

CONCUSSION IN PROFESSIONAL RUGBY LEAGUE

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DECLARATION

This thesis is submitted to the University of Newcastle in fulfilment of the requirements for the degree of Doctor of Philosophy.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library**, being made available for loan and photocopying subject to the provisions of the Copyright Act 1968.

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I hereby certify that the work embodied in this thesis has been completed in collaboration with other researchers. I have included as part of the thesis a statement clearly outlining the extent of collaboration, with whom and under what auspices.

I hereby certify that this thesis is in the form of a series of published papers of which I am a joint author. I have included as part of the thesis a written statement for each co-author, endorsed by the Faculty Assistant Dean (research Teaching), attesting to my contribution to the joint publication.

I acknowledge that the intellectual content of this thesis is the product of my own work, except to the extent that others have contributed in terms of the study conception and design. Contributions in terms of editorial suggestions have also been offered by my supervisors and other colleagues.

Andrew J. Gardner

17 June 2015

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The views and conclusions contained here are those of the author and should not be interpreted as necessarily representing the official policies or endorsements of The University of Newcastle, The National Rugby League (NRL), or any of the funding or supporting bodies acknowledged above.

ABSTRACT

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Concussion in Professional Rugby League

Background

Rugby League is a popular full-contact sport played internationally by 18 full-member test nations of the Rugby League International Federations (RLIF), 21 RLIF affiliate-members, and approximately 32 other unaffiliated nations. The most popular elite, professional, domestic leagues are played in Australia and the United Kingdom. Rugby league game play involves numerous collisions and tackles, and it carries an inherent risk for injury including head trauma. Despite the increased interest in sport-related concussion in recent years, only a limited number of studies have been conducted in rugby league players on this topic, with the large majority of publications only addressing the incidence of concussion as a secondary outcome measure within sports-specific injury focused studies. Additionally, there are currently no published papers on the potential long-term consequences of sport-related concussion in retired professional rugby league players.

Aim/Purpose

This thesis addresses some of the issues related to the identification and acute management of sport-related concussion in professional rugby league players. It also examines the potential long-term consequence of concussion in retired professional rugby league players. One of the overall aims of this thesis was to conduct a systematic review of the literature examining both, (i) concussion in rugby league; and (ii) the use of magnetic resonance spectroscopy in sport-related concussion. These systematic review papers set the scene for the main aims of this thesis, which were to address the identified gaps in the literature, first by identifying the factors associated with concussion in rugby league at the professional level via systematic video analysis of the injury. The purpose of this first study was to described player and injury characteristics, situational factors, concussion signs, and return to play. A secondly aim was to examine the potential long-term consequences of a history of multiple concussions in retired professional rugby league players. The purpose of this second study was to examine the brain neurometabolite concentrations and the cognitive profiles of retired rugby league players who had a history of numerous self-reported concussions.

Methods

Paper 1: This systematic review involved the retrieval of eligible studies pertaining to concussion in rugby league players. Numerous online databases were searched for publication in English from 1900 up to June 2013 using the key search terms: rugby league, league, football; in combination with injury terms: athletic injuries, concussion, sports concussion, sports related concussion, brain concussion, brain injury, brain injuries, mild traumatic brain injury, mTBI, traumatic brain injury, TBI, craniocerebral trauma, head injury, and brain damage. Articles were regarded as relevant and warranting inclusion if they were experimental studies examining concussed rugby league players. Studies were included whether they were conducted with acute or long-term concussed athletes (i.e., there were no restrictions placed on time elapsed since injury).

Paper 2: All National Rugby League clubs were invited to participate in this video analysis study of concussion, three agreed to participate. All players medically diagnosed with a concussion by an experienced team physician from the three participating clubs were included in the study. The digital video footage of games in which each concussion was diagnosed was reviewed. Descriptions pertaining to player's demographic information (i.e., age, height, weight, playing position, and game performance statistics) and return to match play were also recorded. Two raters independently viewed the digital records of events leading to concussion. Relevant variables were pre-determined and data were independently recorded by both raters. In order to reach consensus, all discrepancies between raters resulted in a review of the footage together and a discussion regarding the recorded data. Under circumstances where consensus was not reached, a third rater was to be consulted to make the final determination, however this was not required.

Paper 3: Each use of the 'Concussion Interchange Rule' ('CIR') during the 2014 National Rugby League season was included in the study. There was no video analysis conducted on any event that was not logged and assessed by club medical staff. Access to video footage of the incident was attained through the National Rugby League's Digital Press Pass subscription. All uses of the CIR were independently reviewed by the first author and at least one other author. Two authors were blinded to the study hypotheses but the first author was not blinded. The three raters determined whether any of six signs (loss of consciousness, loss of muscle tone, seizures, clutching of the head, unsteadiness of gait, or possible impairment in cognition or awareness as evidenced by a blank or vacant stare) were present, absent, or indeterminable based on the available footage of the incident for every case. When there was disagreement between the two primary raters (who rated all incidents), both raters reviewed

and discussed those cases in an effort to reach consensus. In the cases where consensus could not be achieved, ratings from a third rater were used.

Paper 4: This systematic review involved the retrieval of eligible studies pertaining to magnetic resonance spectroscopy and concussion in athletes. Numerous online databases were searched for publication in English up to February 2013 using the key search terms: magnetic resonance spectroscopy, nuclear magnetic resonance spectroscopy, neurospectroscopy, spectroscopy, two-dimensional nuclear magnetic resonance spectroscopy, correlation spectroscopy, J-spectroscopy, exchange spectroscopy, nuclear overhauser effect spectroscopy, NMR, MRS, COSY, EXSY, NOESY, 2D NMR, craniocerebral trauma, mild traumatic brain injury, mTBI, traumatic brain injury, brain concussion, concussion, brain damage, sport, athletic, and athlete. Articles were regarded as relevant, and warranting inclusion in the review if they were experimental studies using MRS to determine the presence (or absence) of pathophysiology in concussed athletic samples. Studies were included whether they were conducted acutely or post-acutely (i.e., there were no restrictions placed on time since injury) and whether or not they also used other outcome measures (e.g., conventional MRI, CT, symptom checklists, balance testing, or neuropsychological testing). All retrieved articles were independently assessed for quality using a standardized quality assessment checklist.

Paper 5: Retired professional rugby league players (n=13) were recruited through communication with the club alumni. Exclusion criteria included any medical history of neurosurgery, or any history of a brain tumor requiring radiation treatment, or claustrophobia. Healthy community control subjects similar in age and education were recruited through a research participant registry established by a medical research institute. All participants completed a clinical interview and neurocognitive testing. The total interview and testing time was approximately 135 minutes. The MRS data was collected during a separate, single testing session on all participants as one component of a multiparametric neuroimaging study. The imaging time for the MRS component of the study was approximately 25 minutes; the whole multiparametric acquisition time was approximately 65 minutes. An overall test battery mean was computed by summing and averaging the normative scores (expressed in T score units with a mean of 50 and a SD of 10). Conventional Imaging was performed on a 3 T Siemens Skyra scanner with a 20-channel head coil. MRS voxels were placed in posterior cingulate grey matter (GM) and parietal white matter (WM). Concentrations of glutamate (Glu), glutathione (GSH), *myo*-inositol (mI), *N*-acetylaspartate (NAA), total choline (tCho), creatine+phosphocreatine (tCr), and glutamate+glutamine (Glx) were quantified using LCModel and water scaling.

Results

The systematic review of the rugby league literature identified that very little research had been conducted evaluating concussion. One hundred and ninety nine rugby league injury publications were identified. Thirty-nine (20%) were related in some way to concussion. Of the 39 identified articles, 6 (15%) had the main aim of evaluating concussion, while the other 33 reported on concussion incidence as part of overall injury data analyses. Rugby league concussion incidence rates vary widely from 0.0 to 40.0/1000 playing hours, depending on the definition of concussion injury (game time loss vs. no game time loss). The incidence rates vary across match play versus training session, seasons (winter vs. summer) and playing position (forwards vs. backs). The ball carrier has been found to be at greater risk for injury than tacklers. Concussion accounts for 29% of all injuries associated with illegal play, but only 9% of injuries sustained in legal play.

Video analysis of medically diagnosed concussions during the 2013 National Rugby League (NRL) season identified most concussions (83%) occurred during a high tackle, and all concussed ball carriers were hit high. None of the striking players were concussed. All concussions involved a blow to the head or face. Loss of consciousness was observed in 30% of cases. Only half of the total sample was removed from play, and one athlete who was removed returned to play in the same match. Of the players who were removed from play, the large majority returned to play the following week. Illegal play accounted for 25% of all concussions. The concussion incidence was 14.8 injuries per 1,000 player NRL match hours or approximately one concussion every four games.

The video analysis of the use of the concussion interchange rule (CIR) during the 2014 season identified 167 uses of the CIR. Loss of consciousness was observed in 30.2% of cases. Common observable signs of injury included clutching the head (69.1%), loss of muscle tone (50.0%), unsteadiness of gait (52.5%), and a blank or vacant state (59.9%). Convulsive convulsions were observed in 1.9%. The overall inter-rater reliability for these concussion signs for the two raters was $\kappa = 0.60$ (95% CI = 0.56-0.64), which is considered to be weak to moderate agreement. More than half of the players who used the CIR returned to play later in the same match (56.8%). Of the players who used the CIR, and who had three or more observable signs of possible injury, 46.4% returned to play in the same game. No player used the CIR more than once in the same game. Of the players who were removed from play, the large majority returned the following week. Forwards (69.9%) used the CIR significantly more often than backs (30.1%). Most incidences occurred from a hit up (62.3%) and occurred during a high tackle (80%). The incidence rate was 24.03 uses of the CIR per 1,000 NRL player match hours. This equates to approximately one CIR every 2.41 games in the 2014

NRL season.

The systematic review of magnetic resonance spectroscopy (MRS) in sport-related concussion identified only eleven publications, with varying methodology and results. The review identified 11 publications that met criteria for inclusion, comprised of data on 200 athletes and 116 controls. Nine of 11 studies reported a MRS abnormality consistent with an alteration in neurochemistry. The results support the use of MRS as a research tool for identifying altered neurophysiology and monitoring recovery in adult athletes, even beyond the resolution of post-concussive symptoms and other investigation techniques returning to normative levels.

In new data collected as part of the thesis, the MRS profiles of retired NRL players differed compared to community age- and education-matched control participants. From a clinical perspective, these early middle-aged retired athletes did not report more depression, anxiety, or stress, and they did not have worse cognitive functioning, than control subjects (although one retired player met clinical criteria for mild cognitive impairment [MCI]). They did, however, perform more poorly than controls on non-dominant fine motor coordination and speed, and their balance scores were correlated with lower levels of some neurometabolites. A significant difference between groups was observed in grey matter N-acetylaspartate (NAA), with significantly lower concentrations of NAA found in retired athletes. No significant differences were found in white matter NAA. Secondary analysis found a significant difference between groups in grey matter myo-inositol (mI), with retired players having lower concentrations compared to controls. There was a significant difference in grey matter glutathione, with retired players showing lower concentrations compared to controls. There were no significant difference between groups in grey matter choline or glutamate concentrations. In white matter, there were no statistically significant differences in any of the neurometabolites that were hypothesized to differ (mI, choline, glutamate, or glutathione).

Conclusion

Rugby league is a contact sport with high incidence of concussions, which leads to participants being exposed to numerous concussions during their careers. The current series of studies adds enormously to rugby league concussion literature, which had previously been quite limited, as identified in the systematic review of the rugby league concussion literature (Chapter 2). The current series of studies characterised concussion at the professional level in current rugby league players; identifying antecedent events and risk factors, together with return to play management and decision-making. In addition to investigating current players, this series of studies also investigated cognition and neurometabolites in retired professional rugby league players. While the current series of studies identifies concussion as a common

risk factor for participation in rugby league, the potential long-term consequences for rugby league players with a history of numerous concussions remains a topic requiring further investigation. In the small sample of retired players included in Study 3, not one player expressed significant concerns regarding their cognition and on neuropsychological assessment none of the retired rugby league players performed significantly below their estimated pre-morbid level of intellectual function. So for all intents and purposes the investigation was conducted in ‘asymptomatic’ retired rugby league players, however there were significant neurometabolic differences observed between groups on magnetic resonance spectroscopy. The clinical relevance of this finding also requires further investigation, but it may suggest that MRS is sensitive to possible pre-clinical symptomology that other methodologies (i.e., neuropsychological testing) are not sufficiently sensitive to detect.

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All errors and limitations remaining in this thesis are mine alone.

*“If our brains were so simple that we could understand them,
we would be so simple that we could not”*

- Anonymous

“If you cannot explain it simply, you do not understand it well enough”

-Albert Einstein

“Learning without thought is labour lost”

-Confucius

*The more you know, the more you realise how much you don't know – the less you know the
more you think you know*

-David T. Freeman

“A job well done is its own reward”

-Anonymous

“If the map differs from the terrain, believe the terrain”

- Norse proverb

*“Far and away the best prize that life offers is the chance
to work hard at work worth doing”*

- Theodore Roosevelt

*He will keep in perfect peace...
all those who trust in Him...
whose thoughts turn often to the Lord*

- Isaiah 26:3

PREFACE

PUBLICATIONS & PRESENTATIONS

RELATED PUBLICATIONS PUBLISHED IN PEER-REVIEWED JOURNALS RELEVANT TO THE TOPIC BUT NOT INCLUDED AS CHAPTERS IN THE THESIS:

Iverson GL, Gardner AJ, McCrory P, Zafonte R, & Castellani R. (2015). A critical review of chronic traumatic encephalopathy. *Neuroscience & Biobehavioral Reviews*, in press.

Gardner A, Iverson GL, & McCrory, P. (2014). Chronic traumatic encephalopathy in sport: a systematic review. *British Journal of Sports Medicine*, 48 (2), 84-90.

Gardner AJ, Iverson GL, Williams WH, Baker S, & Stanwell, P. (2014). A systematic review and meta-analysis of concussion in rugby union. *Sports Medicine*, online first August, 20.

Gardner AJ, Tan CO, Ainslie PN, van Donkelaar P, Stanwell P, Levi CR, & Iverson GL. (2014). A Systematic Review of Cerebrovascular Reactivity After Sport-Related Concussion. *British Journal of Sports Medicine*, accepted October, 2014.

Schofield PW, Moore TM, & Gardner A. (2014). Traumatic brain injury and olfaction: a systematic review. *Frontiers in Neurology: Neurotrauma*, 5 (Art. 5).

Gardner A. (2013). The complex clinical issues involved in an athlete's decision to retire from collision sport due to multiple concussions: a case study of a professional athlete. *Frontiers in Neurology: Neurotrauma*, 4 (Art.141), 1-6.

Gardner A, Kay-Lambkin FJ, Stanwell P, Donnelly JD, Williams WH, Hiles A, Schofield PW, Levi CR, & Jones DK. (2012). A Systematic Review of Diffusion Tensor Imaging Findings in Sports-Related Concussion. *Journal of Neurotrauma*, 29 (16), 2521-2538.

REVIEWED ABSTRACTS PUBLISHED IN CONFERENCE PROCEEDINGS:

Gardner AJ, Iverson GL, Wojtowicz M, Levi CR, Makdissi M, Quinn TN, Shultz SR, Wright D, Stanwell P. (2015). *A Systematic Video Analysis of Concussion in the National Rugby League* presented at the *American Academy of Neurology 67th Annual Meeting*, April 18- 25, 2015; Washington, DC, USA.

Gardner AJ, Iverson GL, Wojtowicz M, Levi CR, Kay-Lambkin F, Schofield PW, Zafonte R, Shultz SR, Lin AP, Stanwell P. (2015). *Magnetic Resonance Spectroscopy Findings in Retired Professional Rugby League Players* presented at the *3rd Annual Sports Neuropsychology Concussion Symposium*, May 1-2; Atlanta, GA, USA.

Gardner AJ, Wojtowicz M, Levi CR, Zafonte R, Iverson GL. (2015). *Sports Concussion Assessment Tool – Third Edition (SCAT-3) for Screening Players Suspected of Concussion in the National Rugby League* presented at the *3rd Annual Sports Neuropsychology Concussion Symposium*, May 1-2; Atlanta, GA, USA.

Gardner AJ, Stanwell P, Ellis J, Levi CR, Iverson GL. (2015). *A Video Analysis of Use of the New ‘Concussion Interchange Rule’ in the National Rugby League During the 2014 Season* presented at the *5th International Neuropsychological Society/ Australian Society for Brain Injury Pacific Rim Conference*, July 1-4; Sydney, NSW, Australia.

CONFERENCE PRESENTATIONS:

Gardner AJ, Iverson GL, Wojtowicz M, Levi CR, Makdissi M, Quinn TN, Shultz, SR, Wright, D, Stanwell, P. (2015). *A Systematic Video Analysis of Concussion in the National Rugby League* presented at the *American Academy of Neurology 67th Annual Meeting*, April 18- 25, 2015; Washington, DC, USA.

Gardner AJ, Stanwell P. (2013). *Preliminary cognitive and neuroimaging findings in retired professional rugby league players* presented at the *3rd Australian Neurotrauma Symposium*, 25-26 October, Hobart, TAS, Australia.

NON-PEER REVIEWED PUBLICATIONS:

Gardner A, & Stanwell P. (2012). Riskante Gehirnerschütterungen Chronisch traumatische Enzephalopathie (CTE) als Folge von Kopfverletzungen. *Medical Sports Network – Germany*, 4, 22-25.

Gardner A. (2014). Concussion & Dementia: What are the potential risks for later life cognitive and mental health issues for retired rugby league players? *Men of League Foundation Magazine*, 2, pp17-18.

STATEMENT OF CONTRIBUTION OF OTHERS

Publication 1: Gardner A, Iverson GL, Levi CR, Schofield PW, Kay-Lambkin F, Kohler RM, Stanwell P. (2015). A systematic review of concussion in rugby league. *British Journal of Sports Medicine*, 49(8):495-498.

I, Grant Iverson, attest that Research Higher Degree candidate Andrew Gardner contributed to the conceptualisation, database search, selection of eligible publications, the data extraction, analysis and drafting of the manuscript to the publication entitled “A systematic review of concussion in rugby league.”

Grant L. Iverson

Date: 12 June 2015

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Publication 2: Gardner A.J., Stanwell P, Levi CR, Quinn TN, Makdissi M, Shultz SR, Wright D, Iverson GL. (2015). A video analysis of concussion in the national rugby league: a preliminary study. Brain Injury. Accepted March 21, 2015; Epub ahead of print June 17.

I, Peter Stanwell, attest that Research Higher Degree candidate Andrew Gardner contributed to the conceptualisation, data collection, video analysis coding and documentation, data analysis and drafting of the manuscript to the publication entitled “A video analysis of concussion in the national rugby league: a preliminary study.”

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Publication 3: Gardner, A.J., Iverson, G.L., Stanwell, P., Moore, T., Ellis, J., Levi, C.R. (2015). A Video Analysis of the Use of the New 'Concussion Interchange Rule' in the National Rugby League During the 2014 Season. International Journal of Sports Medicine, (2015) submitted June 8.

I, Grant Iverson, attest that Research Higher Degree candidate Andrew Gardner contributed to the conceptualisation, data collection, video analysis coding and documentation, data analysis and drafting of the manuscript to the publication entitled "A Video Analysis of the Use of the New 'Concussion Interchange Rule' in the National Rugby League During the 2014 Season."

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Publication 4: Gardner, A.J., Iverson, G.L., Stanwell, P. (2014). A Systematic Review of Proton Magnetic Resonance Spectroscopy Findings in Sport-related Concussion. Journal of Neurotrauma, 31(1):1-18.

I, Grant Iverson, attest that Research Higher Degree candidate Andrew Gardner contributed to the conceptualisation, database search, selection of eligible publications, the data extraction, analysis and drafting of the manuscript to the publication entitled “A Systematic Review of Proton Magnetic Resonance Spectroscopy Findings in Sport-related Concussion.”

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I, Grant Iverson, attest that Research Higher Degree candidate Andrew Gardner contributed to the conceptualisation, data collection, and the drafting of the manuscript to the publication entitled “Magnetic Resonance Spectroscopy and Cognitive Findings in Retired Professional Rugby League Players.”

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CHAPTER 1

Introduction

1.1 THE SPORT OF RUGBY LEAGUE

1.1.1 History of the Rugby League Football (Rugby League)

Rugby League Football or Rugby League, is a popular collision sport played between two sides of thirteen players on a rectangular playing field. It originated as a breakaway faction derived from rugby union. In 1895, in Huddersfield, Northern England a Northern Rugby Football Union was developed, independent of the well established Rugby Football Union (RFU). Administrators of a number of clubs in Northern England united to form a Northern Rugby League in 1901. By 1904 the new body had more clubs affiliated to it than the RFU and the popularity of this new sport began to grow (Collins, 2006).

Initially there were no rule changes and the Northern Rugby League maintained the laws of the Rugby Football Union. During the first season of the game, a new rule was introduced, awarding a penalty for a deliberate knock-on. Subsequent new laws were gradually phased in and in 1897 the line-out was abolished. In 1906, two positions in the forwards (the flankers) were disposed of, reducing the number of players on each team to 13 players rather than the 15 players in rugby union. Additionally, the inception of a 'play the ball' had occurred, whereby the player in possession was required to heel the ball back to a team member following a tackle as opposed to a scrum being formed. The scoring structure was also modified such that all types of goals were now only worth two points. With the emergence of this new

code competing for interest, it became necessary to make a distinction between them. It became customary to describe those teams affiliated to the Northern Union as 'playing in the league' while those which remained affiliated to the RFU as playing "rugby union". In 1922, the Northern Union also changed its name to the Rugby Football League and thus over time the sport itself became known as "rugby league" football. In 1966, the International Board introduced a rule that a team in possession was allowed three play-the-balls and on the fourth tackle a scrum was to be formed. This was increased to six tackles in 1972 and in 1983 the scrum was replaced by a handover (Collins, 2006).

Rugby league had similar roots in Australia. It originated following some dissention amongst members of the New South Wales Rugby Union. A meeting was held on 8th August 1907, to organise professional rugby in Australia. At this meeting a decision was made to form a New South Wales Rugby Football League (NSWRFL), to play the Northern Union rules. The recruitment of players for the new game commenced, and a major coup was achieved when the NSWRFL managed to recruit Herbert "Dally" Messenger, the most famous rugby player in Sydney at the time. The NSWRFL competition was first played in 1908 and has been played, in some form, every subsequent year. Rugby league quickly took over from rugby union as the most popular form of football in both New South Wales and Queensland (Heads & Middleton, 2008).

1.1.2 The National Rugby League (NRL)

Currently in Australia the highest level of competition is the National Rugby League (NRL). The NRL is the present-day embodiment of Australia's top-level domestic rugby league competition, which in turn grew from Sydney's club competition. The NRL has 16 competing clubs predominately made up of teams from Sydney but also three Queensland teams, and one team each from Australia Capital Territory (ACT), Victoria and New Zealand. The NRL season is scheduled from Autumn until Spring. The season culminates in the premiership deciding game, the NRL Grand Final, traditionally one of Australia's most popular sporting events (Collins, 2006).

Table 1. Teams in the NRL (2011-2015)

Team Name	Suburb, City	Home Ground	Foundation Year
Brisbane Broncos	Brisbane, Queensland	Suncorp Stadium	1988
Canterbury-Bankstown Bulldogs	Canterbury-Bankstown, New South Wales	ANZ Stadium	1935
Canberra Raiders	Canberra, Australian Capital Territory	GIO Stadium	1982
Cronulla-Sutherland Sharks	Cronulla, New South Wales	Remondis Stadium	1967
Gold Coast Titans	Gold Coast, Queensland	Cbus Super Stadium	2007
Manly Warringah Sea-Eagles	Manly, New South Wales	Brookvale Oval	1947
Melbourne Storm	Melbourne, Victoria	AAMI Park	1998
Newcastle Knights	Newcastle, New South Wales	Hunter Stadium	1988
New Zealand Warriors	Auckland, New Zealand	Mt Smart Stadium	1995
North Queensland Cowboys	Townsville, Queensland	1300 Smiles Stadium	1995
Parramatta Eels	Parramatta, New South Wales	Pirtek Stadium	1947
Penrith Panthers	Penrith, New South Wales	Pepper Stadium	1967
St. George Illawarra Dragons	Kogarah & Wollongong, New South Wales	WIN Jubilee Oval & WIN Stadium	1999
South Sydney Rabbitohs	Redfern, New South Wales	ANZ Stadium	1908
Sydney Roosters	Eastern Suburbs, New South Wales	Allianz Stadium	1908
Wests Tigers	Balmain & Campbelltown, New South Wales	ANZ Stadium, Leichardt Oval & Campbelltown Stadium	2000

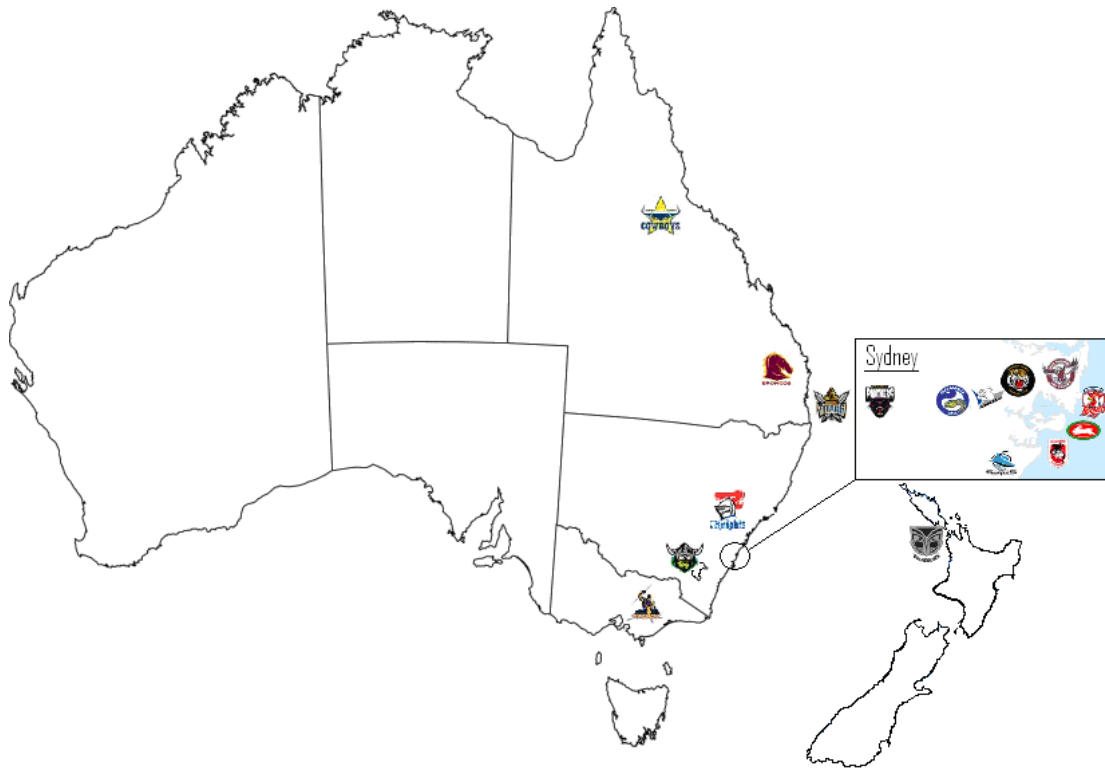


Figure 1. Map of Australian & New Zealand with NRL team locations (2010-2015)

1.1.3 Rules and Playing Positions

Rugby League is well known for its physical demands and toughness. The objective in rugby league is to score more points through tries, goals or field goals than the opposition. Games are played with two halves, each consisting of forty minutes.

The try is the most common form of scoring. A try is awarded when a player applies downward pressure to the ball, in their control, on the ground on or beyond the defending team's tryline (in the in-goal area, see Figure 2 for details). A try is worth four points. A goal is worth two points and may be gained from a conversion of a try or from a penalty. A field goal, or drop goal, is worth one point and is gained by dropping and then kicking the ball on the half-volley between the uprights in open play (Andrews, 1995).

Tackling is a crucial component of rugby league. This is the means by which defending players stop the progress of the opposition. There are a number of rules regarding the execution of a legal tackle, one of which is that only the player holding the football may be tackled. A tackle is completed when that player's progress is halted, or they are put to ground. An attacking team gets a maximum of six tackles to

progress up the field before possession is changed over. Ball control is also an important component in rugby league, as a fumble of the ball in a forward direction on the ground results in a handover. The ball can also be turned over by going over the sideline (Andrews, 1995).

On game day, a team of thirteen starting players and four reserves are recorded on a team sheet. The four reserve players operate as replacement players for the thirteen players on the field. Any player can be replaced by one of the reserve players at any time during the game. However, as opposed to a ‘replacement,’ where the player removed from the field of play is not permitted to return to the game; an individual player may be brought on and off the field (i.e., interchanged) multiple times during the game. At the NRL level there are restrictions placed on the number of interchanges that can be made by a team during a game, that limit being twelve. Prior to the 2014 season there were only two circumstances under which a player could be replaced without this limit being affected; the ‘blood rule’ or an illegal act. In these cases, a player can go to the ‘blood-bin’ to receive treatment and have the blood removed from his body and/or clothing, or if the player was injured by an illegal act that was placed on report. That is, if the opposing player was deemed by the match official to have committed a foul that warrants referral to a match review committee and in the act of committing such a foul a player was injured, then the injured player can be replaced by an interchange player without one of the twelve interchanges being tallied. As a result of ongoing concern pertaining to the acute management of concussion, and the introduction of a variety of rules by other Australian football codes to replace players suspected of sustaining a concussion, the NRL implemented their own changes. In 2014, the NRL introduced a ‘concussion interchange rule,’ which enabled a player suspected of having sustained a concussion to be removed from play and replaced without an interchange being recorded against the concussed player’s team. Team medical staff are given a 15-minute period to assess the player’s suitability to return to play, and if deemed fit, the player may return within the 15-minute period, without an interchange charged against the team.

A rugby league team is made up of six forwards and seven backs each with their own crucial roles to play during a game. The forwards typically apply brute force, carrying out the responsibility for the majority of the physically demanding work; making hit-ups to gain field position and making tackles to defend field position. The backs are

generally smaller, faster and more agile than the forwards. They are often the most creative and evasive players on the field, relying on running, kicking and handling skills, as well as tactics and set plays, to break the defensive line (Andrews, 1995).

The forward positions are traditionally named after the player's position in the scrum, which is one of their key responsibilities during the match. The forward pack consists of a hooker, a lock, two second rowers and two front rowers or props. The backline consists of one fullback, two wingers, two centres and two halves (Andrews, 1995).

Table 2. Rugby League Playing Positions

Number(s)	Position	Description
Backline Positions		
1	Fullback	The name is derived from the fullback's defensive position where the player drops out of the defensive line to cover the behind from kicks and runners breaking the line. In attack the fullback will typically make runs into the attack or support a runner in anticipation of a pass out of the tackle
2 & 5	Wing	The wingers are normally the fastest players in a team and play on the perimeters of the field (the wings). Wingers also drop back on the last tackle to cover the left and right sides of the field for kicks while the fullback covers the middle.
3 & 4	Centre	The centres are positioned one in from the wings and together complete what is known as the three-quarter line. Their primary role is to create attacking opportunities for their team and defend against those of the opposition.
6	Five-Eighth	Most of the backline play is facilitated by the halfback and five-eighth. They are also generally responsible for the last tackle options and kicks in general play.
7	Halfback	The halfback is also responsible for feeding the scrum when in possession.
Forward Pack Positions		
8 & 10	Prop	These positions tend to be largest players on field. They are positioned in the centre of the line. The prop will be an "enforcer" and in attack, will give their team momentum by charging at the defence aggressively.
9	Hooker	The player commonly ascribed to the role of dummy-half. In defence the hooker usually defends in the middle of the line against the opposition's props and second-rowers. The hooker will be responsible for organising the defence in the middle of the field. In attack as dummy-half this player is responsible for starting the play from every play-the-ball by either passing the ball to the correct player or running the ball out of the dummy-half position themselves.

11 & 12	Second Row	The modern day second row is very similar to a centre and is expected to be faster, more mobile and have more skills than the prop and will play amongst the centres, providing strength in attack and defence when the ball is passed out to the wings.
13	Lock	The lock covers the entire field on both attacking and defending duties

Note. Position description information adopted from Andrews (1995).

The rugby league field of play is depicted in Figure 2 (below). It is bordered on either side by the touchlines, with each end of the field possessing an in-goal area (bordered by the deadball line and the tryline, along with the touch in-goal lines on either side).

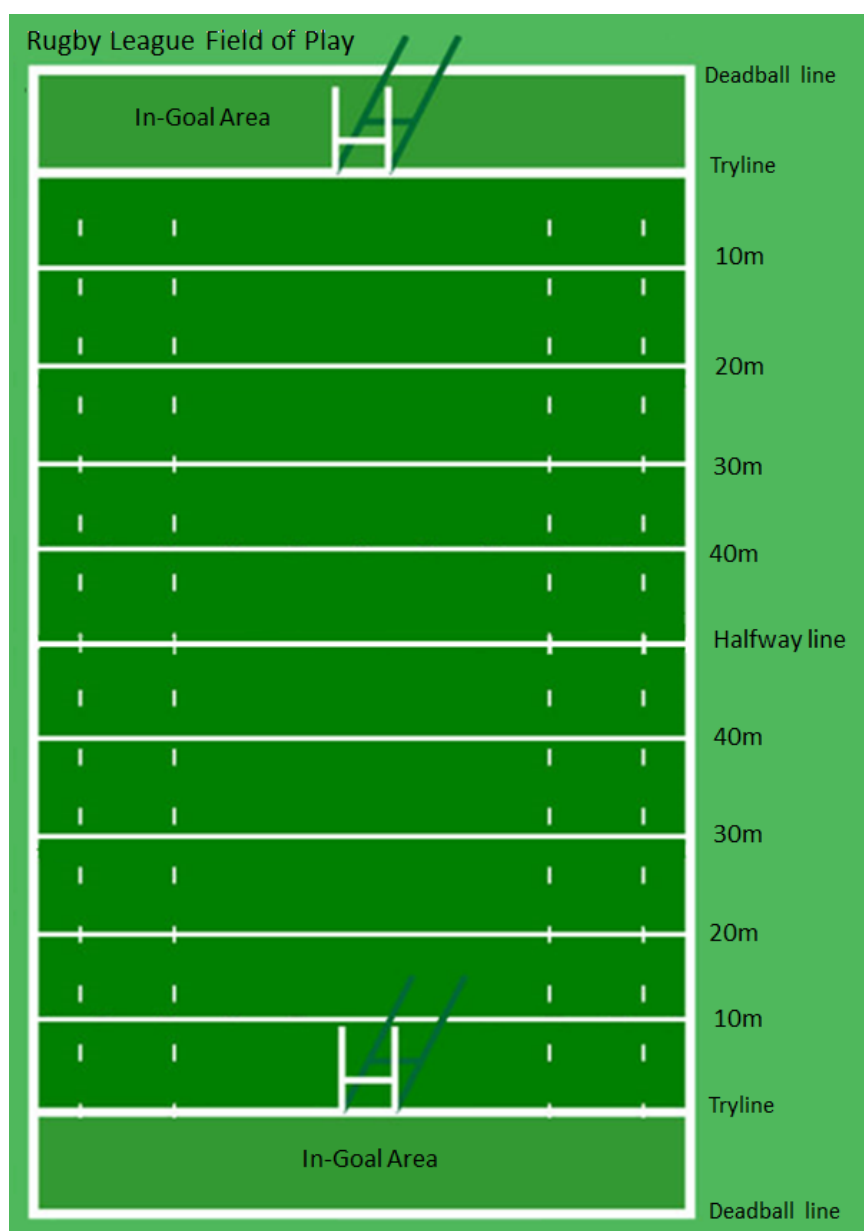


Figure 2. Rugby League Field of Play.

1.1.4 The National Rugby League's Concussion Policy

The NRL have adopted a concussion policy for a number of years, although this policy has been more formalised recently and closely monitored during the 2014 season. In 2014, the policy included a 'concussion interchange rule' (CIR) that enabled the removal of a player suspected of having sustained a concussion without the use of an interchange. The club doctor is given 15 minutes to assess the player before making a decision on his suitability to return to play. If cleared, the player may return to play, if not returned to play then an interchange is recorded for that player.

One of the expectations of the policy is that the Sports Concussion Assessment Tool - 3rd edition (SCAT-3) is administered to assist in forming the return to play decision (further details about the SCAT-3 are provided below). In addition to this sideline screening assessment tool, post-acute assessment of cognitive function may also be conducted with the computerised neuropsychological test, CogSport (further details about the CogSport test are provided below). The implementation of the CogSport program in the NRL pre-dates the more recent concussion policy.

1.1.4.1 Sports Concussion Assessment Tool – Third Edition (SCAT-3)

The Sports Concussion Assessment Tool – Third Edition (SCAT-3) is a standardised screening tool used to evaluate an athlete who may be suspected of having sustained a concussion in the acute and sub-acute stages. It is typically used in a sideline evaluation, once the player has been initially removed from play (McCrory et al., 2013). The SCAT-3 is freely available for downloading without restriction to anyone but as the SCAT-3 was designed for medical professionals, it is recommended that only medical professionals familiar with its administration use this tool. The SCAT-3 incorporates the Maddocks' questions (Maddocks & Dicker, 1989; Maddocks, Dicker, & Saling, 1995) and the Standardized Assessment of Concussion (SAC) (McCrea, 2001; McCrea, Kelly, Kluge, Ackley, & Randolph, 1997; McCrea et al., 1998; McCrea, Randolph, & Kelly, 2000), brief assessment of orientation, attention and memory function (Concussion in Sport Group, 2013). However, the SCAT-3 was not designed to be used as a sole basis upon which to diagnose or exclude a concussion and should not be used in the absence of clinical judgement. Importantly,

from a clinical perspective, an athlete may have sustained a concussion even if their SCAT-3 performance is found to be within the ‘normal’ range (Concussion in Sport Group, 2013).

1.1.4.2 CogSport

CogState Ltd.’s CogSport© (Collie, Maruff, McStephen, & Darby, 2003) is a computerized neuropsychological battery that requires approximately 15-20 minutes to complete. It requires responses to playing card stimuli. There are four subtests: Detection, Identification, One Card Learning and One Back. A number of performance based scores are produced for each subtest, including a standard score, time to complete the test, accuracy percentage, hits, misses and anticipation errors (responses to stimuli that are either too quick or occur prior to the stimuli being presented) (greater detail regarding neuropsychological testing is provided in the neuropsychological assessment section below).

1.2 THESIS OBJECTIVES

1.2.1 Overall Aims, Objectives & Study Hypothesis

The aim of this body of research was to examine a number of issues related to concussion in rugby league during both the acute and chronic phases post-injury. Initially it was considered important to establish the circumstances upon which concussions occur in the NRL.

To achieve this objective a systematic video analysis of antecedents and characteristics of medically diagnosed concussions was conducted (see chapter 3) in three participating clubs during the 2013 season. During the 2014 season, where the ‘new’ ‘concussion interchange rule’ was introduced for the first time, a similar systematic video analysis was conducted of antecedents and characteristics of the incidences that lead to the rule being used for all sixteen NRL clubs during the season (see chapter 4). This study hypothesized that: (i) the incidence of use of the concussion interchange rule will be proportionally greater than the incidence of medically diagnosed concussions observed in the three NRL clubs from the 2013 season; (ii) the concussion interchange rule would be used more frequently with

forwards than backs given forwards typically have greater body mass and are involved in more tackles; (iii) that the rule would be used more often with the hooker position than other positions because that position is generally held by smaller forwards, who generally complete high tackle counts; and (iv) that the ‘hit up’, where the ball carrier charges directly into an organised defensive line, will be the most frequent type of play resulting in the use of the CIR.

A systematic review of the MRS and sport-related concussion literature was also conducted to examine the use of this MR technique in current and former athletes (chapter 6). From a chronic perspective, a prospective sample of retired rugby league players was recruited to examine possible long-term effects of concussion from a cognitive and neurochemistry perspective (see chapter 7). The primary hypothesis was that NAA would be reduced in retired players compared to the control participants. Four a priori secondary hypotheses were also considered. First, it was hypothesized that mI would be elevated in retired players compared to control participants; second, it was hypothesized that Cho will be elevated in retired athletes compared to control participants; third, it was hypothesized that the concentration of glutamate would be reduced in retired players compared to the control participants; and finally it was hypothesized that the concentration of GSH will be reduced in retired players compared to the control participants.

1.2.2 Methodology

1.2.2.1 Participants

Study 1: All National Rugby League (NRL) players who sustained a concussion during the 2013 season (n=19) from the three participating clubs were included in this study.

Study 2: All National Rugby League (NRL) players who used the ‘concussion interchange rule’ during the 2014 NRL season (n=167) were included in study 2.

Study 3: Participants for study 3 were 13 retired professional rugby league players and 13 controls of similar age and education who had no history of neurotrauma or participation in contact sports. Retired players were recruited through the Newcastle Knights ‘Old Boys’ and control subjects were recruited through the local community.

1.2.2.2 Design and Data

Study 1: following confirmation from the club medical doctor of a diagnosed concussion, the PhD candidate reviewed video footage of each incident. The presence or absence of signs of concussion (i.e., loss of consciousness, body going limp, blank or vacant stare, wobbly legs, clutching head, or evidence of a concussive convulsion), along with player characteristics, details of the game play (i.e., time of game, type of play, tackle number in the set, location on the field, body region of initial impact, secondary impact [where applicable], and whether the concussion occurred as a result of foul play), together with information pertaining to return to play, were recorded.

Study 2: An analysis of the video footage of 167 events where the ‘concussion interchange rule’ (‘CIR’) was used during the 2014 NRL season was conducted. Similar to study 1 methodology, the PhD candidate reviewed video footage of each use of the rule and recorded the presence or absence of signs of concussion (i.e., loss of consciousness, body going limp, blank or vacant stare, wobbly legs, clutching head, or evidence of a concussive convulsion), along with information pertaining to player characteristics, game play (i.e., time of game, type of play, tackle number in the set, location on the field, body region of initial impact, secondary impact [where applicable], and whether the concussion occurred as a result of foul play) and return to play.

Study 3: All participants (n=26) completed a clinical interview, psychological and cognitive testing, and MRS investigation. MRS voxels were placed in unilateral-occipital grey matter and parietal white matter. Concentrations of glutamate (Glu), glutathione (GSH), *myo*-inositol (mI), *N*-acetylaspartate (NAA), total choline (tCho), creatine+phosphocreatine (Cr+PCr), and glutamate+glutamine (Glx) were quantified using LCModel.

1.2.3 Systematic Literature Reviews Methods

1.2.3.1 Systematic Review of the Rugby League Concussion Literature

Eligible articles were determined via online database searching, hand-searching reference lists and performing cited reference searches. Only articles published in English from 1900 up to June 2013 pertaining to concussion in rugby league athletes were considered. The online databases of PubMed, PsycINFO, MEDLINE, EMBASE, SPORTDiscuss and Web of Science were searched, using the key search terms: rugby league, league, football; in combination with injury terms: athletic

injuries, concussion, sports concussion, sports related concussion, brain concussion, brain injury, brain injuries, mild traumatic brain injury, mTBI, traumatic brain injury, TBI, craniocerebral trauma, head injury and brain damage. All articles included in the initial search were then reviewed to assess eligibility for inclusion in this review. Articles were regarded as relevant and warranting inclusion if they were experimental studies examining concussed rugby league players. Only observational, cohort, correlational, cross-sectional and longitudinal studies were included.

1.2.3.2 Systematic Review of the Magnetic Resonance Spectroscopy (MRS)

Sports Concussion Literature

Eligible articles were determined via online database searching, hand-searching reference lists and performing cited reference searches. Only articles published in English up to February 2013 pertaining to concussion and Magnetic Resonance Spectroscopy in athletes were considered. The online databases of PubMed, PsycINFO, MEDLINE, EMBASE, SPORTDiscuss and Web of Science were searched, using the key search terms and combinations of these terms: magnetic resonance spectroscopy, nuclear magnetic resonance spectroscopy, neurospectroscopy, spectroscopy, two-dimensional nuclear magnetic resonance spectroscopy, correlation spectroscopy, J-spectroscopy, exchange spectroscopy, nuclear overhauser effect spectroscopy, NMR, MRS, COSY, EXSY, NOESY, 2D NMR, craniocerebral trauma, mild traumatic brain injury, mTBI, traumatic brain injury, brain concussion, concussion, brain damage, athlete, athletic, and sport. All articles included in the initial search were then reviewed to assess eligibility for inclusion in this review. Articles were regarded as relevant and warranting inclusion if they were experimental studies examining MRS in concussed athletes. Eligible articles were independently assessed for quality using the quality assessment checklist selected for its generic comprehensiveness and currency. The criteria list included questions pertaining to both study relevance and validity. The criteria format included designation of studies as positive, neutral or negative.

1.3 LITERATURE REVIEW - SPORT-RELATED CONCUSSION

1.3.1 The Athlete

Modern sport is a highly competitive and lucrative commercial product, with the health of its major stakeholders, the athletes, regarded as a vital asset. The status of the athlete's cognitive health is one of the most important factors in maintaining a high level of athletic performance (Collie, Darby, & Maruff, 2001).

The rates of participation for Australian children aged 5-14 years in at least one sport outside of school hours revealed 1.7 million, or 63%, participated in such activities, and 1.2 million people aged 15 years and over (6.9%) participated in at least one form of football (i.e. soccer, rugby union, rugby league or Australian Rules Football). These football codes have among the highest rates of concussion worldwide. The reported incidence ranges from 5.9–9.8 concussive injuries per 1000 player hours, which equates to about five injuries per team per season (Australian Bureau of Statistics, 2008, 2009, 2011).

1.3.2 Prevalence of Sport-related Concussion

In the United States (US) incidence rates for sport-related concussion were recently revised by the Centers for Disease Control and Prevention (CDCP) from approximately 300,000 annually in the 1990s to as many as 3.8 million annually (CDC, 2009; Koh, Cassidy, & Watkinson, 2003; Tommasone & Valovich McLeod, 2006).

Comprehensive collegiate injury data has been collected by the National Collegiate Athletic Association (NCAA) Injury Surveillance System (ISS) since 1982. In 1999, NCAA ISS reported 4.2 concussion injuries per 1000 athletic exposures, with football game injury rates at 2.2 injuries per game for a team of 50 athletes. The equivalent rate for practice injury was reported as 4.7 injuries per game (Guskiewicz et al., 2003a). When considering all injuries sustained in NCAA competition, concussions generally account for approximately 4–10% of all injuries (Hootman, Dick, & Agel, 2007).

1.3.3 Contemporary Definitions of Concussion

Definitions of concussion have been developing over the past half a century and are likely to develop further with ongoing discoveries and advancements in knowledge of this unique condition. A variety of contemporary definitions have appeared in the professional literature but there is no universally accepted definition of concussion. The first attempt to resolve this confusion was proposed by the Committee on Head Injury Nomenclature of the Congress of Neurological Surgeons in 1966. They purported a “consensus” definition that concussion is “a clinical syndrome characterized by immediate and transient post-traumatic impairment in neural function, such as alteration of consciousness, disturbance of vision, equilibrium, etc. due to brain stem involvement due to mechanical forces” (Maroon et al., 2000). The American Medical Association and the International Neurotraumatology Association subsequently endorsed this definition and it has represented the most popular definition by far (Lovell, 2009a).

In 1996, the National Football League’s Mild Traumatic Brain Injury Committee offered the following definition of concussion:

...as a traumatically induced alteration in brain function, manifested by an alteration of awareness or consciousness, including but not limited to a loss of consciousness, “ding,” sensation of being dazed or stunned, sensation of “wooziness” or “fogginess,” seizure, postconcussion syndrome, including persistent headaches, vertigo, near-syncope, cognitive dysfunction, memory disturbances, hearing loss, tinnitus, blurred vision, diplopia, visual loss, personality change, drowsiness, lethargy, fatigue and inability to perform usual daily activities (Pellman, Viano, Tucker, Casson, & Waeckerle, 2003).

A number of definitions have also been published by professional organizations. In 1997, the American Academy of Neurology defined concussion in the following way:

A trauma-induced alteration in mental status that may or may not involve a loss of consciousness. Confusion and amnesia are the hallmarks of concussion. The confusional episode and amnesia may occur immediately after the blow to the head or several minutes later (American Academy of Neurology, 1997).

In 1999, the American Orthopedic Society for Sports Medicine defined concussion as follows:

Any alteration in cerebral function caused by a direct or indirect (rotation) force transmitted to the head resulting in one or more of light-headedness, vertigo, cognitive and memory dysfunction, tinnitus, blurred vision, difficulty concentrating, amnesia, headache, nausea, vomiting, photophobia, or a balance disturbance. Delayed signs and symptoms may also include sleep irregularities, fatigue, personality changes, an inability to perform usual daily activities, depression, or lethargy (Wojtys et al., 1999).

The Concussion in Sport (CIS) Group defined concussion this way:

A complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces. Several common features that incorporate clinical, pathological and biomechanical injury constructs that may be used in defining the nature of concussive head injury include:

1. Concussion may be caused either by a direct blow to the head, face, neck, or elsewhere on the body with an “impulsive” force transmitted to the head.
2. Concussion typically results in the rapid onset of short-lived impairment of neurological function that resolves spontaneously.
3. Concussion results in neuropathological changes, but the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury.
4. Concussion results in a graded set of clinical syndromes that may or may not involve loss of consciousness. Resolution of the clinical and cognitive symptoms typically follows a sequential course.
5. Concussion is typically associated with grossly normal neuroimaging studies (Aubry et al., 2002).

As each of the above definitions suggest, broadly speaking a concussion is generally a result of abrupt acceleration and deceleration of the brain within the skull. The

acceleration/deceleration forces may lead to linear and/or rotational movement of the brain whereby brain tissue moves against itself inside the skull, increasing the risk for cognitive and neurobehavioral deficits (Team Physician Consensus Statement, 2006).

1.3.4 *The Management of Sport-related Concussion*

Concussion is among the most complex injuries to diagnose, assess and manage in sports medicine. The effects of concussion are not confined to one domain. Instead, concussion is known to produce a constellation of self-reported symptoms and impairments of cognitive functioning, balance and other functional capacities during the acute phase (e.g., initial 24 hours). Athletes, to varying degrees, experience a complex combination of symptoms and exhibit deficits across multiple domains of functioning. Indeed, there is no perfect test or marker for an immediate diagnosis of concussion in the sporting environment (McCrea, Iverson, Echemendia, Makdissi, & Raftery, 2013). Tests do not diagnose whether a concussion has occurred in an athlete, rather, tests provide objective data on the physiological, cognitive, psychological and behavioural changes associated with the injury. These multidimensional components assist the clinician with an overall diagnostic formulation. As such, clinical diagnosis is based largely on the observed injury mechanism, signs and symptoms. Thus diagnosis of a concussion is a clinical judgment, ideally made by a medical professional. No one tool should be used solely to make, or exclude, the diagnosis of concussion in the absence of clinical judgement. Importantly, an athlete may have sustained a concussion even if their performance on screening or other measures is considered to be within normal limits (McCrory et al., 2013).

Although symptom assessment remains a critical component of the assessment process, some athletes may under-report concussions by almost 50% (McCrea et al., 2003) and therefore attention has been focused on the validation of objective measures for managing sport-related concussion. One method for managing concussive injuries adopts an individualized approach that includes a baseline and post-injury evaluation. However other approaches include a post-injury assessment only with comparison made to normative data, either option is considered to be clinically appropriate (Aubry et al., 2002; Guskiewicz et al., 2004; Guskiewicz,

Riemann, Perrin, & Nashner, 1997; Lovell, 2009a). Further details specific to neuropsychological assessment are discussed in chapter 5.

1.4 LITERATURE REVIEW – NEUROCOGNITIVE ASSESSMENT

Neuropsychological testing of concussed athletes has resulted in rapid expansion of sport-related concussion knowledge (Lovell, 2008). The utility of neuropsychological testing in assessing concussion was proposed as early as the 1880s (Walton, 1883), and has been documented empirically since the early 1980s (Rimel, Giordani, Barth, Boll, & Jane, 1981). Barth and colleagues at the University of Virginia in the late 1980s (Barth et al., 1989), demonstrated the potential usefulness of neuropsychological testing to monitor and document cognitive recovery in the first week following a sport-related concussion and it is considered a valid method for monitoring post-injury cognitive changes (McCrory et al., 2013).

The neuropsychological sequelae typically associated with sport-related concussion during the acute stages tend to include communication problems and perceptual and/or conceptual disturbances. Such deficits manifest as slowed information processing speed, poor attention and concentration, slowed reaction time and psychomotor speed, reduced new learning and working memory, and executive dysfunction (e.g., inhibitory control, flexibility and problem solving) (Aubry et al., 2002; Barr & McCrea, 2001; Barr, McCrea, & Randolph, 2008; Boutin, Lassonde, Robert, Vanassing, & Ellemberg, 2008; Casson, Pellman, & Viano, 2009; Covassin, Stearne, & Elbin, 2008; Erlanger, Kutner, Barth, & Barnes, 1999; Goldberg & Dimeff, 2008; Henry, Gross, Herndon, & Furst, 2000; Lovell, 2009a, 2009e; Mahone, 2007; McCrory et al., 2005; Meehan & Bachur, 2009; Mooney et al., 2007; Mrazik, 2000; Roebuck-Spencer, Sun, Cernich, Farmer, & Bleiberg, 2007). Language and visuospatial skills tend to be preserved following sport-related concussion (Lezak, Howieson, & Loring, 2004). Traditionally, cognitive assessments conducted in athletic populations utilised ‘pencil and paper’ neuropsychological measures (Barth et al., 1989; Collins et al., 1999). Many athletes with concussions have neuropsychological decrements detectable using conventional paper–pencil neuropsychological tests (and computerized neuropsychological tests, discussed below) in the initial hours, days, and potentially weeks post-injury (Karr,

Areshenkoff, & Garcia-Barrera, 2014). Specifically, Broglio and colleagues (2007) indicated that a high percentage of symptomatic athletes, on the day of injury, exhibited a significant decline on both computerised and pencil and paper cognitive tests. There were also 15-30% of athletes who were impaired on testing despite self-reported symptom recovery, although it was also reported that 10-25% of symptomatic athletes demonstrated no significant decline on neuropsychological tests (Broglio, Macciocchi, & Ferrara, 2007).

The primary focus of the initial post-concussion cognitive research tended to relate to retrograde amnesia and memory retention (Yarnell & Lynch, 1970). The results demonstrated that athletes developed progressive retrograde amnesia and memory difficulties approximately 3 to 20 minutes after a concussion. Despite this relative success in detecting cognitive deficits, it became apparent that only assessing memory-related performance was not an effective way to evaluate the multi-dimensional cognitive sequelae typically observed following sport-related concussion. As a result, the early focus on memory was expanded in subsequent studies to include multiple neurocognitive domains including processing speed, reaction time, attention and concentration as well as complex problem solving (Barth et al., 1989). Concussed athletes were found to consistently perform poorly on these multidimensional neuropsychological tests (Barth et al., 1989).

Computerised neuropsychological tests have been adopted as a core component of many concussion management programs (Macciocchi, Barth, Alves, Rimel, & Jane, 1996; Resch et al., 2013) and have been validated against paper-and-pencil tests (Allen & Gfeller, 2011; Collie, Maruff, Makdissi, et al., 2003) and post-concussion symptoms scores (Allen & Gfeller, 2011; Chen, Johnston, Collie, McCrory, & Ptito, 2007; Collie, Maruff, Makdissi, et al., 2003; Driscoll, Monte, Solomon, Krueger, & Grafman, 2013; Lau, Collins, & Lovell, 2011; Resch et al., 2013), with overall specificity and sensitivity of 80-90% (Lau et al., 2011). Neuropsychological assessment may also be useful in the absence of baseline data where appropriate local normative data is available (Echemendia et al., 2013). Computerised tests were developed in the 1990s to provide an alternative to traditional tests and are now used almost exclusively in many sports settings. The baseline - post-injury paradigm involves testing an athlete during the pre-season prior to their participation in a sport

or a given season. In the event of a concussion, the athlete's post-injury performance is compared to their own individual baseline performance to determine whether evidence of neurocognitive disturbance is present or absent (Echemendia & Julian, 2001). Theoretically, possessing individual baseline cognitive performance is considered to improve the diagnostic accuracy when compared to post-injury performances by limiting variance associated with pre-injury confounding variables. However, the pre-post injury assessment model may introduce error because test interpretation must take into account the test's psychometric properties (e.g. test-retest reliability) and the inherent error surrounding multiple testing sessions (i.e. serial post-injury assessment) that often occur at varying time intervals post-baseline and post-injury (Broglio, Ferrara, Macciocchi, Baumgartner, & Elliott, 2007; Comper, Hutchison, Magrys, Mainwaring, & Richards, 2010; Echemendia, 2010; Elbin, Schatz, & Covassin, 2011; Schatz, 2010). Test-retest reliability is particularly relevant, when considering that traditional pencil and paper tests were not originally designed for serial assessment over short-intervals (as may be required in concussed athletes to track their cognitive recovery). Importantly, neuropsychological tests that possess a low test-retest reliability increase the reliable change (RC) metrics, thereby potentially limiting the value of baseline examinations (Broglio, Ferrara, et al., 2007; Mayers & Redick, 2012; Randolph, McCrea, & Barr, 2005; Resch, Macciocchi, & Ferrara, 2012). Traditional tests have been studied in combination with computerised batteries to assess construct validity (Maerlender et al., 2012; Maruff et al., 2009).

Neuropsychological assessment and management models in sport-related concussion are designed to promote the screening of large numbers of athletes in order to establish an individual standard for each athlete. The model is distinctly different from more traditional models of neuropsychological evaluation that utilize extensive, time-consuming test batteries. The baseline evaluation is not designed to represent a comprehensive assessment but is targeted to assess cognitive domains that are most often affected by concussion, such as memory, attention and concentration, speed of mental processing, and reaction time (R. S. Moser et al., 2007). It is considered standard practice that an athlete's cognitive performance must return to baseline or better, both at rest and exertion, before returning to play, in order to avoid the possibility of more serious, cumulative injury during the vulnerable recovery period (Kontos, Collins, & Russo, 2004; R. S. Moser et al., 2007).

The combined use of traditional and computerised neuropsychological tests in applied settings has been referred to as a 'hybrid' neuropsychological testing approach (Comper et al., 2010). Both formats possess strengths and weaknesses in comparison to one another but typically the neuropsychologist administered pencil and paper method enables a more thorough and comprehensive assessment of more cognitive domains than the computerised format offers. Involvement of a neuropsychologist also enables the ability to document qualitative information and allows differential diagnosis considerations, and the assessment of other neurological or psychiatric conditions, that may masquerade as a concussion (Randolph et al., 2005). However, the conventional pencil and paper methods were originally designed to examine gross impairment at a single point in recovery not to be serially administered to detect the often very minor deficits in cognition frequently observed in sport-related concussion. Furthermore, conventional pencil and paper tests are time consuming and require trained, on-call clinical personnel to be properly administered (Lovell, 2006; Lovell & Collins, 1998; Schatz, Pardini, Lovell, Collins, & Podell, 2006). This method of assessment may be feasible at the professional level, however very few collegiate and high school programs have implemented this approach given the limitations of time, personnel and finances (Kontos et al., 2004).

The field of neuropsychology has also contributed significantly to the development of standardized sideline concussion assessment tools (Barr & McCrea, 2001; McCrea et al., 2013; McCrea et al., 1998), objective methods of symptom assessment (Gioia, Schneider, Vaughan, & Isquith, 2009; Lovell, 2006; Lovell & Collins, 1998; Randolph et al., 2009), and office-based assessments (Gioia, Collins, & Isquith, 2008). A sideline assessment (i.e. cognitive screening) may be conducted in the acute stage, either on-field or on the sideline, with more formalised testing conducted in the sub-acute and/or chronic stage (contingent upon recovery and clinical indications) (Echemendia et al., 2012; Echemendia et al., 2013; King, Brughelli, Hume, & Gissane, 2014; McCrory et al., 2013). Cognitive recovery largely overlaps symptom resolution, but may also occur following symptom recovery. Even in the absence of self-reported symptoms and overt physical signs, the neuropsychological assessment may be sufficiently sensitive to detect (Ellemberg, Henry, Macciocchi, Guskiewicz, & Broglio, 2009; Johnson et al., 2011; McCrory et al., 2005; McCrory et al., 2009;

Williamson & Goodman, 2006) and quantify subtle cognitive changes post-concussion, and importantly monitor cognitive recovery (Ellemberg et al., 2009; Johnson et al., 2011; McCrory et al., 2009; McCrory et al., 2013). Concussion management programs that use a neuropsychological assessment to assist in clinical decision-making regarding return-to-activity have been instituted across a number of levels of sports competition (i.e. professional, collegiate/varsity and high school).

1.4.1 Computerised Neuropsychological Test Batteries

With the advancement of technology, and acknowledged inherent limitations of the conventional 'pencil and paper' neuropsychological tests, a number of traditional measures were developed into computerized test batteries. Several researchers have developed computerized neuropsychological testing batteries and symptom evaluations for sport-related concussive injury that enable quick and efficient baseline evaluations of large groups of athletes (Collie et al., 2004; Collie, Maruff, Makdissi, et al., 2003; Erlanger et al., 2003; Erlanger, Feldman, Kaplan, Theodoracopulos, & Kutner, 2000; Erlanger et al., 2001; Lovell, 2008; Lovell & Collins, 2002). The use of comprehensive computerized neuropsychological batteries has largely supplanted the use of traditional neuropsychological measures in most concussion management programs (Bruce & Echemendia, 2009). Neuropsychological testing of sport-related concussion in the computerized format has several advantages and few limitations compared with conventional testing procedures, including; time efficiency, ease of information storage, randomization and alternative forms, automated scoring and measurement accuracy. This inevitably results in an increase in the validity of detecting subtle changes in cognitive processes, particularly those related to speed of response (Lovell, 2009a). In essence, a computerized approach has been considered to be more sensitive, reliable, practical, and certainly more cost-effective than conventional pencil and paper approaches. Because computerized neuropsychological testing is self-paced and self-directed, trained athletic trainers and other properly trained sports medicine staff members can administer baseline and follow-up tests (Randolph, McCrea, & Barr, 2005). However this perceived advantage also has a distinct limitation, in that there is no real opportunity for the neuropsychologist to observe the athlete completing the test directly (i.e. qualitative information regarding the athlete cannot be collected and used for assisting with clinical decisions).

Table 3. *Properties of Conventional ‘Pencil & Paper’ and Computerized Neuropsychological Tests.*

	Conventional ‘pencil & paper’	Computerized tests
Psychometric		
Alternative forms	None or very few	Infinite
Stimulus randomization	Within test only	Within test, between test & between subjects
Test-retest reliability	Wide range	Generally high for RT
Normative data	Mainly cross sectional, little	Very little for most tests
Practice effects	Large due to lack of alt forms	Small: alternative forms and randomization
Output	Level of performance	Level of performance and variability
Practical considerations		
Administration time	1min-4hrs	1min-2hrs
Support required	NP or trained technician for admin	Self-admin and auto scored
Accessibility	Poor – requires a NP	High – may be internet delivered
Data storage and analysis	Time consuming and costly	Automated

Note. NP: Neuropsychologist; RT: Response time; LT: longitudinal; alt: alternative; auto: automatic; admin: administration.

1.4.2 Limitations of Neuropsychological Testing

Despite the accumulating evidence supporting the clinical utility of neuropsychological tests for detecting and monitoring recovery from sport-related concussion, a number of limitations have also been documented (Collie et al., 2001; Echemendia et al., 2013; Randolph & Kirkwood, 2009; Randolph, McCrea, & Barr, 2005). Randolph, McCrea and Barr (2005) highlighted a number of shortcomings of both the conventional and computerized neuropsychological assessment tools and challenged the need for neuropsychological testing in managing an athlete’s recovery from a concussive injury. The authors provide a strong case that neuropsychological tests offer nothing to further return to play decisions and are therefore of no clinical benefit. The argument suggests that if an athlete is symptomatic no current guidelines permit return to play. Therefore, testing an athlete while symptomatic can add no value to clinical decision-making. Furthermore, at the time of their review, there was a lack of support in the literature for the ability of neuropsychological tests to detect residual neuropsychological impairments following resolution of concussive symptoms, implying neuropsychological testing could not add clinical value to management and return to play decision making. For this reason and the failure of

neuropsychological tests to meet other psychometric criteria (e.g. reliable change indices, adequate reliability, failure to develop psychometrically coherent test composite indexes) the authors proposed, “no neuropsychological tests have met the necessary criteria to support a clinical application at this time.” The review also highlighted that the real risks involved in premature return to play have never been clearly defined, and no assessment technique or management intervention has ever been demonstrated that result in risk modification.

1.5 LITERATURE REVIEW – MAGNETIC RESONANCE SPECTROSCOPY

Concussion in an athlete is typically caused by accelerations or decelerations of the head involving both linear (translational) and rotational forces (Elson & Ward, 1994). Once considered injuries that were completely transient in nature, it is now understood that when forces are applied to the brain with sufficient magnitude, long-term changes in structure and function can be observed in a subset of neurons and glia. Importantly, acceleration/ deceleration (A/D) forces differentially affect grey and white matter.

In an effort to demonstrate that movement of the brain within the cranial vault may be even more complex than was originally considered, Bayly and colleagues (2005) used MRI to observe that consistent mild accelerations of the head inside the imaging coil generate a remarkable amount of movement of the brain. Three subjects were asked to repeatedly allow the head to fall a short distance downward while lying in the supine position. Results revealed that tethering loads may be borne by the vascular, neural, and dural elements that bind the brain to the base of the skull. These biological tethers cause the brain to compress and stretch in the anterior-posterior plane followed by rotation backward and upward relative to the skull (Bayly et al., 2005).

When the brain moves within the cranial vault, stretching and compression can affect neuronal cell bodies, axons, and organelle as well as glial cells. The acute neurometabolic and neurochemical change that can occur in neurons following stretch or compression commence with a disruption of the neuronal cell membrane and axon

due to stretching resulting in ion movement across the plasma membrane, widespread release of neurotransmitters (most importantly excitatory amino acids such as glutamate), and influx of calcium ions. Further metabolic disruptions are caused by damage to mitochondria (Staal, Dickson, Chung, & Vickers, 2007; Wu, Ying, & Gomez-Pinilla, 2007).

Once an axon is stretched, a pathophysiologic process begins that can lead to structural change and metabolic dysfunction beyond the acute phase. Most studies indicate that it is acute axonal stretch and strain that causes a rapid increase in intracellular calcium. Strain on the axonal membrane causes an abnormal influx of Na^+ through mechanosensitive sodium channels, a reversal of the Na^+ - Ca^{2+} exchangers, and activation of voltage-gated Ca^{2+} channels (Wolf, Stys, Lusardi, Meaney, & Smith, 2001). This in turn causes selective proteolysis or a breakdown of Na^+ channels and progressively increasing levels of intra-axonal Ca^{2+} (Iwata et al., 2004). Dramatic elevations in intracellular calcium stores occur quickly with some estimates being within the first one to six seconds following axonal stretch (Staal, Dickson, Gasperini, Liu, Foa, & Vickers, 2010). The massive influx of Ca^{2+} leads to damage to the axonal cytoskeleton and initiates the pathophysiological process that follows. It is these pathophysiologic events that lead to the genesis of retraction balls, and eventually, secondary axotomy.

It has long been assumed that axons that have been stretched undergo subsequent axonal disconnection. When disconnection occurs close to the cell body, neuronal death ensues (e.g. Giehl, Schacht, Yan, & Mestres, 1997; Bonatz, Röhrig, Mestres, Meyer, & Giehl, 2000) with substantial neuronal atrophy occurring with more distal lesions. New evidence suggests that axonal injury causes (1) persistent neuronal atrophy in neocortex but not neuronal death, and (2) spontaneous structural plasticity (Greer, McGinn, & Povlishock, 2011). Equally important is the fact that injured neurons produce an elongation of their proximal disconnection over a 28-day period, consistent with regeneration and reorganization (Greer et al., 2011). Cortical impact models demonstrate that dendrites can also be affected when exposed to mild forces. Specifically, the dendrites of neurons in injured cortex swell in a manner similar to that described for axons, a condition that will obviously impact post-synaptic potential production (Gao & Chen, 2011). Further, repetitive injuries in cultured cells

result in reduced neurite (developing dendrites and axons in cultured cells) length and number (Kane et al., 2011).

In the presence of high extracellular glutamate (such as occurs during the complex neurometabolic and neurochemical cascade that occurs post-mTBI) extracellular glutamate induces a decline in GLT-1 and GLAST expression in cultured cortical astrocytes (Lehmann, Bette, & Engele, 2009). This of course can be linked to glutamate increases in the extracellular space that occurs in a feed-forward manner. Furthermore, astrocytes and microglia are important mediators of inflammation following concussion. Inflammation in the CNS is driven by the microglia, astrocytes, and peripheral macrophages that are all capable of releasing anti- and pro-inflammatory cytokines, chemokines, neurotransmitters, and reactive oxygen species. Precise regulation of inflammation is essential because of the potential impact on neurogenesis (Whitney, Eidem, Peng, Huang, & Zheng, 2009). It may be the case that astrocyte mediated pro-inflammatory cytokines such as IL-1 α may be involved in increased susceptibility to repetitive injury (Ranaivo, Zunich, Choi, Hodge, & Wainright, 2011).

Concussion is induced by biomechanical forces applied to the brain, and may involve two phases of tissue injury: primary and secondary. While primary injuries are almost immediate and generally irreversible, secondary injuries are delayed and can continue for an extended period of time. The primary injury phase involves direct and indirect mechanical damage from impact and acceleration/deceleration. Secondary injury is the non-mechanical damage that results from a complex metabolic cascade initiated by neuronal cell membrane disruption and axonal stretch, with neuronal membrane deformity leading to ionic flux and release of excitatory neurotransmitters. Attempts to restore homeostasis result in a cellular energy crisis with depletion of cellular energy stores preceding initiation of apoptosis and neuronal death. Furthermore, impaired cerebrovascular autoregulation results in decreased cerebral blood flow (CBF), inflammatory response with activation of microglia, and release of free radicals that are additional mechanisms that can contribute to tissue damage during the secondary injury phase. Although best described in severe TBI, diffuse axonal injury (DAI) occurs in mTBI as well and is recognised as an important determinant of long-term cognitive and neuropsychiatric outcome in mTBI.

Advanced neuroimaging techniques may prove to be vital in understanding the molecular, cellular, and functional mechanisms sport-related concussion (Slobounov, Gay, Johnson, & Zhang, 2012). These techniques can provide information about the cellular and molecular processes arising naturally during concussion and allow for the investigation of post-concussion recovery, for monitoring therapeutic response, as well as potentially providing prognostic information regarding long-term clinical outcome. Magnetic resonance spectroscopy (MRS) can provide insight into metabolic alterations in mTBI through observation and quantification of cerebral metabolites.

1.5.1 Sport-related Concussion and Neuroimaging

Most sport-related concussions are mild in nature, resolve without long-lasting sequelae, seldom requiring hospitalisation and therefore are rarely investigated via neuroimaging. However, a small proportion of athletes may sustain a more severe SRC and routine investigation may be necessary. The advancement of neuroimaging techniques has provided an avenue to investigate and better understand, not only neuronal disease and disorders but also the acute and chronic effects of acquired brain injury.

Magnetic resonance spectroscopy may be capable of detecting changes in glutamate/glutamine, N-acetyl aspartate, and myo-inositol, molecular abnormalities that may serve as markers of brain damage caused by head injuries (Ziegler et al., 2002). Further, measuring tau and phospholipid-tau in cerebrospinal fluid may yield diagnostically useful markers of CTE.

1.5.1.1 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) is used to visualise detailed internal structures. MRI makes use of the property of nuclear magnetic resonance (NMR) to image nuclei of atoms inside the body. The MRI scanner or ‘magnet’ uses a powerful magnetic field to align the magnetisation of certain atoms and radio frequency fields to systematically alter the alignment of this magnetisation. This causes the nuclei to produce a rotating magnetic field detectable by the scanner and this information is recorded to construct an image of the scanned area of the body. The differences in the MRI signal intensity of the grey and white matter permits segmentation of the brain

parenchyma into two separate compartments. Similarly, the extra-axial spaces and the ventricles filled with cerebrospinal fluid (CSF) can also be separated, allowing for volume calculation of the three different tissue-CSF compartments (Bigler & Tate, 2001). Such measurements enable accurate determination of qualitative and quantitative changes in specific brain areas following trauma (Hofman et al., 2001; MacKenzie et al., 2002).

Conventional MRI includes T1-weighted, T2-weighted and fluid attenuated inversion recovery images. These images provide exquisite detail of intracranial and cerebral structure, and can identify occult lesions not visualised on CT, such as small cerebral contusions. One of the measures studied in patients following TBI is the ventricle-to-brain ratio (VBR). This ratio is the total volume of the ventricles divided by the total brain volume. Increased VBR indicates increasing atrophy, and is directly related to the severity of injury. It is reflective of global changes but may disproportionately reflect white matter volume loss compared with that of grey matter (Garnett, Cadoux-Hudson, & Styles, 2001).

Voxel-based morphometry (VBM) is a method of voxel-by-voxel analysis of 3D MRI data. Subsequent to TBI, an individual's VBM has been utilised to locate sites where major differences occur (Prabhu, 2011).

1.5.1.2 Magnetic Resonance Spectroscopy (MRS)

Magnetic resonance spectroscopy (MRS) detects signals from chemical tissue. Neurospectroscopy (MRS of the brain) provides a unique insight into the brain's chemistry. It has been proposed that MRS is a tool that may be used to determine the long term effect of traumatic brain injury, providing an objective method of prognosis and therefore management of this condition. MRS has also been purported to detect much earlier the neuropathological signs of Alzheimer's disease, providing an opportunity for earlier management prior to progression of the disease (Mountford, Stanwell, Lin, Ramadan, & Ross, 2010).

MRS has long been used as a non-invasive method to measure concentrations of various compounds in the brain. Use of higher field strengths enhances the accuracy to determine concentrations of a broader range of metabolites including

neurotransmitters like glutamate, glutamine, gamma-amino butyric acid, and glycine. More recently, the role of MRS in the evaluation of patients with TBI has been studied by a number of groups (Ashwal et al., 2004; Cohen et al., 2007; Gasparovic et al., 2009). Gasparovic and colleagues (2009) reported on preliminary findings which indicated significantly lower levels of grey matter glutamine and higher levels of white matter creatine in subjects with mTBI relative to healthy controls (Gasparovic et al., 2009). Furthermore, creatine levels were predictive of executive dysfunction and emotional distress in the combined groups. It was hypothesised that change in levels of creatine (a critical component of the brain's energy metabolism) and glutamate, may occur following mTBI. Moreover, the different pattern of results for grey and white matter suggests tissue-specific metabolic responses to mTBI. Despite promising findings, the evidence for MRS in prognostication is not yet sufficient for use in routine clinical practice in all patients undergoing MRI for evaluation of TBI (Greer, 2009). The yield of applying newer techniques of obtaining and analyzing the MRS, like multivoxel acquisition and 2D correlation spectroscopy (2D-COSY), needs to be evaluated in the follow-up of athletes following brain injury (Ziegler et al., 2002).

Several studies have demonstrated the value of proton MRS for evaluation of TBI, with findings including significant metabolic alterations in brainstem (Carpentier et al., 2006), splenium of the corpus callosum (Cecil et al., 1998), parietal white matter (WM) (Brooks et al., 2000; Ross et al., 1998; Shutter, Tong, & Hoshouser, 2004), occipital grey matter (GM) (Brooks et al., 2000; Friedman, Brooks, Jung, Hart, & Yeo, 1998; Ross et al., 1998; Shutter et al., 2004), occipital white matter (Friedman, Brooks, Jung, Hart, & Yeo, 1998), frontal lobe white matter (Garnett, Blamire, Rajagopalan, Styles, & Cadoux-Hudson, 2000; Garnett et al., 2001), and the thalamus (Uzan et al., 2003). These reports have primarily studied subjects with more severe degrees of injury, and have used single-voxel spectroscopy acquisition methods to evaluate changes in these metabolites in a few normal-appearing brain locations. To evaluate metabolite changes from a wider extent of the brain, a few studies have used multi-voxel single slice spectroscopic imaging (MR spectroscopic imaging, or MRSI) (Holshouser et al., 2006; Macmillan et al., 2002; Marino et al., 2007; Signoretti et al., 2002), or volumetric MRSI methods (Govindaraju et al., 2004; Kirov et al., 2007), with analyses based on metabolite ratios from user-selected regions of interest. These

studies confirmed that subtle and widespread metabolite changes can occur in subjects with even mild TBI, and that these can occur remote from any MRI observed lesion (Govind et al., 2010).

1.6 LONG-TERM CONCERNS FOR RETIRED ATHLETES: CHRONIC TRAUMATIC ENCEPHALOPATHY

There are ongoing concerns regarding the potential long-term effects of concussion and multiple concussions on retired collision sports athletes. Particular concerns have historically been directed toward boxers, but more recently have also included other collision sports athletes like American football players and ice hockey players.

Chronic traumatic encephalopathy (CTE) has been referred to as a neurodegenerative disease with: (i) localized neuronal and glial accumulations of phosphorylated tau (p-tau) involving perivascular areas of the cerebral cortex, sulcal depths, and with a preference for neurons within superficial cortical laminae; (ii) multifocal axonal varicosities and axonal loss involving deep cortex and subcortical white matter; (iii) relative absence of beta-amyloid deposits; (iv) TDP-43 immunoreactive inclusions and neurites; and (v) broad and diverse clinical features (McKee et al., 2013). The aetiology of the modern description of CTE generally has been assumed to be multiple concussions in sports (McKee et al., 2013; Omalu, Hamilton, Kambou, DeKosky, & Bailes, 2010; Stein, Alvarez, & McKee, 2014). However, it also been proposed that a single traumatic brain injury of any severity (Omalu et al., 2010) or multiple mild TBIs in civilians or military service members (McKee et al., 2013; Omalu et al., 2010; Stein et al., 2014) can cause the disease.

From a clinical perspective, the historical description of CTE appears to present two clinical syndromes—one that was progressive and one that did not appear to be progressive (Johnson, 1969; Roberts, 1969; Roberts, Allsop, & Bruton, 1990). Slurred and dysarthric speech, gait problems, Parkinsonism, and cognitive impairment (including dementia) were commonly described. These early case descriptions contain extensive histories of psychiatric illnesses, severe substance abuse, and other medical or neurological problems. The extent to which these problems represent clinical features of CTE, one or more comorbidities, or both is difficult to determine.

Modern CTE has been characterised through retrospective family interviews and revisions of the medical records of post-mortem cases. CTE has been described as including chronic psychiatric problems, substance abuse, aggression, and suicidal behaviour have been linked to the described neuropathology (Baugh et al., 2012; Gavett et al., 2011; Omalu et al., 2011; Omalu et al., 2010), however associating completed suicide with CTE has been questioned (Iverson, 2014; Wortzel, Shura, & Brenner, 2013). McKee and colleagues (2013) have described clinical staging of disease: “Symptoms in stage I chronic traumatic encephalopathy included headache and loss of attention and concentration. Additional symptoms in stage II included depression, explosivity, and short-term memory loss. In stage III, executive dysfunction and cognitive impairment were found, and in stage IV, dementia, word-finding difficulty, and aggression were characteristic.” Clearly, at all stages of neuropathology, the differential clinical diagnoses are complex. This is especially true in the presumed early stages of the disease, where the clinical features might be subtle, nonspecific, and even relatively common in the general population (e.g., headaches or concentration difficulty).

In 2014, a new term related to CTE was coined, Traumatic Encephalopathy Syndrome (TES) (Montenigro et al., 2014). Montenigro and colleagues proposed research criteria for this syndrome having identified and reviewed the documented clinical features of 202 published cases of CTE over the past 100 years. The proposed research criteria for TES consists of four proposed subtypes: (i) TES behavioural/mood variant (i.e., emotionally explosive or depressed), (ii) TES cognitive variant (based on self-report and/or collateral report and low scores on neuropsychological testing), (iii) TES mixed variant (behavioural/mood features and cognitive features), and (iv) TES dementia. The duration of the symptoms must be a minimum of 12 months, and the primary source of exposure to neurotrauma. The individual must have played collision sport for a minimum of six years, with two years at the college level or higher. In the absence of exposure to a sport with repetitive blows to the head, a history of four documented mild TBIs or concussions, or two moderate/severe TBIs, is necessary. To meet diagnostic criteria, patients must also have a minimum of two of the following nine “supportive features”: (i) impulsivity (e.g., excessive gambling, increased or unusual sexual activity, substance abuse, or excessive shopping or unusual purchases); (ii) anxiety (e.g., anxious mood,

agitation, excessive fears, obsessive behaviour, or compulsive behaviour; and the authors note that a formal diagnosis of anxiety disorder would meet this criterion); (iii) apathy (e.g., loss of interest in usual activities, loss of motivation, and/or reduction of voluntary, goal-directed behaviours); (iv) paranoia; (v) suicidality (thoughts or attempts); (vi) significant headache (at least one episode per month for a minimum of 6 months); (vii) motor signs (e.g., dysarthria, dysgraphia, bradykinesia, tremor, rigidity, gait disturbance, falls, and/or other features of parkinsonism); (viii) documented decline (i.e., progressive decline in functioning); or (ix) delayed onset (i.e., usually at least two years after exposure, but delayed onset is not required for diagnosis). The diagnostic criteria for TES are extremely broad and will likely result in very high sensitivity at the expense of specificity (Montenigro et al., 2014).

There are fundamental unanswered questions about long-term health and welfare of retired collision sports athletes, and specifically CTE, with further research on clinical features in athletes with a remote history of repetitive neurotrauma required. Epidemiological studies on the relation between contact sports and neurodegenerative disease are needed. A standardised and precise protocol for studying the neuropathology is also required (e.g., minimum sampling of brain, preferred staining methods with acceptable alternatives, reporting of results, including clinicopathologic correlations). The current state of the science does not allow us to determine the extent to which repetitive neurotrauma uniquely causes, or partially contributes to, specific clinical symptoms such as depression, personality changes, or cognitive impairment. Based on decades of research in AD and other diseases, it is apparent that early stage tau pathology is usually not considered sufficient to cause clinical symptoms or a syndrome. Moreover, retired athletes are not immune to the medical, psychiatric, neurological, or neurodegenerative conditions, disorders, or diseases that affect the general population. The important next step in the process of potentially answering some of the unresolved issues associated with CTE is to conduct large-scale, prospective, longitudinal, clinicopathological studies (Gardner, Iverson, & McCrory, 2013).

CHAPTER 2

PUBLICATION 1: A SYSTEMATIC REVIEW OF CONCUSSION IN RUGBY LEAGUE

Gardner A, Iverson GL, Levi CR, Schofield PW, Kay-Lambkin F, Kohler RM, Stanwell P. (2015).
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This is the first systematic review on concussion in rugby league and has been published in the fourth highest ranked sports medicine journal. The review provided an effective method by which to establish the current state of the concussion literature within the sport in order to identify aspects requiring further investigation.

The systematic review was conceived and conceptualised by the PhD candidate. The database search, selection of included publications, the data extraction, analysis and drafting of the manuscript were also conducted by the PhD candidate.

This study was supported by funding from the NSW Sporting Injuries Committee and the Brain Foundation (Australia); these grant applications were both completed by the PhD candidate.

ABSTRACT

Objectives: Concussion remains one of the inherent risks of participation in rugby league. While other injuries incurred by rugby league players have been well studied, less focus and attention has been directed toward concussion.

Review Method: The current review examined all articles published in English from 1900 up to June 2013 pertaining to concussion in rugby league players.

Data Sources: Publications were retrieved via six databases using the key search terms; rugby league, league, football; in combination with injury terms: athletic injuries, concussion, sports concussion, sports related concussion, brain concussion, brain injury, brain injuries, mild traumatic brain injury, mTBI, traumatic brain injury, TBI, craniocerebral trauma, head injury, and brain damage. Observational, cohort, correlational, cross-sectional, and longitudinal studies were all included.

Results: 199 rugby league injury publications were identified. Thirty nine (20%) were related, in some way, to concussion. Of the 39 identified articles, six (15%) had the main aim of evaluating concussion, while the other 33 reported on concussion incidence as part of overall injury data analyses. Rugby league concussion incidence rates vary widely from 0.0 to 40.0 per 1,000 playing hours, depending on the definition of injury (time loss versus no time loss). The incidence rates vary across match play versus training session, seasons (winter versus summer), and playing position (forwards versus backs). The ball carrier has been found to be at greater risk for injury than tacklers. Concussion accounts for 29% of all injuries associated with illegal play, but only 9% of injuries sustained in legal play.

Conclusion: In comparison with other collision sports, research evaluating concussion in rugby league is limited. With such limited published rugby league data, there are many aspects of concussion that require attention, and future research may be directed towards these unanswered questions.

INTRODUCTION

Originating in the north of England in the late nineteenth century, rugby league has become a popular team collision sport played throughout the world at a variety of competition levels (1). It is a physical sport involving numerous collisions and tackles. Each team, consisting of thirteen players on the field, is allowed six tackles with the ball. The ball cannot be thrown forward but must be carried forward or kicked down field. At the completion of each set of six tackles, the ball is immediately given to the opposing team to commence their set of six tackles. The same players, therefore, engage in both offensive and defensive roles, depending upon which team is in possession of the ball. The game is played non-stop, except for a serious player injury, for two 40-minute halves. The overall objective of the game is to carry the ball over the goal line of the opponent to score a try (2). In Australia, rugby league is a popular contact sport. There are approximately 167,533 registered players with 368,869 involved in school competition and 893,965 involved in development club programs (3).

With the improvements in professionalism and commercialisation of sports such as rugby league, an increase in the value of the athlete as a commodity has occurred. Injuries sustained by players are now of considerable financial importance both to the individual player and to their club. Participation in rugby league, at any level, carries inherent risk for injury (4), including concussion.

Sport-related concussion is a common injury (5-7), and these injuries might be more prevalent than initially thought because some concussions go unrecognised (8). Approximately 90% of concussions in sport occur without loss of consciousness (9-12); thus, they can be difficult to detect and they might be under-diagnosed. Concussions are caused by accelerations or decelerations of the head involving both linear (translational) and/or rotational forces, and there is tremendous interest in

trying to better understand the biomechanics of this injury (e.g., 13-17). Concussions have a large adverse effect on cognition and balance in the first 24 hours following injury, with resolution of these deficits occurring within about one week according to group studies (18,19). There is evidence that a minority of athletes do not experience rapid recovery in cognitive functioning (20), and this subgroup might be obscured in statistical analyses applied to larger groups of athletes (21). Younger athletes might take longer to recover. In a prospective study of high school football players (22, 23), approximately 42-47% were deemed functionally recovered by one week (see Figure 1, page 503) (23) and it was not until four weeks that 84-94% were considered recovered.

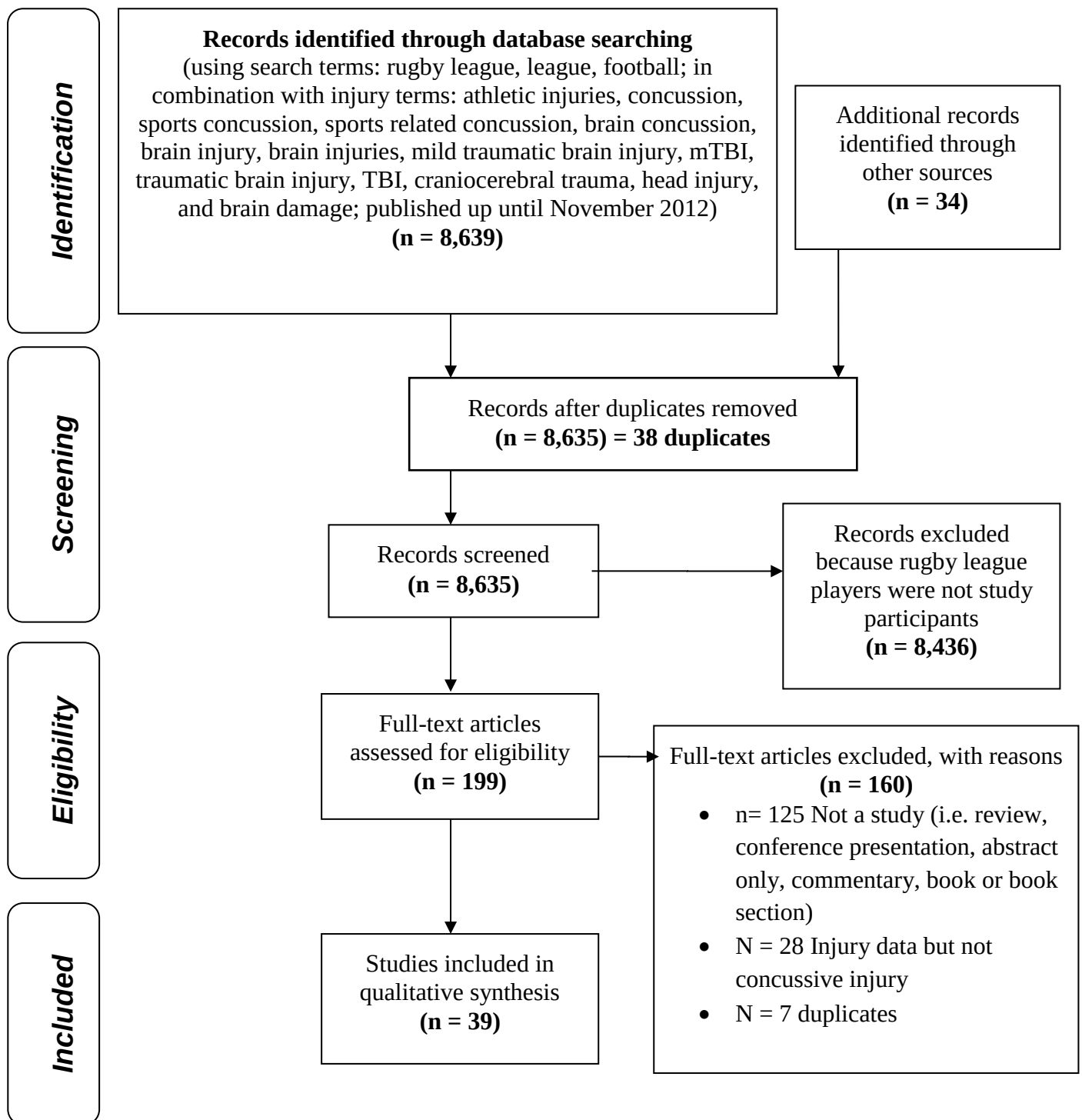
Concussion in sport has been the topic of media attention recently, thus raising awareness in the participants of collision sports, parents, and the general community, but also sports medicine physicians and researchers. The aim of this review was to systematically evaluate the available evidence on concussion in rugby league.

METHODS

The review was conducted in two stages. In stage 1, articles were retrieved via online database searching, hand-searching reference lists, and performing cited reference searches (see Fig. 1). The current review examined all articles published in English from 1900 up to June 2013 pertaining to concussion in rugby league athletes. The online databases of PubMed, PsycINFO®, MEDLINE®, EMBASE, SPORTDiscuss™, and Web of Science were searched, using the key search terms: rugby league, league, football; in combination with injury terms: athletic injuries, concussion, sports concussion, sports related concussion, brain concussion, brain injury, brain injuries, mild traumatic brain injury, mTBI, traumatic brain injury, TBI, craniocerebral trauma, head injury, and brain damage. The reference lists of articles retrieved for inclusion in the review were searched to identify other relevant articles.

Key articles retrieved via online databases and through hand searching reference lists were also used for further searches using the Web of Science Cited Reference function. During stage 2, the titles and abstracts of articles were reviewed to assess eligibility for inclusion in this review. Articles were regarded as relevant and warranting inclusion if they were experimental studies examining concussed rugby league players. Studies were included whether they were conducted with acute or long-term concussed athletes (i.e., there were no restrictions placed on time elapsed since injury) and independent of examination techniques used to assess these players (e.g., neuroimaging, symptom checklist, balance testing, or neuropsychological testing). Where there was uncertainty about whether a study should be included based on the review of the title and abstract, the full article was retrieved. Only observational, cohort, correlational, cross-sectional, and longitudinal studies were included.

Figure 1. PRISMA Flow Diagram



RESULTS

A total of 8,639 articles were identified using the search strategy outlined in Figure 1. The initial search strategy was far reaching and had limited restrictions, in order to identify all articles eligible for inclusion. Due to the nature of the initial search, a considerable number of citations were not relevant largely due to the use of the term “football”, which yielded over 7,500 citations pertaining to American football, rugby union, Australian football, and/or ‘soccer’ research. After all identified citations were screened, 199 were retrieved and screened for eligibility. Of the 199 articles, 125 were not research studies (i.e., conference presentation, abstract only, commentary), 28 were excluded on the basis that the participants were not athletes (i.e., they were not sports-related concussion cases), and seven duplicates were identified on closer inspection. The final outcome following this screening process resulted in the inclusion of 39 articles for this review (33 related to concussion incidence (1, 24-54) and 6 specifically examining concussion (55-60).

There were 18 published articles that reported the incidence of concussion per 1,000 playing hours (1, 25, 27-31, 36, 37, 39, 40, 47, 48, 51, 55, 61-63) (see Supplementary Table 2). Incidence rates varied widely from 0.0 (27, 31) to approximately 40.0, with differences in sampling and methodology likely explaining a large amount of this variation (37). Concussions are less common in rugby league than other types of injuries such as contusions, muscular strains, joint injuries, abrasions, and lacerations (4, 24, 28, 33, 61). The incidence of concussion has been observed to remain consistent over consecutive seasons. Between 13-17% of all players sustained a concussion over three consecutive seasons (55). However, studies on the incidence of injuries in rugby league are confounded by inconsistencies in the injury definitions used. Initial attempts at a standard definition for injury were not achieved, yet recently an international consensus opinion on the definition of injury

has been accepted (4). Some studies used the strict criterion of a missed match (time loss) as the injury definition, and others used a medical treatment (non-time loss) to define the injury. These variations in the definition of injury are highlighted by considering that up to 85% of all playing injuries, and up to 82% of all training injuries, are ‘non-time loss’ injuries. Non-time loss concussions account for approximately 71% of all concussions (46), suggesting that the most reliable studies in this body of literature estimate concussion incidence between 8.0 and 17.5 injuries per 1,000 player hours (1, 62).

Tackling has been identified as the most common cause of concussion in rugby league (30, 36, 53), with the tackled player reportedly more vulnerable to injury than those players making the tackle (61). It is therefore not surprising, given the reported forces induced on the bodies of players involved in the tackle (64), and the high number of tackles that occur each game (61), that the incidence of concussion in rugby league is relatively high (see Supplementary Tables 1 and 2 for a review). Playing position (forwards versus backs) might also influence the risk for concussion. The forwards (who typically possess a bigger physique and are involved in more contact/tackles during the game) might be at greater risk for injury than backs (28, 40). King, Hume, and Clark (61) reported that the tackle-related concussion occurred most frequently to the ball carrier when tackled at the shoulder or mid-torso height, in their blind vision, when involving two or more tacklers, and in the final quarter of matches. Of all injuries associated with illegal play, 29% were concussions, whereas only 9% of injuries sustained in legal play were concussions (53).

Compared to the rates of concussion during match play (34.6 per 1,000 playing hours), one study reported that the rates of concussion during training were 0.3 per 1,000 playing hours (33). A reduction in training loads (i.e., reduced by 1.7 versus 0.7 per 1,000 training hours) was also found to reduce the injury rates in rugby

league players and resulted in greater improvements in maximal aerobic power (31). Another study reported 32-37 injuries per 1,000 playing hours compared to 1.0 per 1,000 training hours by reducing training loads (37). Variations in concussion rates were also observed across seasons, with winter injuries occurring at a rate of 3.35 per 1,000 playing hours and summer 2.51 per 1,000 playing hours, with a winter/summer risk ratio of 0.75 (39). Despite little attention being given to the possible effects of history of concussion, one study reported that 62% of concussed athletes had sustained a previous concussion. This study also found 30% of players sustained a concussion in the current playing season (59). As a comparison, the rates of injuries during match play have been estimated to range between 1.68 (36) and 104.8 (27) for contusions, 9.2 (36) and 261.9 (27) for muscular strains, 12 (61) and 65.5 (27) for joint injuries, and 0 (27) and 40 (37) for concussions during 1,000 hours of match play.

In a New Zealand (NZ) economics study, concussions were associated with the highest mean cost per injury type, accounting for 6.3% of total injury costs, despite representing only 1.8% of the total injury entitlement claims (61). The incidence of concussion varied among ethnicity, with NZ Maori (n=62; 10.4 injuries per 1,000 playing hours) recording significantly more concussions than other ethnic groups (NZ European: n=41; 6.9 injuries per 1,000 playing hours; Pacific People: n=17; 2.9 injuries per 1,000 playing hours; Asian: n=0; others/unknown: n=31; 5.2 injuries per 1,000 playing hours). Total cost and mean cost per concussion was found to vary across ethnic groups in this study (NZ Maori: \$2,363,000 New Zealand dollars (mean cost per concussion \$38,118); NZ European: \$86,000 (mean cost per concussion \$2,097); Pacific People: \$44,000 (mean cost per concussion \$2,588); Asian: \$0; others/unknown: \$239,000 (mean cost per concussion \$7,709) (50).

The level of knowledge among players and officials regarding concussion and the opinion of players regarding the importance of management, researchers reported that 54% knew of a concussion policy in rugby league but only 8% could identify the three week mandatory stand-down requirement; and 78% reported a seven day stand-down as the requirement for recovery from concussion. Loss of consciousness was reported to be required in the definition of concussion by 39% of respondents. Overall concussion knowledge was low at 42% ($\pm 20\%$). Trainers/medics recorded the highest overall concussion knowledge. Misconceptions regarding this injury appear to be common (60). King and colleagues (49) reported that fewer than 34% of injured athletes sought medical clearance for return to sports participation for match play, and fewer than 25% for return to training. It was also reported that up to 75% of players felt that time off for rehabilitation was too long, especially for concussion with the three week mandatory stand-down period (49). Interesting, a survey of club coaches found that 55% of respondents who had a player with a concussion ($n=52$) had not sought medical clearance for a concussed player before returning them to match or training activities (60).

Hinton-Bayre, Geffen, and Friis (55) conducted the most thorough study to date examining the epidemiology and consequence of concussion in rugby league. The authors found the incidence of concussion remained relatively stable across the three seasons of observation. They reported 9.84 concussions per 1,000 playing hours in first grade (the highest level of club competition); 7.87 concussions per 1,000 playing hours in reserve grade (the second tier of club competition); 5.90 concussions per 1,000 playing hours in age-group (u/21s & u/19s) competitions. Loss of consciousness occurred in only six cases (12%), and individual players sustaining a subsequent injury accounted for seven (16%) of all concussive injuries. Unlike previous studies, Hinton-Bayre, Geffen, and Friis did not observe any playing

positions that were more vulnerable to concussion. Players in possession of the ball (players being tackled) were not concussed significantly more frequently than defensive players (players making the tackle). There were two recorded concussions that occurred when neither player in the collision had possession of the ball. The reported mechanisms of injury were as follows: 40% (n=17) head high tackles, 35% (n=15) head contact with the ground, and head contact with opposing player's body (n=5). The most common self-reported post-concussion symptoms were as follows: headache (n=35), unsteadiness (n=22), visual disturbance (n=19), dizziness (n=11), and nausea (n=10).

DISCUSSION

Concussions in rugby league are common. The incidence rates vary dramatically in large part due to how the injury has been defined across studies. However, using the more liberal injury definition, there appear to be between 8.0 and 17.1 injuries per 1,000 player hours. One study suggested that a substantial minority of athletes (e.g., 13 to 17%) will sustain this injury at least once over the course of three playing seasons (55). The rate of injury is much higher in match play than in training (33, 37). There is some evidence that forwards are at greater risk for injury (28, 40); the ball carrier appears to be statistically more likely to get injured than the tackling player (61). Concussion rates are disproportionately high for illegal play (53). This finding provides governing bodies of the sport with an opportunity to modify risk by implementing greater sanctions, which hopefully would modify the playing behaviour of participants and reduce concussion rates.

The definitions of concussion in past rugby league studies have not been consistent with international recommendations (65). Over the past decade, several agreement statements and consensus statements have set out standardised injury definitions for injury (66-71). In contrast, most rugby league studies have used a strict

criterion of a missed match (time loss) as the injury definition, and a number of other studies have incorporated a less strict injury definition that includes the player merely receiving medical treatment (non-time loss). Future researchers are encouraged to use consensus-based definitions of this injury (71).

The majority of rugby league studies addressed injury rates. There were only six studies that addressed other issues. The topics of these studies were diverse and mostly non-overlapping, including a comprehensive audit of concussion in rugby league (55), examination of the psychometric properties of screening (59) and cognitive tests in concussed rugby league footballers (56, 57), retrospectively examining concussive convulsions (58), and assessing concussion knowledge among rugby league club stakeholders (60). King and colleagues (60) found that misconceptions about concussion appear to be common in players, trainers, and coaches. This highlights a weakness in the education of rugby league stakeholders and the importance of widespread education. Education dissemination could be a collaborative effort between the governing bodies, and the elite level, which plays a crucial role in the filtering of all educational messages to the community and the grass roots levels.

Research focused on studying the acute consequences and best management strategies in current players, and the potential longer term outcomes of concussion in retired players is needed. Future research could, for example, use video analysis to determine whether certain playing styles (e.g., tackling, ball carrying, or running techniques) or playing positions, are associated with increased risk for injury (72-76). Future research in the areas of prevention, injury identification and medical management, and risk for long-term outcomes will be of benefit to current athletes, trainers, and coaches.

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AUTHOR CONTRIBUTIONS

Andrew Gardner developed the concept, methodology, conducted the literature search and structure of the review. He wrote the entire content included in the manuscript, figure and tables.

Grant Iverson assisted with the development of the concept and methodology. He also provided considerable editing and comment on all sections, the figure, and tables to finalise the manuscript.

Chris Levi, Peter Schofield, Frances Kay-Lambkin, Ryan Kohler, and Peter Stanwell provided expert input to the final draft of the manuscript.

COMPETING INTERESTS

Andrew Gardner has a clinical practice in neuropsychology involving individuals who have sustained sports-related concussion (including current and former athletes). He has received travel funding from the Australian Football League (AFL) to present at the Concussion in Football Conference in 2013. Previous grant funding includes the NSW Sporting Injuries Committee, the Brain Foundation and the Hunter Medical Research Institute, supported by Jennie Thomas.

Grant Iverson, Ph.D. has been reimbursed by the government, professional scientific bodies, and commercial organisations for discussing or presenting research relating to mild TBI and sport-related concussion at meetings, scientific conferences, and symposiums. He has a clinical and consulting practice in forensic neuropsychology involving individuals who have sustained mild TBIs. He has received research funding from several test publishing companies, including ImPACT Applications, Inc., CNS Vital Signs, and Psychological Assessment Resources (PAR, Inc.). He is a

co-investigator, collaborator, or consultant on grants relating to mild TBI funded by several organisations, including, but not limited to, the Canadian Institute of Health Research, Alcohol Beverage Medical Research Council, Rehabilitation Research and Development (RR&D) Service of the US Department of Veterans Affairs, Vancouver Coastal Health Research Institute, and Roche Diagnostics Canada.

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Supplementary Table 1. Studies examining concussion in rugby league players

Author (year)	Aims Purpose	Findings
King, Hume, & Clark (2012)	To examine the nature of rugby league tackles associated with injuries	The majority of injuries occurred in the tackle situation. More injuries occurred to the ball carrier than the tackler. Tackle-related injuries occurred most frequently to the ball carrier when tackled at the shoulder or mid torso height, in their blind vision, when involving two or more tacklers, and in the fourth quarter of matches.
King, Hume, Milburn, & Gianotti (2009)	To provide an epidemiological overview of rugby league injuries and associated costs in NZ over 8 years.	Although the cost of concussion over the study period only accounting for 1.8% of the total injury entitlement claims, concussion accounted for 6.3% of the total costs and had the highest mean cost per injury type (\$25,347).
King & Gissane (2009)	To describe differences in injury risk between different amateur participation levels.	No significant differences were observed between division 1 and division 2 teams for concussions.
Gabbett (2008)	Incidence of injury in junior rugby league.	The overall incidence of injury was 56.8 per 1,000 playing hours. Incidence of concussion was 4.6 per 1,000 playing hours.
Hodgson, Standen & Batt (2006)	Analysis of injury rates after the seasonal change in rugby league	The incidence of injuries in summer remained higher than that found in winter. The increase observed in concussion did not reach significance.
King, Gabbett, Dreyer, & Gerrard (2006)	To examine the incidence of injury in NZ rugby league sevens tournament	Over the two days of competition 76 injuries were observed. One concussion was recorded; equated to 6.5 per 1,000 playing hours.
Gabbett (2005a)	Playing position & injuries in rugby league	The hooker and props were found to have the highest incidence of injury of any playing positions. Concussion incidence was 5 per 1,000 playing hours in forwards versus 3 in backs; props recorded an incidence of 6 per 1,000 playing hours, backrowers and outside backs 4, and hookers and halves 2.
Gabbett (2005b)	To examine the influence of the limited interchange rule on the Incidence of injury	A 30% reduction in overall risk of injury was reported during matches played under the limited interchange rule in comparison to matches played under the unlimited interchange rule. Concussion (which also included 'open wound injuries to the head' in this study) had an increased risk of 0.59 under the limited interchange rule versus the unlimited interchange rule.
Gabbett & Domrow (2005)	Investigate the risk factors for injury in sub-elite rugby league	The incidence of injury was 55.4 per 1,000 playing hours. Injuries were most commonly sustained while being tackled and while tackling. The rate of concussion was 3 per 1,000 playing hours.
Gabbett (2004)	Investigate if reductions in pre-season training loads reduced the incidence of training injuries in rugby league footballers	A reduction in training loads reduced training injury rates in rugby leagues players and resulted in greater improvements in maximal aerobic power. Concussion rates were reduced from 1.7 versus 0.7 per 1,000 training hours.
Hrysomallis	To evaluate the impact energy	When compared to the Head Injury Criterion (HIC) values for the bare headform drops, the headgear on average

Author (year)	Aims Purpose	Findings
(2004)	attenuation of headgear using a yielding headform and no-rigid impact surface	reduced the HIC values by approximately 50%. 1/7 headgear tested generated HIC values below 1,000 for side of the head impacts. It appears that headgear thickness on the front and sides should be at least 15mm in order to offer adequate impact energy attenuation.
Gabbett (2004)	Influence of training and match intensity on injury rates in rugby league	Match-play injury-rate (any type of injury) was highly correlated with the intensity, duration, and load of matches. A significant positive relationship was present between the incidence of overall training injury (any type of injury) and the intensity, duration, and load of training sessions. Concussive injuries: Match (n=36) 34.8 per 1,000 playing hours; Training (n=1) 0.3 per 1,000 training hours.
McIntosh, McCrory, & Finch (2004)	To examine the impact energy attenuation performance of foam	Attenuation of impact energy could be increased by increasing foam thickness. The 16mm thick Honeycomb headgear model performed significantly better than the 10mm standard model.
Gissane et al. (2003)	To determine the incidence of injury in professional rugby league, in terms of major injuries and over 3 day injuries.	Very high injury rates; 563 per 1,000 players. Concussive injuries: Minor (n=10); over 3 days (n=2), and major (n=2).
Gissane, Jennings, Kerr, & White (2003)	To report the injury incidences over a period of five summer seasons and four winter seasons to examine the shift in playing seasons	Professional rugby league footballers doubled their risk of being injured; up to a 100% increase. Both forwards and backs demonstrated an increase in injury. The tackle is the most common mechanism for injury. Concussive injuries: summer (n=10) 4.02 per 1,000 playing hours; winter (n=8) 3.35 per 1,000 playing hours; Summer/winter risk ratio 1.20.
Gabbett (2003)	To document the incidence of injury in semi-professional rugby league footballers over two consecutive seasons	Overall playing incidences of injury of 824.7 per 1,000 player-position game hours, with First grade players having the highest incidence of injury (1055.3 per 1,000 player-position game hours). Rates of missed matches were higher in the present cohort (67.7 per 1,000). Concussive injuries: Playing injuries approximately 32-37 per 1,000 playing hours; Training injuries approx. 1 per 1,000 training hours.
Gabbett (2002)	Document the incidence of injuries in amateur rugby league sevens	Overall injury rate was 283.5 per 1,000 playing hours. This represents a 76.5% increase in rates of injury from the same cohort participating in conventional rugby league. Incidence of injury increased significantly when participating in consecutive matches. No concussions were observed in the study cohort.
Gissane, Jennings, White, & Cumine (1998)	To ascertain different injury rates from winter to summer seasonal play	Increased rates and risk of injury associated with summer competition in both forwards and backs. Injury rates in summer increased despite exposure decrease by one-third. Concussion: winter (n=8) 3.35 per 1,000 playing hours; summer (n=1) 2.51 per 1,000 playing hours; winter/summer risk ratio 0.75.
Gissane,	To document the differences in	The forwards/backs overall injury risk ratio was 1.50; 492 injuries [277 (56.3%) forwards, 215 (43.7%) backs].

Author (year)	Aims Purpose	Findings
Jennings, Cumine et al. (1997)	the incidence of injury between rugby league forwards and backs	Concussion: forwards (n=22) 11.1 per 1,000 playing hours; backs (n=13) 5.60 per 1,000 playing hours; total (n=35) 8.10 per 1,000 playing hours.
Stephenson, Gissane, & Jennings (1996)	To describe the incidence of injury in one professional rugby league club over a period of four seasons	Overall injury rate of 114 injuries per 1,000 playing hours. This incidence was reduced to 34 injuries per 1,000 playing hours, if injury definition restricted to those that miss a subsequent game due to the injury. Most common site of injury head and neck (33.3%) of the overall injury incidence. Concussion: first team (n=18) 8.0 per 1,000 playing hours; A team (n=17) 9.0 per 1,000 playing hours; total (n=35) 8.0 per 1,000 playing hours.
Gibbs (1993)	To study the incidence and nature of injuries sustained by players in all three teams of a professional rugby league football club over three seasons	Over the three playing seasons 141 injuries were observed, 44.9 injuries per 1,000 playing hours. Concussion (n=5 players) made up 6% of all injuries. Four concussions were minor (only missed one subsequent game), the other was a player who had three injuries. Games missed following each incident: 1, 4, and the rest of the season (2 games), respectively. 23 other players were treated on the field for mild concussion that did not require removal from play or missing subsequent games.
Seward, Orchard, Hazzard, & Collinson (1993)	To establish a comparative injury profile across the major football competitions in Australia at the elite level	Rugby league reported a total of 1,214 injuries during the season. The most common injury reported was head and facial lacerations (11.4%), followed by concussion at 8.5% of all reported injuries. These injuries were particularly common among forwards.
McKenna et al. (1986)	Public hospital admissions due to sporting injuries in New Zealand	A total of 5,108 admission due to sporting injuries were recorded during 1981-82. The overwhelming majority of injuries (80%) were sustained participating in winter sports (i.e., the warm season). 58.1% of cases were involved in 'rugby' (league and union). 504 'rugby' concussions were documented, which represents 70% of all documented concussions, 17% of all injuries in 'rugby' (the second most common behind fractures), and 10% of the overall injuries recorded. Concussion incidence is likely to be considerably higher, because these statistics are only for those injuries resulting in an admission to hospital.
Alexander, Kennedy, & Kennedy (1979)	Describe the pattern and incidence of one season of injuries in the top three grades of a NSW rugby league club	204 total injuries equating to one injury per 3.6 hours of play. Concussion (n=13) 3.6% of injuries, 10 occurred to front-row players.
Lingard, Sharrock, & Salmond (1976)	To identify the incidence, nature, and severity of sports injuries during the winter in New Zealand	Overall a total of 2,529 cases were documented across a variety of sports [rugby league n=192 (7.6%)]. A total of 124 central nervous system head injuries were recorded across all sports, only 87 resulted in a hospital admission. In rugby league, 4.2% of injuries were central nervous system head injuries (n=7).
Gissane, Hodgson, & Jennings (2012)	Describe the injury rates in rugby league in terms of those injuries that require players to miss	Overall 85% of all playing injuries and 82% of all training injuries are non-time loss injuries. Non-time loss concussions accounted for 71% of all concussions. Note: prior to 2012 it was possible to be classified as having a concussion and not miss any playing time.

Author (year)	Aims Purpose	Findings
	matches and those that do not.	
O'Connor (2011) ^{REF}	NRL injury report 2010	Concussions were sustained at an injury rate of 3.3 per 1,000 playing hours (n=27) at the NYC level, and 4.3 per 1,000 playing hours (n=30) at the NRL level. All incidences were recorded in games, with neither level recording a single incidence of concussion at training. Concussion represented 6.4% and 4.6% of the overall injury incidence in the NYC and NRL, respectively. 31 NYC games (mean: 1.3) were missed during the 2010 season as a result of a concussion (1.9 missed games per club). 55 NRL games (mean: 1.8) were missed during the 2010 season as a result of a concussion (3.4 missed games per club).
O'Connor (2012)	NRL injury report 2011	Concussions were sustained at an injury rate of 3.4 per 1,000 playing hours at the NYC level, and 4.2 per 1,000 playing hours at the NRL level. On average 1.7 (NYC) and 2.2 (NRL) concussions occurred per club during the 2011 season. Concussion represented 5.5% and 5.3% of the overall injury incidence in the NYC and NRL, respectively, and 6.8% and 6.4% of game injuries, respectively. An average of 1.0 NYC and 1.7 NRL games were missed during the 2011 season as a result of a concussion, equating to 1.7 and 3.8 games missed per club, respectively.
King, Hume, & Clark (2010)	Player perspectives on return to play after a match or training injury in amateur rugby league	In 2008, concussion resulted in missed matches (n=8; i.e., 17.0% of overall match injuries) but not training (n=0). Incidence of concussion match injury was 17.8 per 1,000 playing hours. In 2009, concussion resulted in missed matches (n=5; 11.4% of overall match injuries) and training (n=1; 5.0% of overall training injuries). Incidence of concussion match injury was 10.7 per 1,000 playing hours, and 0.2 per 1,000 training hours. Less than 33.3% of athletes sought medical clearance for return to sports participation for match play, and less than 25% for return to training post-injury. 75% of players felt that time off for rehabilitation was too long, especially for concussion with the three week mandatory stand-down period.
King, Hume, Milburn, & Gianotti (2009)	Injury surveillance, claims, and costs by ethnicity and other demographics in New Zealand rugby league	Concussion represented 0.5% ($\pm 0.4\%$) of all injury claims but 1.3% ($\pm 2.4\%$) of the overall injury costs. NZ Maori (n=62; 10.4 injuries per 1,000 playing hours) recorded significantly more concussions than other ethnic groups (NZ European: n=41; 6.9 injuries per 1,000 playing hours; Pacific People: n=17; 2.9 injuries per 1,000 playing hours; Asian: n=0; others/unknown: n=31; 5.2 injuries per 1,000 playing hours). Total cost and mean cost per concussion varied by ethnic group (NZ Maori: \$2,363,000 (mean cost per concussion \$38,118); NZ European: \$86,000 (mean cost per concussion \$2,097); Pacific People: \$44,000 (mean cost per concussion \$2,588); Asian: \$0; others/unknown: \$239,000 (mean cost per concussion \$7,709).
King (2006)	Incidence of injuries in the 2005 NZ national junior rugby league competition	74 total injuries were recorded with an overall incidence rate of 217.3 per 1,000 playing hours. Total recorded concussions (n=5) represented an incidence of 14.7 per 1,000 playing hours and 6.8% of the overall injury data. At the under 16s level (n=1 concussion) incidence of 4.3 per 1,000 playing hours and 2.0% of the overall injury data.

Author (year)	Aims Purpose	Findings
		At the under 18s level (n=4 concussions) incidence of 18.5 per 1,000 playing hours and 17.4% of the overall injury data.
King & Gabbett (2009)	Injuries in NZ semi-professional rugby league	Limited concussion details, beyond graphical representation of incidence of injury, approximately 6.0 per 1,000 playing hours.
Norton & Wilson (1995)	Rugby league injuries and patterns	352 injuries in 313 players, equivalent to 621 injuries per 1,000 players and 4.8 injuries per 1,000 playing hours. Concussion represented 11.8% of the total injury data. Restricted teams reported somewhat higher proportion of concussions compared with other grades. All concussions were reported to have been sustained in tackles. Of all injuries associated with illegal play, 29% were concussions. Only 9% of injuries sustained in legal play were concussions. Headgear was worn by 10.4% of players who sustained a head injury or concussion. Headgear was worn by 8.4% of players who did not sustain a head injury or concussion.
Hume & Marshall (1994)	Sports injuries in NZ: an exploratory analysis	Reported 3 fatal injuries in rugby league (not specifying cause), representative of 4.3% of all fatal injuries with an incidence of 0.41 per 100,000 players per year. A total of 102 injuries in rugby league, representative of 2.3% of all sporting injuries recorded, with an incidence of 137.82 per 100,000. Across all sports, hospitalisation due to concussion (n=421) represented 9.6% of all injuries, ED presentation (n=47) represented 1.5% of all injuries and sports injury clinic appointments (n=24) represented 3.9% of all injuries.
<i><u>Rugby League Studies with a Concussion Focus</u></i>		
Hinton-Bayre, Geffen, & Friis (2004)	Record the incidence of concussion in rugby league including the circumstances leading to concussion, injury incidence, mechanism leading to concussion, how the injury was recognised and the frequency of presenting signs and symptoms, across three seasons.	Concussion incidence remained relatively stable across the three seasons; 13-17% of all players. Loss of consciousness occurred in only 12% cases. 16% of recorded concussions were repeat injuries. All playing position were vulnerable to concussion, although the incidence of injury was not significantly different between forwards and backs in contrast to results from other studies. 9.84 concussions per 1,000 playing hours in first grade; 7.87 concussions per 1,000 playing hours in reserve grade; 5.90 concussions per 1,000 playing hours in age-group (u/21s & u/19s) competitions. Offensive players were not concussed significantly more frequently than defensive players (9.68 v 6.45 per 1,000 playing hours); only two concussions occurred when neither player in the collision had possession of the ball. Identification of a concussion was most frequently made when a player remained motionless on the ground (n=21); a player admitted problems subsequently (n=10); and observed unsteadiness (n=7). Mechanism of injury: 40% (n=17) head high tackles, but only 7 resulted in a penalty; 35% (n=15) head contact with the ground; and head contact with opposing players body (n=5). Most common self-reported post-concussion symptoms: headache (n=35), unsteadiness (n=22), visual disturbance (n=19), dizziness (n=11), and nausea (n=10).
Hinton-Bayre & Geffen (2002)	Severity of concussion and neuropsychological assessment	No relationship was observed between concussion severity grade and cognitive impairment for the severity grading systems used (AAN, Cantu, or Colorado Medical Society).

Author (year)	Aims Purpose	Findings
	results	Cognitive deficits were observed regardless of the severity rating within 2 days post-concussion. The percentage of rugby league footballers impaired at 10 days post-concussion was consistent across severity classifications. PTA was the only salient predictor of impairment at 2 days, although neither its presence nor duration was related to recovery. Players experiencing a loss of consciousness did not appear more likely to demonstrate impairment. The overemphasis of grading systems/classifications on loss of consciousness requires greater consideration and the effects of the mildest concussion may be underestimated.
Hinton-Bayre, Geffen, & McFarland (1997)	Study 1: examine alternate form equivalence, test-retest reliability, and practice effects on standardised measures of processing speed. Study 2: examine the sensitivity of the selected psychometric measure to the acute effects of concussion.	Study 1: Established alternate forms and test-retest reliability of measures expected to be sensitive to the effects of concussion on cognitive functioning. Study 2: Illustrated that timed tasks (silly sentences, Symbol Digit, and Digit Symbol) were performed more poorly following concussion. Silly sentences was found to be most sensitive.
McCrory, Bladin, & Berkovic (1997)	Retrospectively studied concussive convulsions in elite Australia rules and rugby league footballers	Only two cases of elite rugby league concussive convulsion during 15 playing seasons. Outcomes for a player experiencing a concussive convulsion were universally good. Concussive or impact convulsions are a non-epileptic phenomenon, and are not associated with structural brain injury. Antiepileptic medication is not indicated and prolonged absence from sport is unwarranted.
King, Clark, & Gissane (2012)	To determine whether the King-Devick sideline test and the Sports Concussion Assessment Tool (SCAT-2) could identify concussions in amateur rugby league footballers	12 games (414.5 match exposure hours) of a 24 game season were observed, three concussions were identified by team medics and two were found post-match by King-Devick testing. Three players identified on-field had significantly longer King-Devick test times (median increase greater than 5s) and reported greater post-concussion symptoms compared with their own baseline performance. Concussion incidence 12.1 per 1,000 match hours. Internal consistency of the three King-Devick testing cards was: card 1: 0.72, card 2: 0.78, and card 3: 0.76. Player cohort (n=50) self-reported history of concussion: 30% (n=15) of players sustained a concussion in the current playing season. 62% (n=31) reported a previous concussion history. 31 players (25.8%) were removed from play, with five (16.1%) receiving a subsequent medical clearance to return-to-play. Median number of days that players were removed from play was 17.5 (range 2-21) days.
King, Hume, & Clark (2010)	Assess the knowledge of first aid, concussion recognition and management, and injury	Concussion knowledge questionnaire Part III: "concussion recognition, management and prevention knowledge" consisted of 38 closed- and open-ended questions on concussion recognition, management, and prevention knowledge.

Author (year)	Aims Purpose	Findings
	prevention of local rugby league club administrators, coaches, and other team management in NZ	95 people (50 coaches, 13 managers, 15 trainers/medics, 14 club committee personnel and 3 referees) completed the questionnaire. Male:Female ratio 83%:17%, mean age 38 years (± 10 years), 55% (n=52) had a current first-aid certificate. Only 54% of coaches had a rugby league coaching qualification; 54% of managers had a rugby league manager's qualification, 13% of trainer's had a rugby league trainer's qualification, and 100% of referees had a rugby league refereeing qualification. All respondents indicated that they knew what the term concussion meant; 98% responded that sports-related concussion could influence players' social and work activities. 75% knew how to recognise a concussion in players but only 58% had discussed the consequences of a concussion with a player. 85% identified that playing while recovering from a concussion could lead to long-term complications. 70% insist a concussed player should see a doctor before returning to play or train, and 26% of non-coaches would check with the coach before they could return a player to play or training. 54% knew of a concussion policy in rugby league but only 8% could identify the three week mandatory stand-down requirement. 78% reported a seven day stand-down as the requirement for recovery from concussion. 55% of respondents who had a player with a concussion (n=52) had not sought a medical clearance for a concussed player before returning them to match or training activities. Only 33% ($\pm 14\%$) of respondents correctly identified concussive symptoms. 53% endorsed the wearing of head gear as a means to aid concussion prevention. More trainers (80%) supported this statement than coaches (62%) or managers (54%). Loss of consciousness was reported to be required for a concussion to have occurred by 39% of responses. Overall concussion knowledge was low at 42% ($\pm 20\%$). Trainers/medics recorded the highest overall concussion knowledge. Misconceptions regarding SRC appear to be common.
Note, NYC: national youth competition; NRL: National Rugby League; NZ: New Zealand; ED: emergency department.		

Supplementary Table 2. Studies reporting on concussion incidence

Author (year)	Concussion incidence	Injury Definition	Level of Play	Number of teams and seasons	Ranking of concussion frequency among all other injuries, rates of overall injury, and rates of concussion
King et al (2012)	Ball carrier 6 per 10,000 tackle events & 12 per 1,000 match hours; Tackler 4 per 10,000 tackle events & 8 per 1,000 match hours. Concussion Risk ratio Ball Carrier:Tackler = 1.4	An injury that rendered the player unavailable for selection in the next match	Professional	One team, two seasons (48 matches; 830 playing hours)	Equal 4 th ; 18 concussions / 266 total injuries
King et al (2009)	Division 1: 12.9; Division 2: 27.2; overall 17.5.	Injuries defined as both: transient (did not miss a game), and missed game injuries.	Amateur	Two teams, two seasons (53 matches; 951 hours)	Least frequent injury category recorded
Gabbett (2008)	4.6	Any pain or disability suffered by a player during a match that resulted in the player missing a subsequent match.	Junior	One team, four seasons (84 matches)	5 th most frequent type of injury
King et al (2006)	Total 6.5; Semi-Professional 10.6; Amateur 0.	Any pain or disability suffered by a player during a match that resulted in the player missing a subsequent match.	Semi-Professional & Amateur	20 teams, 1 'sevens' tournament (47 games)	Equal 6 th ; 1 concussion / 76 total injuries
Gabbett (2005)	Forwards: 5; Backs: 3; Outside Backs: 4; Halves & Hooker: 2; Backrowers: 4; Props: 6.	Any pain or disability suffered by a player during a match that resulted in the player missing a subsequent match.	Semi-Professional	156 players over two seasons	Forwards equal 5 th , 5 / 80 total injuries; Backs equal 5 th , 3 / 57 total injuries.
Gabbett (2005)	Unlimited Interchange: 5.1; Limited Interchange: 3.0; Limited/Unlimited Interchange RR: 0.59	Any pain or disability suffered by a player during a match that resulted in the player missing a subsequent match.	Semi-Professional	One club, three seasons (two under Unlimited Interchange; one under Limited Interchange rules)	Unlimited Interchange equal 4 th , Limited Interchange equal 5 th .
Gabbett et al (2005)	3.0	Any pain or disability suffered by a player during a match that resulted in the player missing a subsequent match.	Semi-Professional	One club, four seasons	5 th
Gabbett	Training injuries: Year	Any pain or disability suffered by a	Semi-	One club, three seasons	2001: 10 th ; 2002: 8 th ; 2003:

Author (year)	Concussion incidence	Injury Definition	Level of Play	Number of teams and seasons	Ranking of concussion frequency among all other injuries, rates of overall injury, and rates of concussion
(2004)	2001: 0; Year 2002: 1.7 Year 2003: 0.7	player during a match that resulted in the player missing a subsequent match.	Professional		10 th .
Hinton-Bayre et al (2004)	1 st Grade: 9.84; Res. Grade: 7.87; Age-Grade: 5.90	The team physician made a clinical diagnosis of concussion	Professional	Two clubs, three seasons	NR: Concussion only
Gissane et al (2003)	Summer: 4.02; Winter: 3.35 Summer:Winter RR: 1.20	Any pain or disability suffered by a player during a match that resulted in the player missing a subsequent match.	Professional	One club, nine seasons (five summer and four winter seasons)	Summer: 6 th Winter: equal 4 th
Gabbett (2003)	NR graphically represented. Match: Forward: slightly less than 40.0; Backs: slightly less than Forwards total. Training: Forwards: less than 1; Backs: 0.	Any pain or disability suffered by a player during a match that resulted in the player missing a subsequent match.	Semi-Professional	156 players, two seasons	Match: Forwards: 7 th ; Backs: 6 th . Training: Forwards: 11 th ; Backs: 13 th .
Gissane et al (1998)	Winter: 3.35 Summer: 2.51	A physical impairment received during a competitive match which prevented a player from being available for selection for the next competition game.	Professional	One club, four seasons	Winter: Equal 4 th , (8 / 72 total injuries) Summer: equal 5 th (1 / 20 total injuries)
Jennings et al (1997)	Forwards: 11.1 Backs: 5.6 Total: 8.1	The onset of pain or a disability that occurred while playing.	Professional	One club, four seasons	Forward: 6 th (22 / 277 injuries) Backs: 7 th (13 / 215 injuries) Total: 6 th (35 / 492 injuries)
Stephenson et al (1996)	All players: 8 1 st team: 8 A team: 9	The onset of pain or disability that occurred while playing rugby league football	Professional	Four seasons (249 games)	All players: 8 th (35 / 492 injuries) 1 st team: 8 th (8 / 297 injuries) A team: 7 th (17 / 195 injuries)
O'Connor (2011)	NRL: 4.3 NYC: 3.3	Any injury that was sustained during a first grade NRL game (or NYC game) or training session that resulted in missed game time.	Professional	Sixteen clubs, one season	NRL: 5 th ; NYC: 7 th

Author (year)	Concussion incidence	Injury Definition	Level of Play	Number of teams and seasons	Ranking of concussion frequency among all other injuries, rates of overall injury, and rates of concussion
O'Connor (2012)	NRL: 4.2 NYC: 3.4	Any injury that was sustained during a first grade NRL game (or NYC game) or training session that resulted in missed game time.	Professional	Sixteen clubs, one season	NRL: Equal 5 th NYC: 5 th
King (2006)	Total: 14.7 u/16: 4.3 u/18: 18.5	Any pain or disability suffered by a player during a match that required advice and/or treatment	Junior	Four teams, one season	Total: 6 th (5 / 74 total injuries) u/16: equal 9 th (1 / 49 total injuries) u/18: 2 nd (4 / 23 total injuries)
King & Gabbett (2009)	NR, graphically represented, approx. 6.	Any pain or disability suffered by a player during a match that required advice and/or treatment	Semi-Professional	Eight teams, one season	7 th
Note. Incidence reported as number of injuries per 1,000 playing (or training) hours; RR: risk ratio; Res: Reserve; NR: not reported; NYC: national youth competition; u/: under; approx.: approximately.					

PUBLICATION 2: A VIDEO ANALYSIS OF CONCUSSION IN THE NATIONAL RUGBY LEAGUE: A PRELIMINARY STUDY

Gardner AJ, Stanwell P, Levi CR, Quinn TN, Makdissi M,
Shultz SR, Wright D, Iverson GL. (2015).
Brain Injury. Accepted March 21, 2015.

This is the first video analysis of concussion in rugby league and has been accepted for publication in the seventh highest ranked rehabilitation journal. This video analysis is the first study to identify common game-play, and player characteristics leading to *medically diagnosed concussion* in the National Rugby League. This study also provided detail pertaining to video signs of concussion and return to play.

The video analysis was conceived and conceptualised by the PhD candidate. The data collection, video analysis coding and documentation, data analysis and drafting of the manuscript were also conducted by the PhD candidate.

This study was supported by funding from the NSW Sporting Injuries Committee and the Brain Foundation (Australia); these grant applications were both completed by the PhD candidate.

ABSTRACT

The aim of the present study was to conduct the first video analysis of concussion in the National Rugby League (NRL) and to describe player and injury characteristics, situational factors, and time to return to play. Videos of 20 medically diagnosed concussions for three clubs during the 2013 NRL season were reviewed. The concussion incidence was 14.8 injuries per 1,000 player NRL match hours, or approximately one concussion every four games. Most injuries (83%) occurred during a high tackle, and all injured ball carriers were hit high. None of the striking players were injured. All injuries involved a blow to the head or face. Loss of consciousness was observed in 30% of cases. Only half of the total sample was removed from play, and one athlete who was removed returned to play in the same match. Of the players who were removed from play, the large majority returned the following week. Illegal play accounted for 25% of all concussions. In summary, concussions in the NRL are common. Future studies may include larger numbers to validate this preliminary data, and may also investigate other levels of play and age ranges.

INTRODUCTION

Rugby league is a full-contact sport where participants are involved in numerous collisions and tackles. The game is played continuously in two 40-minute halves.¹ Like other contact sports, participation in rugby league, carries inherent risk for injury,² such as contusions, muscular strains, joint injuries, abrasions, and lacerations.³ The reported incidence of concussion in rugby league varies across studies, ranging from 0.04,⁵⁻⁶ to approximately 40.0 concussions per 1,000 player match hours. The wide variation in incidence rates is likely explained in large part by the differences in sampling and methodology (for review see Gardner et al⁷).

Video analysis of injury mechanisms is a unique method for objectively examining important characteristics or risk factors for injuries, which may ultimately provide sport-specific information for reducing the incidence of concussion.⁸⁻⁹ This has been previously demonstrated in video analysis studies of other sport-related injuries,¹⁰⁻¹¹ and specifically for concussion in other full-contact sports such as boxing,¹² soccer,¹¹ taekwondo,¹³ ice hockey,^{8,14} and lacrosse.¹⁵ To date there are no published studies on video analysis of concussion in rugby league. With the advancement of technology and the professionalism of rugby league at the elite level, an array of high quality video footage of National Rugby League (NRL) matches is now available. This wealth of information enables an analysis of match-play characteristics and injury mechanisms among NRL players. The aim of the current study was to analyze the video recordings of medically diagnosed concussions among three participating National Rugby League clubs during the 2013 season, with the objective of describing the player and injury characteristics, the match situational factors, recovery time, and return to play.

METHODS

All National Rugby League clubs were invited to participate in this study, three agreed to participate. All players medically diagnosed with a concussion by an experienced

team physician from the three participating clubs were included in the study. The digital video footage of games in which each concussion was diagnosed was reviewed. Descriptions pertaining to player's demographic information (i.e., age, height, weight, playing position, and game performance statistics) and return to match play were also recorded.

Procedure

Two raters (AG and TQ) independently viewed the digital records of events leading to concussion. Raters viewed each event using Quicktime Player V.7.7.5 software. Relevant variables were pre-determined and data were independently recorded by both raters. Raters were allowed to view the event as many times as required, in any playback speed deemed necessary to record relevant information for each variable. In order to reach consensus, all discrepancies between raters resulted in a review of the footage together and a discussion regarding the recorded data. Under circumstances where consensus was not reached, a third rater (PS) was to be consulted to make the final determination, however this was not required. Given the small sample size and the qualitative nature of this video analysis, the results are presented descriptively, and the incidence of concussion was calculated as the number of incidences per 1,000 player hours.

RESULTS

A total of 20 concussions were reported. There was one player who sustained two concussions (24 days apart) during the season, meaning data was collected on 19 players. This represents an incidence rate of 14.8 concussions per 1,000 NRL player match hours, which equates to approximately one medically diagnosed concussion every four games at the elite level.

Player Characteristics

All but one of the recorded concussions involved contact with an opposition player. Those players who delivered the contact that resulted in the concussive injury were classified as the 'striker'. On average, strikers were 188.4 cm tall (SD=5.4, range 178-198) and

weighed 101.9 kg (SD=7.1, range 82-110). Height and weight were not significantly different between the strikers and those who were injured ($p > .05$). Playing position was determined through match reports and verified by viewing the game footage. Forwards sustained 40% (8/20) of concussions and backs 60% (12/20). Fullbacks sustained 5% (1/20), wingers 15% (3/20), centres 20% (4/20), halfbacks 10% (2/20), five-eighth 10% (2/20), back rowers 5% (1/20), props 20% (4/20), and hookers 15% (3/20) of reported concussions.

How Do Concussions in the NRL Occur?

There were eleven concussions recorded by the ball carrier as compared to eight as a tackler. In one case, a player sustained a concussion while not in possession of the ball or in engaging in a tackle. This occurred to a defender who was contesting a cross-field kick. The number of players engaged in the tackle in which the concussion occurred varied. There were eight injuries sustained when there were two tacklers involved and seven concussions when there was one tackler involved. There were four cases of three tacklers being involved. In 83% (15/18) of tackles that resulted in concussion, the tackles were made high (i.e. the initial contact was made above the waist, to the upper torso or head) whereas only three concussions were sustained when the initial contact was below the waist. There were two incidences where the player lost his footing and fell into the impact. All ball carriers ($n=11$) who sustained a concussion were hit high. Of the tacklers ($n=8$) seven injuries were coded; three tacklers were making a low tackle and four tacklers were tackling high.

All concussive injuries were incurred by players who were struck in the head/face. The injured players were struck via a range of modalities: by the striking player's shoulder (7/20, 35%), knee (4/20, 20%), head (4/20, 20%), torso (2/20, 10%), elbow and forearm (1/20, 5% each). Interestingly, none of the striking players that caused the concussion sustained an injury. Secondary contact was observed in 25% (5/20 cases). Secondary contact involved impact with the playing surface in four out of five cases. The other secondary impact occurred as a result of a second defender joining in on the execution of a tackle as the

ball carrier was falling to the ground, and the defender's knees struck the player in the face. One-fifth of injuries (4/20 cases) were a result of foul play, with each of these incidents being placed on report by the match official.

Where Do Concussions in the NRL Occur?

Eleven concussions were recorded in the middle corridor, with nine observed in the side corridor. There were six (30%) concussions sustained in the defensive third, five (25%) in the midfield defensive third, four (20%) in the midfield attacking third, and five (25%) in the attacking third of the field.

When Do Concussions Occur?

There were nine concussions sustained in the first half and eleven sustained during the second half. When dividing the match minutes into quarters, more than half of concussions occurred in the final 20 minutes of either half (i.e., minutes 21-40 and 61-80 of the match; $n=13/20$). Regarding the tackle number in the set, there were no concussions recorded for tackle zero (which occurs irregularly during a game) or for tackle number three. Tackles one and four were associated with seven injuries each, while tackles five and tackle two were associated with four and two concussions, respectively.

Observable Signs of Injury

All injuries were coded for observable signs, such as loss of consciousness, body going limp, convulsive convulsion, clutching of the head, wobbly legs, and a blank/vacant stare. Loss of consciousness was observed in 30% (6/20) cases. There were no observable convulsive convulsions. There were 45% (9/20) of cases that resulted in the player's body going limp following the impact. Players who lost consciousness did not clutch their heads immediately following the impact, but of the remaining cases 50% (7/14) did so. Video footage was not always available (or conclusive) to determine whether the concussed player was demonstrating a blank or vacant stare post-injury. Of the available cases in which this could be coded, 53% (8/15) of players were observed to have a blank or vacant stare. Of the

concussed players who returned to their feet following the injury (n=18), two-thirds demonstrated balance problems through video evidence of ‘wobbly legs’. Considering all the observable signs simultaneously (i.e., loss of consciousness, clutching of head, blank stare, and balance problems), 80% had one or more of these visible signs on video. Considering the three observable signs most reflective of an injury to the brain (i.e., loss of consciousness, blank stare, and balance problems) simultaneously, 70% had one or more of these signs.

Medical Attention, Removal from Play, and Return to Play

Of the 20 cases, 19 (95%) were attended to on the field. Only 50% of cases (10/20) were removed from play. All players who appeared to have sustained a loss of consciousness were removed from play. Of the 10 players who were removed from play, one player returned to play in the same game (he had not sustained visible loss of consciousness). In the 10 cases where the concussed player was removed from play, the time taken and the mechanism by which they were removed was recorded. Seven (70%) players walked from the field assisted by the trainer, one player walked off unassisted, one player was taken on a stretcher, and one on the medicab. For the players who walked off (8 cases), the average time from injury to removal from play was 90 seconds (SD =20.4, Range = 60 - 113). The two more serious injuries that required the stretcher and the medicab to remove the players from the field took 7:24 and 4:55, respectively.

In the current data set, 50% of cases remained in play following their concussion and one (5%) returned to play during the same game. All of these players who remained in the game following their injury played again in the next match (i.e., none missed a match). Of those players who were removed from play and did not return to play in the same game, eight of nine cases, returned to play the following game (range: 5-19 days following); in two cases the club had a bye the following week.

DISCUSSION

This paper summarises the breakdown of the antecedent events and contextual factors associated with concussion in the NRL. It also provides a number of descriptive characteristics of NRL players, from three participating clubs, with medically diagnosed concussion over a single season. In a sport where body contact and tackling is an integral part of the game, it is not surprising that all concussion events resulted from a blow to the head or face delivered by an opponent.

The present study revealed an incidence rate of 14.8 concussions per 1,000 player NRL match hours or approximately one concussion every four games at this level. The overt signs of concussion were apparent on video analysis in the large majority of cases. The acute recognition, identification, and management of this injury on the sideline is important, and these overt signs, although not present in all cases, appear to be reliable indications that a player has sustained an injury and should be removed from play for further assessment.

Three-quarters of concussions occurred from high tackles, of which only 25% were considered illegal play, despite the initial contact for all cases being to the head or face. Stricter enforcement of the high tackle rule might result in fewer injuries.

Half of the players medically diagnosed with a concussion remained in play and another player returned to play during the same game. Of those players who were removed from play and did not return to play in the same game, eight of nine cases returned to play the following game. None of the athletes who remained in the game following their injury missed the next match.

Previous concussion surveillance studies in other contact sports,^{8,12-15} have collected data on more concussions than the current study,^{8,14} across more than one season,^{8,14-15} and have been able to conduct statistical analyses across some sport-specific factors and in turn provide recommendations regarding concussion management^{8,14} or coaching sport-specific technique.¹³ For example, a taekwondo video review found the striking participant delivering

a roundhouse kick to the temporal area of the head to an opponent in a closed stance position resulted in numerous concussions and recommended development of blocking skills.¹³ Whereas participants in combat sports like boxing¹² and taekwondo¹³ typically anticipate impacts, concussion in other contact sports such as ice hockey,^{8,14} lacrosse,¹⁵ and rugby league often occur in athletes who do not anticipate the impact. All published surveillance studies have been conducted at the professional or elite level. In some of those studies, the striking players were taller and weighed more than the players who sustained a concussion.^{8,14} In addition, player to opponent contact was reported as the predominant mechanism for concussion, typically directed to the head.^{14,15} Similar to the rugby league data, illegal play accounted for approximately one in four lacrosse¹⁵ and ice hockey concussions.¹⁴

There are limitations associated with a study of this nature. First, only three of sixteen eligible clubs participated, which limits the generalizability of the findings. Second, the current results may not accurately reflect the incidence or circumstances of concussion at other levels of play (e.g. semi-professional or amateur levels) or across other age ranges. Third, the study was conducted over a single season, which resulted in a relatively number of concussions being included for analysis. Nonetheless, several important issues highlighted in this paper are applicable to the rugby league community at large. Further video-analysis investigation with larger numbers of concussions is warranted to validate this preliminary data and enable statistical analysis of the data, which will allow additional questions to be systematically addressed. Future studies may also investigate other levels of play and samples that include a younger age range.

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PUBLICATION 3: A VIDEO ANALYSIS OF THE USE OF THE NEW ‘CONCUSSION INTERCHANGE RULE’ IN THE NATIONAL RUGBY LEAGUE

Gardner AJ, Iverson, GL, Stanwell P, Moore, T, Ellis J, Levi CR.

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This is the first systematic video analysis of the use of the ‘concussion interchange rule’ in the National Rugby League during the first season that this new rule was introduced and is under review with a top 20% of sports science journals. This video analysis is a follow up to the medically diagnosed concussion video analysis described in chapter 3, and is the first study to identify common game-play, and player characteristics leading to *suspected concussion*, and the use of the ‘concussion interchange rule’ in the National Rugby League. This study also provided detail pertaining to video signs of concussion and return to play. The video analysis was conceived and conceptualised by the PhD candidate. The data collection, video analysis coding and documentation, data analysis and drafting of the manuscript were also conducted by the PhD candidate.

This study was supported by funding from the NSW Sporting Injuries Committee and the Brain Foundation (Australia); these grant applications were both completed by the PhD candidate.

A Video Analysis of Use of the New ‘Concussion Interchange Rule’ in the National Rugby League During the 2014 Season

ABSTRACT

During the 2014 season, the National Rugby League (NRL) in Australia introduced a new ‘concussion interchange rule’ (CIR) to improve player health and welfare. We conducted a video analysis of the use of the CIR during the first season of its implementation and described player and injury characteristics, situational factors, concussion signs, and return to play. There were 167 reported uses of the CIR. Loss of consciousness (LOC) was observed in 32.3% of cases, loss of muscle tone in 53.7%, clutching the head in 70.0%, unsteadiness of gait in 66.0%, and a vacant state in 66.4%. More than half of the players who used the CIR returned to play later in the same match (56.8%). Forwards (69.9%) used the CIR significantly more often than backs (30.1%). Most incidences occurred from a hit up (62.3%) and occurred during a high tackle (80%). The results of this video analysis suggest that return to play guideline adherence and the accuracy of clinical return to play assessments warrant further review.

Key Terms: concussion; video analysis; injury management; return to play.

INTRODUCTION

Rugby league is a popular full-contact sport played internationally by 18 full-member test nations of the Rugby League International Federations (RLIF), 21 RLIF affiliate-members and approximately 32 other unaffiliated nations. The most popular elite, professional, domestic leagues are played in Australia and the United Kingdom. The game is played between two teams of thirteen players each, with four interchange players. At the professional level, interchanges are limited to 12 per team for the duration of the game. The game is played continuously in two 40-minute halves; if there is a draw at the end of regulation play then 'golden point' extra time is played for a maximum of 10 minutes each half or until one team scores to win the game [8]. Rugby league game play involves numerous collisions and tackles, and as is the nature of participation in any contact sport, rugby league carries an inherent risk for injury including head trauma [13].

The reported incidence of concussion in rugby league varies across studies. The rates of 'non-time loss injuries' range from 8.0 to 14.7 [12] concussions per 1,000 player match hours, with most past estimates ranging from 3.0 to 5.1 per 1,000 match hours. Sampling and methodological variations are likely to explain these reported differences in rates [4]. In a video analysis of medically diagnosed concussions in three National Rugby League (NRL) clubs from the 2013 season, the incidence was found to be 14.8 concussions per 1,000 player match hours or one concussion every four games [5]. The incidence of concussion at one NRL club over a 15 year (1998-2012) period was reported to be 28.33 concussion per 1,000 player match hours [20].

The NRL has implemented a number of steps aiming to improve player health and welfare in the area of concussion including the introduction of the concussion interchange rule, making the shoulder charge illegal, and the introduction of financial sanctions for perceived breaches of concussion policy. Following the 2013 season completion, the NRL in

Australia reviewed their concussion policy and enacted an updated policy that involved mandatory removal from play of any player suspected by sideline club training and/or medical staff of having sustained a concussion, in line with the international consensus statement from the Concussion in Sport Group [16]. During the latter rounds of the 2014 NRL competition, and during the 2014 finals series, the sideline visual assessment by club staff of a possible concussion was supported by the availability of immediate access to video review. The policy also included a 15-minute assessment window for a club medical officer to complete the Sports Concussion Assessment Tool 3rd edition (SCAT-3) and any other assessment deemed necessary. If the player, following this assessment, is then cleared to return to play and is able to do so within the 15 minute assessment period, then the team is not penalized an interchange (i.e., the team receives a ‘free interchange’). The criteria for a player to be “cleared” to return to play is based on the clinical judgment of full recovery made by club medical staff, allowing the player to return to the match in which they were removed under the CIR. If the player is cleared to return to play outside of this 15-minute assessment window, then the team is charged with an interchange. In the event that an athlete is not cleared to return to play, the interchange is not tallied against the injured player’s team.

The use of multi-angle capture slow-motion video footage is a unique and objective method to analyse mechanisms and characteristics of sports injuries. One of the main aims in doing so is to potentially provide sport-specific information on the mechanisms of injury and biomechanics with the long-term aim of reducing the incidence of concussion [3,9]. Video analysis studies of other sport-related injuries have been helpful in this regard [1,2]. Video analyses of concussions have also been conducted in other sports such as boxing [18], soccer [1], taekwondo [14], ice hockey [9,10], and lacrosse [15]. The NRL is a professional league with every match televised live, offering a wealth of information for analysis of match-play characteristics and injury mechanisms. Using video analysis of an injury ‘live’ (i.e., during

the match) throughout the 2014 season was at the discretion of each club, who all had access to their own video feed in the ‘coaches box’ during a match. During the 2014 final series, the NRL piloted providing a sideline video feed for club medical staff to review footage of injuries, especially concussions.

The aim of the current study was to conduct an “off-line” (post-match) analysis of multi-angle slow motion video recordings of cases where the concussion interchange rule was used in the National Rugby League during the 2014 season, with the objective of describing the player and injury characteristics, the match situational factors, player recovery time, and return to play time intervals as determined by the sideline concussion assessment and management process. We hypothesized that: (i) the CIR would be used more frequently with forwards than backs given forwards typically have greater body mass and are involved in more tackles; (ii) the rule would be used more often with the hooker position than other positions because that position is generally held by smaller forwards who generally have a high tackle count; and (iii) the ‘hit up’, where the ball carrier charges directly into an organized defensive line, will be the most frequent type of play resulting in the use of the CIR.

METHODS & MATERIALS

Each use of the CIR (i.e., clinically identified possible concussive events) during the 2014 National Rugby League season was included in the study. There was no video analysis conducted on any event that was not logged and assessed by club medical staff. The first author obtained information on the use of the rule (i.e., the player’s name and round in which the CIR was used). This information was provided by the NRL football operations manager and the NRL chief medical officer. Access to video footage of the incident was attained through the National Rugby League’s Digital Press Pass subscription. Online match reports were accessed via the NRL website. The digital video footage of incident for which the CIR

was used was reviewed. The player's demographic information (i.e., age, height, weight, playing position, and game performance statistics) and information regarding return to match play were also recorded from open access (public domain) online sources (<https://matchcentre.nrl.com> and <http://live.nrlstats.com>). All uses of the CIR were independently reviewed by the first author and at least one other author. Two authors were blinded to the study hypotheses but the first author was not blinded. The first author has experience in the identification of concussion on the sideline at this level. The other raters, although long-term followers of the sport, had no prior experience identifying concussion (one was an experienced referee of the sport). The three raters determined whether any of six signs (loss of consciousness, loss of muscle tone, seizures, clutching of the head, unsteadiness of gait, or possible impairment in cognition or awareness as evidenced by a blank or vacant stare) were present, absent, or indeterminable based on the available footage of the incident for every case. When there was disagreement between the two primary raters (who rated all incidents), both raters reviewed and discussed those cases in an effort to reach consensus. In the cases where consensus could not be achieved, ratings from a third rater were used. The final consensus decision data were used in the frequency data described in the Results section below. This study was approved by the University Human Ethics Committee. The methodology used was in compliance with the ethical standards of the International Journal of Sports Medicine [7].

Procedure

The digital records of events leading to the use of the CIR were independently reviewed by two authors (and sometimes three) using Quicktime Player V.7.7.5 software. The NRL digital press pass enabled review of full match replays provided by the broadcaster of each game. There was not however, the opportunity for the researchers to review specific incidences from multiple angles or in slow motion, except as provided by the broadcaster in

replaying the incident. Relevant variables were pre-determined and data was recorded, using identical methodology as used in the 2013 season video surveillance.[5] The incident was reviewed as many times as required in any playback speed deemed necessary to document relevant information.

Return to play during the same game was obtained by reviewing the full match replay, while the return to match play for those players who were not cleared to return to play in the same game in which they were taken from the field under the CIR was obtained by reviewing subsequent match reports from the NRL website. To confirm the match reports were accurate, video footage of the game identified as the player's returning game were reviewed to confirm that the player had taken part in that game.

Field of Play

For the purpose of distinguishing between locations on the field, it was divided into twelve sections across the length and breadth of the field of play. The breadth of the field of play was divided into three regions. The middle portion of the field between the 20 meter marking inside each sideline was defined as the 'middle corridor.' The 'side corridor' refers to the portion of the field on both sides between the 20 meter marking inside the sideline and the sideline itself. The length of the field of play was divided into four sections; the 'defensive quarter', whose boundaries include the in-goal area through to the 20 meter line at the defensive end of the field. The 'midfield defensive quarter' which runs from the 20 meter line to the halfway line; the 'midfield attacking quarter' which runs from the halfway line to the 20 meter line at the attacking end of the field; and the 'attacking quarter' which encompasses the area of play from the 20 meter line to the in-goal area at the attacking end of the field.

Statistical Analysis

Most of the analyses in this paper are descriptive. Pearson χ^2 test was used to compare proportional differences. For cases that involved contact with another player, the players' heights and weights were compared using independent *t*-tests. Inter-rater reliability analyses using Cohen's kappa (κ) statistics were used to determine consistency among the two raters for (i) the overall rating of all concussion signs, and (ii) each of the six individual signs. Cohen's kappa is considered to be the most appropriate method for calculating IRR in a study design with two raters [6]. Unlike the total percent agreement, Cohen's kappa considers the proportional agreement that could occur simply by chance. The κ coefficients are calculated by considering the proportion of rater agreement and the expected proportion [6]. Using the interpretations of κ described by McHugh [17], κ agreement was categorized as almost perfect ($>.90$), strong ($.80-.90$), moderate ($.60-.79$), weak ($.40-.59$), minimal ($.21-.39$) and none ($0-.20$). All analyses were performed using IBM SPSS Statistics V.22.0 and used two-sided tests for significance at the 0.05 level, with 95% CIs.

RESULTS

The CIR was used 167 times in the NRL during the 2014 season. There were five cases in which an incident leading to the use of the rule could not be identified on review of the video footage available leaving the total number of cases in the current study at 162. The CIR was used for 94 players on one occasion, 22 players on two occasions, and 6 players on three or more occasions throughout the season. There were no players who used the CIR more than once in the same match. Taking into account the players with multiple CIR use, data was available on a total of 122 individual players. The incidence rate was 24.03 (95% CI =20.68-27.91) uses of the CIR per 1,000 NRL player match hours. This equates to approximately one CIR use every 2.41 games in the 2014 NRL season.

Inter-Rater Reliability (IRR)

The overall IRR for the concussion signs for the two raters was $\kappa = 0.60$ (95% CI = 0.56-0.64), which is considered to be weak to moderate agreement [17]. The IRRs for each individual sign were as follows: loss of consciousness = 0.68 (95% CI = 0.61-0.74), seizure = 0.70 (95% CI = 0.69-0.71), unsteadiness of gait = 0.64 (95% CI = 0.57-0.71), clutching of the head = 0.50 (95% CI = 0.46-0.54), loss of muscle tone = 0.45 (95% CI = 0.42-0.49), and blank or vacant stare = 0.36 (95% CI = 0.29-0.43). The modest inter-rater reliabilities were due in part to the many indeterminable ratings from one of the raters, but there were also disagreements about the presence of individual signs. The third rater was needed to facilitate a consensus decision for the frequency calculations in 94 cases.

Observable Signs of Possible Concussion

All uses of the CIR were coded for observable signs. Overt loss of consciousness (LOC) was observed in 31.3% cases (50/160, there were two case where LOC could not be determined). There were three (1.9%) players who demonstrated observable signs of seizure-like activity. The player's body went limp with apparent loss of muscle tone following the impact in 53.7% of cases (87/162). Players clutched their heads 70.0% of the time immediately following the impact (112/161). The angles of view available in the video footage were not always appropriate to determine whether the injured player had a blank or vacant stare following injury. Of the available cases in which this could be coded (n=146), 66.4% of players were observed to have a blank or vacant stare suggesting impairment of awareness and/or cognition. Of the concussed players who returned to their feet following the injury and for whom video footage was available (n=144), 66.0% had observable balance problems in keeping with gait ataxia. Eighty-nine of 162 (55.9%) of players had three or more observable signs concurrently.

Overall, there were 83 players (53.2%) who returned to play in the same game (video footage was not available for 3 cases). Of the 80 cases with video footage, 23.8% (n=19) had video evidence of LOC; 50% (n=40) had evidence of loss of muscle tone; 72.5% (n=58) clutched their head following contact; 52.5% (n=42) had video evidence of gait ataxia; and 47.5% (n=38) had video evidence of a blank or vacant stare (see Table 1). No player with video evidence of a seizure-like activity returned to play in the same game. Of the 50 players with observed LOC, 38.0% returned to play in the same game (i.e., 19/50). There were 18 players who had no observable signs of concussion on review of the video footage of the incident that lead to the player being removed from play under the CIR. For this group, we had return to play data on 15, and 80.0% (12/15) returned to play in the same game. There were 70 players who demonstrated three or more of the four primary observable signs, where 42.9% (30/70) returned to play in the same game. Of the 66 players who required physical or motorised assistance from the field following the event, 74.2% (49/66) experienced three or more observable signs of injury. In this group overall, 36.4% (24/66) returned to play in the same game.

Table 1. Summary of video analysis findings.

	Total Sample			No Return to Play			Returned to Play		
	(N=162)			(n=76)			(n=80)		
	Yes	No	Missing	Yes	No	Missing	Yes	No	Missing
	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Loss of Consciousness	30.9 (50)	67.9 (110)	1.2 (2)	40.8 (31)	57.9 (44)	1 (1.3)	23.8 (19)	75 (60)	1.3 (1)
Loss of muscle tone	53.7 (87)	46.3 (75)	0 (0)	59.2 (45)	40.8 (31)	0 (0)	50 (40)	50 (40)	0 (0)
Clutching Head	69.1 (112)	30.2 (49)	0.6 (1)	68.4 (52)	31.6 (24)	0 (0)	72.5 (58)	26.3 (21)	1.3 (1)
Unsteadiness of gait	54.3 (88)	34.6 (56)	11.1 (18)	59.2 (45)	26.3 (20)	14.5 (11)	52.5 (42)	38.8 (31)	8.8 (7)
Vacant Stare	58.6 (95)	30.2 (49)	11.1 (18)	72.4 (55)	19.7 (15)	7.9 (6)	47.5 (38)	37.5 (30)	15 (12)
Seizure	1.9 (3)	98.1 (159)	0 (0)	3.9 (3)	96.1 (73)	0 (0)	0 (0)	100 (80)	0 (0)

Note. Return to play data was missing for 6 of the 162 athletes; therefore the total sample size for the ‘no return to play’ and ‘returned to play’ variables is 156.

Medical Attention, Removal from Play, and Return to Play

Of the 162 cases, 147 (90.7%) were rapidly assessed on the field and overall 90.1% of cases were immediately removed from play (five players remained in play until the next break in play before being removed from the field). All players who, on video evidence, sustained LOC were removed from play. Of the 146 cases where the concussed player was removed from play, the time taken for the player to be removed could be calculated in 101 (60.5%) of cases, with the average time for removal of the player of 99 seconds (SD= 70, range: 25-366 seconds).

Of those players who were removed from play but returned later in the game (n= 83/146, 56.8%), one (1.2%) player who was removed from play with physical assistance (two trainers in that instance) returned to play later in the same game; 23 (27.7%) players who were removed from play with physical assistance (one trainer) returned to play later in the same game; 30 (36.1%) of players who walked off unassisted returned to play later in the same game; all four players who ran off the field unassisted were returned to play; and four of the five who were not removed from the game until the next break in play returned to play later in the same game.

For the 83 players who returned to play in the game in which the CIR was used, 85.5% (71/83) played the following week (5-9 days later), 3 (3.6%) missed one match, and returned between 10-16 days following injury, and for 10.8% (9/83) there was missing data on when they played their next match. For the 78 players who did not return to play in the game in which they were removed from play under the CIR, 61.5% (48/78) returned to play the following game (between 5-9 days following injury), 12.8% (10/78) missed one match and returned in two weeks, 5.1% (n=4) returned in three weeks, 5.1% (n=4) returned 4 weeks or more following injury. For 12.8% (n=10) data were missing on when they returned to play. Note that the missing data for the return to play is a reflection of some of the uses of the rule

being made in a player's final game of the season and therefore there are no additional games played in the 2014 season.

The mechanism by which the player was removed from play was; five (3.5%) players remained in play until the next break in play, at which point they walked from the field unassisted; four (2.7%) players ran from the field unassisted; 52 (35.1%) walked off unassisted; 43 (29.1%) walked from the field assisted by a trainer; 15 (10.1%) walked off assisted by two trainers; one (0.7%) player was removed from play on a stretcher; and seven (4.7%) players were removed from play on the Medicab. There were 21 cases where there was insufficient video footage to determine how the player left the field, although it is highly likely that they left the field unassisted, because the game was typically stopped and video footage was available for the injuries where they required assistance. None of the players who were removed on the stretcher (n=1) or via the Medicab (n=7) returned to play. Despite missing data on the 'unsteadiness of gait' variable, all eight of these players demonstrated three observable signs of concussion on video analysis. Of the 146 players who were removed from play under the rule, 83 (56.8%) of players returned to play in the same game.

Player Characteristics

All but three (1.9%) of the recorded uses of the CIR involved contact with an opposition player. Those players who delivered the contact that resulted in the use of the rule were defined as the 'striking player'. On average, the striking players were 186.4 cm tall (SD=5.6, range 172-200) and weighed 102.5 kg (SD=10.2, range 81-133). The injured players were 185.7 cm tall (SD=5.4, range 172-200) and weighed 99.9 kg (SD=8.7, range 84-122). There was no significant difference in height [$t(332) = 1.2, p = 0.25$], but the striking players weighed marginally more than the injured players [$t(332) = 2.51, p = 0.013$]. Playing position was determined through match reports and verified by viewing the game footage. Interchange players accounted for 21.0% (34/167) of the uses of the rule. The CIR was used

with forwards on 57.4% (93/167) of occasions and with backs on 24.7% (40/167) of occasions. When considering the total number of player position exposures [i.e., 301 games multiplied by the number of players in each position on the field (12 forwards, 3,612 exposures, and 14 backs, 4,214 exposures)]; this represents a significant, proportional difference between the forwards and back positions [X^2 (1, 7,826) = 30.76, $p < .001$; RR = 2.7, 95% CI = 1.85-3.99]. Rates of use of the CIR by player position was as follows: fullbacks 4.2% (7/167), wingers 5.4% (9/167), centers 9.6% (16/167), halfbacks 1.8% (3/167), five-eighth 3.0% (5/167), lock 10.2% (17/167), second rowers 22.8% (38/167), props 14.4% (24/167), and hookers 8.4% (14/167). Some positions have two players on the field (i.e., winger, center, second row, and prop). Considering the number of players per position, the use of the rule occurred fewer than 5% of the time with wingers, halfbacks, five-eighths, and center, and more than 10% of the time with second rowers and locks. Of interest is that neither the absolute percentages or comparative rates indicated that the hooker position was over-represented in the use of the CIR (14 uses with 602 exposures) compared to all other positions combined [153 uses of the rule with 7,224 exposures; X^2 (1, 7,826) = 0.12; $p = 0.74$].

Circumstances When the Concussion Interchange Rule Was Used

There were 70 (43.2%) uses of the CIR with the ball carrier compared to 89 (54.9%) with a tackler and three (1.9%) incidences where the injured player was neither the ball carrier nor the tackler. The number of players engaged in the tackle in which a player was injured varied. There were 35 (21.0%) uses of the rule when there was only one player involved in the tackle. There were 55 (32.9%) uses where two tacklers were involved, 62 (37.1%) where three tacklers were involved, and five when there were four tacklers involved. In 95% (154/162) of cases it was possible to determine whether the initial contact between the ball carrier and the tackler was either defined as high (i.e., the initial contact was made above the

waist, to the upper torso or head) or low (i.e., initial contact was made below the waist). In 79.9% (123/154) of the injuries, the tackles were made high. Virtually all of the ball carriers who were injured were hit high (96.9%; 63/65). For the tacklers, 67% (59/88) were injured when making a high tackle and 33% (29/88) were injured in the process of making a low tackle. The tackler was most frequently injured when there were three players involved in the tackle (38/88; 43.2%), and the ball carrier was most frequently injured when there were two players (28/69; 40.6%) or three players (24/69, 34.8%) involved in the tackle.

The overwhelming majority (95.8%, 160/162 cases) of players removed from play under the CIR were struck in the head/face (in one case the information for the initial contact variable was not coded due to insufficient video footage). The striking player was rarely injured (4.4%; 7/158). Secondary contact was observed in 15.4% (25/162) of cases, with most of these cases involving impact with the playing surface (80%, 20/25). Referee identified and reported foul play accounted for 11.7% (19/162) of injuries, with 84.2% (16/19) of these players being placed on report by the match official.

There were 21 different plays or situations that were coded for the 162 uses of the CIR. The 'hit up' was the most common play that resulted in using the CIR, accounting for 62.3% of instances; no other play accounted for more than 5% of the CIR use. A common circumstance leading to the use of the rule was a tackler making a tackle high from the ball carrier making a hit up (25.7% of all uses of the CIR).

Where Do Incidences Occur?

There were 122 (75.3%) uses of the rule that occurred in the middle corridor, whereas 40 (24.7%) were observed in the side corridor. There were 36 (22.2%) uses of the rule that occurred in the defensive quarter, 51 (31.5%) in the midfield defensive quarter, only five (3.1%) in the midfield attacking quarter, and 70 (43.2%) in the attacking quarter of the field.

When Do Incidences Occur?

There were 88 (54.3%) uses of the rule in the first half, 73 (45.1%) during the second half, and one (0.6%) during golden point extra time. Regarding the tackle number in the set, there was one (0.6%) use of the rule for tackle zero (which occurs irregularly during a game). There were 32 (19.2%) uses for the first tackle, 28 (16.8%) uses for the second tackle, 31 (18.6%) for the third tackle, 32 (19.2%) for the fourth tackle, 31 (18.6%) for the fifth tackle, and 7 (4.2%) for the sixth tackle.

DISCUSSION

This paper summarizes antecedent events and contextual factors associated with the implementation of the CIR in the NRL during its first season of use. It also provides descriptive characteristics of players and game situations. There were three a priori hypotheses. First, as hypothesized, the concussion interchange rule was used more frequently with forwards than backs. The second hypothesis was not supported; the rule was not used more often with the hooker position based on absolute percentages or based on comparing the rate of the rule for this position. The rule was used more frequently for forwards than for backs with both the second rower and the lock position using the rule more than 10% of the time. Third, as hypothesized, the 'hit up' was the most frequent type of play resulting in the use of the concussion interchange rule. Of the 21 coded plays or situations in which the rule was used, the hit up (62.3% of cases) was the only play that accounted for more than 5% of the rule use.

The inter-rater reliabilities for the concussion signs were weak to moderate [17]. This was likely due to multiple factors, including differences in experience between the raters and difficulty in observing or quantifying the signs (which in some cases are subtle and/or subjective) leading to one rater using the indeterminate code much more often than the other primary rater. This was most evident in the rating of a blank/vacant stare, which appears to be

a very subjective sign to code on video analysis. Notably, a significant factor influencing inter-rater reliability is restricted ranges (e.g., coding video evidence of overt signs of concussion as present, absent, or indeterminable). Having well quantified constructs of interest, like the more objective factors included in the National Hockey League's (NHL) Heads-up checklist (HUC) [11], generally results in greater inter-rater reliabilities [6]. For example, the Heads-up checklist validation study found 8/15 factors had a κ value greater than 0.6 for two naïve raters and 11/15 for two expert raters. However, this tool does not require raters to code overt concussion signs such as those conducted in the current study. To the authors' knowledge this is the first video analysis study to examine evidence of concussion signs in a large cohort of contact sport athletes. This study is also unique because a trainer or doctor identified the athlete from the sideline as potentially having suffered a concussion that required further investigation; the athletes were not necessarily diagnosed with concussion.

There was a high rate of return to play in the same game for players who had observable signs of concussion on post-hoc video analysis. It should be recognized that the reported signs were apparent on video review, with the "off-line" process allowing the incidents to be watched repeatedly, in slow motion and from multiple angles, if necessary. However, it is noteworthy that this opportunity was not afforded to the medical staff, who are typically positioned on the sideline, at ground level, sometimes with obstructed view of the play. It can be extremely difficult for the doctor to see these signs from their position on the sideline. Moreover, the medical staff undertake a direct clinical assessment, are able to gauge the players clinical neurological status, and make an on-the field diagnosis. The purpose of this paper was to retrospectively review characteristics on video footage of events identified first hand and assessed and managed in real-time. The extent to which some of the signs observed on video (e.g., clutching head or a vacant stare) are reliable indicators of clinically

defined concussion is not well understood. Moreover, those signs might resolve rapidly and when evaluated clinically the athletes might not show evidence of concussion on the sideline. The difficulties encountered in sideline identification and assessment (e.g., the elusive nature of concussion, the heterogeneity, sensitivity and specificity of the sideline assessment tools, and the potential evolving nature of concussive injury) are documented [19] and some athletes undoubtedly continue to play after an injury to their brain. More research is needed to improve our ability to rapidly and accurately identify concussion, especially the milder end of the spectrum, during the course of a game or match.

There are limitations associated with a study of this nature. It proved to be difficult to code many of the video footages for specific signs of concussion. Little is known about the reliability and accuracy with which observers can do this. Importantly, there was no verification sought for the final diagnosis of players who did not return to play in the same game in which they were removed from play under the CIR. That is, some players who remained out of play may not have been diagnosed with a concussion. Importantly, the design of the study is such that we can make no inference about the overall sensitivity of the current concussion surveillance system given the lack of an accepted “gold standard” identification system. In this analysis we did not undertake what could potentially be regarded as some form of standard such as an independent expert observer review of the match video record to identify all concussion events. Hence, the data collected does not provide an indication of the incidence of those players who sustained a possible concussion but were not captured under the CIR. Further, this is not a study of medically diagnosed concussion as no direct clinical assessments were undertaken. Therefore, we can make no comment on the appropriateness of the return to play assessments given we have no information on the sidelines assessment process, the possibility of concomitant injuries, nor any agreed upon standard to measure observed results against. Other issues to note are this is, to our knowledge, the first report on

the application of a CIR in the first season of its implementation in a professional sport. One can assume that, as club officials became accustomed to the new rule they may have established different thresholds for removing and returning players under the rule. A less conservative approach may account in part for the number of players (56.8%) who were medically cleared to return to play in the same game following their second clinical assessment. Importantly also, the study was conducted over a single season, as opposed to multiple seasons. The return to play measurement was based on return to play at the NRL level. No data was available to assess possible return to play at lower levels of the game. Finally, it is recognized that there were a variety of reasons, beyond a diagnosis of concussion, for the player to not return to play at the NRL level. All of these factors could not be controlled for and may bias the return to play data.

Future rugby league video analysis may investigate other levels of play and samples that include a younger age range. A more comprehensive examination of all tackles throughout the entire season may also establish base-rates of certain at-risk plays and provide a clearer picture of the incidence of injury by type of play. Reviewing video footage of injuries provides a unique insight into the characteristics and possible risks associated with contact sports, like rugby league. Injury data from video analysis of specific injuries, like concussions, can inform the development of prevention strategies to reduce or minimise identified risks.

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PUBLICATION 4: A SYSTEMATIC REVIEW OF PROTON MAGNETIC RESONANCE SPECTROSCOPY FINDINGS IN SPORT- RELATED CONCUSSION

Gardner A, Iverson GL, Stanwell P.

Journal of Neurotrauma (2014) 31(1), 1-18.

This is the first systematic video analysis of magnetic resonance spectroscopy in concussion. It has been published in the 76th highest ranked (top 30%) neuroscience journal. The review examined the methodology (i.e., data acquisition and post-processing techniques) and findings of all MRS publications in concussed athlete samples.

This systematic review was conceived and conceptualised by the PhD candidate. The data was collected, collated and analysed by the PhD candidate, and the manuscript was authored by the PhD candidate.

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A Systematic Review of Proton Magnetic Resonance Spectroscopy Findings in Sport-Related Concussion

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Abstract

Traditional structural neuroimaging techniques are normal in athletes who sustain sports-related concussions and are only considered to be clinically helpful in ruling out a more serious brain injury. There is a clinical need for more sophisticated, non-invasive imaging techniques capable of detecting changes in neurophysiology following injury. Concussion is associated with neurometabolic changes including neuronal depolarization, release of excitatory neurotransmitters, ionic shifts, changes in glucose metabolism, altered cerebral blood flow, and impaired axonal function. Proton magnetic resonance spectroscopy (^1H -MRS, or simply MRS) is capable of measuring brain biochemistry and has the potential to identify and quantify physiologic changes following concussion. The focus of the current review is to provide an overview of research findings using MRS in sport-related concussion. A systematic review of articles published in the English language, up to February 2013, was conducted. Articles were retrieved via the databases: PsychINFO, Medline, Embase, SportDiscus, Scopus, Web of Science, and Informit using key terms: magnetic resonance spectroscopy, nuclear magnetic resonance spectroscopy, neurospectroscopy, spectroscopy, two-dimensional nuclear magnetic resonance spectroscopy, correlation spectroscopy, J-spectroscopy, exchange spectroscopy, nuclear overhauser effect spectroscopy, NMR, MRS, COSY, EXSY, NOESY, 2D NMR, craniocerebral trauma, mild traumatic brain injury, mTBI, traumatic brain injury, brain concussion, concussion, brain damage, sport, athletic, and athlete. Observational, cohort, correlational, cross-sectional, and longitudinal studies were all included in the current review. The review identified 11 publications that met criteria for inclusion, comprised of data on 200 athletes and 116 controls. Nine of 11 studies reported a MRS abnormality consistent with an alteration in neurochemistry. The results support the use of MRS as a research tool for identifying altered neurophysiology and monitoring recovery in adult athletes, even beyond the resolution of post-concussive symptoms and other

investigation techniques returning to normative levels. Larger cross-sectional, prospective, and longitudinal studies are required to understand the sensitivity and prognostic value of MRS within the field of sport-related concussion.

Key Words: concussion, athlete, magnetic resonance spectroscopy.

Introduction

Sport-related concussions are traumatic brain injuries on the very mild end of the neurotrauma spectrum. These injuries can cause severe symptoms and impair balance and cognitive functioning—especially in the first 24 hours following injury (1, 2). Functional recovery, as assessed by self-reported symptoms, balance testing, and cognitive testing, occurs within a few days to one month in the vast majority of athletes (3, 4). Structural neuroimaging techniques, such as computed tomography (CT) and conventional magnetic resonance imaging (MRI), are seldom helpful for identifying the pathophysiology associated with this injury. Rather, they are used to rule out more serious injuries and associated macroscopic abnormalities (e.g., contusions, hemorrhage). However, MRI techniques such as diffusion tensor imaging (DTI) (5, 6) and magnetic resonance spectroscopy (MRS) (7) provide non-invasive, *in-vivo* indices of pathophysiology associated with moderate and severe traumatic brain injury (8), and these imaging techniques have the potential to reveal changes associated with sport-related concussion.

MRS is a neuroimaging technique that provides non-invasive, *in-vivo* measurement of biochemistry and thus allows for assessment of the underlying metabolic changes that accompany disease throughout the body. The clinical application of MRS originated in the late 1980s and early 1990s (9-15) where the initial focus was directed to the brain and the term *neurospectroscopy* was coined to refer to MRS of the brain. MRS is a logical technology to use with injured athletes because concussion is believed to be associated with a “neurometabolic cascade.” Giza and Hovda (16) described the primary elements of the pathophysiologic / neurometabolic cascade of concussion and described the concept of metabolic vulnerability occurring in brain tissue following a concussion. In brief, these elements involve abrupt neuronal depolarization, release of excitatory neurotransmitters,

ionic shifts, changes in glucose metabolism, altered cerebral blood flow, and impaired axonal function (16).

According to this model, biomechanical forces to the brain induce ionic shifts resulting in acute and subacute changes in cellular physiology. There is an abrupt, indiscriminant release of neurotransmitters and unchecked ionic fluxes, which include the binding of excitatory transmitters, such as glutamate, to the N-methyl-D-aspartate (NMDA) receptor. This is the catalyst for neuronal depolarization [i.e., the efflux of potassium (K^+) and influx of calcium (Ca^{2+})]. The sodium-potassium (Na^+-K^+) pump subsequently becomes overactive, in an effort to restore the neuronal membrane potential during the acute stage. In order for this process to occur, resources such as adenosine triphosphate (ATP) are required in increasing quantity by the Na^+-K^+ pump, and as a consequence a substantial acceleration in glucose metabolism occurs to facilitate this process. This is believed to result in a cellular energy crisis, due to disparity between glucose supply and demand (hypermetabolism), and this energy crisis occurs within the context of a number of other processes including diminished cerebral blood flow (16, 17). Consequently, the concussed brain commences a phase of depressed metabolism following the initial period of accelerated glucose utilization. During this period, the energy crisis may be exacerbated by persistent increases in Ca^{2+} that are thought to impair mitochondrial oxidative metabolism with cell death a potential consequence. Increased intra-axonal calcium flux has been shown to disrupt neurofilaments and microtubules, impairing post-traumatic neural connectivity (16). Thus, following even a single sport-related concussion, cerebral pathophysiology can be adversely affected for weeks (17, 18).

Overview of MRS

Proton magnetic resonance spectroscopy (MRS) is a powerful technique to study endogenous biochemistry in the human brain non-invasively. It is capable of assessing the

neurochemical profile of *in-vivo* brain tissue and thus providing biomarkers of neurological disorders even in cases where a lesion is not observed in MR images (19, 20). The non-invasive quality of this technique makes it suitable not only for diagnostic purposes but also longitudinal follow-up studies. It has proved to be a powerful adjunct to the clinical assessment for numerous conditions, including stroke, brain tumors, epilepsy, neurodegeneration, and metabolic disorders (19-22).

A water-suppressed brain ^1H (proton) MR spectrum typically displays a number of signals that correspond to several brain metabolites. These signals are characterized by one or more peaks with a certain resonance frequency, line width (full width at half maximum of the peak's height), line shape (e.g., Lorentzian or Gaussian), phase, and area. The peaks are separated owing to differences in resonance frequency, which are caused by the difference in the chemical environment of the different nuclei. The molecular structure of a particular metabolite is reflected by a typical peak pattern. The area of a peak is directly proportional to the number of nuclei that contribute to it and to the concentration of the metabolite to which the nuclei belong.

Approximately 25 metabolites are currently considered to be measurable in the human brain by *in-vivo* MRS methods. All metabolites have a normal concentration that generate a pattern of resonances that are similar across individuals unless underlying pathology is present (22). Thus, diagnostic information can be obtained with neurospectroscopy by either comparing the numeric values of metabolite ratios or absolute concentrations with those obtained from control cohorts. Figure 1 identifies the key brain metabolites of a typical spectrum obtained from a 29 year old healthy volunteer at 1.5 T (23).

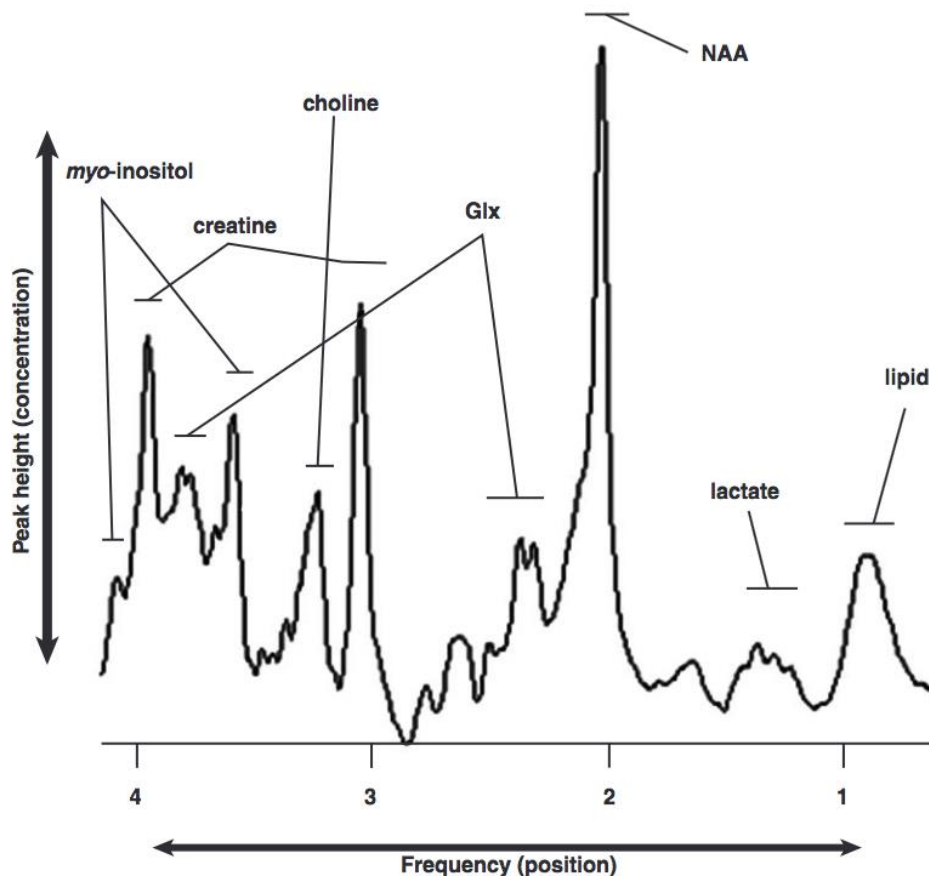


FIG. 1. Proton magnetic resonance spectrum representation acquired at magnetic field strength of 3 tesla. The main individual metabolite peaks are labeled, with the x-axis representing chemical shift in parts per million (ppm) and y-axis indicating amplitude or concentration of the chemical.

The cerebral metabolites that have been reported on previously in MRS of sports-related concussion include: N-acetylaspartate (NAA), Creatine (Cr), Choline (Cho), Glutamine (Gln) and glutamate (Glu), Myo-inositol (mI), and Lactate (Lac). These metabolites are discussed below.

N-acetylaspartate (NAA): An amino-acid derivative synthesized in neurons and transported down axons, concentrations within the human brain are among the most abundant of all neurochemicals, in the order of 10 $\mu\text{mol/g}$ (20). NAA is regarded as a neuronal marker with almost exclusive localization in neurons, with the concentration of NAA in the brain correlated with the number of measured neurons (22). Despite its abundance among cerebral tissue, the exact biological function of NAA is unclear (7). Three distinctive processes are associated with the biosynthesis of NAA: mitochondrial phosphorylating capacity, cell

energy state and ATP level, and acetyl-CoA availability. Interestingly, NAA possesses capacity to be synthesised within an energy surplus environment (i.e., high ATP and acetyl-CoA concentration) because of indirect high-energy expenditure. Accordingly, it may be possible for the brain energy state to be measured via observing the concentration of NAA (24, 25).

NAA levels have been observed to decrease in neuropathological conditions correlating with the degree of degeneration in humans (26). Further, NAA levels have been observed to recover subsequent to transient ischemia and brain injury without neuronal death, suggesting it as a marker of neuronal functionality rather than neuronal density (20). The acetyl moiety of NAA is clearly visible in *in-vivo* spectra at 2.02ppm.

Creatine (Cr): The primary resonance of creatine is at 3.02ppm and is primarily due to creatine (Cr) and phosphocreatine (PCr), which are in constant rapid enzymatic chemical exchange. Phosphocreatine plays a crucial role in adenosine triphosphate (ATP) synthesis and is therefore used as the central energy marker of both neurons and astrocytes. The creatine-phosphocreatine equilibrium is thought to be a mechanism for energy transport from the mitochondrial producing site to the synaptic consumption at the nerve terminals. Total creatine concentration is commonly assumed to be stable in the normal brain spectrum, and is thus often used as an internal standard to scale other metabolites. However, its concentration may change in pathological conditions (19, 20), with age (20), and between grey and white matter (27), and it has been found to be altered by acute brain injury (28).

Choline (Cho): The main choline resonance in the brain spectrum resonates at 3.21 ppm. Cho-containing compounds are essential for membrane lipid synthesis and act as precursors for the biosynthesis of the neurotransmitter acetylcholine (20). Total choline concentration (including free Cho and phosphorylated-choline metabolites) in the human brain is initially elevated in neonates, but slowly decreases to young adult concentrations by

about age 4 years at which point they become positively correlated with age (29). The observed age-associated increase in Cho is believed to be a reflection of the increased release of water-soluble Cho-containing compounds from cell membranes, as a result of higher membrane turnover (30).

Glutamine (Gln) and glutamate (Glu): Glu and Gln are relatively abundant amino acids in the human brain (31). Both are involved in brain neurotransmission with observable resonances in *in-vivo* spectra that lie between 2.12 and 2.35 ppm (β - γ region) as well as 3.74 and 3.75 ppm (α -region). Glu is the major excitatory neurotransmitter in the human brain; a component of intermediary energy metabolism; a precursor for glutamine, GABA, and glutathione; and a building block of proteins (32, 33). Gln is a precursor and storage form of glutamate located within astrocytes (31). (Govindaraju, Young, & Maudsley, 2000) Due to their spectral overlap they are often evaluated together as the sum of Glu + Gln, and referred to as Glx.

Myo-inositol (mI): Inositol has several isomers, one of which is myo-inositol (mI), which provides the greatest contribution to the resonance observed in *in-vivo* spectra obtained from the human brain. Myo-inositol generates four groups of resonances: a doublet-of-doublets centered at 3.52 ppm and a triplet at 3.61 ppm are the two prominent multiplets each corresponding to two protons. Myo-inositol is by itself not usually diagnostic; however, when evaluated in combination with other metabolites, it becomes a diagnostic “modifier” in diseases that affect choline concentration and it contributes specificity in certain diagnoses (eg, dementia) (23). mI is generally considered to be a marker for gliosis, which has been demonstrated to be increased in a number of neurological disorders (20).

Lactate (Lac): The *in-vivo* signal from lactate is observed as a doublet at 1.33 ppm. Lactate is one marker for energy metabolism, with lactate generated and released by astrocytes thought to serve as an energy substrate for neurons, especially during synaptic

activity (34) and during re-oxygenation following stroke (35). Healthy tissues do not have sufficient lactate to be detectable by *in-vivo* MRS. However, lactate can be detected in the brain when neural tissue is oxygen deprived and also following mitochondrial damage (23).

Another cerebral metabolite of interest, but has not been investigated in *in-vivo* studies in sport-related concussion, are macromolecules. Macromolecules co-resonate proximal to lipid and lactate at 0.93, 1.24, 1.43, 1.72, 2.05, 2.29, and 3.00 ppm (referred to as M1-M7, respectively). Although the precise nature of these macromolecules is unclear, they can be identified as broad resonances that underlie 0.9-3.0 ppm in conventional short echo MRS (TE < 35 ms) and demonstrate diagnostic promise across MRS modalities. It has been proposed that the increased macromolecule resonances at 0.9 and 1.3 ppm may represent a biochemical marker of myelin fragments (36), and consequently it is possible that characterizing these resonances may provide additional diagnostic value to proton MRS (37, 38).

Data Acquisition

In-vivo proton spectroscopy is collected from a narrow frequency range of approximately 4 parts per million (ppm), within which lies most clinically significant proton resonances. In addition, endogenous water occupies nearly 80% of brain tissue and must be suppressed for the detection of metabolites of lower concentration. Additionally, signals from extra-cerebral tissue, such as subcutaneous fat, can cause artefacts that compromise the quality of *in-vivo* spectra. This necessitates that MRS be collected from a well-defined, spatially dependent, volume of interest (referred to as a voxel), or from multiple voxels that cover a larger volume of interest. *In-vivo* studies generally use voxels between 3-8cm³; however, with higher magnetic field scanners, voxels as small as 1cm³ can be studied. Nevertheless, when the voxel size is reduced, so is the amount of tissue present within the

voxel, and the measurement time must be increased to maintain a consistent signal-to-noise ratio.

Two types of localization methods in *in-vivo* MRS are commonly used: single voxel spectroscopy (SVS) and chemical shift imaging (CSI). Single voxel spectroscopy (SVS) methods make use of modulated, frequency selective radiofrequency (RF) pulses applied in the presence of a pulsed gradient field. To select a volume, three selective pulses are applied, one after the other, in the presence of mutually orthogonal field gradients. The intersection of the three excited planes defines the voxel from which data is collected. CSI technique can collect an array of spectra from a single plane, or from the whole brain. Phase-encoding gradients are employed to encode the spatial dimensions, and the MR signal is collected in the absence of any gradient in order to maintain the spectroscopic information. Each acquired voxel contains a MR spectrum that allows for the assessment of the metabolic profile of a specific location or allows for visualization of the spatial distribution of specific metabolites of interest. CSI also allows for the acquisition of smaller volumes than in single voxel techniques (as small as 0.4cm^3 at higher magnetic field strength). However, CSI methods are intrinsically affected by inhomogeneity across the large measured volume that can adversely impact on spectral resolution and require long data acquisition times (22).

There are two common approaches used for voxel localization: stimulated echo acquisition mode (STEAM) (39) and point-resolved spectroscopy (PRESS) (40). In STEAM localization is achieved by three consecutive slice-selective 90° radiofrequency (RF) pulses that generate a stimulated echo from the region of interest with full localization achieved in a single scan without the need for phase cycling. In PRESS localization is achieved following the application of a slice-selective 90° RF pulse followed by two slice-selective 180° RF pulses that generate a spin echo from the ROI. The principal advantage of PRESS over

STEAM localization is the additional SNR gained in the collection of a spin echo over a stimulated echo (22).

Echo time (TE) is another important variable chosen before the commencement of data collection. *In-vivo* spectra are collected as either short TE (typically 20-35ms), or as long TE measurements (TE > 135ms). Short TE measurements are preferable to minimize J-modulation of coupled spin systems, which form the majority of MR detectable cerebral metabolites, and to reduce signal losses caused by T2 relaxation (20). Additionally short TEs allow for the evaluation of an extended neurochemical profile including myo-inositol, glutamate, glutamine, and macromolecules which adds to the diagnostic power of neurospectroscopy (7). Long TE measurements benefit from a less complicated appearance, improved water suppression, and a flatter baseline. Also at long TE, lipid signals are significantly reduced, allowing for the evaluation of metabolites that may have been obscured by strong lipid resonances. However, the choice of long TE comes at the expense of SNR (as much as 40% reduction) as well as the reduction in the number of diagnostic markers with signals mainly from resonances with uncoupled spins (7).

Spectral Processing and Analysis

MR spectroscopy processing typically involves converting the time domain signal to the frequency domain with metabolite evaluation carried out in the frequency domain, the time domain, or a combination of both. Semi-quantitative analysis of metabolites can then be undertaken with measurement of peak amplitudes being the simplest form of analysis. A further approach to quantification involves determining the area of a certain peak in the frequency domain. Here the operator selects a frequency range, which preferably contains only one peak, and then performs numeric integration. However, this approach is an adequate method only if the resonances are well separated without any baseline fluctuations. Unfortunately, this is rarely the case, because most *in-vivo* spectra suffer markedly from

spectral overlap and baseline fluctuations. Peak fitting involves a further complexity in obtaining metabolite quantification in which either an operator, or an algorithm, selects all important metabolites and makes coarse estimations of their resonance frequency, line width, and peak intensity. Subsequently, a fit is performed by using a least-squares optimization algorithm, which iteratively fits all peaks to a line-shape model function, so that the fitted spectrum resembles the experimental spectrum as closely as possible. In general, this method proves to be fairly robust with respect to spectral overlap. However, if the actual line shapes deviate substantially from Gaussian or Lorentzian model functions, the algorithm will not be able to fit the peaks accurately (22).

The incorporation of metabolite a priori knowledge can further enhance quality of spectral fit, and thus accuracy of quantification. All known signal parameters, such as relative frequencies, amplitude ratios, scalar coupling, and phases of resonances, that are characteristics of a certain metabolite, can be implemented as constraints in the fitting routine. Prior knowledge is the only way of enhancing, by reducing the degrees of freedom, the accuracy of fitted model parameters for a given data set. These methods can account for complexities like multiplet structures due to coupling and thus enhance quality of quantification (41). Common approaches include the AMARES method (42) in jMRUI (43), LCModel (44) and MIDAS software (45). (Maudsley et al., 2009) Prior knowledge methods can also include specific basis sets that predict how metabolites will respond to a specific pulse sequence as well as taking into account the type of imager, magnetic field strength, echo time, repetition time and reduce MRS post-processing burden as well as limiting operator dependence during analysis.

Metabolite Ratios

Metabolites' levels are most frequently reported as ratios, rather than absolute concentrations with creatine the most frequent denominator (46). This approach assumes that

creatine remains stable in both normal brain (control subjects) and in diseased brain; however, this approach of using creatine has recently been called into question (20, 46). If, using this approach, a change in the ratio of metabolite peaks is observed, it remains unclear which metabolite concentration actually changes. For this reason absolute concentration methods are recommended as the preferred method metabolite analysis (20, 41, 46).

Matched controls

Several studies have demonstrated metabolite changes between different brain regions, associated with age and between genders (19, 45, 47). For these reasons it is advisable that spectroscopy studies for clinical or research purposes use age-, gender-, and anatomically matched spectra from control subjects for comparison. These spectra should be recorded with identical techniques and on the same scanner as those performed in patients.

Objectives

In the current review, studies that used MRS to investigate brain injuries in athletes were considered. The aim of this review was to systematically evaluate the currently available evidence on the efficacy of MRS for (i) diagnostic prediction, (ii) value of prognostic information, and (iii) enhancing understanding of pathophysiology accompanying sport-related concussion. Observational, cohort, correlational, cross-sectional, and longitudinal studies were all included in the current review.

Methods

The review was conducted in three stages. In stage 1, articles were retrieved via online database searching, hand-searching reference lists, and cited reference searches (see Figure 2). The online databases of PsychINFO, Medline, Embase, SportDiscus, Scopus, Web of Science, Informit, and Dissertations and Theses were searched. Keywords and combinations of these words were used to search the databases comprehensively: magnetic resonance spectroscopy, nuclear magnetic resonance spectroscopy, neurospectroscopy,

spectroscopy, two-dimensional nuclear magnetic resonance spectroscopy, correlation spectroscopy, J-spectroscopy, exchange spectroscopy, nuclear overhauser effect spectroscopy, NMR, MRS, COSY, EXSY, NOESY, 2D NMR, craniocerebral trauma, mild traumatic brain injury, mTBI, traumatic brain injury, brain concussion, concussion, brain damage, sport, athletic, and athlete. Articles were limited to those that were published in English-language journals up to February 2013. The reference lists of articles retrieved for inclusion in the review were hand-searched to identify other relevant articles. Key articles retrieved via online databases and hand-searching reference lists were also used for further searches using the Web of Science Cited Reference function. The results of cited reference searches were narrowed using the key words magnetic resonance spectroscopy or MRS; concussion or sports-related concussion; sport; and athletic or athlete. This was undertaken to capture the most relevant articles for further evaluation. The review of the references acquired from the database search results was carried out by two authors independent of one another (AG and PS).

During stage 2, the titles and abstracts of articles were reviewed to assess eligibility for inclusion in this review. Articles were regarded as relevant, and warranting inclusion in the review if they were experimental studies using MRS to determine the presence (or absence) of pathophysiology in concussed athletic samples. Studies were included whether they were conducted acutely or post-acutely (i.e., there were no restrictions placed on time since injury) and whether or not they also used other outcome measures (e.g., conventional MRI, CT, symptom checklists, balance testing, or neuropsychological testing). If there was uncertainty about whether a study should be included based on the review of the title and abstract, the full article was retrieved.

In stage 3, all retrieved articles were independently assessed for quality using a standardized quality assessment checklist selected for its generic comprehensiveness and

currency, as previously described (5, 48). The methodological quality of the included studies was scored according to the criteria lists developed for both primary research and review articles. The criteria list included questions pertaining to both study relevance and validity. Validity questions consider a number of dimensions including: the research question and aims; participant and control selection criteria; prevention or acknowledgement of potential biases; exposure and intervening factors; appropriateness of statistical analyses; and whether conclusions are supported by results. The criteria answer format includes designation of studies as positive, neutral, or negative. A study qualified for a positive score if it included: (i) an appropriate selection of study participants and matched controls; (ii) intervention(s) described in detail; and (iii) measures that are reliable and valid. Negative criterion was assigned to studies if at least six of the ten validity questions were not met. The neutral criterion was assigned to studies that had not fully met the positive criteria above, but nevertheless offered some valid information.

The checklist considered whether: the research question was clearly stated, the selection of study subjects/patients was free from bias, the study groups were comparable, the method of handling withdrawals was described, blinding was used to prevent introduction of bias, interventions or procedures and any comparison(s) were described in detail, outcomes were clearly defined and the measurements reliable and valid, statistical analyses were appropriate for the study design and type of outcome indicators, conclusions were supported by the results with biases and limitations taken into consideration, and the potential bias due to the study's funding or sponsorship was disclosed (see Table 4).

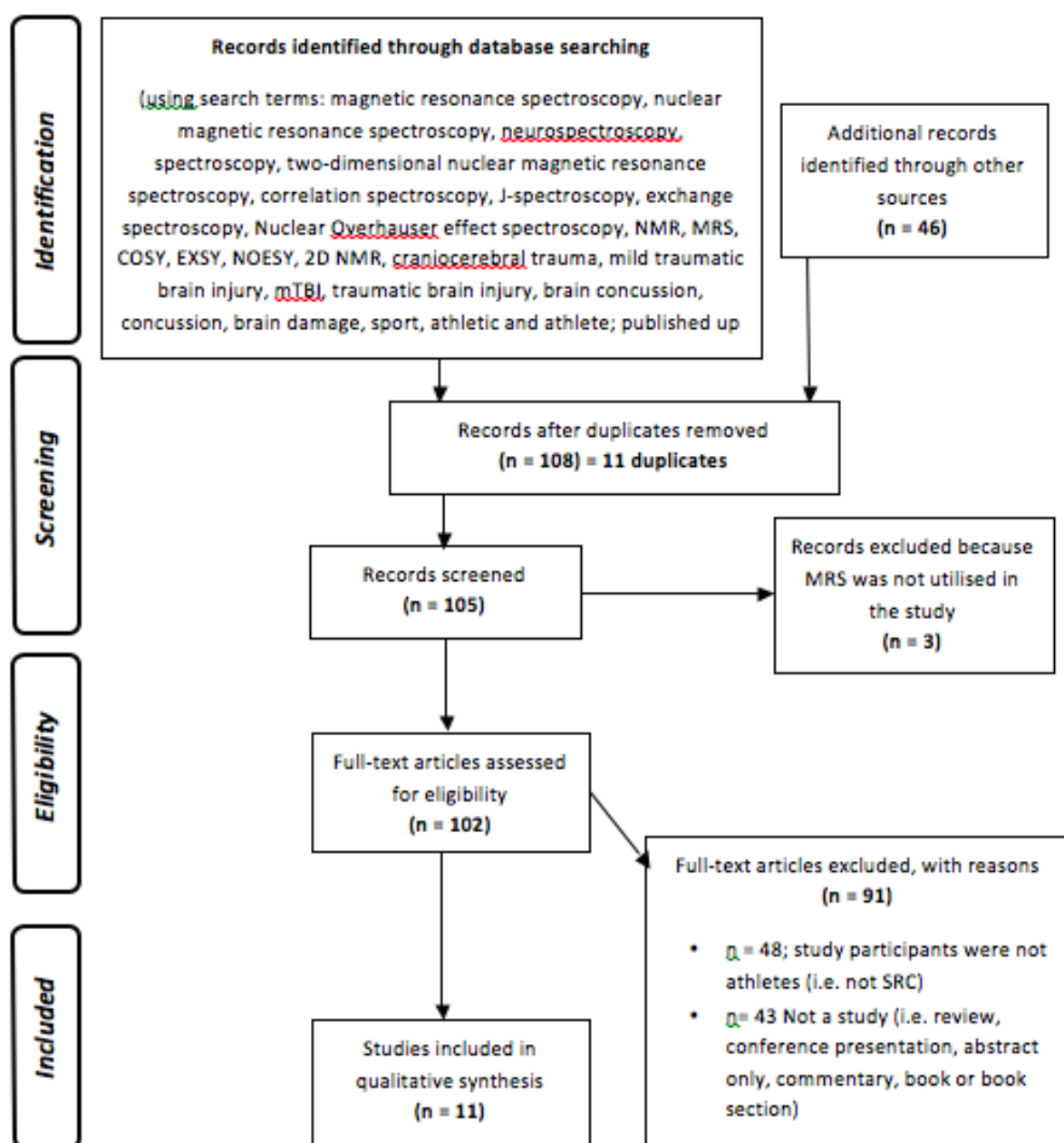


Figure 2. PRISMA Flow Diagram

Data Extraction

Data was extracted from the identified studies, including (i) participant demographics (athletes and control subjects); (ii) characteristics of participants (sport, exposure to concussion, concussive history); (iii) MRS paradigms (technique and data extraction); (iv) time lapsed [immediate (minutes to hours), acute (1-14 days), sub-acute stage (2-4 weeks), prolonged and chronic stages (greater than four weeks)]; (v) brain regions studied; (vi) results of the study; (vii) study comments (see Tables 1, 2, 3 and 4 for data extraction results).

Methodological Quality Assessment

Two authors (AG and PS) independently scored the included articles according to the quality assessment criteria using the checklists described above. Consistency was attained without further discussion across all eleven articles.

Results

A total of 119 articles were identified using the search strategy outlined in Figure 2. The initial search strategy was extremely liberal in order to capture all possible articles for inclusion in this review. Of identified citations, 108 were screened following removal of duplicates, with 102 retrieved and screened for eligibility. Due to the nature of the initial liberal approach to searching for relevant articles, 48 were excluded on the basis that the participants were not athletes (i.e., not sport-related concussion cases). Of the remaining 54 articles, 43 were excluded because they were not research studies (e.g., conference presentation, abstract only, commentary). The final outcome following this screening process resulted in the inclusion of eleven articles for this review.

The quality assessment resulted in ten studies with positive study quality ratings and one with negative study quality rating. None of the identified studies were rated with neutral quality ratings when assessed against the pre-specified standardized criteria. The negative rating was assigned to one of the studies because of limited information pertaining to the

study methodology and MRS parameters, potential participant selection bias, and the absence of a control group (see Table 1 for the quality assessment results).

Table 1. Quality Assessment Rating Results

[illegible]

A total of 200 athletes participated across the eleven studies, with the results of 116 ‘neurologically intact’ control participants also reported. One study also included three idiopathic Parkinson’s disease cases (49). Two of eleven studies involved only male samples (50, 51), two studies did not report on gender (49, 52), and one did not report on gender for the control group (53). Of the seven studies that included a mixture of both genders, five reported on the gender split in athletes (54) and controls (55-57), whereas the other two studies reported on the overall sample only (53, 58). In total, of the studies identifying gender, 219 males and 95 females were represented in the overall sample. However, aside from one study (54), possible gender differences were not fully explored. In terms of the sports represented, two studies involved boxers (49, 52), one used ice hockey players (54), and one used American footballer players (51). Four studies included a mixed sample of contact sport athletes (53, 57, 58) and the remaining three did not report the sports in which athletes participated (50, 55, 56) (see Table 2). Notably, two studies identified significant changes in NAA concentrations in asymptomatic athletes (55, 56), and one study identified similar NAA changes in athletes where the results of other measures (like computerized cognitive testing) were found to be normal (50).

Table 2. Study Characteristics

Refs	N		Sex		Age		Time Post-Injury		Symptoms	Method for Diagnosis	Injury severity (rating scale; GCS, PTA, LOC)	Symptoms	Concussion Definition	Concussion History	Level of Play	Sports	Follow-Up period (If any)
	Athletes	Controls	M	F	Range	Mean (SD)	Mean	SD									
Chamard et al (2012) ⁵⁵	45	0	25	20	M: 20-26; F: 18-37	M: 22.2 F: 20.2	Initial: <72hrs; F/U: 2 wks & 2 mths	NR	PCS	One physician and one non-physician observation and self-report	SCAT-2: GCS and Maddocks Score	SCAT-2 & ImPACT	Clinically diagnosed using an observed or self-reported mechanism (such as a blow to the head or body) and immediate or delayed neurological signs or symptoms	NR	Varsity	Ice Hockey	Two follow-up time periods: 2 days and 2 months
Cimatti (2006) ⁵³	5 (1 not a SRC)	0	NR	NR	NR	NR	1: 36-48hrs; 1: <24hrs; 2: NR	NR	NR	NR	NR	NR	NR	NR	NR	4 Boxers; 1 NR ball sport	N/A
Davie et al (1995) ⁵⁰	3	3 iPD; 3 ctrls	NR	NR	S: 45-69; C: 49-72	S: 55.3 (12.3) C: [iPD]; median 56yrs C: median 59yrs	S: Case 1: 21yrs Case 2: 25yrs Case 3: 34yrs. Mean= 26.7yrs	6.7yrs	Delayed onset	Self-report	Number of KOs sustained	NR	NR	Case 1: 1 KO in 75 A and 25 P bouts; Case 2: 3 KOs in 1 A and 24 P bouts; Case 3: 0 KOs in ? A & 30-40 P bouts.	P	Boxing	N/A
Henry et al (2010) ⁵¹	12	12	24	0	NR	S: 22.1 (0.77) C: 23 (0.71)	81.9 hrs	46.7 hrs	PCS	Intervarsity sports team's physician and physiotherapists	AAN (1997). GCS at time of injury 13-15 (mild).	Recorded using PCSC, individual total symptoms score reported but not the specific	AAN (1997).	S: mean 1.67; SD 0.4. C: nil Hx.	University level intervarsity sports	NR	N/A

Refs	N		Sex		Age		Time Post-Injury		Symptoms	Method for Diagnosis	Injury severity (rating scale; GCS, PTA, LOC)	Symptoms	Concussion Definition	Concussion History	Level of Play	Sports	Follow-Up period (If any)
	Athletes	Controls	M	F	Range	Mean (SD)	Mean	SD									
												symptoms					
Henry et al (2011) ⁵²	16	8	all	nil	NR	S: 22.1 (1.7) C: 22.8 (1.53)	Initial: < 5 days mean = 81.9 h; F/U: mean = 6.4 mths; Ctrl F/U: 18.2 mths	Initial: SD = 46.7 h; F/U: 0.4 mths; Ctrl F/U: 10.3 mths	14/16 subjects self-reported Sx on initial imaging. NR at F/U.	Intervarsity sports team's physician and physiotherapists	AAN (1997)	Recorded using PCSC, individual total symptoms score reported but not the specific symptoms	AAN (1997).	1 conc. = 8 2 conc. = 6 3 conc. = 2	University level intervarsity sports	Football	All results seen on initial Ax were observed at F/U
Johnson , Gay et al (2012) ⁵⁷	28	20	S: 13 C: 10	S: 15 C: 10	NR	S: 20.2 (0.8) C: 20.3 (1.5)	11.4 days	6.1 days	All subjects underwent testing within 24hrs of symptom resolution	Certified Athletic Trainer	NR	SCAT-2	NR	1 conc. = 9 2 conc. = 10 ≥3 conc. = 9	University level intervarsity sports	NR	N/A
Johnson , Zhang et al (2012) ⁵⁶	15	15	S: 6 C: 7	S: 9 C: 8	NR	S: 20.6 (1.2); C: 20.4 (0.8)	10.8 days	NR	All subjects underwent testing within 24hrs of symptom resolution	Certified Athletic Trainer	Grade 1 Cantu Guidelines	SCAT-2	NR	No history of previous mTBI	University level intervarsity sports	NR	N/A
Maugans et al (2012) ²⁸	12	12	18	6	S: 11-15 C: NR	S: 13.4 (1.2) C: NR	1 st (<72hrs): 44.8 hrs; 2nd (14-days): NR; 3 rd (>30-days): 70 days	1st: 19.5; 2nd: NR 3rd: 46.10	NR	Licensed healthcare professional in accordance with the International Conference on Concussion in Sport.	LOC reported in 2 subjects. Exclusion criteria included "focal neurologic al injury" and "pathology on clinical imaging". One	<72hrs: mean 27.8 (6.9); 3 days: mean 11.2 (4.4); 30 days: mean 3.8 (1.24); Ctrl Group: mean 4.1	Zurich (3rd SIC)	0 conc. = 9 1 conc. = 3 (greater than one year ago)	High School	Football (n=8) Soccer (n=3) Wrestling (n=1)	Two follow-up time periods: 14 days and greater than 30 days post-injury

Refs	N		Sex		Age		Time Post-Injury		Symptoms	Method for Diagnosis	Injury severity (rating scale; GCS, PTA, LOC)	Symptoms	Concussion Definition	Concussion History	Level of Play	Sports	Follow-Up period (If any)
	Athletes	Controls	M	F	Range	Mean (SD)	Mean	SD									
											participant did not complete the third testing session due to post concussion symptoms requiring medical attention.	(1.3).					
Vagnozzi et al (2008) ⁵⁴	13	5	8	5	S: 20-32 C: NR	S: 25.85 (3.6) C: NR	1 st : 3 days 2 nd : 15 days 3 rd : 30 days. 2 nd conc. (n=3) 4 th : 45 days	NR	PCS	NR	NR	Recorded using PCSC, specific individual symptoms reported but not the total symptoms scores	“Traumatically induced alteration in mental status, not necessarily with LOC”	NR	“Nonprofessional”	Kick Boxing (n=6) Boxing (n=3) Soccer (n=2) Rugby (n=1) Alpine Skiing (n=1)	Follow-up time periods: single concussion group (n=10): 14 and 30 days; double concussion group (n=3): 14, 30 and 45 days.
Vagnozzi et al (2010) ⁵⁸	40	30	S:31 C:23	S:9 C:7	NR but inclusion reported as 16-35 yrs	S: 26.5 (5.5) C: 27.6 (3.6)	1 st : 3 days, 2 nd : 15 days; 3 rd : 22 days, 4 th : 30 days	NR	PCS	Referred either by on-field personnel or, in the case of hospital admission, by emergency room doctors. The final selection of a patient candidate to be enrolled in the study was carried	78% of participants reported PTA; PTA < 5 min, 8/31 (25.6%); PTA 5–10 min, 5/31 (16.1%); PTA 10–15 min, 9/31 (29%); PTA >15 min, 9/31	Recorded using PCSC, group symptoms reported but not the total symptoms scores	“Traumatically induced alteration in mental status, not necessarily with LOC”	NR	5 P, 35 A	Soccer (n=11) Kick boxing (n=6) Rugby (n=5) Horse Riding (n=4) Boxing (n=4) Bike riding (n=4) Alpine skiing	Three follow-up time periods: 3, 15, 22 and 30 days

Refs	N		Sex		Age		Time Post-Injury		Symptoms	Method for Diagnosis	Injury severity (rating scale; GCS, PTA, LOC)	Symptoms	Concussion Definition	Concussion History	Level of Play	Sports	Follow-Up period (If any)
	Athletes	Controls	M	F	Range	Mean (SD)	Mean	SD									
										out by the investigators on the basis of the presence of post-concussive symptoms, either at the time of the first MRI or in case of symptom clearance.	(29%); 48% of participants reported LOC at the time of impact, with an estimated duration varying from 15-90s.					(n=3) Basketball (n=3)	
Vagnozzi et al (2012) ⁵⁹	11	11	S: 8 C: 3	S: 8 C: 3	S: 16-35; C: NR	S: 24.6 (6.4) C: 25.9 (5.7)	1 st : 3 days, 2 nd : 15 days; 3 rd : 30 days, 4 th : 45 days	NR	SCAT-2; PCS	NR	GCS= ≥ 14; no anatomical lesion on conventional MRI; normal neurological exam; Cho:Cr differs from controls	Recorded using PCSC from SCAT-2, group symptoms reported but not the total symptoms scores	“Traumatically induced alteration in mental status, not necessarily with LOC”	NR	A	Soccer (n=4) Boxing (n=3) Rugby (n=1) Alpine Skiing (n=1) Kick Boxing (n=1) Basketball (n=1)	Three follow-up time periods: 3, 15, 30 & 45 days

Note. S: Concussed subjects; C: Control subjects; NR: not reported; N/A: not applicable; hrs: hours; s: seconds; PCSC: post-concussion symptoms checklist; iPD: idiopathic Parkinson’s disease; KOs: knock outs; A: amateur; P: professional;
Hx: history; Cho: choline; Cr: creatine; M: male; F: Female; SD: standard deviation; AAN: American Academy of Neurology Quality Standards Subcommittee and Neurology AAO (1997)

Table 3. MRS Study Characteristics.

Study	Anatomical Structures Examined	MR Specifications	MRS Acquisition & Voxel Size (mm)
Chamard et al (2012) ⁵⁵	Corpus callosum	3 tesla	SVS PRESS (TE 35ms, TR 2000ms, 128 acquisitions) Voxel: 10x20x30mm
Cimatti (2006) ⁵³	SVS: Bilateral frontal cortical-subcortical white matter MRSI: Immediately above the corpus callosum.	1.5 tesla	SVS No parameters given 2D MRSI PRESS (TE 272ms, TR 1500ms) VOI: 130x100x18mm
Davie et al (1995) ⁵⁰	Lentiform nucleus.	1.5 tesla	SVS STEAM (TE 272ms, TR 2270ms) Voxel: 3.4 to 6.0mL
Henry et al (2010) ⁵¹	Bilateral: i. Hippocampus ii. Dorsolateral prefrontal cortex (DLPFC) iii. Primary motor cortex (M1)	3 tesla	SVS PRESS (TE 30ms, TR 1500ms, 256 acquisitions) Voxel: hippocampus (20x40x16mm), DLPFC (16x16x16mm), and M1 (16x20x32mm)
Henry et al (2011) ⁵²	Bilateral: i. Dorsolateral prefrontal cortex (DLPFC) ii. Primary motor cortex (M1)	3 tesla	SVS PRESS (TE 30ms, TR 1500ms, 256 acquisitions) Voxel: DLPFC (16x16x16 mm), and M (16x20x32mm)
Johnson, Gay et al (2012) ⁵⁷	Genu and splenium of the corpus callosum.	3 tesla	3D MRSI PRESS (TE 135ms, TR 1510ms, 1 signal average) VOI: 120x120x80mm Voxel: 10x10x12.5mm
Johnson, Zhang et al (2012) ⁵⁶	Genu and splenium of the corpus callosum.	3 tesla	3D MRSI PRESS (TE 135ms, TR 1510ms, 1 signal average) VOI: 120x120x80mm Voxel: 10x10x12.5mm

Study	Anatomical Structures Examined	MR Specifications	MRS Acquisition & Voxel Size (mm)
Maugans et al (2012) ²⁸	Anterior cingulate gyrus; left dorsolateral prefrontal white matter; left thalamus.	3 tesla	SVS PRESS (144ms, TR 3000ms) Voxel 8mL
Vagnozzi et al (2008) ⁵⁴	Bilateral, cortical–subcortical frontal white matter	3 tesla	SVS PRESS (TE 144ms, TR 2000ms, 128 acquisitions) Voxel: 15x15x15mm
Vagnozzi et al (2010) ⁵⁸	Site 1 & 2: Bilateral, cortical–subcortical frontal white matter Site 3: Frontal lobe white matter	Site 1: 3 tesla Site 2: 1.5 tesla Site 3: 3 tesla	Site 1: SVS PRESS (TE 144ms, TR 2000ms, 128 acquisitions) Voxel: 15x15x15mm Site 2: SVS PRESS (TE 144ms, TR 2000ms, 128 acquisitions) Voxel: 15x15x15mm Site 3: 2D MRSI STEAM (TE 135ms, TR 2000ms, 3 signal averages) VOI: 240x240x15mm Voxel: 15x15x15mm
Vagnozzi et al (2012) ⁵⁹	Bilateral, cortical–subcortical frontal white matter	3 tesla	SVS PRESS (TE 144ms, TR 2000ms, 128 acquisitions) Voxel: 15x15x15mm
Note. SVS: single voxel spectroscopy; MRSI: magnetic resonance spectroscopic imaging; VOI: volume of interest; PRESS: point-resolved spectroscopy; STEAM: stimulated echo acquisition mode; TE: time to echo; TR: time to repeat; ms: milliseconds; mm: millimetre; mL: millilitre; DLPFC: dorsolateral prefrontal cortex.			

Table 4. Post-Processing Steps & MRS Data Analysis Methodology

Chamard et al (2012)⁵⁸ • LCModel • Metabolites evaluated (NAA, Glu, Cr, & mI) as ratios with creatine as denominator • Only metabolites with CRLB < 20% were evaluated
Cimatti (2006)⁵³ • Vendor software • Metabolites evaluated as ratios (NAA/Cr, Cho/Cr, & NAA/Cho) • No indication of spectral quality
Davie et al (1995)⁵⁰ • Analysis package not specified • Metabolites expressed as concentrations (mmol/L) using water scaling and relaxation correction • NAA, Cr & Cho evaluated • No indication of spectral quality
Henry et al (2010)⁵¹ • LCModel • Metabolites evaluated (NAA, Glu, Cr, Cho & mI) as ratios with creatine as denominator • Only metabolites with CRLB < 20% were evaluated
Henry et al (2011)⁵² • LCModel • Metabolites evaluated (NAA, Glu, Cr, & mI) as ratios with creatine as denominator • Only metabolites with CRLB < 20% were evaluated
Johnson, Gay et al (2012)⁵⁷ • jMRUI using AMARES • Metabolites evaluated as ratios (NAA/Cho, NAA/Cr, and Cho/Cr) • No indication of spectral quality
Johnson, Zhang et al (2012)⁵⁶ • Vendor software (Siemens Spectroscopy Card) • Metabolites evaluated as ratios (NAA/Cho, NAA/Cr, and Cho/Cr) • No indication of spectral quality
Maugans et al (2012)²⁸ 1. Quantitative analysis • LCModel • Metabolites expressed as concentrations (mmol/L) using water scaling and relaxation correction • Metabolites evaluated were NAA, Cr, Cho, lactate • NAA CRLB < 15% for data inclusion 2. Semi-quantitative analysis • Vendor software (Philips SpectroView) • Metabolites evaluated (NAA, Cr, Cho & lactate) as ratios with creatine as denominator • 99% of collected spectra met criteria for analysis

Vagnozzi et al (2008)⁵⁴

- Vendor software (Philips SpectroView)
- Metabolites evaluated (NAA, Cr, & Cho) as ratios with creatine as denominator
- No indication of spectral quality

Vagnozzi et al (2010)⁵⁸

Site 1:

- Analysis package not specified
- Metabolites evaluated as ratios (NAA/Cho, NAA/Cr and Cho/Cr)
- No indication of spectral quality

Site 2:

- Analysis package not specified
- Metabolites evaluated as ratios (NAA/Cho, NAA/Cr and Cho/Cr)
- No indication of spectral quality

Site 3:

- Vendor software (Siemens, Spectroscopy Card)
- Metabolites evaluated as ratios (NAA/Cho, NAA/Cr and Cho/Cr)
- No indication of spectral quality

Vagnozzi et al (2012)⁵⁹

- Vendor software (Philips SpectroView)
- Metabolites evaluated (NAA, Cr, & Cho) as ratios with creatine as denominator
- No indication of spectral quality

Note. LC: linear combination; NAA: N-acetylaspartate; Glu: glutamate; Cr: creatine; Cho: choline; mI: Myo-Inositol; LA: lactic acid; ¹H-MRS: proton magnetic resonance spectroscopy; CRLB: Cramer-Rao Lower Bound.

Findings across studies were varied, but generally when an abnormality was reported, the NAA concentrations were reduced (9/11 studies) in the concussed athletes compared with controls (see Table 5). Significant changes in Glu were observed in 2/3 studies using short TE (50, 51). One of these studies, utilizing a short TE, SVS acquisition, reported a reduction in mI as well as Glu (51). However, one study detected no metabolic change across groups (58), and another found no metabolic changes between concussed versus non-concussed athletes (54). In these two studies, Chamard and colleagues (54) studied the corpus callosum while Maugans and colleagues (58) studied three separate brain regions (anterior cingulate gyrus, left dorsolateral prefrontal white matter, and left thalamus). Other studies detected statistically significant changes in a variety of neuroanatomical regions, including frontal white matter (50-53, 57), primary motor cortex (50, 51), genu and splenium of the corpus callosum (55, 56), and the lentiform nucleus (putamen and globus pallidus) (49).

Two studies specifically examined the acute effects of concussion without looking at the subacute stage (50, 52); both of these studies conducted scanning within four days of the injury. One study identified NAA decrements in half of the six non-boxing athletes, and in only one of four boxers (52). In the other study, a significant decrease in NAA was observed in the dorsolateral prefrontal cortex and in the motor cortex (M1) in addition to significant decreases in Glu in M1 (50). The findings of decreases in NAA, in the above mentioned acute studies, were consistent with the acute findings on other MRS studies that examined both acute and subacute phases (51, 53, 57).

Repeated or follow-up MRS was conducted in five of the 11 identified studies (51, 53, 54, 57, 58). Three out of five of these studies reported significantly decreased levels of NAA in the dorsolateral prefrontal cortex and motor cortex (50), and the frontal cortical-subcortical juncture (53, 57), and decreased Glu and mI in the motor cortex (50). More specifically, Henry and colleagues reported persisting decreases in NAA:Cr levels in the dorsolateral

prefrontal cortex over time (6 month post-injury follow up), decreased levels of Glu:Cr in the motor cortex in the acute phase but recovery in the chronic phase, and equivalent mI:Cr levels in the acute phase but significant differences emerged over time. Vagnozzi and colleagues (53) reported on the recovery of NAA levels within frontal white matter and found a decrease of 18.5% at day three, with a 3% recovery observed at day 15 and then full recovery observed at day 30 following injury. In three athletes that sustained a second concussion (at 10, 12, and 13 days post initial injury), recovery of NAA levels was found to be prolonged but recovery was complete by 45 days post-initial injury. Vagnozzi and colleagues (57) once again reported acute changes in NAA:Cr (-17.6%) and NAA:Cho levels (-21.4%) within frontal white matter at day three following injury with gradual recovery monitored at days 15 and 22, and complete recovery at day 30. These findings were observed regardless of the different magnetic field strength or mode of MRS acquisition employed in this multi-site study. The final study of the four studies that included follow-up MRS investigation did not identify any significant differences between adolescent athletes and age-match controls (58).

Three of ten studies conducted MRS in the subacute and/or chronic stage (49, 55, 56). Two of these studies were conducted with asymptomatic athletes who were scanned within 24-hours of self-reported symptom resolution (55, 56), and these scans were conducted on average 10-11 days following injury. Johnson and colleagues (56) reported reduced NAA:Cr and NAA:Cho concentration in the genu, but not the splenium, of the corpus callosum. The second of the Johnson and colleagues studies (55) reported reduced NAA:Cr and NAA:Cho concentration in the genu and the splenium of the corpus callosum. The third study (49) examined three retired professional boxers (24-27 years post-retirement) who had a diagnosis of Parkinson's disease (PD). These boxers had a significant reduction in NAA in the putamen and globus pallidus compared to patients with idiopathic PD and an age-matched control

group. There was no report on the possible Time X Group effect (i.e., did the magnitude of group differences change with time).

The MRS data acquisition and post-processing techniques used across the 11 studies varied considerably (see Tables 3 and 4). Seven of eleven studies used a single voxel spectroscopy (SVS) method (49-51, 53, 54, 57, 58), three used a multi-voxel approach (52, 55, 56), and one multi-site study used both methods (57). Three studies employed a short TE acquisition (50, 51, 54), with the other eight studies utilizing long TE acquisition (49, 52, 53, 55-59). In addition, only 2/11 studies (49, 52) were conducted at a magnetic field strength of 1.5 tesla; eight ((50, 51, 53-56, 58, 59) were conducted at the higher magnetic field strength of three tesla (one multicentre study (57) used both 1.5 and three tesla).

Spectral post-processing was undertaken using vendor software in 6/11 cases, with LCModel used in 4/11 studies, jMRUI (AMARES) in 1/11 study, and no spectral processing package specified in 3/11 studies. Maugans and colleagues (58) undertook analyses using both vendor and LCModel, and Vagnozzi and colleagues (57) was a three site study, where one site used vendor analysis and two sites did not specify the type of analyses. Metabolite ratios were reported in 9/11 studies with creatine used as the most common denominator. Maugans and colleagues (58) used LCModel with metabs in mmol/L and the vendor software using ratios with creatine as the denominator. Only the studies using LCModel reported on data quality stating that only metabolites with Cramer-Rao lower bounds (CRLB) with a threshold of either <15% (58) or <20% (50, 51, 54) applied to select metabolites for analysis. Maugans and colleagues (58) stated that 99% of collected spectra met criteria for analysis.

Table 5. Relation Between MRS Results and other Methodologies

Refs/ Findings	Other Outcome Assessments	Results of other Assessments	Correlation among Results of MRS and other Measure(s)/Findings	Abnormality Detected	
				MRS	Other Methodology
Chamard et al. (2012) ⁵⁵	- Brain MRI exam incl. DTI and SWI - SCAT2 - ImPACT	NR	NR	NSAD	NR
Findings:	- There were no significant MRS findings in concussed versus non-concussed athletes. - Non-concussed female athletes had decreased NAA over the course of the season.				
Cimatti (2006) ⁵³	Brain MRI exam	NR	NR	NAA:Cr & NAA:Cho lowered compared to standard values	N/A
Findings:	- The NAA values 36-48 hours post-injury were lower in two subjects with concussion. - In the four boxing subjects, only one had lower NAA:Cr and NAA:Cho in comparison to the standard values. < 24hrs post boxing bout, diminution of the value of Cr.				
Davie et al. (1995) ⁵⁰	- Neurological examination - Brain MRI exam	- Neurological examination presented as case studies with varying results. - MRI revealed discrete periventricular or subcortical white matter high signal lesions. There were no high signal lesions present in the basal ganglia. - In three iPD cases, there were small periventricular or subcortical white matter lesions present on T2 weighted MRI and a moderate degree of low signal extending from the globus pallidus into the medial border of the putamen. - Cavum septi pellucidi in one boxer	NR	NAA lowered in lentiform nucleus.	- MRI: periventricular or subcortical white matter high signal lesions - In iPD, 3 instances of periventricular or subcortical white matter lesions and a moderate degree of low signal extending from the globus pallidus into the medial border of the putamen.
Findings:	- The concentrations of NAA from the lentiform nucleus in the three ex-boxers were all significantly lower compared to age matched controls. - There was no significant difference in the concentration of NAA in the iPD group compared with the controls. - There was no significant difference in the concentrations of Cr or Cho between the three groups.				
Henry et al. (2010) ⁵¹	- Brain MRI exam - PCSC - NP Ax	- Structural MRI: NR - NP Ax: NSAD	- PCSC: NAA/Cr & Glu/Cr in M1 were negatively correlated with symptom severity. - PCSC – symptom clusters:	- Significant decrease in glutamate in M1. - Significant	N/A

Refs/ Findings	Other Outcome Assessments	Results of other Assessments	Correlation among Results of MRS and other Measure(s)/Findings	Abnormality Detected	
				MRS	Other Methodology
			Glu/Cr – cranial symptom cluster in M1 significantly correlated after correcting for multiple comparisons.	decrease in NAA in DLPFC & M1.	
Findings:	• Significant decrease in glutamate in M1. • Significant decrease in NAA in DLPFC and M1. • No change observed in the hippocampus. • Metabolic changes in M1 negatively correlated with self-reported symptom severity despite comparable NP testing results.				
Henry et al. (2011) ⁵²	• PCSC • Brain MRI exam	• Total symptom scores revealed a significant interaction, where there was a significant effect of time, and a main effect of group, where concussed athletes were significantly more symptomatic in the acute post-injury phase, but were statistically similar to controls in the chronic post-injury phase	NR	• Significant decrease in NAA in DLPFC in both acute and chronic phases • Trend toward a decrease in Glu in M1 at both time points	• Acute phase athletes more symptomatic than controls
Findings:	• In the DLPFC, NAA:Cr levels remained lower in the concussed group across time. • M1 revealed variable changes; concussed athletes showed recovery of Glu:Cr level across time. • In M1 the mI:Cr levels were similar between groups in the acute phase but significantly different in the chronic phase. • Glu:Cr in M1 tended to distinguish between groups at both time points				
Johnson, Gay et al. (2012) ⁵⁷	• SCAT2 ('returned to normal') • BESS ('returned to normal') • Clinical information on concussive injury history • Brain MRI exam (no abnormality detected at MRI)	N/A: SCAT2 and BESS used for clinical assessment and decisions regarding recovery and clearance to return-to-play, not for research data • Structural MRI - NAD	• An increased number of previous concussions was not correlated with progressive reduction of NAA:Cr & NAA:Cho in the genu or splenium of the corpus callosum.	• Significant decrease in NAA:Cr & NAA:Cho in genu of the corpus callosum	N/A
Findings:	• Significant decrease in NAA:Cr and NAA:Cho in the genu of the corpus callosum in 'recovered' concussed athletes • No evidence of progressive reduction of NAA:Cr & NAA:Cho in the genu or splenium of the corpus callosum as a result of a greater number of previous concussions				

Refs/ Findings	Other Outcome Assessments	Results of other Assessments	Correlation among Results of MRS and other Measure(s)/Findings	Abnormality Detected	
				MRS	Other Methodology
	• Findings only in the genu, and not the splenium, of the corpus callosum				
Johnson, Zhang et al. (2012) ⁵⁶	• Routine protocol of the Pennsylvania State University Sports Concussion Program • Brain MRI exam	N/A: The Pennsylvania State University Sports Concussion Program used for clinical assessment and decisions regarding recovery and clearance to return-to-play but not for research data • Structural MRI - NAD	N/A	• Significant decrease in NAA:Cr and NAA:Cho in genu and splenium of the corpus callosum	N/A
Findings:	• In the genu and the splenium, NAA:Cr and NAA:Cho were significantly lower in ‘recovered’ concussed athletes				
Maugans et al. (2012) ²⁸	• ImPACT • Brain MRI exam incl. DTI, SWI • PC-MRA (for CBF)	• Statistically significant differences in mean total CBF values were found between the two groups. • All other measures examined did not reveal any statistically significant differences between the two groups. • Routine Brain MRI: NAD • DTI: NAD • SWI: NAD	N/A	NSAD	• CBF: Mean total • CBF values reduced in concussed versus control participants.
Findings:	• There were no significant MRS findings in the concentration of NAA or NAA:Cr ratio levels over time for the concussed participants. • ImPACT: Initial post-injury total symptoms score differed significantly and resolved at the day 14 follow-up. Reaction time composite scores were significantly different at initial and 14-day follow up and had returned to control levels by the final testing session.				
Vagnozzi et al. (2008) ⁵⁴	• PCSC • Brain MRI exam	NR: Singly concussed athletes asymptomatic at day 3; doubly concussed athletes asymptomatic at day 30 • MRI: NSAD.	N/A	Singly concussed: NAA:Cr decreases at day 3, modest recovery by day 15. Doubly concussed: NAA:Cr decreases at day 3, persisted following second concussion (prior to day 15) at day 30.	N/A
Findings:	• Concussion opens a temporal window of brain metabolic imbalance, the closure of which does not coincide with resolution of clinical symptoms. • The recovery of brain metabolism is not linearly related to time. • A second concussive event prolonged the time of NAA normalization by 15 days. • Singly concussed athletes, at 3-days post-injury had a decrease of				

Refs/ Findings	Other Outcome Assessments	Results of other Assessments	Correlation among Results of MRS and other Measure(s)/Findings	Abnormality Detected	
				MRS	Other Methodology
	18.5% compared to controls in NAA:Cr. • Only a 3% recovery was observed at 15-days • Full recover of the NAA:Cr ratio was observed at 30-days post-injury • These patients reportedly were asymptomatic at approximately 3 days post injury. • The second concussive injury group (N=3 occurred before the 15-day follow up) had a similar decrease of the NAA:Cr ratio at 3 days • At 15-days following the second injury, a further diminution of NAA:Cr occurred (with respect to singly concussed athletes). • At 30-days, NAA:Cr remained significantly different, with respect to singly concussed athletes • At 45-days post-injury, there was recovery of the NAA:Cr with respect to control patients. • This group of patients was asymptomatic at 30 days post injury. • NAA may be helpful for assessing the full cerebral metabolic recovery after concussion, thereby suggesting its future use in assisting with return to play decision making				
Vagnozzi et al. (2010) ⁵⁸	• PCSC • Brain MRI exam	• Athlete self-reported post-concussion symptom resolution between 3 and 15 days • MRI: NSAD.	• Detectable metabolic change was observed beyond the self-reported symptom resolution.	NAA:Cr & NAA:Cho changes observed beyond day 15 post-injury.	N/A
Findings:	• Athletes with concussion exhibited the most significant alteration of metabolite ratios at Day 3 post-injury (NAA:Cr -17.6%, NAA:Cho -21.4%). • On average, metabolic disturbance gradually recovered, initially in a slow fashion and, following Day 15, more rapidly. • At 30 days post-injury, all athletes showed complete metabolic recovery. • Symptom resolution occurred between 3 and 15 days post-concussion. • Comparison of spectroscopic data, obtained in controls using different field strength and/or mode of acquisition, did not show any difference in the brain metabolite ratios.				
Vagnozzi et al. (2012) ⁵⁹	• PCSC from SCAT2 • Brain MRI exam	• Athlete self-reported post-concussion symptom resolution between 11 and 19 days (M=15.2 SD=2.6 days) • MRI: NSAD	• Detectable metabolic change was observed beyond the self-reported symptom resolution.	NAA:Cr & NAA:Cho changes observed beyond day 30 post-injury. Cho:Cr changes observed beyond 15 days post-injury.	N/A
Findings:	• NAA:Cr was increased at 3 and 15 days post injury. • NAA:Cr was decreased at 30 days but returned to normal at 45 days. • NAA:Cho was decreased at 3 and 15 days post injury, slightly lower than controls at 30 days, and recovered at 45 days. • Cho:Cr increased at 3 and 15 days, resolved by 30 days.				

Discussion

This review identified only 11 studies that have used MRS with athletes who have sustained concussions. Nine of these studies report statistically meaningful differences in MR spectra between controls and athletes. Together, these findings suggest that (i) metabolic disruption continues beyond the resolution of symptoms and other objective measures in some athletes, and (ii) MRS can detect such changes.

In the two studies that did not find spectral changes, Chamard and colleagues (54) studied the corpus callosum with a SVS, short echo time (TE 35ms, voxel size 6cm^3 and 128 acquisitions) technique and Maugans and colleagues (58) studied three separate brain regions (anterior cingulate gyrus, left dorsolateral prefrontal white matter, and left thalamus) with a SVS, long echo time (TE 144ms, voxel sizes hippocampus 12.8cm^3 , DLPFC 4.1cm^3 , M1 10.2cm^3 , and 256 acquisitions) technique. Both studies (54, 58) used the user independent LCModel program to evaluate their data and only studied metabolites with Cramer-Rao lower bounds (% SD) less than 20%. Chamard and colleagues (54) did not use a control group for comparison. Maugans and colleagues (58) recruited age and gender matched controls. Both studies conducted the initial assessment within 72-hours post-injury and at two follow ups (at two weeks and approximately 2 months). In general, both studies were methodologically sound from an MRS perspective. Although Maugans and colleagues (58) potentially missed some metabolites by using long TE acquisition, given the fact there was no reported change in NAA, and all other neuroimaging measures also revealed no significant differences, it is unlikely that Glu would have demonstrated significant change either. Though Chamard and colleagues (54) used a short TE acquisition, giving them access to the full neurochemical profile, they studied only one brain location, the corpus callosum. Two other studies with single brain location

methodology in the corpus callosum (55, 56) found no significant differences, although once again there were limitations related to using long TE acquisition and the range of metabolites that are visible with this methodology.

The most significant finding across the nine studies that identified spectral changes was a reduction in NAA. Change in Glu was the next most common metabolite change (50, 51), with Henry and colleagues (51) also reporting a change in mI. Only three studies (50, 51, 54) could examine these metabolites (i.e., Glu and mI) because they used the short TE technique (thus, they were able to assess the full neurochemical profile accessible to proton MRS). The use of the long echo time (TE) MRS technique (53, 57) does not allow for the characterization of the full neurochemical profile accessible with *in-vivo* MRS thus potentially limiting the sensitivity of the technique. Thus, the use of long TE acquisitions in concussion research may be viewed as a methodological limitation because this approach might have missed some important neurometabolic data (given that two of the three studies that employed short echo demonstrated a significant decrease in Glu; with one study also demonstrating a significant decrease in NAA in the primary motor cortex and a decrease in NAA in the dorsolateral prefrontal cortex) (50).

There was considerable variability in MRS collection and analysis across studies. These differences included 2/11 studies (49, 52) undertaken at a magnetic field strength of 1.5 tesla with 9/11 undertaken at 3 tesla; one multi-site study pooled results collected at both 1.5 and 3 tesla field strengths (57); with the studies undertaken at 3 tesla having the advantages of inherent increases in spectral resolution and SNR per unit time. Additionally, 3/11 studies employed a short TE technique (50, 51, 54) and 8/11 studies used a long TE technique. Furthermore, 8/11 used a well-defined volume of interest within the brain from which to record spectroscopy (SVS

technique) with the highest possible spectral quality, and others used a CSI technique which can compromise final spectral quality.

A number of studies either used vendor software for spectral processing and evaluation or did not mention the analysis package used. Only 4/11 studies (50, 51, 54, 56) used post-processing techniques (LCModel and AMARES in jMRUI) capable of incorporating prior knowledge of metabolites of interest that are capable of maximizing spectral information available in MRS studies. Furthermore, only 4/11 studies commented on metrics related to spectral quality stating that only metabolites with Cramer-Rao lower bounds (CRLB) <20% (50, 51, 54) or CRLB <15% (58) were included in spectral analysis. Only 2/11 studies (49, 58) studied metabolites as concentrations (mmol/L); 9/11 studies reported on metabolites as ratios (mostly commonly with creatine as the denominator).

The decision to evaluate metabolites as ratios in the majority of studies and not in absolute units (e.g. mmol/L) assumes that the chosen denominator remains stable across different brain regions and participants, and presupposes that the chosen denominator is not involved in the pathologic process under investigation. The use of creatine as a stable denominator in *in-vivo* brain MRS has recently been challenged (20, 46) in control subjects and is likely to have special relevance in brain injury studies (46) because the magnitude of results may be weakened if both metabolites are affected.

In addition, there were differences in age- and gender-matched controls, as well as considerable variability in brain regions under examination. Previous studies have shown that control subjects should be matched on gender and age as closely as possible (45, 47, 60), and should compare spectra collected from the same brain region as the comparison sample or experimental group (45, 47).

Diagnostic Potential of MRS in Sports-Related Concussion

Nine studies found MRS changes in athletes versus control subjects. Five of six studies found MRS changes in the acute / sub-acute stages (greater than 72hrs) post-injury. MRS changes in 9/11 studies were detected in the weeks, months, and in one study, years following injury (in boxers who had Parkinson's disease). As such, MRS might have some diagnostic potential. However, more studies are required with greater numbers, combined with cross-validation with other more established measures. Information regarding effect sizes and Bayesian diagnostic accuracy will be necessary before drawing conclusions about clinical usefulness in individual athletes. At present, MRS is experimental and insufficient data has been published to recommend that it be used clinically or diagnostically.

Challenges in Applying MRS Data to Diagnosis, Prognosis, or Return-to-Play Decision Making

Rodent brain injury models have revealed a window of metabolic 'brain vulnerability', defined as a distinct period of metabolic imbalance, due to an altered energy state and decreased NAA concentrations (24, 25, 61). (Hovda, Yoshino, Kawamata, Katayama, & Becker, 1991; Tavazzi et al., 2007; Vagnozzi et al., 2007) It has been proposed that the post-injury energy imbalance is due, in the most part, to mitochondrial malfunctioning (62). Vagnozzi and colleagues (57) suggest that concussion-induced imbalance of neuronal energy metabolism considerably hampers NAA normalization and that normalization of NAA concentrations may only occur following complete recovery of the cerebral energy state. The findings of the majority of studies included in the current review report a period of metabolic alteration in injured athletes (49-53, 55-57). The ability of MRS to detect ongoing residual metabolic deficits, despite the resolution of symptoms and the return to 'normal' on

other clinical measures (i.e., the athletes would otherwise have been cleared to return to play) (55, 56), is potentially of considerable clinical significance. One study with adolescents, however, did not replicate these results (58). This study employed a long TE, single voxel spectroscopy technique that reduced sensitivity to cerebral metabolites with short T2 relaxation times (e.g., glutamine, glutamate, mI). They also listed their criteria for metabolite inclusion, stating that only metabolites with Cramer-Rao lower bounds of < 15% were evaluated. Interestingly, this study also investigated several other MRI metrics including DTI, susceptibility-weighted imaging, and vascular metrics (cerebral blood flow (CBF)) and reported significant findings only in CBF. In addition, there were no significant differences on cognitive measures.

A major limitation in the MRS of sports-related concussion literature is the lack of detailed information regarding individuals' concussion histories. It is well recognized that concussion history, injury dynamics, severity, and clinical presentations are heterogeneous. Only three out of 11 studies reported individual data (49, 53, 58) (see Table 2). This was particularly evident in terms of concussion severity, history of previous concussion, and reported post-concussion symptoms, all of which provide important information that could be correlated with individuals' MRS findings. The difficulty with recall bias in obtaining valid retrospective data on the number and nature of past concussions has been noted previously (63). Only Maugans and colleagues (58) reported individual data on number of previous concussions. Information pertaining to the exposure levels, such as years of play, position played, and number of bouts (in the boxing cases) was also often absent. Thus, it is not known in some cases whether the MRS data acquired represent the sequelae of the current concussion, a previous history of concussions, or a combination of both. Although the inclusion criteria for one study excluded previous

concussion history in the past twelve months from the athlete group (55), using this criterion still resulted in the inclusion of three athletes with a prior history of one concussion. Other studies in the current review either did not report on the concussion history (52, 53, 57), reported concussion history as group data (50), or provided individual data but did not correlate it with individual performance on any other outcome measures (i.e., individual MRS results) (49, 51, 56). Moreover, there may be gender differences relating to the susceptibility and recovery from concussion (64-67), and gender differences have been demonstrated in MRS findings (47, 60). Therefore, it will be important to investigate for gender effects in future studies.

The absence of studies examining sensitivity and specificity of MRS for sport-related concussion, and the lack of longitudinal studies involving a reasonably large cohort of injured athletes, is a considerable shortcoming of this literature. There are also no studies involving test-retest reliability, or how to interpret reliable or clinically significant change in individual athletes. In addition, there is no consensus pertaining to the ideal methodology, with a variety of methods used to measure metabolite concentrations. The availability of additional metabolites, such as glutamate and mI, might add to the sensitivity and specificity of MRS measures (as shown in severe TBI). Therefore, adoption of short echo time methods or other means of obtaining additional biochemical measures would be advantageous (7). Finally, although follow-up data have been published, there has been no published longitudinal study in SRC that correlates initial MRS results with long-term outcomes. For example, whether or not the observed decrease in NAA during the acute phase following injury or, for that matter, at any time over the course of recovery is predictive of worse outcome requires far more investigation.

Future research may also be directed toward examining the correlation between concussion severity, the extent to which NAA decreases, and the timing of recovery trajectories. Exploring potential metabolic changes associated with a second or multiple concussions also requires further consideration. It is also of practical use to correlate the MRS findings with other clinical tools (such as neuropsychological tests).

Conclusions

The review identified 11 studies that have used MRS in concussed athletes. These studies suggest that MRS can identify neurophysiological changes, even beyond the resolution of post-concussive symptoms, balance problems, and cognitive deficits. In the future, MRS studies might more clearly delineate the natural history of cellular changes following concussion, which could be translated into better clinical management. Some methodological recommendations for future MRS studies are listed below.

1. Use absolute metabolic concentration as a means for analyzing spectral data, rather than studying metabolite ratios (46).
2. Use an appropriate echo time to study metabolites of interest; short TE, in order to maximize the observation of all possible metabolites and thus provide maximum information related to the neurochemical profile of the brain region under investigation (20); long TE to provide a flatter spectral baseline and improved water and lipid suppression.
3. Use an automated analysis package (e.g., LCModel, AMARES) to minimize operator dependence and maximize incorporation of spectral prior knowledge (41).

4. Provide data in publications on the quality of the spectra and their fitting results as proposed by Kreis and colleagues (68) (e.g., full-width half maximum, CRLB value for metabolite inclusion, fitting residual).
5. Use appropriately age-matched controls and match 1:1 for gender. Report gender data separately.
6. Collect MRS data in the acute stage (while the athlete remains symptomatic, commonly within 48 hours following injury) and then follow up studies to monitor long-term metabolic change and correlate these with athlete recovery. Obtaining MRS data in conjunction with other more validated clinical methods such as post-concussion symptoms, balance, and cognition will assist with interpretation of MRS data.

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CHAPTER 6

PUBLICATION 5: MR SPECTROSCOPY FINDINGS IN RETIRED PROFESSIONAL RUGBY LEAGUE PLAYERS

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This is the first study of retired rugby league players. It is also the first study to report on magnetic resonance spectroscopy findings in rugby league. It is currently under review in the 7th highest ranked (top 4%) Orthopedics and Sports Medicine journal. This study was conceived and conceptualised by the PhD candidate. The data was collected and collated by the PhD candidate following processing by co-author A/Prof. Stanwell. The initial drafts (and final veto) of the manuscript was authored by the PhD candidate.

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MR Spectroscopy Findings in Retired Professional Rugby League Players

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Abstract

Retired professional Rugby League players have had considerable lifetime exposures to concussions. Magnetic resonance spectroscopy (MRS) is capable of measuring brain biochemistry and has the potential to identify and quantify altered physiological metabolism associated with neuronal viability, gliosis, and neurotransmission. This study examined brain neurometabolite concentrations in retired rugby league players who had a history of numerous self-reported concussions. Participants were 13 retired professional rugby league players with an extensive history of concussion and participation in contact sports, and 13 matched controls (age and education) who had no history of neurotrauma or participation in contact sports. All completed a clinical interview, psychological and cognitive testing, and MRS investigation. MRS voxels were placed in posterior cingulate grey matter (GM) and parietal white matter (WM). Concentrations of glutamate (Glu), glutathione (GSH), *myo*-inositol (mI), *N*-acetylaspartate (NAA), total choline (tCho), creatine+phosphocreatine (tCr), and glutamate+glutamine (Glx) were quantified using LCModel and water scaling. There were no significant differences between retired athletes and controls on measures of depression, anxiety, or cognitive functioning. The retired athletes reported significantly greater alcohol use ($p < .01$; Cohen's $d = 1.34$), and they had worse manual dexterity using their non-dominant hand ($p = .03$; $d = .74$). Retired players had significantly lower concentrations of GM NAA ($p = .04$; $d = .65$), GM mI ($p = .04$; $d = .91$), and GM GSH ($p < .01$, $d = 1.43$). They did not differ in concentrations of other hypothesized neurometabolites. These findings suggest that MRS might be sensitive to biochemical differences in athletes long after their athletic careers have ended in the absence of clinical differences in cognitive performance and self-reported psychological functioning.

Introduction

Rugby League is a popular full-contact sport played internationally by 18 full-member test nations of the Rugby League International Federations (RLIF), 21 RLIF affiliate-members, and approximately 32 other unaffiliated nations. It involves numerous collisions and tackles, and carries an inherent risk for injury,¹⁻³ including concussions and sub-concussive blows to the head.⁴ In a video analysis of medically diagnosed concussions in three National Rugby League (NRL) clubs from the 2013 season, the incidence was 14.8 concussions per 1,000 player match hours or one concussion every four games.⁵ The incidence of concussion at one NRL club over a 15 year (1998-2012) period was reported to be 28.33 concussion per 1,000 player match hours.⁶

There is considerable concern about the possible long-term effects of multiple concussions and sub-concussive blows sustained during an athletic career and their possible effects on cognitive health later in life.⁷⁻¹⁶ Advanced neuroimaging in retired athletes has mostly involved former football players and boxers.^{12,17-21} Researchers have examined the microstructure of white matter, for example, using diffusion tensor imaging (DTI),^{20,21} and neural activation using functional magnetic resonance imaging (fMRI)^{19,22} in several studies. Magnetic resonance spectroscopy (MRS) is an imaging modality that has been used with retired athletes from diverse sports.²³⁻²⁷ MRS is a powerful, non-invasive, neuroimaging technique that provides in-vivo measurement of endogenous biochemistry of the human brain.²⁸

In-vivo MRS is able to report on neurometabolites that provide insight into neural function, inflammation, axonal injuries, and possible pathologies. Numerous neurometabolites can be quantified such as N-acetyl aspartate (NAA), a biomarker of neuronal integrity; myo-inositol (mI) which is involved in glial cell growth; glutamate

(Glu) which is the major excitatory neurotransmitter in the human brain and a component of intermediary energy metabolism; choline (Cho) which is considered a measure of membrane synthesis or degradation; and glutathione (GSH), which is a vital constituent of cells throughout the body, acting as a redox buffer, and as cofactor for signal transduction, antioxidant defense, and electrophile defense, especially in the brain.²⁹ GSH is thought to be involved in the pathogenesis of several neurodegenerative diseases.

The majority of the literature on neurometabolic changes related to sports concussion has focused on active players during the acute post-injury phase.³⁰ Five studies have been conducted using MRS with retired athletes, but none in Rugby League player samples.^{23–27} All five studies reported significant findings on various neurometabolites, suggestive of neuroinflammation and/or neurodegeneration, but the results are not consistent due in large part to methodological differences across studies. The methodology and results of these studies are summarized in Table 1.

Table 1. MRS publications in retired athletes.

[illegible]

Author	N	Age (years)	Education (years)	Sport	Years of exposure	Years since exposure	Control Group (n)	Control Group Age	Education (years)	Voxel Location(s)
Lin et al (2015)	5	M: 43.6; SD: 10.8	NR	3 AF, 1 Wrestler, 1 Baseball	11-28	3-25	5 Non-professional athletes	M: 45.2; SD: 12.6	NR	PCG
MR Parameters: 2D L-COSY; 70 cm wide bore Siemens Verio (Siemens AG, Erlangen, Germany) using the operating software. VB17 using the 32 channel head coil, using 64 increments with 8 averages, and a repetition time (TR) of 1.5 seconds resulting in an acquisition time of 12.8 minutes. The data were acquired from a voxel in the PCG (size 3 Å~ 3 Å~ 3 cm3), acquired vector size 1,024 points; acquisition time 512 ms; spectral width in F2 2,000 Hz and spectral width in F1 1,250 Hz (0.8 ms increment size). Metabolites Examined: NAA, Cho, Cr, Glu, Glx, Aspartate, mI, Lysine, Threonine, GABA Other Measures: NR ‘a semi quantitative exam via person interview’ Findings: (i) Lysine/Cr no diffs; (ii) Glx >30% higher in retired athletes; (iii) Cho 65% higher in retired athletes; (iv) fucosylated glycans increased by 60% in retired athletes; (v) Phenylalanine, increased by 46% in retired athletes; (vi) mI was not found to be significantly different										
Koerte et al (2015)	11	M: 52.0; SD: 6.8; Range: 40-70	NR	Soccer	At least one season at Pro level	NR	14 non-contact sports	Mean: 46.9 SD: 7.9	NR	PCG
MR Parameters: 2D L-COSY; 3T Magnetom Verio, Seimens Healthcare, with a 32-channel head coil array. Imaging parameters were: MP-RAGE: TR = 1800 ms, TE = 3.06 ms, FOV = 256, voxel size = 1x1x1 mm3, iPAT, acceleration factor 2; 3D T2-Blade: TR = 3000 ms, TE = 400ms, FOV = 250 mm, voxel size=1x1x1 mm3, iPAT, acceleration factor 2. MRS acquired single voxel point-resolved spectroscopy (PRESS) using a short TE = 30ms, TR = 2000ms, voxel size = 20x20x20 mm3, 128 averages. CRLB less than 20% were used for each neurochemical estimation. Metabolites Examined: NAA, Cr, Cho, Glu, GSH, mI. Ratios with Cr as denominator Other Measures: Clinical information, TMT A & B, ROCF, BESS Findings: Significant differences: Higher Cho/Cr; mI/Cr. No difference: NAA/Cr; Total Cr. Levels correlated with number of headers performed each week and lifetime estimates of headers. GSH/Cr significantly correlated with lifetime estimates of headers but not to number of headers performed each week. TMT B correlated with GSH/Cr+PCr. No other cognitive correlations										
Present Study	13	M: 37.3; SD: 4.8; Range: 30-44	M: 12.2; SD: 5.1; Range: 10-16	Rugby League	M: 6.1 years; Md: 8.0; IQR: 3.5-8.7; Range: 4 months – 13 years	M: 5.7; Md: 5.0; IQR: 3.2-8.2; Range: 4 months – 16 years	13	M: 37.3; SD: 2.1; Range: 30-45	M: 13.0; SD: 2.8; Range: 10-18	Parietal WM PCG
MR Parameters: 3T Siemens Skyra scanner with a 20-channel head coil. Placement of the MRS voxels was selected based on T1-weighted images acquired with a 3D MPRAGE sequence (TR/TE/TI:2300/3.03/900ms; flip angle: 9°; 192 sagittal slices with 1mm thickness, FOV_{APxFH}:256x256 mm², matrix: 256x256 pixels). SVS acquisitions were acquired from two brain regions. Spectral quality was assessed using: (i) the signal-to-noise ratio (SNR); and (ii) the line width as provided by LCModel output. Metabolites Examined: NAA, Cr, Cho, Glu, GSH, mI, Glx Other Measures: Clinical information, DASS-21; HPS, WMS-III Information and Orientation, RAVLT, RCFT, WAIS-IV: Digit Span, Similarities, Coding, Symbol Search, Stroop Test, COWAT, TMT A & B, Grooved Pegboard, BESS Findings: Significant differences: reduced GM NAA - medium ES; reduced GM mI – large ES; reduced GM Glu – medium ES; reduced GM GSH – medium ES; No difference: WM NAA - small ES; WM and GM Cho – small ES; reduced WM GSH – medium ES.										

Note. AF: American Football; IH: BDI-II: Beck Depression Inventory – 2nd edition; BESS: Balance Error Scoring System; DASS-21: Depression, Anxiety, Stress Scale – 21 item; ES: Effect size; GM: Grey matter; HPS: Hunter Pain Scale; IH: Ice Hockey; IQR: Inter-quartile range (95% confidence interval); M: mean; Md: Median; MMSE: Mini-Mental Status Exam; MTL: medial temporal lobe; N/A: not applicable; NR: not reported; PCG: posterior cingulate gyrus; PFC: prefrontal cortex; RAVLT: Rey Auditory Verbal Learning Test; RCFT: Rey Complex Figure Test; SDMT: Symbol Digit Modalities Test; SVS: Single voxel spectroscopy; TMT: Trail Making Test; WM: white matter.

MRS has also been used to detect and monitor metabolic change in aging,^{31,32} mild cognitive impairment (MCI),^{33,34} and other neurodegenerative diseases.^{35–38} Specifically, patients with MCI have elevated hippocampal levels of mI/Cr and increased levels of GSH in spectra collected from the anterior and posterior cingulate.³³ In Alzheimer's disease (AD), the metabolite NAA/Cr ratio is reduced in spectra collected from bilateral posterior cingulate gyri and inferior precunei.³⁶ Meta-analysis of MRS findings in healthy aging revealed reduced frontal NAA and increased parietal choline and creatine.³¹ Interpreting MRS results through observing patterns of metabolic change is generally considered a more robust method for identifying potential pathologies than single measure changes.³⁷ For example in neurodegenerative disease, because neuron cell loss is common, decreased NAA is typically observed, and as a result of reduced neurotransmission, glutamate is also reduced.³⁹ In contrast, in cases of acute neuroinflammation where energy metabolism and gliosis may be increased, it is common for glutamate and mI to be elevated,⁴⁰ while GSH³³ is simultaneously reduced.²⁵

To our knowledge, there are no prior studies examining MRS in retired rugby union or rugby league players. This study examined neurometabolites in retired professional rugby league players between the ages of 30-45 years. In this study several hypotheses were informed by the assumption that these athletes have had enormous exposure to both concussion and other blows to the head during their athletic careers, and this might have resulted in alterations in physiological metabolism that could hasten the onset MCI or neurodegenerative disease. Given that NAA is thought to be a marker of neuronal viability and whole brain NAA has been found to be reduced in patients with MCI and AD,⁴¹ our primary hypothesis was that NAA would be reduced in retired players compared to the control participants. An

additional four *a priori* secondary hypotheses were also considered. First, it was hypothesized that mI would be elevated in retired players compared to control participants because mI is believed to be important in neurodevelopmental synaptogenesis, axonal growth, and myelination; it is generally assumed to be a marker of gliosis and researchers have reported that mI is increased in the context of neuroinflammation;⁴² and it is elevated in MCI and AD patients^{31,34,36,43} and in retired athletes.⁴⁴ Second, it was hypothesized that Cho will be elevated in retired athletes compared to control participants because Cho is considered to be a marker for cellular proliferation or tissue damage,^{45,46} and it has been reported to be elevated in retired athletes.⁴⁴ Third, it was hypothesized that the glutamate would be reduced in retired players compared to the control participants because glutamate is considered to be a proxy marker for neuronal loss and is found to be reduced in Alzheimer's disease.⁴⁷ Fourth, it was hypothesized that the GSH will be reduced in retired players compared to the control participants because dysregulation of glutathione homeostasis is implicated in the induction and progression of neurodegenerative diseases.^{29,48}

Materials And Methods

Participants

Retired professional rugby league players (n=13) were recruited to the current study through communication with the club alumni, who distributed information pertaining to the study to their members. Exclusion criteria included any medical history of neurosurgery, or any history of a brain tumor requiring radiation treatment, or claustrophobia (i.e., they were unable to tolerate being inside the MRI machine for neuroimaging). Healthy community control subjects similar in age and education were recruited through a research participant registry established by a medical research

institute. The retired players and the control subjects were selected from larger samples of players (N = 26) and controls (N = 18) based on the number of subjects who were within the specified age range. The study is ongoing with the goal to recruit a larger sample of older retired players who could be analyzed separately.

Procedures

All participants completed a clinical interview and neurocognitive testing with the lead author (AG). The clinical interview collected data pertaining to demographic information, medical and concussion history, together with patient reported outcome measures. Immediately following the interview, neurocognitive testing was completed. The total interview and testing time was approximately 135 minutes. The MRS data was collected during a separate, single testing session on all participants as one component of a multiparametric neuroimaging study. The imaging time for the MRS component of the study was approximately 25 minutes; the whole multiparametric acquisition time was approximately 65 minutes.

Measures

The administration battery included patient reported outcome measures and neurocognitive tests. The patient reported outcome measures were as follows; the Depression, Anxiety, Stress Scale 21-item (DASS-21),⁴⁹ the Rivermead Post Concussion Symptoms Questionnaire,⁵⁰ Alcohol Use Disorders Identification Test (AUDIT),⁵¹ Brief Pain Inventory (BPI).⁵² Cognitive testing measuring attention, processing speed, learning and memory, and fluid executive function were administered as part of the neurocognitive test battery. The Advanced Clinical Solutions (ACS) Test of Premorbid Functioning (TOPF)⁵³ was also administered to establish an estimated premorbid level of intellect for each participant. In total each participant's cognitive performance was based on 12 test scores, collected from the

following tests, using the following normative data sets: the Mitrushina and colleagues⁵⁴ meta-norms were used to convert raw data to standard scores for the Rey Auditory Verbal Learning Test (RAVLT),⁵⁵ Rey Complex Figure Test (RCFT) immediate recall and delayed recall,⁵⁶ Trail Making Test (TMT) A and B,⁵⁷ the Controlled Oral Word Association Test (COWAT) FAS⁵⁸ and animal fluency, and the Stroop condition 3 - inhibition task.⁵⁹ The Wechsler Adult Intelligent Scale 4th Edition (WAIS-IV)⁶⁰ Australian and New Zealand norms were used to convert the raw data to standard scores for the following subtests: digit span (backwards and sequencing), symbol search, and coding. An overall test battery mean was computed by summing and averaging the normative scores (expressed in T score units with a mean of 50 and a SD of 10).

Conventional Imaging

Imaging was performed on a 3 T Siemens Skyra scanner with a 20-channel head coil. Placement of the MRS voxels was selected based on T1-weighted images acquired with a 3D MPRAGE sequence (TR/TE/TI:2300/3.03/900ms; flip angle: 9°; 192 sagittal slices with 1mm thickness, FOV_{APxFH}:256x256 mm², matrix: 256x256 pixels).

Single-Voxel Spectroscopy

Single voxel spectroscopy (SVS) acquisitions were acquired from two brain regions. The first volume of interest encompassed a region predominantly rich in grey matter in the occipito-parietal region (encompassing posterior cingulate and precuneus). The second volume of interest encompassed an area predominantly rich in white matter in the parietal white matter. For all subjects MRS voxels were positioned using the T1-weighted MPRAGE volumetric acquisition for guidance with care taken to avoid the lateral ventricles in the case of parietal white matter.⁶¹ For convenience,

these regions will subsequently be referred to simply as grey matter or white matter. The posterior cingulate was selected because it is one of the most homogenous regions of the brain allowing for sound technical quality and strong reproducibility.⁶² Moreover, the posterior cingulate region is considered to be a good indicator of neurochemical changes in other neuroanatomical regions.^{37,62}

A short echo time (TE) PRESS (point resolved spectroscopy)⁶³ single voxel sequence was used for all measurements (TE: 40 ms; TR: 2000 ms; 2048 sampled complex FID points, spectral bandwidth: 2 kHz) with the TE chosen to enhance quantification of glutamate.⁶⁴ The data were measured with and without water suppression to obtain separate metabolite and water spectra with water spectra providing an internal water reference to scale the measured metabolite signals. Automatic first- and second-order MR shimming was followed by manual fine-tuning of the shim gradients to maximize B₀ field homogeneity in all experiments (peak linewidths of unsuppressed water: 12–15 Hz). The transmitter rf-frequency was set to 2.3 ppm for the acquisition of the metabolite spectrum, and to 4.7 ppm (water resonance) for the acquisition of the water spectrum, to minimize chemical shift misregistration and thus ensuring nearly equally located volumes for the water-suppressed and non-suppressed measurements.

Spectral Analysis

Localized spectra were quantified in LCModel (version 6.3-0G)⁶⁵ to evaluate the concentrations of metabolites that were scaled against the water signal from non-water-suppressed spectra. LCModel analyzes in-vivo spectra as a linear combination of complete model spectra of the individual metabolites in-vitro, which are defined in an appropriate basis set. In this study a simulated basis set was employed for the PRESS sequence parameters used in this study and included the following 17

metabolites: alanine (Ala), aspartate (Asp), creatine (Cr), phosphocreatine (PCr), gamma-amino-butyric acid (GABA), glucose (Glc), glutamine (Gln), glutamate (Glu), glycerophosphocholine (GPC), phosphocholine (PCho), glutathione (GSH), *myo*-inositol (mI), lactate (Lac), *N*-acetyl-aspartate (NAA), *N*-acetylasparylglutamate (NAAG), scyllo-inositol (sIns), and taurine (Tau). The following calculations were also reported in the LCModel output: GPC+PCho, NAA+NAAG, Cr+PCr (tCr), and Gln+Glutamate (Glx). Metabolites were fitted in the chemical shift range between 0.5 and 4.2 ppm to take into account baseline distortions caused by broad macromolecular resonances, which were also included in the model spectra basis set as simulated singlets at 0.9, 1.5, 2.1, and 3.0 ppm.⁶⁶ Model metabolites and concentrations used in the basis set are fully detailed in the LCModel manual (<http://www.s-provencher.com/pages/lcm-manual.shtml>).

Data quality was ensured by using established criteria⁶⁷ and included: (i) excluding spectra with a line width full width at half-maximum (FWHM) exceeding 0.1 ppm; (ii) excluding spectra with poor signal-to-noise ratio (SNR) (≤ 20); and (iii) visually inspecting all spectra for the presence of abnormal features such as asymmetric line shapes, and excluding those with artefacts. Following spectral quality assurance, we applied strict criteria for assessing metabolites reporting only on metabolites with Cramer-Rao lower bounds (CRLB) less than, or equal to, 15% (excellent reliability): Glu, GSH, mI, NAA, GPC+PCho (tCho), Cr+PCr (tCr), and Glx in grey matter, and GSH, mI, NAA, GPC+PCho (tCho), Cr+PCr (tCr), and Glx in white matter. Glutamate was also analysed in white matter where CRLB were less than, or equal to, 20% (but greater than 15%, i.e. acceptable reliability) in the case of glutamate in a minority of cases.

Relaxation and Partial-Volume Correction

All spectroscopic voxels were placed to maximize one tissue type, either grey matter or white matter. These tissues have different water concentrations⁶⁸ and exhibit different T1 and T2 relaxation time constants for both metabolites^{69–71} and water.^{72–74} Furthermore, metabolite signals originate only from grey matter and white matter, whereas water signal arises from grey matter, white matter, and cerebral spinal fluid (CSF). Accordingly, to compensate for the variable amount of water signal included in each spectroscopy voxel, T1-weighted images were segmented into grey matter, white matter, and CSF masks using Statistical Parametric Mapping-8 (SPM8) (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>). Each voxel was subsequently re-aligned with the grey matter, white matter, and CSF masks using spatial information regarding the voxel location, and the fractions of each tissue class estimated. Metabolite concentrations were then computed, correcting for partial-volume and T1 and T2 relaxation effects, using methods described previously.⁷² This involved correcting the LCModel results for each voxel according to the equation below.

$$[M] = \frac{[M]_{LCM} \times (f_{GM} \times R_{H2O_GM} + f_{WM} \times R_{H2O_WM} + f_{CSF} \times R_{H2O_CSF})}{(1 - f_{CSF}) \times R_M}$$

Eq. 1

In this equation, $[M]_{LCM}$ is the concentration in mmol kg⁻¹ of MR visible water (mmolal) as reported by LCModel and using tissue water as a concentration reference; f_{GM} , f_{WM} , and f_{CSF} are the water density fractions for grey matter, white matter, and CSF,^{68,75} respectively; and the R_{H2O} terms are the relaxation attenuation factors for the water signal in each tissue class, based on reported values for T1 and T2^{72–74} and the equation $R_{H2O_y} = \exp[-TE/T_{2_H2O_y}](1 - \exp[-TR/T_{1_H2O_y}])$, where $T_{1_H2O_y}$ and $T_{2_H2O_y}$ are the T1 and T2 relaxation times of water in compartment y, TE is the sequence echo time, and TR is the repetition time. Similarly, R_M is the relaxation attenuation

factor for the metabolite signal in either grey matter or white matter.^{69,71,76} The fractional water densities appearing in Eq. [1] were calculated using the estimated tissue volume fractions obtained by tissue segmentation using SPM8 by taking into account the relative water densities (WD) in each volume fraction using the equation below.

$$f_x = \frac{f_{x_vol} \times WD_x}{f_{GM_vol} \times WD_{GM} + f_{WM_vol} \times WD_{WM} + f_{CSF_vol} \times WD_{CSF}}$$

Eq. 2

In this equation, the various terms refer to the volume fractions and associated water densities of each tissue or CSF (i.e., x= grey matter, white matter, or CSF). In this study, we used T1 and T2 values of 1,304 ms and 93 ms for grey matter⁷⁴, 660 ms and 73 ms for white matter⁷⁴, and 4,000 ms and 2,470 ms for CSF, respectively.^{72,73} Likewise, water densities used were grey matter=0.78, white matter=0.65, and CSF=0.97,^{68,75} Estimates of metabolite T1 and T2 values at 3T were drawn from published data,^{69–71} except in the case of GSH where concentration values were corrected for water relaxation attenuation but not for metabolite relaxation attenuation due to a lack of reported T1 and T2 values for GSH in human brain.

Results

Participant Descriptives

The average age of the retired player group was 37.3 years (SD: 4.8, range 30-44) and average level of education was 12.2 years (SD: 5.1, range 10-16). The control group's average age was 37.3 years (SD: 2.1, range 30-45), and education was 13.0 years (SD: 2.8, range 10-18). Retired players reported an average of 28.5 (median = 20; IQR = 5.5 - 41; range 3-100) concussions, with an average of 6.5 (median = 3; IQR = 1.5 - 6; range 0-20) concussions with loss of consciousness sustained during

their careers. Players had been retired for between 4 months and 13 years ($M = 6.1$, $Md = 8.0$, $IQR = 3.5-8.7$ years). Four players had retired during the previous 12 months. The time since the most recent concussion ranged between 4 months and 16 years ($M = 5.7$, $Md = 5.0$, $IQR = 3.2-8.2$ years). On a scale of 1 (no concern) to 7 (extremely concerned), players rated their concern about how their concussion history might be affecting their current and future cognitive health as $M=3.8$ (Range 1-7). The retired players group did not report repeating any grades in school or hyperactivity. There were two cases of attendance in special education classes, reading problems, and spelling problems. Two retired players reported a family history of dementia in either their parents and/or grandparents. No retired player reported current prescription medication use. With regard to marital status, five retired players were married at the time of the assessment, five had never married, and three were divorced. Three retired players reported a history of arthritis (compared to one control), two reported a history of depression (compared to one control), and two reported a history of headache. None of the retired players reported a history of hypertension, diabetes, myocardial infarction or cardiac-related conditions, thyroid condition, liver disease, stroke, syphilis, neurosurgery, meningitis, or other psychiatric conditions. One retired player met criteria for probable MCI based on a clinical interpretation of his neuropsychological test results (i.e., he had six scores out of 12 below the 10th percentile).

In the control group, there was one subject who reported repeating a school year, attendance in special education classes, reading problems, and spelling problems, and one subject who reported hyperactivity. Five control participants reported a family history of dementia in either their parents and/or grandparents. Two control participants reported current prescription medication use (for depression and

arthritis). Twelve were married at the time of the assessment and one had never married. A history of headache was reported by eight control subjects. None reported a history of hypertension, diabetes, myocardial infarction or cardiac-related conditions, thyroid condition, liver disease, stroke, syphilis, neurosurgery, meningitis, or other psychiatric conditions. No control subjects met criteria for probable MCI based on a clinical interpretation of their neuropsychological test results.

Spectral Quality

The mean ($\pm$ standard deviation) for measurement SNR and line width in both regions was 31.17 (± 2.27) and 0.061 (± 0.013) ppm for grey matter and 29.79 (± 4.22) and 0.047 (± 0.022) ppm for white matter, respectively. There were no significant group differences (control vs. retired athlete) for measurement SNR ($P=0.36$) or line width ($P=0.07$) in grey matter. In white matter there was no significant difference in line width ($P=0.36$), but there was a significant difference in SNR ($P=0.03$). The mean ($\pm$ standard deviation) for Cramer-Rao lower bounds in both regions were glutamate 6.17 ± 0.37 , GSH 9.17 ± 1.18 , mI 4.79 ± 0.50 , NAA 2.33 ± 0.47 , GPC+PCho 3.08 ± 0.28 , Cr+PCr 2.00 ± 0.00 , and Glx 5.17 ± 0.47 for grey matter, and glutamate 7.58 ± 3.13 , GSH 9.75 ± 1.27 , mI 4.88 ± 1.05 , NAA 3.04 ± 0.68 , GPC+PCho 2.17 ± 0.47 , Cr+PCr 2.04 ± 0.20 , and Glx 6.50 ± 1.32 for white matter. There were no significant differences in CRLB in grey matter or white matter for any measured metabolites (grey matter: P-values ranged from 0.17 to 0.72; white matter: p-values ranged from 0.09 to 0.79). All spectra included for analyses were free of artefacts. The metabolite concentrations obtained in control subjects in this study are similar to those reported in numerous other studies.^{33,76–78}

MRS

MRS results are presented in Table 2. Non-parametric Mann-Whitney tests were used for all comparisons. One-tailed tests were used to examine the directional primary hypothesis of reduced NAA in retired players compared to control participants. There was a significant difference between groups in grey matter NAA with significantly lower concentrations of NAA found in retired athletes ($U=51.0$, $p=.04$; one-tailed p value; Cohen's $d=.65$, medium effect size). No significant differences were found in white matter NAA ($p=.07$; Cohen's $d=.20$). Spearman correlations between NAA and lifetime concussion history were non-significant in both the white matter and grey matter in the retired athletes.

Table 2. Primary, Secondary, and Exploratory Comparisons Between Groups

	Retired Players		Controls			
Clinical Tests	M	SD	M	SD	p	Cohen's d
Depression, Anxiety, Stress Scale						
Depression	3.23	5.57	2.31	2.56	.70	.23
Anxiety	3.23	5.07	2.62	2.99	.89	.15
Stress	9.38	9.00	7.23	4.36	.88	.32
AUDIT	9.85	4.18	4.62	3.64	0.004	1.34
Rivermead PCSQ Total Score	10.92	11.07	6.46	7.24	.54	.49
Cognition Composite T Score ¹	50.68	5.93	52.03	5.93	.56	.23
Grooved Pegboard: Dominant Hand (T scores)	40.38	10.59	44.85	8.91	.40	.46
Grooved Pegboard: Non-Dominant Hand	44.08	6.87	49.69	8.39	.03	.74
BESS Total Raw Scores	16.46	3.95	14.62	5.94	.44	.38
Metabolites in Grey Matter						
Glutamate (Glu)	9.48	1.25	10.36	1.48	0.07	0.64
Glutathione (GSH)	1.12	0.25	1.47	0.24	0.003	1.43
GSH/tCR	0.32	0.07	0.39	0.07	0.05	1.00
myo-Inositol (mI)	5.67	0.90	6.54	1.02	0.04	0.91
N-acetyl-aspartate (NAA)	10.17	1.40	11.17	1.66	0.04*	0.65
Choline (GPC+Pch)	1.29	0.18	1.25	0.12	0.98	0.07
NAA+NAG	10.71	1.54	11.38	1.81	0.37	0.40
Creatine (Cr)	7.16	0.83	7.84	0.95	0.11	0.76
Glx (glutamate/glutamine)	14.82	2.77	17.37	2.85	0.04	0.91
Metabolites White Matter						
Glutamate (Glu)	6.62	0.98	6.11	1.06	0.11	0.50
Glutathione (GSH)	1.02	0.50	1.23	0.67	0.82	0.36
GSH/tCR	0.33	0.14	0.38	0.16	0.52	0.33
myo-Inositol (mI)	5.19	1.19	5.47	1.65	0.94	0.20
N-acetyl-aspartate (NAA)	8.22	1.17	8.49	1.52	0.70	0.20
Choline (GPC+Pch)	1.81	0.20	1.81	0.45	0.46	0.00
NAA+NAG	9.78	0.74	9.73	0.76	0.98	0.07
Creatine (Cr)	6.27	0.23	6.34	0.93	0.94	0.12
Glx (glutamate/glutamine)	9.30	2.84	10.44	3.39	0.52	0.37

Note. *One-tailed p-value used for the single directional primary hypothesis. All of the secondary hypotheses were directional but we did not use one-tailed p-values due to increased risk for type 1 statistical errors due to multiple comparisons; ¹Cognitive Composite Score is the mean of RAVLT Total, Rey Complex Figure Immediate Recall and Delayed Recall, Trails A, Trails B, WAIS-IV Symbol Search, WAIS-IV Coding, WAIS-IV Digits Span Backwards and Sequencing, Phonemic and Semantic Fluency, and Stroop Inhibition T Scores; Rivermead PCSQ= Rivermead Post Concussion Symptom Questionnaire.

Secondary analyses examining concentration differences in grey and white matter mI, Cho, glutamate, and glutathione were also conducted. Although all hypotheses were directional, two-tailed p values were used due to increased risk for Type 1 statistical errors due to multiple comparisons. No further adjustment was done to reduce risk for Type 1 errors given that the small sample sizes and associated

reduced power increase the likelihood of Type 2 errors. There was a significant difference between groups in grey matter mI ($U=44.00$, $p=.04$; Cohen's $d=.91$), with retired players having lower concentrations compared to controls. There was a significant difference in grey matter glutathione, with retired players showing lower concentrations compared to controls ($U=27.0$, $p<.01$, Cohen's $d=1.43$). There was no significant difference between groups in grey matter choline ($p>.05$; Cohen's $d=.64$) or glutamate ($p>.05$; Cohen's $d=.64$) concentrations, although the differences between groups had medium effect sizes. In white matter, there were no statistically significant differences in any of the neurometabolites that were hypothesized to differ (mI, Cho, Glu, or GSH). The reader is encouraged to view the effect sizes in Table 2 because the analyses were under-powered due to small sample sizes and some of the nonsignificant grey matter effect sizes were medium to large. In contrast, the effect sizes in white matter were mostly small. Exploratory Spearman correlations between lifetime concussion history and mI, Cho, Glu, and GSH were nonsignificant in both white matter and grey matter in the retired athletes.

Cognitive and Self-Report Measures

Non-parametric Mann-Whitney tests were used for all comparisons because of small sample sizes, violations to the assumptions of normality, and skewness in some variables. The two groups were similar on age and education (all $ps>.05$). A cognition composite score was calculated using the mean of the Rey Auditory Verbal Learning Test Total score, Rey Complex Figure Immediate Recall and Delayed Recall, Trails A, Trails B, WAIS-IV Symbol Search, WAIS-IV Coding, WAIS-IV Digits Span Backwards and Sequencing, Phonemic and Semantic Verbal Fluency, and Stroop Inhibition T Scores for each participant. There was no significant difference between groups on this cognition composite score ($p>.05$; $d=0.23$). Performance on balance

testing (i.e., BESS scores), fine motor functioning (i.e., Grooved Pegboard T Scores), psychological distress (i.e., DASS Anxiety, Stress, and Depression scores), and post-concussion symptoms total score (i.e., Rivermead Post-Concussion Questionnaire Scale; RPCQS) were also compared between groups. There was a significant group difference in non-dominant hand performance on the Grooved Pegboard test, with retired players showing worse performance compared to controls ($U=41.0$, $p=.03$; $d=.74$). There was also a significant difference in AUDIT scores (i.e., Alcohol Use Disorders Identification Test), with retired players scoring higher than controls ($U=28.5$, $p<.01$; $d=1.34$). The breakdown of retired players and controls by AUDIT classification ranges was as follows: Abstainer = 0 players and 1 control, Low Risk = 4 players and 10 controls, Hazardous Level = 7 players and 2 controls, Harmful = 1 player and 0 controls, and High Risk = 1 player and 0 controls. There were no significant differences between groups (all $ps >.05$) on BESS scores ($d=.38$); DASS Depression ($d=.23$), Anxiety ($d=.15$), or Stress scores ($d=.32$); post-concussion symptoms ($d=.49$); or in dominant-hand performance on the Grooved Pegboard Test ($d=.46$).

Post-hoc exploratory analyses examining potential associations between psychological distress (i.e., DASS Depression, Anxiety, and Stress scores), cognition (i.e., cognition composite T scores), balance (i.e., BESS scores), fine motor functioning (i.e., Grooved Pegboard Test T Scores), post-concussion symptoms (i.e., RPCQS), and MRS metabolites were run within retired rugby players using Spearman correlations (Table 3). In retired athletes there were significant negative correlations between BESS scores and grey matter glutathione ($r=-.76$; $p <.01$), grey matter glutathione/creatine ($r=-.67$; $p<.05$), and grey matter Glx ($r=-.80$; $p<.01$) concentrations. BESS scores were also negatively associated with white matter

glutathione ($r = -.58$; $p < .05$), choline ($r = -.57$; $p < .05$), and creatine ($r = -.62$; $p < .05$) concentrations. There was also a significant positive correlation between AUDIT scores and white matter glutamate ($r = .61$ $p < .05$). All other associations for retired athletes were non-significant (all p s > 0.05 ; see Table 3). There were no significant correlations between AUDIT scores, BESS scores, and Grooved Pegboard performance in retired athletes (all p s $> .05$). For completeness, the same correlation matrix was computed within the control subjects. There were many more significant correlations within the control group than within the retired athlete group (see Table 3). There were some consistencies in the correlations between neurometabolites and the clinical measures in both groups, but overall the results were not consistent and difficult to interpret.

Table 3. Exploratory Spearman Rho Correlations between MRS Metabolites and Cognition, Psychological, and Balance Variables within Retired Rugby Players and Controls

Metabolite	DASS Depression		DASS-Anxiety		DASS-Stress		AUDIT		mBESS Total		GP-Dom		GP-Nondom		Cognition Composite		Rivermead PCSQ	
	RA	Con	RA	Con	RA	Con	RA	Con	RA	Con	RA	Con	RA	Con	RA	Con	RA	Con
Grey Matter																		
Glutamate (Glu)	-.24	.17	.04	.01	.21	.54	-.28	.65*	-.04	.01	-.44	.51	.44	.13	.05	-.13	.17	.27
Glutathione (GSH)	.25	.08	.14	-.03	.12	.14	-.06	.09	-.76**	.37	.09	.06	-.07	.17	-.05	.39	.08	.29
GSH/tCr	.34	.17	.17	.13	.13	-.08	-.08	-.30	-.67*	.36	.40	-.19	-.22	.26	-.23	.58*	.02	.23
Myo-Inositol (mI)	.23	.23	.41	.18	.52	.51	.03	.47	-.20	.06	-.30	.42	.32	-.12	-.20	-.14	.47	.36
N-acetyl-aspartate	-.06	-.06	.12	.08	.24	.36	-.30	.58*	-.06	.06	-.40	.31	.27	-.25	-.01	-.58*	.31	.25
Choline (GPC+Pch)	.09	-.03	.15	-.24	.16	.42	-.37	.70**	-.06	.16	-.22	.62*	.08	.07	-.39	-.03	.27	.17
NAA+NAAG	-.27	-.12	-.10	.02	.04	.30	-.07	.61*	.40	.09	-.46	.25	.36	-.34	.09	-.56*	.09	.17
Creatine (Cr)	-.23	.16	.05	.16	-.03	.45	-.06	.59*	-.26	.00	-.39	.35	.17	-.11	.17	-.30	.20	.26
Glx	.04	.10	.14	.08	.03	.45	-.14	.40	-.80**	.22	-.11	.40	.06	.01	.07	.09	.14	.32
White Matter																		
Glutamate (Glu)	.08	-.08	-.03	-.33	-.08	.12	.61*	.14	-.29	-.54	.23	.25	.06	-.15	.21	-.01	-.32	-.67*
Glutathione (GSH)	-.01	.03	-.19	.05	-.26	-.47	-.05	-.48	-.58*	.16	.27	-.22	-.39	.07	.13	.34	-.15	.01
GSH/tCr	.08	-.08	-.18	-.07	-.03	-.42	-.32	-.41	-.41	.21	.31	-.13	-.52	.04	.05	.37	-.24	-.02
myo-Inositol (mI)	-.10	.29	-.10	.24	-.20	-.38	-.05	-.51	-.51	-.05	.04	-.22	.02	.09	.04	.26	.08	.12
N-acetyl-aspartate	.04	-.08	.03	-.15	-.07	-.49	.42	-.45	-.37	.15	.46	-.21	.06	.03	.03	.19	-.33	-.04
Choline (GPC+Pch)	.02	-.04	-.22	.07	-.29	-.62*	.16	-.59*	.57*	.17	-.01	-.35	-.17	.06	.09	.24	-.04	.07
NAA+NAAG	-.05	.12	.22	.17	-.04	-.34	.49	-.37	-.49	.22	.47	-.08	.34	.24	-.18	.10	-.42	.23
Creatine (Cr)	-.19	.23	-.09	.06	-.42	-.43	.31	-.51	-.62*	.05	.21	-.25	-.04	.29	.16	.40	-.10	.05
Glx	.07	-.25	-.01	-.15	-.11	-.67*	.40	-.56*	-.37	.35	.33	-.50	-.06	.06	.26	.30	-.12	-.11

Note: RA= Retired athletes (N=13); Con= Control subjects (N=13); DASS=Depression Anxiety and Stress Scale, mBESS=modified Balance Error Scoring System, Glx=glutamate/glutamine; GPC= Glycerophosphocholine; GP-Dom=Grooved Pegboard for dominant hand, GP-Non-Dom=Grooved Pegboard for Non-Dominant Hand; Pch= Phosphocholine; NAA= N-acetylaspartate; NAAG= N-acetylasparatylglutamate; Rivermead PCSQ= Rivermead Post Concussion Symptom Questionnaire; tCr=total creatine; *p<.05; **p<.01.

Discussion

Rugby League is a full-contact collision sport with tremendous exposure to subconcussive blows to the head and concussions. This sample of retired players estimated a median of 20 concussions over their lifetime, with most reporting between five and 40 prior concussions. They estimated experiencing a median of three concussions with loss of consciousness (LOC), with most reporting between one and six injuries with LOC. This study examined brain neurometabolite concentrations in retired professional rugby league players compared to healthy age-matched controls with no history of concussion using MRS. It was predicted that neuronal viability would be reduced in retired athletes compared to controls secondary to their history of numerous prior concussions and long-exposure to collision sport. As predicted in the primary hypothesis, retired professional rugby league players had significantly reduced *N*-acetylaspartate (NAA) in grey matter with a medium effect size compared to age matched controls. However, there was no significant difference in NAA between the groups in the white matter, and the effect size in white matter was small. NAA in grey matter and in white matter was not correlated with lifetime history of concussion or any clinical outcome measures in the retired athletes.

For the present study, we chose locations to maximize one tissue type per voxel location (i.e., parietal WM and posterior cingulate GM), not specific brain regions of possible vulnerability. It is possible that findings relating to NAA, and other neurometabolites, would have differed if different brain regions were selected for study. Reduction in NAA concentrations may be associated with multiple factors and this has been found in several clinical populations. For example, in neurodegenerative diseases reduced NAA has been observed in AD (posterior cingulate cortex, bilateral medial frontal gyri, and bilateral occipital lobes)^{79–81} and

Parkinson's disease (anterior and posterior cingulate gyri, presupplementary motor area, substantia nigra).^{82,83} Reduced NAA has been found in other brain regions (not the ones in the present study) in people with frontotemporal dementia (motor cortex, frontal white matter, and corticospinal tracts),⁸⁴ major depressive disorder and bipolar disorder (right prefrontal cortex and left prefrontal white matter),^{85,86} chronic pain (particularly neuropathic pain),⁸⁷ high-risk vascular risk factors (prefrontal cortex),⁸⁸ alcohol use disorder (frontal cortices, frontal white matter, and cerebellar vermis),^{89–92} and chronic drug abuse (basal ganglia, frontal white matter, dorsolateral prefrontal cortex, and parietal white matter).^{93–96} Although some prior studies have shown reduced NAA in association with alcohol abuse, and the retired athletes had greater alcohol use than the controls, their level of drinking was far less than reported in previously published MRS studies.

It was hypothesized that *myo*-inositol (mI) would be increased in the retired rugby players; it was not. In fact, grey matter mI was significantly lower in retired athletes than in control subjects, with a large effect size. There was no difference in white matter mI. The lower mI did not appear to be attributable to issues with water suppression, or voxel placement, or metabolic or hepatic conditions among participants. The retired players had greater alcohol use than the control subjects, but not to the point where we would anticipate cirrhosis or toxic hepatitis underlying the mI finding. Although these mI results are inconsistent with findings from one other study of retired athletes in other collision sports,⁴⁴ the results in that study were mixed with reductions in the hippocampus and the motor cortex but increased in the mesial temporal lobe and prefrontal cortex. These mI results are also inconsistent with the theory that there might be active neuroinflammation and the theory of neurodegeneration similar to MCI or AD.^{31,34,36,43}

It was hypothesized that choline (Cho) would be elevated in retired athletes, due to membrane turnover, similar to the results of Tremblay and colleagues.⁴⁴ However, the levels of Cho in the brains of athletes compared to controls in both grey matter and white matter were virtually identical. Because glutamate might be a marker for neuronal loss in neurodegenerative disease, such as in AD,⁴⁷ it was hypothesized that glutamate would be reduced in retired players. Consistent with this hypothesis, glutamate was lower in grey matter in the retired athletes, with a medium effect size. However, there was a non-significant trend for it to be increased in white matter in the athletes (with a medium effect size). This trend may be due to a CRLB of 15-20 for WM Glu in a few cases, whereas in all other metabolites the CRLB was ≤ 15 (i.e., less robust). This possibility is supported by the CRLB for Glx (Glu + Gln) which was less than 15 for both GM and WM, and was reduced in retired athletes versus controls. Hence the greater Glu in WM might be due, in part, to worse localized shim results in WM versus GM. Glutamate in grey matter and in white matter was not correlated with lifetime history of concussion or any clinical outcome measures in the retired athletes.

Finally, it was hypothesized that glutathione (GSH) would be reduced in retired players compared to the control participants, because lower GSH is expected in other neurodegenerative diseases like AD, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis.^{29,48} GSH was lower in both grey matter and white matter, but not significantly lower in white matter (small-medium effect size). In grey matter, it was significantly lower with a very large effect size. In the retired athletes, there was a significant negative correlation between GSH and BESS scores in both grey matter and white matter meaning that lower GSH was associated with worse balance. There were no other significant correlations between GSH and the clinical outcome measures, and GSH was not associated with lifetime concussion history.

A number of studies have used MRS in groups of retired professional athletes from different contact sports.²³⁻²⁷ De Beaumont and colleagues⁴⁴ examined 30 former male university-level athletes (i.e., ice hockey and football players) aged 51-75 years; 15 athletes reported a history of concussion (sustained between 29-53 years ago) and 15 reported no past history of concussion. There was a non-significant trend ($p = 0.57$) for the N-acetylaspartate to water ratio to be higher in MRS collected from the left primary motor cortex compared to those athletes with no self-report prior history of concussion. Further secondary analysis revealed a significant Age*Group interaction for glutamate, suggesting that the aging affect on glutamate levels might be significantly exacerbated in former athletes with a history of concussion. Furthermore, the glutamate results were positively correlated with motor learning in concussed athletes. Using the same sample as described above, Tremblay and colleagues⁹⁸ collected MRS images from different brain regions [i.e., bilateral medial temporal lobe (MTL) and bilateral prefrontal cortex (PFC)]. Elevated *myo*-inositol (mI) and reduced choline (Cho) was observed in the left MTL (but not the right MTL), and elevated choline in the right PFC (but not the left PFC). The mI results were correlated with poorer performance on delayed visual memory tasks. Davie and colleagues²³ examined three former professional boxers diagnosed with a Parkinsonian syndrome and found significantly reduced levels of *N*-acetylaspartate (NAA) in lentiform nucleus when compared to matched controls and patients with idiopathic Parkinson's disease. The extent to which these findings are related to the diagnosis of PD, a history of repetitive neurotrauma through boxing, or both is not known. Two recent studies of retired athletes used single voxel, 2D Localized Correlated Spectroscopy (L-COSY) located in the posterior cingulate gyrus.^{24,25} Lin and colleagues²⁵ examined five retired athletes with a history of repetitive concussions

(3 former American football players, 1 former wrestler, and 1 former baseball player), with an average age of 43.6 years and an 11 to 28 year history of exposure to sports compared to healthy controls. Participants were assessed between 3 and 25 years following retirement. Increased glutamine/glutamate and choline were reported in retired athletes, with no differences found in NAA or mI. Koerte and colleagues²⁴ examined eleven retired soccer players with no history of concussions, with an average age of 52.0 years. Increased Cho/Cr, and mI/Cr were reported in these athletes, but no differences were found in the NAA/Cr ratio. Similar to the present study, both Lin and colleagues²⁵ and Koerte and colleagues²⁴ used the posterior cingulate gyrus as the region of interest. In retired NFL players,²⁵ significantly increased glutamate, choline, and other molecules, were observed, but no significant changes in NAA or mI. In retired professional soccer players,²⁴ mI and Cho were both elevated and mI and GSH correlated with lifetime estimates of heading of the soccer ball. The present study observed distinct findings of significantly reduced NAA, GSH, and mI in retired professional rugby league players. To date, there is not a consistent pattern, or conclusive underlying neurobiology, associated with MRS findings in retired contact sport athletes.

Given that the retired players were early middle age, and the sample sizes were small, we did not anticipate significant differences on the clinical outcome measures—although given their extensive history of multiple concussions and long-exposure to collision sports it was certainly possible. There were no meaningful differences between the groups in symptoms of depression, anxiety, stress, or cognitive functioning. There was a significant difference in AUDIT scores between groups, with a very large effect size, illustrating that the retired rugby players reported more alcohol use. There was a non-significant trend, with a medium effect size, for

retired players to report more post-concussion-like symptoms. There was no significant difference between the groups on a composite score of cognitive functioning, which incorporated simple and complex attention, working memory, processing speed, learning and memory, verbal fluency, and inhibitory control tasks. On a measure of fine motor dexterity and speed, retired players performed significantly worse with their non-dominant hand, and there was a non-significant trend for them to perform worse with their dominant hand (with a medium effect size). There was no significant difference between the groups in balance and postural stability, as measured by the Balance Error Scoring System (BESS), but there was a non-significant trend for the retired athletes to have worse performance ($d=.38$; small-medium effect size).

As seen in Table 3, exploratory correlations within the athlete group revealed significant negative correlations between some of the neurometabolites and the BESS scores, illustrating that worse balance is correlated with lower concentrations of these metabolites. Additional research with larger samples is needed to further examine whether retired athletes have worse fine motor functioning or balance than expected, and whether there is a clear neurobiological underpinning to this finding. Rugby league players sustain numerous injuries to their hands and fingers throughout their career, so it is possible the peripheral factors contributed to the difference found on the Grooved Pegboard test—but this would not explain the correlations between BESS scores and the neurometabolites.

As is the case in most MRS studies, our results are limited by the nature of a cross-sectional study with modest numbers of participants. Small sample sizes are common in many neuroimaging studies with athletes, irrespective of the MR parameters used, given the labor intensive and expensive nature of the research, and

recruitment challenges.^{99–101} It is also important to note that, to date, the results of MRS studies with retired athletes have yielded diverse and inconsistent results (see Table 1). This is likely due, at least in part, to small sample sizes, heterogeneity within and between samples, and different methodologies. Small imaging studies involving extensive statistical analyses also are prone to chance or spurious findings—and when clinical measures are correlated with neurometabolites, significant findings often occur such as the exploratory correlations identified in the control group in Table 3.

In conclusion, we have measured, for the first time, changes in brain chemistry in retired rugby league athletes. These results suggest reduced neuronal viability and possible evidence of neuroinflammation, with an unexplained reduction in myoinositol. Overall, the findings should be considered preliminary, because of the 10 hypothesis-driven primary and secondary statistical analyses, only two were statistically significant. Therefore, these findings require replication. Further research is necessary to clarify the extent to which retired athletes have evidence of neurochemical changes in their brains and the potential etiology and pathophysiology of these differences.

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Discussion and Conclusion

7.1 SUMMARY OF MAIN RESULTS

Concussion in rugby league is an under-studied topic. The current thesis sought to expand the knowledge and understanding of rugby league concussion by conducting video analysis of concussion in professional rugby league and to evaluate the cognitive and neurometabolic profiles of retired professional rugby league players.

The video analysis studies demonstrated an incidence rate for diagnosed concussions of 14.8 concussions per 1,000 player match hours (95% confidence interval: 9.60-22.91), approximately one concussion every four games, whereas the incidence rate for the use of the concussion interchange rule was found to be 24.03 uses per 1,000 player match hours (95% confidence interval: 20.68-27.91), approximately one use of the rule every 2.4 games. Compared to similar sport (rugby union), these rates are considerably higher. In professional rugby union incidence rates of 0.40 concussions per 1,000 player match hours have been reported (Gardner, Iverson, Williams, Baker, & Stanwell, 2014). In the small sample of medically diagnosed concussion from three NRL clubs during the 2013 season, LOC was observed in 30% of cases, there were no observable incidences that involved convulsive convulsions, in 45% of cases the player's body went limp following the impact, 50% of player clutched their head, a blank or vacant stare post-injury was observed in 53% of players, and two-thirds of cases demonstrated balance problems. Considering all the observable signs simultaneously (i.e., loss of consciousness, clutching of head, blank stare, and balance problems), 80% had one or more of these visible signs on video. Considering the three

observable signs most reflective of an injury to the brain (i.e., loss of consciousness, blank stare, and balance problems) simultaneously, 70% had one or more of these signs. In the second video analysis study, the incidents surrounding a player's use of the concussion interchange rule (CIR) were reviewed. The CIR was used within the forward positions, significantly more often, than in backline player positions [$(X^2(1, 7,826) = 30.76, p < .001; RR = 2.7, 95\% CI = 1.85-3.99)$]. A number of signs of concussion were observed on video analysis, with overt LOC observed in 30.2% cases, 1.9% of players demonstrated observable signs of seizure-like activity, the player's body went limp with apparent loss of muscle tone following the impact in 50% of cases, 69.1% of players clutched their heads immediately following the impact, a blank or vacant stare following injury was observed in 66.4% of players, and 60.3% of players demonstrated balance problems in keeping with gait ataxia. There were 35.2% of players who demonstrated three or more observable signs concurrently. Overall, 53.2% of players returned to play in the same game. Of those, 23.8% had video evidence of LOC; 45% had evidence of loss of muscle tone; 72.5% clutched their head following contact; 50% had video evidence of gait ataxia; and 47.5% had video evidence of a blank or vacant stare.

In a small sample of retired professional rugby league players with varying history of self-reported concussions, no significant differences emerged between the retired players and a control group on measures of depression, anxiety, or cognitive functioning were observed. However, retired athletes had worse manual dexterity using their non-dominant hand, significantly lower concentrations of grey matter NAA, grey matter mI, and grey matter GSH. There were no significant differences in planned comparisons of the other metabolites examined.

7.2 INTEGRATION OF RESULTS AND CONTRIBUTION TO THE FIELD

Rugby league is a popular international, full contact sport with a history dating back to 1895 (Collins, 2006). While sport-related concussion is a topic that has garnered considerable medical, research, and community interest over the past few decades (Moser, 2007), there are few concussion-related studies in rugby league players (Gardner, Iverson, Levi, et al., 2014). The increased interest in sport-related

concussion has provided advancements in the clinical understanding of the recovery trajectory and improvements in diagnosis and management, for example it is now well established that symptom and cognitive recovery typically occur between 7-10 days for the majority of concussed athletes (Bleiberg et al., 2004; McCrea et al., 2005; McCrea et al., 2003). The understanding of the physiological changes and recovery mechanisms remains less clear, with a few studies in this emerging area that have used advanced neuroimaging techniques suggesting that biochemical changes that occur post-concussion may persist beyond the resolution of symptoms and cognitions (Gardner, Iverson, & Stanwell, 2014). It has also been demonstrated that biochemical changes that occur in the brain following concussion can persist even when the athlete is 'clinically asymptomatic,' possibly identifying a post-concussion window of vulnerability during which an increased risk for further neurotrauma may be increased, unbeknownst to the athlete. This suggests that some athletes may be unwittingly exposing themselves to potentially dangerous levels of risk. Despite these advances in concussion research and knowledge, and the risk to participants of collisions sports like rugby league to concussive injuries, concussion research in rugby league players to date, has been sparse (Gardner, Iverson, Levi, et al., 2014).

The aim of the current series of studies was to explore a number of research questions pertaining to concussive injury in current and retired professional rugby league players. The research program and series of studies has examined the rugby league player cross-sectionally. That is, current professional NRL players and retired professional NRL players with and without a history of concussion (many had a history of numerous concussions during their careers).

Following the initial systematic review of the concussion literature within the sport of rugby league, which identified a very limited number of studies in this area, the first two studies endeavoured to characterise concussion in professional rugby league players by conducting video analysis of medically diagnosed concussion (in the 2013 season) and uses of the concussion interchange rule (in the 2014 season), in addition to evaluating the management of concussion at this level of play.

The practical value of video replay is now well-established in rugby league, as a tool for reviewing an official's on-field decisions through the so-called 'video referee,' or

as a day-to-day teaching aid for coaches, players and match officials. From a research perspective, accessing the readily available video footage enables the opportunity for unique investigation of sports specific injuries, including concussion. The analysis of video for understanding injury etiology is not a novel approach, however with recent advances in digit technology, improved visual acuity and access to high resolution footage is far superior than that which has been previously available. Identifying potential risk factors for concussion in rugby league is an important manner in which to modify these risks through methods like the implementation of rule and regulation changes. These two studies were the first to identify the circumstances surrounding concussive injury in rugby league (at the professional level), and the first to document return to play decision-making, in addition to associating the signs identified on video analysis with return to play.

The duration of loss of consciousness (LOC) is considered to be a sound measure of traumatic brain injury (TBI) severity (Jennett & Teasdale, 1981), for example in the context of sport-related concussion the presence of LOC (despite this typically being for a very brief period of time in sport-related concussion) is considered to be a more severe injury than one that does not involve LOC (Marion, Grimes, Kelly, & Flores, 2013). Concussive convulsions are relatively uncommon but dramatic phenomenon in collision sport (McCrory, Bladin, & Berkovic, 1997). In the current studies evidence of concussive convulsion, comprising an initial period of tonic stiffening followed by myoclonic jerks were observed in three (1.9%) players in the 2014 season study but were not observed in any of the twenty cases in the 2013 season study. There is a literature attesting to the difference between convulsions that occur within seconds of concussion – which are not considered to be an epileptic phenomenon; and post-traumatic epileptic seizure (seizures that occur early [within one week] or late [after one week]) (McCrory et al., 1997). This literature notes that concussive convulsions have not emerged as a risk factor for post-traumatic epilepsy in severe head injury (Walker, Caveness & Critchley, 1969), they are not associated with structural brain injury, antiepileptic treatment is not indicated and prolong absence from sport is not warranted (McCrory et al., 1997; McCrory & Berkovic, 2000). Loss of muscle tone (i.e., body going limp) was also considered as a strong indicator of concussion but is typically brief and transient, so may not always be visible even on video analysis. Pathologically, loss of muscle tone (flaccidity) is most commonly related to a

peripheral nerve deficit. Loss of muscle tone was evidence in 45% of players in the 2013 season study and 50% players in the 2014 season study. Dizziness/balance problems has been established as a common acute sign post-concussion (Peterson, Ferrara, Mrazik, Piland, & Elliott, 2003) and has been demonstrated in up to 77% of concussion cases (Guskiewicz et al., 2003c). On video, balance problems are generally evidenced by unsteadiness of gait (or gait ataxia). The mechanism for this symptom may be related to inner ear disturbance, from a vestibular mechanism, or brain stem alterations (Cavanaugh et al., 2005; Guskiewicz, 2011; Guskiewicz, Perrin, & Gansneder, 1996). In the current video analysis studies, gait ataxia was observed in two-thirds of players in the 2013 season study and 52.5% players in the 2014 season study. Possible impairment in cognition or awareness as evidenced by a blank or vacant stare typically required the camera to zoom in and provide an unobstructed view of the player's face. This material was not available in every case, on occasions game-play continued and the broadcast did not return to the player, or did not return within sufficient time to determine the presence or absence of a vacant stare, on other occasions medical staff and other players surrounding the player obstructed the view of the players face. In addition, this variable is relatively subjective, that is the definition of a "vacant" look is difficult to describe, but for these studies was determined by a lack of focus of the eyes on the person attending to the injured player. Further the reviewers of the video footage were not always aware of whether the evidence that they had coded represented a difference from the 'usual appearance' of the player involved. Clutching of the head was a non-specific characteristic that was relatively inconsistently observed in cases of concussion. In addition, unlike many of the other signs used in the video analysis of concussion, clutching of the head may not have been related to the blow the player sustained but rather for other reasons like being disappointed with the play, facial injury, or adjusting their mouth guard or other protective equipment, for example.

Both video analyse studies (chapters 2 and 3) identified a minority of players were returned to play during the same game despite demonstrating signs of concussion on video review. Based on the evidence of these signs and return to play decision making, LOC was not always considered by club medical staff as a key indicator of concussion. In the medically diagnosed concussion study no player who experienced a LOC was returned to play in the same game, however there were 23.8% of players

demonstrating LOC who were cleared to return to play in the study reviewing the use of the concussion interchange rule. Other signs, and combinations of these signs, were not considered as clear indicators of concussion and a minority of players were returned to play despite video evidence. An important point to labour here however is that there was no indication that the club medical staff making the return to play decisions were aware of, or had personally observed, the signs that were seen and reported on video analysis by the researchers. This point once again highlights that LOC, which was observed in approximately one-third of cases (30% [6/20] players in study 1 and 30.2% [49/159] of players in study 2) is perhaps a more obvious sign observed live, from the sideline by club medical staff and is considered to be a stronger indicator that a concussion had occurred and therefore the player should not be returned to play during the same game.

The purpose of the video analysis was not an assessment of the competence of the referee in executing their responsibilities appropriately. On video review, there were a number of plays that were determined by the on-field referee to be illegal, however there were a number of cases where the determination of illegal play was made by the video referee on review, and yet further still a number of cases where contact was made with the head but no penalty was awarded. Approximately 29% and 25% of concussions analysed were not awarded a penalty on the play; therefore, the behaviour that produced many of the concussions in these samples were not considered illegal during the game. It is important to note that there are a number of rules in place in the NRL that can influence acceptable player behaviour. For example, any tackle that is considered to be careless, reckless or dangerous is penalizable and most contact with the head falls under one or more of these categories. Given the definitions of both of these penalties, there is merit in enforcing current rules and regulations. However, it is presumptive to assume that a significant decreased in the incidence of concussion in the NRL would occur. If a rule-based approach (including the enforcement by referees) were the only solution, the concussion incidence rate would approach zero. However, simultaneously implementing stronger sanctions for illegal play, together with stricter enforcement of rules may result in the successful reduction of concussion incidences.

Research linking a career in collision sports with later life cognitive, psychiatric, behavioural and/or neuropathological consequences remains a topic of contention and debate (Gardner et al., 2013; Iverson, 2013; McCrory, Meeuwisse, Kutcher, Jordan, & Gardner, 2013). The fundamental challenge within the CTE literature is the lack of empirical methodology for determining whether the problems described in retired athletes are unrelated or related in a small, medium, or large way to the neuropathology of CTE versus the neuropathology associated with aging and/or other medical, psychiatric, neurological, and neurodegenerative diseases (Iverson, Gardner, McCrory, Zafonte, & Castellani, 2015). While there has now been steadily emerging evidence that some retired National Football Players (NFL) players have mild cognitive impairment (Randolph, Karantzoulis, & Guskiewicz, 2013), neuroimaging evidence of microstructural changes in white matter (Guskiewicz et al., 2005; Hart et al., 2013; Strain et al., 2013), functional changes in brain metabolism (Hampshire, MacDonald, & Owen, 2013) and molecular changes (Coughlin et al., 2015) disproportionate to their age, there has not been any research conducted in retired rugby league players, and less still investigation of cognition and brain metabolism. Magnetic resonance spectroscopy is an advanced MRI technique that provides a non-intrusive insight into neurometabolites. A review of the MRS and sport-related concussion literature identified eleven studies up to February 2013, but comparison of results across studies was limited due to enormous variation in methodology. The review provided recommendations for MRS application to future sport-related concussion research to aid in comparison across studies.

In the final study in this series, a sample of retired rugby league players with a high number of previous exposures to concussion, examined the cognitive status and neurometabolic profile of participants. Results demonstrated that despite no differences between retired rugby league players and match controls on self-reported depression, anxiety or stress, cognitive assessment, there were group differences on aspects of MRS (namely, reduced NAA, mI, glutamate and glutathione in grey matter). They did, however, perform more poorly than controls on non-dominant fine motor coordination and speed, and their balance scores were correlated with lower levels of some neurometabolites. These results are consistent with recent MRS findings in retired NFL players (Lin et al., 2015). MRS is a powerful, non-invasive, neuroimaging technique that provides in-vivo measurement of endogenous

biochemistry of the human brain (Duarte, Lei, Mlynárik, & Gruetter, 2012). Only three studies have been conducted using MRS in retired athletes (Davie et al., 1995; De Beaumont et al., 2013; Tremblay et al., 2013). De Beaumont and colleagues (2013) reported a near significant between-group effect for N-acetylaspartate in MRS collected from the left primary motor cortex compared to those athletes with no self-report prior history of concussion in 15 former, male, university-level ice hockey and football players aged 51-75 years. Further analysis that involved correcting glutamate and NAA levels with advancing age revealed a significant Age*Group interaction for glutamate, but not for NAA. Tremblay and colleagues (2013) reported on the same cohort as but with MRS collected from different brain regions. They collected spectra from bilateral medial temporal lobe (MTL) and bilateral prefrontal cortex (PFC) and reported elevated *myo*-inositol (mI) and reduced choline (Cho) in the left medial temporal lobe (but not the right MTL), and elevated choline in the right PFC (but not the left PFC). The mI results were correlated with poorer performance on delayed visual memory tasks. Davie and colleagues (1995) examined three former professional boxers, diagnosed with a Parkinsonian syndrome, and found significantly reduced levels of *N*-acetylaspartate (NAA) in lentiform nucleus when compared to matched controls and idiopathic Parkinson's disease patients. The extent to which these findings are related to the diagnosis of PD, a history of repetitive neurotrauma through boxing, or both is not known. MRS has also been shown to be capable of detecting subclinical change associated with accelerated ageing and/or neurodegenerative disease. MRS has been used to detect and monitor metabolic change in aging (Lin, & Rothman, 2014; Wilson, Quarrie, Milburn, & Chalmers, 1999), mild cognitive impairment (MCI) (Duffy et al., 2014; Tumati, Martens, & Aleman, 2013) and other neurodegenerative diseases (Griffith et al., 2008; Kantarci et al., 2007; Lin, Harris, & Wong, 2005; Magierski & Sobow, 2014).

This series of investigations has considerably increased the current rugby league concussion literature. Previously, there were only seven studies examining a diverse range of topics of concussion in rugby league such as knowledge of concussion, cost of concussion to the community, tackle characteristics and the incidence of concussion. This series has now considered game play and player characteristics that lead to concussion, incidence rates and also the first study to report on retired rugby league players' cognitive function and neurometabolic profiles.

7.3 CLINICAL MANAGEMENT OF CONCUSSION IN PROFESSIONAL RUGBY LEAGUE

The Australian Rugby League Commission (ARLC), the governing body of rugby league in Australia (including the NRL competition), have already implemented a number of recommendations stemming from the video analysis studies' by enacting a number of strategies for reducing the incidence of concussion, and improving concussion management and welfare for current players. For example, the concussion policy has been revised twice during the past two seasons. These revisions have included the recent extension of specific signs, like any type of facial injury, as indicators for the removal from play of a player under the CIR. The data obtained from the video analysis studies (chapters 3 and 4) certainly support these initiatives.

One of the important strategies was the close monitoring of the policy to ensure compliance from all NRL clubs. This has included a request for an explanation regarding individual case management where it is perceived by the ARLC that a player has been miss-managed. More critically, financial sanctions for non-compliance of the policy (by way of large club fines) have also improved player concussion management. The inclusion of the CIR at the beginning of the 2014 season, which enabled a player suspected of having sustained a concussion to be replaced without penalty to their team in terms of using up an interchange when the concussed player is removed from play, appears to have increased the incidence of concussion management but has also provided an avenue for players to report concussions and feel less inclined to be letting the team down by leaving the field of play.

During the latter part of the 2013 season, the shoulder charge (an act by a defensive player in leading with their shoulder to strike the ball carrier to limit their progress) was outlawed, as it had resulted in a number of more horrific injuries included concussion. Harsher individual penalties (i.e., a greater number of weeks suspended) for foul play that resulted in contact with an opponent's head were also implemented.

During the 2014 season's final series, a pilot program was trialled of a sideline video surveillance system, which was subsequently rolled out at all games for the start of the 2015 season. Video feed is now available on the sideline from the television broadcaster to all club medical staff to review any incident of suspected concussion to assist with removal from play, and return to play decision making. All club medical staff were briefed on the signs to be looking for on video replay that indicate a concussion may have occurred. This information is also recorded and submitted to the NRL governing body each week along with other examination documentation (e.g., the player's SCAT-3 performance).

The beginning of the 2015 season has also encouraged discussion regarding independent (from the club) medical care for managing concussion and making clinical decisions regarding return to play. The video analysis studies in this thesis have found that a minority of players demonstrating signs of concussion on video analysis are returned to play during the same game, however they do not provide support or otherwise for an independent doctor to be involved in the management of concussion for professional rugby league players. The argument for an independent doctor being involved in the management of concussed players is primarily based on the premise that a club doctor has a perceived conflict of interest, given they are employed by the club, and the club has a vested interest in the performance of the team and in keeping their players on the field. This was not a variable of interest in these current video analysis studies. The video analysis data does however, support the use of video surveillance and the identification of certain signs for the diagnosis of concussion and the introduction of the sideline injury surveillance system is beneficial in this regard. Creating and validating a video checklist for the identification of concussion in rugby league is also recommended. Such a checklist should include the signs used in the current video analysis studies (i.e., loss of consciousness, loss of muscle tone, convulsive convulsions, clutching of the head, unsteadiness of gait, or possible impairment in cognition or awareness as evidenced by a blank or vacant stare) with individuals trained in the art of coding the circumstances of concussion in rugby league.

Concern regarding later life cognitive, psychiatric, and behavioural deficits in retired collision sports athletes is a major health concern and currently a topic garnering

considerable attention in the media and general public. At present there are no published studies examining retired rugby league players, making this the first study to document clinical, cognitive and neurometabolic profiles in this important group. Neuropsychological assessment is known to be sensitive in detecting cognitive deficits and as such cognitive testing has been used to support the clinical diagnosis of mild cognitive impairment (Ramakers et al., 2015) and many neurodegenerative diseases (Rabin et al., 2012), as well as normal healthy aging (St John, Tyas, & Montgomery, 2015). Further, considerable cognitive insights have also been provided by longitudinal, aging studies (Gelber, Launer, & White, 2012; Jorm, Masaki, Petrovitch, Ross, & White, 2005; Snowden, 1997, 2003; White et al., 2005). The retired professional rugby league sample in this study were middle-aged and reported a considerable concussion history, with an estimated average self-reported lifetime history of 20 concussions, most reporting between five and 40 prior concussions, and an estimated average life time history of three concussions with loss of consciousness (LOC), with most reporting between one and six injuries with LOC. From a clinical perspective, these early middle-aged retired professional rugby league players did not report more depression, anxiety, or stress, and they did not have worse cognitive functioning, than control subjects (although one retired player met clinical criteria for MCI). Whether a history of multiple concussions during a career in professional rugby league results in adverse cognitive, psychiatric, and behavioural effects in older samples of retired players is unknown.

This series of publications has reviewed the relevant literature, analysed video in current players with diagnosed and suspected concussion, and reviewed retired players' neurometabolic and neuropsychological profiles. These studies have found:

- Systematically reviewing the rugby league literature identified that very little research evaluating concussion had been conducted compared to many other collision sports (only 199 rugby league injury publications were identified).
- Rugby league concussion incidence rates vary widely from 0.0 to 40.0/1000 playing hours, depending on the definition of concussion injury (game time loss vs. no game time loss).
- The incidence rates vary across match play versus training session, seasons (winter vs. summer) and playing position (forwards vs. backs).

- The ball carrier has been found to be at greater risk for injury than tacklers.
- Video analysis of medically diagnosed concussions during the 2013 National Rugby League (NRL) season identified most concussions (83%) occurred during a high tackle, and all concussed ball carriers were hit high.
- None of the striking players were concussed.
- All concussions involved a blow to the head or face.
- Loss of consciousness was observed in 30% of cases.
- Only half of the total sample was removed from play, and one athlete who was removed returned to play in the same match.
- Of the players who were removed from play, the large majority returned to play the following week.
- Illegal play accounted for 25% of all concussions.
- The concussion incidence was 14.8 injuries per 1,000 player NRL match hours or approximately one concussion every four games.
- The video analysis of the use of the concussion interchange rule (CIR) during the 2014 season identified 167 uses of the CIR.
- Loss of consciousness was observed in 30.2% of cases.
- Common observable signs of injury included clutching the head (69.1%), loss of muscle tone (50.0%), unsteadiness of gait (52.5%), and a blank or vacant state (59.9%). Concussive convulsions were observed in 1.9%.
- The overall IRR for the concussion signs for the two raters was $\kappa = 0.60$ (95% CI = 0.56-0.64), which is considered to be weak to moderate agreement.
- The IRRs for each individual sign were: loss of consciousness = 0.68 (95% CI = 0.61-0.74), seizure = 0.70 (95% CI = 0.69-0.71), unsteadiness of gait = 0.64 (95% CI = 0.57-0.71), clutching of the head = 0.50 (95% CI = 0.46-0.54), loss of muscle tone = 0.45 (95% CI = 0.42-0.49), and blank or vacant stare = 0.36 (95% CI = 0.29-0.43).
- More than half of the players who used the CIR returned to play later in the same match (56.8%).
- Of the players who used the CIR, and who had three or more observable signs of possible injury, 46.4% returned to play in the same game.
- No player used the CIR more than once in the same game.
- Of the players who were removed from play, the large majority returned the

following week.

- Forwards (69.9%) used the CIR significantly more often than backs (30.1%).
- Most incidences occurred from a hit up (62.3%) and occurred during a high tackle (80%).
- The incidence rate was 24.03 uses of the CIR per 1,000 NRL player match hours. This equates to approximately one CIR every 2.41 games in the 2014 NRL season.
- The systematic review of Magnetic Resonance Spectroscopy (MRS) in sport-related concussion identified only eleven publications, with varying methodology and results.
- The review identified 11 publications that met criteria for inclusion, comprised of data on 200 athletes and 116 controls.
- Nine of 11 studies reported a MRS abnormality consistent with an alteration in neurochemistry.
- The results support the use of MRS as a research tool for identifying altered neurophysiology and monitoring recovery in adult athletes, even beyond the resolution of post-concussive symptoms and other investigation techniques returning to normative levels.
- The MRS profiles of retired NRL players differed compared to community age- and education-matched control participants.
- From a clinical perspective, these early middle-aged retired athletes did not report more depression, anxiety, or stress, and they did not have worse cognitive functioning, than control subjects (although one retired player met clinical criteria for mild cognitive impairment [MCI]).
- They retired players (as a group) did, however, perform more poorly than controls on non-dominant fine motor coordination and speed, and their balance scores were correlated with lower levels of some neurometabolites.
- A significant difference between groups was observed in grey matter N-acetylaspartate (NAA), with significantly lower concentrations of NAA found in retired athletes.
- No significant differences were found in white matter NAA.

- Secondary analysis found a significant difference between groups in grey matter myo-inositol (mI), with retired players having lower concentrations compared to controls.
- There was a significant difference in grey matter glutathione, with retired players showing lower concentrations compared to controls.
- There were no significant difference between groups in grey matter choline or glutamate concentrations.
- In white matter, there were no statistically significant differences in any of the neurometabolites that were hypothesized to differ (mI, choline, glutamate, or glutathione).

7.4 RECOMMENDED PRIORITIES FOR FUTURE RESEARCH

It is recommended that future research consider:

- A study reviewing video footage of the entire season to identify the signs of concussion used in the current video analysis studies (i.e., loss of consciousness, loss of muscle tone, concussive convulsions, clutching of the head, unsteadiness of gait, or possible impairment in cognition or awareness as evidenced by a blank or vacant stare) to determine the incidence of possible missed concussions (i.e., concussion that were not diagnosed or potentially managed). In addition, collecting base rates for other game play characteristics (i.e., tackles made for each playing position, location on the field tackles are made, tackle number in each set) will provide a comprehensive, sport-specific, evidenced-based risk analysis.
- Creating and validating a video checklist for coding relevant information related to concussion in rugby league to be used clinically for identifying concussion is recommended; similar to the Heads Up Checklist (HUC) created by Hutchison and colleagues for the National Hockey League (Hutchison, Comper, Meeuwisse, & Echemendia, 2013a, 2013b).
- Research examining return to play decision making may evaluate whether specific signs of concussion as evidenced on video analysis, individually or in combination, are related to performance on sideline cognitive screening,

balance testing or visual saccades and how such signs may be used in return to play decision-making.

- Video analysis of concussions sustained at other levels of play such as the NSW and Queensland Cups, and in other age groups like the National Youth Championship (under 20's), Jersey Flegg (under 18's) and Harold Matthews (under 16's) competitions is recommended to see whether the findings at the NRL level translate to other levels of play and age groups, or whether there are other unique aspects in these competitions.
- Interpretation of MRS results, taken at one time point is difficult. As such, it is recommended that longitudinal studies be conducted to assist with interpreting the data collected on the initial assessment in terms of prognosis and/or the prediction of other aspects (e.g., cognitive performance, diffusion tensor imaging). It is recommended that this starts with players early in their professional career, and continues over the course of their playing lifetime, and into retirement.

In conclusion, the current series of research identified a limited number of studies had been conducted looking at concussion in rugby league players. This series of studies adds to this literature on many fronts including the characterisation of the events that lead to concussion (and concern over possible concussive injury) at the professional level, as well as examining the potential for long-term consequences in retired rugby league players with a history of numerous concussions. These are the first studies to examine these areas.

While this series of studies adds considerably to this rugby league concussion literature, further investigation is required in order to advance the concussion knowledge in rugby league. Specifically, in terms of the potential for long-term consequences in retired rugby league players a prospective, longitudinal, clinicopathological study is required.

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MAGMA, 14(1), 45-49.

Appendix A

Relevant peer review publications during PhD candidature peripheral to the PhD theme:

1. Iverson GL, Gardner AJ, McCrory P, Zafonte R, & Castellani R. (2015). A critical review of chronic traumatic encephalopathy. *Neuroscience & Biobehavioral Reviews*, in press.

This paper, published in the highest rated neuroscience review journal, reviewed the literature on chronic traumatic encephalopathy, differential diagnosis considerations and the current science behind claims that concussion leads to dementia for some athletes. The PhD candidate worked closely with the lead author to conceptualise the review, assisted in conducting the database search and data extraction, provided editorial comment and provided final veto for the submission of this manuscript for publication.

2. Gardner A, Iverson GL, & McCrory, P. (2014). Chronic traumatic encephalopathy in sport: a systematic review. *British Journal of Sports Medicine*, 48 (2), 84-90.

This paper, published in the third highest rated sports medicine journal, reviewed the historical literature for all reported cases of CTE in the literature. It was also the first paper to introduce the concept that the definition of this putative disease process has changed from the classical ‘dementia pugilistica’ described, in the main, in boxers, to the modern chronic traumatic encephalopathy described in other contact sports athletes. The PhD candidate conceived this systematic review and collaborative with the co-authors on the conceptualisation. The database search for relevant publication and the selection of included cases in the manuscript, the data extraction and drafting of the paper were conducted by the PhD candidate.

3. Gardner AJ, Iverson GL, Williams WH, Baker S, & Stanwell, P. (2014). A systematic review and meta-analysis of concussion in rugby union. *Sports Medicine*, online first August, 20.

This paper, published in the highest rated sports medicine journal, is the first review to collate and review all publications on concussion in rugby union players. It examined the incidence of the injury, protective equipment, concussion knowledge, cost to the community and neuropsychological assessment. The PhD candidate conceived and conceptualised this systematic review. All aspect of the review were conducted by the PhD candidate including the database search for relevant publications and the selection of included publications in the manuscript, the data extraction and drafting of the paper.

4. Silverberg N, Gardner AJ, Brubacher J, Panenka L, & Iverson GL. (2014). Systematic review of multivariable prognostic models for mild traumatic brain injury. *Journal of Neurotrauma*, online first September, 15.

This paper, published in a journal ranked in the top 25% of all neuroscience journals, reviewed the mTBI literature on prognostic models. This is the most comprehensive review of the literature on this topic. The PhD candidate worked closely with the lead author to conceptualise the review, conducted the data extraction and provided editorial comment and provided final veto for the submission of this manuscript for publication.

5. Gardner AJ, Tan CO, Ainslie PN, van Donkelaar P, Stanwell P, Levi CR, & Iverson GL. (2014). A Systematic Review of Cerebrovascular Reactivity After Sport-Related Concussion. *British Journal of Sports Medicine*, accepted October, 2014.

This paper, published in the third highest rated sports medicine journal, is the first review to examine CVR through transcranial Doppler ultrasound. The PhD candidate conceived and conceptualised this systematic review. All aspect of the review were conducted by the PhD candidate including the database search for relevant publications and the selection of included

publications in the manuscript, the data extraction and drafting of the paper.

6. Schofield PW, Moore TM, & Gardner A. (2014). Traumatic brain injury and olfaction: a systematic review. *Frontiers in Neurology: Neurotrauma*, 5 (Art. 5).

This paper reviewed the TBI literature across all severities on olfactory dysfunction and testing. The PhD candidate worked closely with the lead and co-author to conceptualise the review, conducted the database search and data extraction and provided editorial comment and final veto for the submission of this manuscript for publication.

7. Gardner A. (2013). The complex clinical issues involved in an athlete's decision to retire from collision sport due to multiple concussions: a case study of a professional athlete. *Frontiers in Neurology: Neurotrauma*, 4 (Art.141), 1-6.

This was a clinical case study of a professional athlete with a history of concussion and subjective cognitive concerns. It outlined some important clinical considerations for advising athletes regarding retirement decision-making due to medical concerns, specifically concussion in this instance. It is self-explanatory as the sole-author that the PhD candidate conducted all aspects of the clinical case study.

8. McCrory P, Meeuwisse WH, Kutcher JS, Jordan BD, & Gardner A. (2013). What is the evidence for chronic concussion-related changes in retired athletes: behavioural, pathological and clinical outcomes? *British Journal of Sports Medicine*, 47 (5), 327-330.

This paper, published in the third highest rated sports medicine journal, reviewed the literature on concussion outcomes in retired athletes. The PhD candidate worked closely with the lead author to conceptualise the review, assisted in conducting the database search and data extraction, provided editorial comment and provided final veto for the submission of this manuscript for publication.

9. Gardner, A., Kay-Lambkin, F.J., Stanwell, P., Donnelly, J.D., Williams, W.H., Hiles, A., Schofield, P.W., Levi, C.R., & Jones, D.K. (2012). A Systematic Review of Diffusion Tensor Imaging Findings in Sports-Related Concussion. *Journal of Neurotrauma*, 29 (16), 2521-2538.

This paper, published in a journal ranked in the top 25% of all neuroscience journals, reviewed the DTI literature in concussed athlete samples. The PhD candidate conceived and conceptualise the review, conducted the database searches, inclusion of studies that meet relevant criteria, extraction of all relevant data, manuscript drafting and editing and final veto on the submission of the manuscript for publication.