac.uk

Ethics Chair:

Dr Lisa Leaver
Ethics Chair
Washington Singer Laboratories
Perry Road
Exeter
EX4 4QG

Email: l.a.leaver@exeter.ac.uk

Appendix C

Apriori power calculations

Hypothesis 1

SRC frequency and neurocognitive variables
Power Calculation – G*Power output table
Correlation: Bivariate normal model

Tails	2
Correlation pH1	0.3
α err prob	0.005 (Bonferroni corrected for 10 correlations)
Power(1-β err prob)	0.8
Correlation p H0	0
Lower critical r	-0.23
Upper critical r	0.23
Total sample size	142
Actual power	0.80

Hypothesis 2

SRC frequency and DTI metrics
Power Calculation – G*Power output table
Correlation: Bivariate normal model

Tails	2
Correlation pH1	0.3
α err prob	0.008 (Bonferroni corrected for 6 correlations)
Power(1-β err prob)	0.8
Correlation p H0	0
Lower critical r	-0.23
Upper critical r	0.23
Total sample size	130
Actual power	0.80

Hypothesis 3

STOP-IT measures and DTI metrics
Power Calculation – G*Power output table
Correlation: Bivariate normal model

Tails	2
Correlation pH1	0.3
α err prob	0.004 (Bonferroni corrected for 12 correlations)
Power(1-β err prob)	0.8
Correlation p H0	0
Lower critical r	-0.23
Upper critical r	0.23
Total sample size	148
Actual power	0.80

Table 1 – *Effect sizes of DTI measures and neuropsychological performance in studies of mTBI and SRCs*

Study reference	**Subjects**		**DTI measure**	**White matter tract/neuro cognitive test**	**Sig. level (p value)**	**Effect size**
	Patients mTBI Acute stage	Patients mTBI chronic stage				
Veeramuthu et al., 2015	30	30	FA	Superior longitudinal fasciculus	T-test 0.024	**Cohen's d** 0.45
			FA	Genu corpus callosum	T-test 0.011	**Cohen's d** 0.51
			FA	Anterior limb of internal capsule	T-test 0.016	**Cohen's d** 0.48
			FA	Superior longitudinal fasciculus/language tasks	Spearman's Rho 0.05	r: 0.40
			FA	Superior longitudinal fasciculus/attention tasks	Spearman's Rho 0.05	r:0.41
			FA	Splenium of corpus callosum/visuo-spatial tasks	Spearman's Rho 0.05	r:0.40
	Athletes SRC	Athletes no SRC				
Zhang et al., 2010	15	15	ADC (MD)	Left dorso-lateral pre-frontal cortex	T-test 0.002	Cohen's d 1.05
			ADC (MD)	Right dorso-lateral pre-frontal cortex	T-test 0.001	Cohen's d 1.15

Table 2 – *Effect sizes reported for neurocognitive effects in studies of multiple concussion.*

Study reference	**Subjects**		**Neurocognitive measure**	**Statistic test/ Significance**	**Effect size Cohen's d**
	Athletes	Controls			
Iverson et al., 2012	26	26	Verbal memory	MANOVA 0.028	0.63
Gardener et al., 2010	34	39	IMPACT: Impulse control score Visual motor speed	MANOVA 0.024 0.013	0.88 0.55
Iverson et al., 2004	19	19	IMPACT: memory composite score	ANOVA 0.015	0.83

Appendix D - Post-hoc sensitivity analysis

Hypothesis 1 - SRC frequency and neurocognitive variables

Sensitivity analysis – G*Power output table

Correlation: Bivariate normal model

Tails	2
α err prob	0.005 (Bonferroni corrected for 10 correlations)
Power (1-β err prob)	0.8
Total sample size	40
Correlation p H0	0
Lower critical r	-0.43
Upper critical r	0.43
Correlation pH1	0.53

Hypothesis 2 - SRC frequency and DTI metrics

Sensitivity analysis – G*Power output table

Correlation: Bivariate normal model

Tails	2
Correlation pH1	0.3
α err prob	0.008 (Bonferroni corrected for 6 correlations)
Power (1-β err prob)	0.8
Total sample size	40
Correlation p H0	0
Lower critical r	-0.41
Upper critical r	0.41
Correlation pH1	0.51

Hypothesis 3

STOP-IT reaction time and DTI metrics

Sensitivity analysis – G*Power output table

Correlation: Bivariate normal model

Tails	2
Correlation pH1	0.3
α err prob	0.004 (Bonferroni corrected for 12 correlations)
Power (1-β err prob)	0.8
Total sample size	40
Correlation p H0	0
Lower critical r	-0.44
Upper critical r	0.44
Correlation pH1	0.54

Appendix E: Dissemination statement

The results of this study will be disseminated to interested parties through feedback, journal publication and presentation.

Dissemination to participants.

As stated on the participant information sheet participants will be informed of the results of the study. Participants have been provided with details of who to contact, should they require further information.

Journal Publication

It is expected that the study will be submitted for publication with the Journal of the International Neuropsychological Society (Impact factor 2.63).

Presentation

On 12th June 2017, my research findings were presented to an academic audience, for peer review, as part of the Doctorate in Clinical Psychology at the University of Exeter.

Appendix F – Supplementary materials

Table 1. *Participant inclusion and* exclusion criteria

Inclusion criteria	Exclusion criteria
• Student enrolled at the University of Exeter • Subjects will be English native speakers. • Subjects will be over the age of 18. • There will be no upper limit of time since last SRC for the rugby players. • Controls will not have a history of head injury.	• Significant medical or psychiatric co-morbidity. • Mental health difficulties (diagnosis or self-disclosure question 14 of the demographic questionnaire). • Participants with contraindications to MRI (see Appendix B). • Less than 18 years old. • Diagnosis of learning disability • Participant unable to provide informed consent. • History of acquired brain injury (e.g. anoxic brain injury, stroke, tumour) • SRC acquired within last 10 weeks. • Present pain levels as described on page 42. • Disturbed sleep as described on page 42.

Table 2. *Sports played by the control participants*

Participant	Sport
Control 1	Rowing
Control 2	Rowing
Control 3	Rowing
Control 4	Rowing
Control 5	Rowing
Control 6	Running
Control 7	Running
Control 8	Cycling/climbing
Control 9	Running/sailing
Control 10	Ultratrail running/climbing
Control 11	Athletics/swimming
Control 12	Squash

Table 3. *Validity and reliability of neuropsychological tests*

Measure	**Validity**	**Test – retest reliability**
Speed and Capacity of Language Processing Test	**Lexical decision task**: Performance on the part of the test remains relatively stable when other neurocognitive domains are impaired and appears sensitive to information processing in early stage of mTBI. It shows good convergent validity with other measures of pre-morbid function such as Mill Hill Vocabulary (.60-.71 and the Wechsler verbal IQ (r=.61) and full IQ (r=.58), it has an internal consistency of 0.83. **The speed of comprehension test:** The convergent validity for this test is also good. It correlates with the NART .60, semantic categorization 0.55 and vocabulary 0.50. Internal consistency in a small sample was reported to be 0.84-0.87.	Test-retest reliability range from 0.64 to 0.88. The test-retest reliability reported is between .78-.93. Practice effects have been found
CogState battery	It is widely used tool with published normative data employed to identify cognitive and psychological difficulties such as mild cognitive impairment, schizophrenia and mTBI (Paul Maruff et al., 2013). The battery has good reported construct validity (r=.49-.83) and good criterion validity for mTBI, schizophrenia and HIV related dementia (Maruff et al., 2009).	
STOP-IT test	This is an experimental test that is widely used but validity measures are not yet available.	
The Stroop colour and word test (Stroop).	The speed condition of the test shows sensitivity to PCS. The interference score convergence validity is moderate (r-.33 response inhibition; r=.55 difference score between Trails test A and B).	Test-retest reliability is reported to be good (r=.83,0.74, 0.67 for the three conditions respectively) although practice effects are present.

The COWA test	This test has good internal consistency (0.83) and test-retest reliability (0.77; d=0.26) Practice effects are present at short intervals	Test-retest reliability (0.77; d=0.26) Practice effects are present at short intervals
Trail making test.	The test is sensitive to closed head injury and Part A shows a positive association with PCS. The construct validity for visual search of the test ranges from moderate to high (.36 to .93) and moderate for Part B on other measures of speed of processing.	Test-retest reliability (A=0.55 and B=0.75). Practice effects are present at short intervals

Information source: Strauss, Sherman & Spreen, 2006.

Appendix G - Instructions for manuscript submission – Journal of the International Neuropsychological Society

Instructions for contributors

Aims and Scope

The *Journal of the International Neuropsychological Society* is the official journal of the International Neuropsychological Society, an organization of over 4,500 international members from a variety of disciplines. The *Journal of the International Neuropsychological Society* welcomes original, creative, high quality research papers covering all areas of neuropsychology. The focus of articles may be primarily experimental, applied, or clinical. Contributions will broadly reflect the interest of all areas of neuropsychology, including but not limited to: development of cognitive processes, brain-behavior relationships, adult and pediatric neuropsychology, neurobehavioral syndromes (such as aphasia or apraxia), and the interfaces of neuropsychology with related areas such as behavioral neurology, neuropsychiatry, genetics, and cognitive neuroscience. Papers that utilize behavioral, neuroimaging, and electrophysiological measures are appropriate.

To assure maximum flexibility and to promote diverse mechanisms of scholarly communication, the following formats are available in addition to a *Regular Research Article: Brief Communication* is a shorter research article; *Rapid Communication* is intended for "fast breaking" new work that does not yet justify a full length article and is placed on a fast review track; *Case Report* is a theoretically important and unique case study; *Critical Review* and *Short Review* are thoughtful considerations of topics of importance to neuropsychology and include meta-analyses; *Dialogue* provides a forum for

publishing two distinct positions on controversial issues in a point-counterpoint format; *Special Issue* and *Special Section* consist of several articles linked thematically; *Letter to the Editor* responds to recent articles published in the *Journal of the International Neuropsychological Society*; and *Book Review,* which is considered but is no longer solicited.

Originality and Copyright

To be considered for publication in the *Journal of the International Neuropsychological Society*, a manuscript cannot have been published previously nor can it be under review for publication elsewhere. Papers with multiple authors are reviewed with the assumption that all authors have approved the submitted manuscript and concur with its submission to the *Journal of the International Neuropsychological Society.*

A Copyright Transfer Agreement, with certain specified rights reserved by the author, must be signed and returned to the Editor-in-Chief by the corresponding author of accepted manuscripts, **prior to publication**. This is necessary for the wide distribution of research findings and the protection of both author and the society under copyright law. If you plan to include material that has been published elsewhere and is under copyright of a third party, you will need to obtain permission to re-use this material in your article. A form may be provided for this purpose by the editorial office. Alternatively, many publishers use an online system for such requests. It is the responsibility of the authors to obtain permissions to re-use material from elsewhere. For information regarding rights and permissions concerning the *Journal of the International Neuropsychological Society*, please contact Marc Anderson (manderson@cambridge.org) or Adam Hirschberg (ahirschberg@cambridge.org).

Disclosure

Potential conflicts of interest include funding sources for the reported study (e.g., a test validation study financially supported by a test publisher, a study supported by an insurance company), personal or family financial interest in a test or product or with a company that publishes a test that is being investigated in the manuscript or competes with a test that is being investigated in the manuscript. Other conflicts include employment, consultancies, stock ownership or medicolegal work. For the latter, information about whether the author's medicolegal work is largely for one side should be reported. This list of potential conflicts is not all inclusive, and it is the responsibility of each author to ensure that all of their "potential conflicts" are reported in the Acknowledgment section of the paper.

Disclosure pertains to all authors. It is the corresponding author's ethical responsibility to explicitly check with each of his/her co-authors to ensure that any real or apparent conflict of interest is appropriately disclosed. Authors should err on the side of full disclosure, and if authors are uncertain about what constitutes a relevant conflict, they should contact the Editorial Office (jins@cambridge.org). The intent of this disclosure is not to prevent an author with a significant financial or other relationship from publishing their work in the Journal of the International Neuropsychological Society, but rather to provide readers with adequate information to form their own judgments about the work.

Compliance with institutional research standards for animal or human research (including a statement that the research was completed in accordance with the Helsinki Declaration should be included in the methods section of the manuscript.

Manuscript Submission and Review

The Journal of the International Neuropsychological Society uses online submission and peer review. Paper submissions are not accepted. Authors who are not able to submit their manuscripts online are asked to contact the editorial office at: jins@cambridge.org.

The website address for submissions is: http://mc.manuscriptcentral.com/jins. Complete instructions are provided on the website.

Prior to online submission, please consult http://www.nlm.nih.gov/mesh/ for 6 keywords or mesh terms that are different from words in the title. Accurate mesh terms will increase the probability that your manuscript will be identified in online searches. Please follow the instructions carefully to avoid delays. The menu will prompt the author to provide all necessary information, including the manuscript category, the corresponding author including postal address, phone and fax numbers, and e-mail address, and suggested reviewers.

The website will automatically acknowledge receipt of the manuscript and provide a manuscript reference number. The Editor-in-Chief will assign the manuscript for review to an action editor and at least two other reviewers. Every effort will be made to provide the author with a review within 6 to 10 weeks of manuscript assignment. Rapid Communications will be reviewed within 4 weeks. If the Editor requests that revisions be made to a manuscript before publication, a maximum of 3 months will be allowed for preparation of the revision, except in unusual circumstances.

Manuscript Length

In order to increase the number of manuscripts that can be published in the *Journal of the International Neuropsychological Society*, please adhere to the following length requirements. Please provide a word count on the title page for the abstract and manuscript (not including abstract, tables, figures, or references). Manuscripts will be returned if they exceed length requirements.

Regular Research Article: Maximum of 5,000 words (not including abstract, tables, figures, or references) and a 250 word abstract. Regular Research Articles are original, creative, high quality papers covering all areas of neuropsychology; focus may be experimental, applied or clinical. Brief and Rapid Communications: Maximum of 2,500 words (not including abstract, tables, figures, or references) and a 200 word abstract, with a maximum of two tables or two figures, or one table and one figure, and 20 references. Brief and Rapid Communications are shorter research articles.

Brief Communication/Rapid Communication: Maximum of 2,500 words (not including abstract, tables, figures, or references) and a 200 word abstract, with a maximum of two tables or two figures, or one table and one figure, and 20 references. Brief and Rapid Communications are shorter research articles.

Case Report: Maximum of 3,500 words with an informative literature review (not including abstract, tables, figures, or references) and a 200 word abstract. Neurobehavioral Grand Rounds are unique case studies that make a significant theoretical contribution.

Critical Review: Maximum of 7,000 words (not including abstract, tables, figures, or references) and a 250 word abstract. Critical Reviews will be considered on any important topic in neuropsychology. Quantitative meta-

analyses are encouraged. Critical Reviews must be preapproved by the Editor-in-Chief. For consideration, please e-mail your abstract to jins@cambridge.org.

Short Review: Maximum of 2,500 words (not including abstract, tables, figures, or references) and a 150 word abstract. Short Reviews are conceptually oriented snapshots of the current state of a research area by experts in that area. Short Reviews must be preapproved by the Editor-in-Chief. For consideration, please e-mail your abstract to jins@cambridge.org.

Dialogue: Maximum of 2,000 words for each segment (not including abstract, tables, figures, or references) and a 150 word abstract, with a maximum of two tables or two figures, or one table and one figure and 20 references. Dialogues provide a forum for two distinct positions on controversial issues in a point counterpoint form. Dialogues must be preapproved by the Editor-in-Chief. For consideration, please e-mail your abstract to jins@cambridge.org.

Special Issue/Special Section: Maximum of 5,000 words (not including abstract, tables, figures, or references) and a 250 word abstract for each article (same as Regular Research Articles). Symposia consist of several thematically linked research articles which present empirical data. Symposia must be pre-approved by the Editor-in- Chief. For consideration, e-mail your proposal to jins@cambridge.org to receive prior approval.

Letter to the Editor: Maximum of 500 words (not including table, figure, or references) with up to five references and one table or one figure. Letters to the Editor respond to recent articles published in the *Journal of the International Neuropsychological Society*.

Book Review: Maximum of 1000 words in length. Include name and affiliations, a title for the review, the author(s)/editor(s), title, publisher, date of publication, number of pages and price. For consideration, e-mail jins@cambridge.org.

Manuscript Preparation and Style

The entire manuscript should be typed double-spaced throughout using a word processing program. Unless otherwise specified, the guideline for preparation of manuscripts is the *Publication Manual of the American Psychological Association (6th edition)* except for references with 3 or more authors (see References section). This manual may be ordered from: APA Order Dept., 750 1st St. NE, Washington, DC 20002-4242, USA.

Pages should be numbered sequentially beginning with the Title Page. The Title Page should contain the full title of the manuscript, the full names and institutional affiliations of all authors; mailing address, telephone and fax numbers, and e-mail address for the corresponding author; and the word count for the abstract and manuscript text (excluding title page, abstract, references, tables, and figures). At the top right provide a short title of up to 45 characters preceded by the lead author's last name. Example: Smith-Memory in Parkinson's Disease. This running head should be repeated at the top right of every following page.

Page 2 should include an Abstract and a list of at least six keywords or mesh terms. Note: structured abstracts must be included with papers submitted after January 1, 2014. A structured abstract must include four header labels: Objective, Method, Results, and Conclusions. A total of six mesh terms

(http://www.nlm.nih.gov/mesh/) or keywords should be provided and should not duplicate words in the title.

The full text of the manuscript should begin on page 3. For scientific articles, including *Regular Research Articles, Brief Communications, Rapid Communications,* and *Symposia*, the format should include a structured Abstract, Introduction, Method, Results, and Discussion. This should be followed by Acknowledgments, References, Tables, Figure Legends, Figures, and optional Appendices and Supplemental Material.

The use of abbreviations, except those that are widely used, is strongly discouraged. They should be used only if they contribute to better comprehension of the manuscript. Acronyms should be spelled out at first mention. Metric system (SI) units should be used.

Appendices and Supplemental Materials may be submitted. Appendices include material intended for print and should be included with the manuscript file. Supplementary material will appear only online and should be submitted as a separate file. Supplementary material is replicated as-is.

The Acknowledgements Section should include a disclosure of conflicts of interest (see above) and all sources of financial support for the paper. In documenting financial support, please provide details of the sources of financial support for all authors, including grant numbers. For example, "This work was supported by the National Institutes of Health (grant number XXXXXXX)". Multiple grant numbers should be separated by a comma and space and where research was funded by more than one agency, the different agencies should be separated by a semicolon with "and" before the final funding agency. Grants

held by different authors should be identified using the authors' initials. For example, "This work was supported by the Wellcome Trust (A.B., grant numbers XXXX, YYYY), (C.D., grant number ZZZZ); the Natural Environment Research Council (E.F., grant number FFFF); and the National Institutes of Health (A.B., grant number GGGG), (E.F., grant number HHHH)."

Tables and Figures should be numbered in Arabic numerals. Figures should be numbered consecutively as they appear in the text. Figures should be twice their intended final size and authors should do their best to construct figures with notation and data points of sufficient size (recommended ≥ 300 dpi) to permit legible photo reduction to one column of a two-column format. Please upload figure(s) in either a .doc, .jpeg, .tiff, or .pdf format. There is no additional cost for publishing color figures. The approximate position of each table and figure should be provided in the manuscript with call-outs: [INSERT TABLE 1 HERE]. Tables and figures should be on separate pages. Tables should have short titles and all figure legends should be on separate pages. All tables and figures must have in-text citations in order of appearance.

Figures submitted in color will appear online in color, but all figures will be printed in black and white unless authors specify during submission that figures should be printed in color, for which there may be a fee. There is no additional cost for publishing color figures in the print version of the journal for corresponding authors who are INS members. For non-members, the cost for publishing color figures in print version of the journal will be $320 per figure with a cap of $1600 per article.

References should be consistent with the *Publication Manual of the American Psychological Association (6th Edition)*. In-text references should be cited as

follows: "...Given the critical role of the prefrontal cortex (PFC) in working memory (Cohen et al., 1997; Goldman-Rakic, 1987; Perlstein et al., 2003a, 2003b)..." with multiple references in alphabetical order. Another example: "...Cohen et al. (1994, 1997), Braver et al. (1997), and Jonides and Smith (1997) demonstrated..."

References cited in the text with two authors should list both names. References cited in the text with three, four, or five authors, list all authors at first mention; with subsequent citations include only the first author's last name followed by et al. References cited in the text with six or more authors should list the first author et al. throughout. In the reference section, for works with up to seven authors, list all authors. For eight authors or more, list the first six, then ellipses followed by the last author's name. Examples of the APA reference style are as follows:

Online/Electronic Journal Article with DOI: Dikmen, S., Machamer, J., Fann, J. & Temkin, N. (2010). Rates of symptom reporting following traumatic brain injury. *Journal of the International Neuropsychological Society*, 16, 401-411. doi:10.1017/S1355617710000196

Scientific Article: Giovannetti, T., Britnell, P., Brennan, l., Siderowf, A., Grossman, M., Libon, D.J., Seidel, G.A. (2012). Everyday action impairment in Parkinson's disease dementia. *Journal of the International Neuropsychological Society*, 18, 787-798.

Book: Lezak, M.D., Howieson, D.B., Bigler, E.D., Tranel, D. (2012). *Neuropsychological Assessment*. New York: Oxford University Press.

Book Chapter: Mahone, E.M. & Slomine, B.S. (2008). Neurodevelopmental disorders. In J.E.Morgan, & J.H. Ricker (Eds.), *Textbook of Clinical Neuropsychology* (pp. 105-127). New York:Taylor & Francis.

Report at a Scientific Meeting: Weintraub, S. (2012, June). Profiles of dementia: Neuropsychological, neuroanatomical and neuropathologic phenotypes. International Neuropsychological Society, Oslo, Norway.

Manual, Diagnostic Scheme, etc.: American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.). Washington, DC: American Psychiatric Association Press.

English Editing

The Research and Editing Consulting Program (RECP) within the International Neuropsychological Society's International Liaison Committee is designed to provide English language editing and statistical consulting to international colleagues who wish to publish their research in English language journals. For additional information see http://www.the-ins.org/the-research-and-editingconsulting-program.

Proofs

The publisher reserves the right to copyedit manuscripts. The corresponding author will receive PDFs for final proofreading. These should be checked and corrections returned within 2 days of receipt. The publisher reserves the right to charge authors for excessive corrections.

Offprints and PDF Files: The corresponding author will receive a free pdf. This pdf can also be mounted on the authors' web pages. Offprints must be ordered

when page proofs are returned. The offprint order form along with the price list will be sent with your PDF.

Open Access

Authors in the *Journal of the International Neuropsychological Society* have the option to publish their paper under a fully Open Access agreement, upon payment of a one-off Article Processing Charge. In this case, the final published Version of Record will be made freely available to all in perpetuity under a Creative Commons license, enabling its reuse and re-distribution. This Open Access option is only offered to authors upon acceptance of an article for publication.

Authors choosing the Open Access option are required to complete the Open Access Transfer of Copyright form. More information about Open Access in the *Journal of the International Neuropsychological Society* can be found here.

For corresponding authors who are INS members, the current APC rate to publish an article Open Access is **$1,000/£630** and for non-members, the current rate is **$2,835/£1,780**.

Please note: APC collection is managed on behalf of Cambridge University Press by RightsLink, who will contact authors following acceptance of their paper.

Green Open Access

Green Open Access is when content is made freely available by the author. This is achieved by depositing the article on the author's web page or in a suitable public repository, often after a specified embargo period. Please see

the table below for a summary of where an author published in the *Journal of the International Neuropsychological Society* may deposit versions of their article:

	Personal Website	Departmental / Institutional Repository	Non-commercial Subject Repository	Commercial Repository and Social Media Sites
Author's Original	At any time	At any time	At any time	At any time
Submitted Manuscript Under Review	At any time	At any time	At any time	At any time
Accepted Manuscript	On acceptance of publication.	On acceptance of publication	On acceptance of publication	Abstract only in PDF or HTML format no sooner than first publication of the full article.
Version of Record	Upon publication	12 months after first publication	12 months after first publication	Abstract only in PDF or HTML format no sooner than first publication of the full article.

Please see the Transfer of Copyright form for further terms and conditions.

Please note: Websites such as 'ResearchGate' or 'Academia.edu' are social media sites, and as such fall under that category within the policy. This means that neither the Accepted Manuscript or the Version of Record may be posted on such sites in its entirety, however authors are free to upload the abstract of their paper.

Posting your Article on PubMed Central

If you have published your article via Open Access within the *Journal of the International Neuropsychological Society*, the publisher will post your article on

PubMed Central if the work was funded by relevant funders such as NIH, Wellcome, and several others, detailed here (Method B on the PMC submission guidelines).

However, in all other cases, it is the responsibility of the author to post their article on PMC if they have received any NIH awards. Please click here to determine applicability.

Under the current terms and conditions, you may submit the Accepted Manuscript version of your article to PubMed Central immediately after the article has first been published online. You may also post the published version of your article (Version of Record) on PubMed **one year after online publication.**

Please click here to follow NIH instructions on how to submit your Accepted Manuscript to PubMed Central, and follow Method C instructions.