Veränderungen der Mikrostruktur des Gehirns bei Kontaktsport-Athleten

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Inhaltsverzeichnis

1 Abkürzungsverzeichnis

AD	axiale Diffusivität
CT	Computertomografie
DTI	Diffusionsbildgebung, diffusion tensor imaging
FA	fraktionale Anisotropie, fractional anisotropy
FSL	FMRIB Software Library
ImPACT	Immediate Postconcussion Assessment and Cognitive Test
MRT	Magnetresonanztomographie
RD	radiäre Diffusivität, radial diffusivity
SCAT2	Sport Concussion Assessment Tool-2
SHT	Schädelhirntrauma
TE	Echozeit (echo time)
TR	Repetitionszeit (repetition time)
TBSS	tract based spatial statistics
Trace	mittlere Diffusivität, mean diffusivity

1 Publikationsliste

Diese Dissertation basiert auf folgenden Publikationen:

1. Takeshi Sasaki, Ofer Pasternak, **Michael Mayinger**, Marc Muehlmann, Peter Savadjiev, Sylvain Bouix, Marek Kubicki, Eli Fredman, Brian Dahlben, Karl Helmer, Andrew Johnson, Jeffrey Holmes, Lorie Forwell, Elaine Skopelja, Martha Shenton, Paul Echlin, and Inga Koerte:
   Hockey Concussion Education Project, Part 3. White matter microstructure in ice hockey players with a history of concussion: a diffusion tensor imaging study.
   (Journal of Neurosurgery 2014, Impact Factor: 4,6)

2. **Michael Mayinger**, Kian Merchant-Borna, Jakob Hufschmidt, Marc Muehlmann, Isabelle Weir, Boris Rauchmann, Martha Shenton, Inga Koerte, Jeffrey Bazarian:
   White matter alterations in college football players: a longitudinal diffusion tensor imaging study.
   (Brain Imaging Behavior 2017, Impact Factor 2016: 4,0)

2 Zusammenfassung

Diese Doktorarbeit ist auf der Grundlage von zwei wissenschaftlichen Studien entstanden. Die hieraus hervorgegangenen Veröffentlichungen wurden 2014 im Journal of Neurosurgery und 2017 im Journal Brain Imaging and Behavior veröffentlicht.

Hintergrund: Das Schädelhirntrauma (SHT) ist eine der häufigsten Verletzungen bei Kontaktsportarten wie Eishockey oder American Football. Ein leichtes SHT führt zu akuten Symptomen wie Gleichgewichts-, Bewusstseinsstörungen und Übelkeit. Bei 15-30% der Betroffenen protrahiert die Symptomatik und es können sich Spätfolgen wie Konzentrationsstörungen oder Depression entwickeln. Es wird außerdem für möglich gehalten, dass auch nach häufig wiederholten leichten Traumata des Kopfes, ohne akute Symptome, ein erhöhtes Risiko für Spätfolgen besteht. Obwohl die genauen Folgen noch unklar sind, konnte bereits mehrfach ein Zusammenhang zwischen wiederholten leichten Traumata und kognitiven Einschränkungen gezeigt werden. Da in herkömmlichen bildgebenden Verfahren (Computertomografie (CT) und Magnetresonanztomografie (MRT)) meist keine Veränderungen sichtbar sind, war es bildmorphologisch bisher schwer, die möglichen Auswirkungen von Traumata zu detektieren und zu analysieren.

Die moderne Diffusions-Tensor-Magnetresonanztomographie (diffusion tensor imaging - DTI) kann Veränderungen des Gehirns bei Patienten nach leichtem SHT erfassen und damit Hinweise auf strukturelle Schädigungen, insbesondere der weißen Substanz, geben. Ähnliche Veränderungen wurden nun auch erstmals nach relativ leichten Traumata, ausgelöst durch Kopfbälle oder Zusammenstößen von Sportlern beim American Football, beschrieben. Dies könnte durch eine frühere Diagnose die gezielte Therapie und Prävention der Spätfolgen der Traumata entscheidend verbessern.

Die Hypothese dieser kumulativen Dissertation ist, dass mittels DTI, durch leichtes SHT (Arbeit 1) oder wiederholte nicht klinisch symptomatische Erschütterungen des Kopfes (Arbeit 2) verursachte Veränderungen des Gehirns erfasst und im longitudinalen Verlauf analysiert werden können.

Arbeit 1 untersuchte die weiße Substanz in den Gehirnen von Eishockeyspielern mit einem leichten, teilweise mehrere Jahre zurückliegenden, SHT in der Vorgeschichte im Vergleich mit Spielern ohne diagnostizierte SHT. Mittels DTI wurden 16 Eishockeyspieler mit Zustand nach leichter SHT und 18 Spieler, welche bislang kein SHT erlitten hatten, untersucht. Zudem wurde eine kognitive Testung mittels zwei neuropsychologischer Testbatterien durchgeführt (ImPACT und SCAT2). Tract-Based Spatial Statistics (TBSS) wurde verwendet, um fraktionale Anisotropie (FA), radiale Diffusivität (RD), axiale Diffusivität (AD) und Trace zwischen den Gruppen zu vergleichen.
Bei der Gruppe mit Zustand nach leichtem SHT zeigte sich sowohl eine signifikante Erhöhung von FA und AD, als auch eine signifikante Erniedrigung von RD und Trace im Vergleich zur Gruppe ohne SHT ($p < 0.05$). Die Bereiche mit erhöhter FA, erniedrigter RD und erniedrigter Trace befanden sich im posterioren Teil der rechten Capsula interna, der rechten Corona radiata und des rechten Temporallappens. Diese Ergebnisse zeigten einen Zusammenhang zwischen leichten SHTs und Veränderungen in der Mikrostruktur der weißen Gehirnsubstanz. Die Zunahme der FA zusammen mit Abnahme der RD kann neuroinflammatorische oder neuroplastische Prozesse des Gehirns widerspiegeln.

Arbeit 2 hat das Ziel longitudinale Veränderungen zu detektieren, die bei American Footballspielern, ohne symptomatisches SHT, also nur durch leichte repetitive Traumata verursacht, nach einer gespielten Saison auftreten und diese im weiteren Verlauf zu beobachten. Arbeit 2 untersucht 19 jugendliche American Footballspieler und 5 Kontrollen. Alle Studienteilnehmer wurden zu drei Zeitpunkten mittels DTI untersucht: Vor Saisonbeginn (T1), nach Saisonende (T2), und nach einer 6-monatigen Trainingspause (T3). Auch hier wurde TBSS genutzt, um die Diffusionsparameter FA, RD, AD und Trace zwischen allen Zeitpunkten zu vergleichen.

Nach der Saison zeigte sich eine signifikante Zunahme von Trace in einem Cluster, welches sich im Hirnstamm und dem linken Temporallappen befand, und eine signifikante Zunahme von FA im linken Parietallappen. Nach der sechsmonatigen Trainingspause kam es zu einer signifikanten Abnahme von Trace und FA in Clustern, die sich teilweise überschnitten oder in unmittelbarer Nähe zu den initialen Veränderungen lagen.
Bereits nach einer Saison können bei American Football Spielern Veränderungen des Gehirns beobachtet werden. Diese Veränderungen scheinen sich teilweise nach einer Phase von 6 Monaten ohne wiederholte Erschütterungen des Kopfes im Rahmen des Kontaktsportes zurückzubilden, was auf eine Regneration der weißen Substanz hindeutet. Unsere Ergebnisse zeigen, dass American Football Spieler von Spielpausen, in denen sie keinen wiederholten Traumata ausgesetzt sind, profitieren könnten.

3 Summary

This cumulative dissertation is based on two scientific studies. The resulting publications were published in the Journal of Neurosurgery and in Brain Imaging and Behavior.

Background: Concussion is one of the most common injuries in contact sports such as ice hockey or American football. Common symptoms of concussion include confusion, dizziness, headache, nausea and balance problems. In 15-30% of affected individuals, a concussion may result in prolonged symptoms such as concentration disorders or depression.

An increased risk of late effects after repetitive subconcussive head injury (RHI), without showing acute symptoms, is also considered possible. While the full consequences are still unclear, a relationship between RHI and cognitive impairments has been shown.

It has been difficult to detect and analyze the potential effects of concussion, as the brain often appears quite normal on conventional computed tomography (CT) and magnetic resonance imaging (MRI).

A relatively new neuroimaging technique is diffusion tensor imaging (DTI) which is sensitive to subtle changes in the brain of patients with a concussion, indicating structural damage particularly in white matter fiber tracts. Similar changes have now for the first time been described following RHI, when players head the ball in soccer or head blows in football. Earlier detection could substantially improve therapy and prevent late effects of concussion and RHI.

The aim of this cumulative dissertation is to show that DTI can detect concussive and RHI related alterations in the brain's microstructure and to evaluate longitudinal changes.

Paper 1 examines the brain's white matter microstructure by using MR diffusion tensor imaging (DTI) in ice hockey players with a history of concussion compared with players without a history of concussion. Sixteen athletes with a history of concussion and 18 without a history of concussion underwent diffusion MRI on a 3Tesla MR scanner.

Tract-based spatial statistics (TBSS) was used to test for group differences in fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD) and the measure Trace. Cognitive evaluation was performed using two neuropsychological test batteries (ImPACT und SCAT2).
TBSS revealed a significant increase in FA and AD and a significant decrease in RD and Trace in several brain regions in the concussed group compared to the nonconcussed group ($p < 0.05$). The regions with increased FA and decreased RD and Trace included the right posterior limb of the internal capsule, the right corona radiata and the right temporal lobe. Increased AD was observed in a small area in the left corona radiata. DTI measures correlated with neither the ImPACT nor the SCAT2 scores. The results of the current study indicate that a history of concussion may result in alterations of the brain's white matter microstructure in ice hockey players. Increased FA based on decreased RD may reflect neuroinflammatory or neuroplastic adaptions of the brain responding to trauma.

The aim of Paper 2 was to examine longitudinal changes in brain white matter (WM) during one season of collegiate football, followed by six months of no-contact rest using TBS.
Fifteen male collegiate football players and 5 male non-athlete student controls underwent diffusion MR imaging at three time points: prior to the start of the football season (T1), after one season of football (T2), followed by one examination after six months of no-contact rest (T3).
Whole-brain TBSS were used to compare fractional anisotropy (FA), radial diffusivity (RD), axial diffusivity (AD) and Trace between all timepoints. Average diffusion values were obtained for each individual from statistically significant clusters. No athlete suffered a concussion during the study period. After one season of play we observed a significant increase in Trace in a cluster located in the brainstem and left temporal lobe and a significant increase in FA in the left parietal lobe.

After the six-month training break, there was a significant decrease in Trace and FA in clusters that partially overlapped or were in close proximity to the initial changes.

Repetitive head impacts obtained during a single season may result in alterations of the brain's WM microstructure in college football players. These changes appear to return to baseline after 6 months of no-contact rest suggesting indicating recovery. Our results suggest that collegiate football players might benefit from periods without exposure to RHI.

4 Einleitung

Diese kumulative Dissertation ist auf der Grundlage von zwei wissenschaftlichen Studien entstanden (Mayinger et al., 2017; Sasaki et al., 2014). Die Studien untersuchen Veränderungen der Mikrostruktur des Gehirns von Kontaktsportlern, die durch subklinische und klinische Traumata verursacht wurden.

4.1 Klinischer und wissenschaftlicher Hintergrund

4.1.1 Leichtes Schädelhirntrauma bei Kontaktsportathleten

Das Schädelhirntrauma ist eine durch äußere Faktoren versursachte Verletzung des Gehirns, die zu vorübergehenden, funktionellen und strukturellen Veränderungen führt (CDC, 2003). Ätiologisch zählen einmalige, akute und stumpfe Kopfverletzungen, wie beispielsweise Unfälle oder Stürze, zu den häufigsten Ursachen. Bei etwa 80% der Betroffenen tritt nur ein leichtgradiges SHT auf (SHT I, Commotio cerebri). In Kontaktsportarten wird das leichte SHT als eine traumatische, durch biomechanische Kräfte verursachte, Gehirnverletzung definiert (McCrory et al., 2017). Symptomatisch zeigen sich beim leichten SHT typischerweise akute Bewusstseinsstörungen bis zur vorrübergehenden (per Klassifikation max. 30 min) Bewusstlosigkeit, Übelkeit, Erbrechen, kognitiven Defizite und Orientierungsschwierigkeiten.
Bei einer Inzidenz von über 600 Fällen pro 100.000 Einwohnern muss weltweit mit jährlich 40 Millionen Betroffenen gerechnet werden (Cassidy et al., 2004). Noch höher ist das SHT Risiko bei Kontaktsportarten, hier stellt es eine der häufigsten Verletzungsursachen dar (Jarvinen & Lehto, 1993). Für den einzelnen Athleten beträgt das jährliche Risiko ein SHT zu erleiden etwa 20% (Clay, Glover, & Lowe, 2013).
Durch wiederholte leichte SHTs bei Kontaktsportarten kann es auch zu protrahierten und kumulativen Langzeitfolgen kommen, gezeigt in Studien beim Boxen (Gronwall & Wrightson, 1975; Jordan & Zimmerman, 1990; McCrory, Zazryn, & Cameron, 2007) oder American Football (Guskiewicz et al., 2005; Guskiewicz et al., 2003; Henry et al., 2011; McCrea et al., 2003). Als langfristige Spätfolgen wiederholter leichter SHTs, über mehrere Jahre, bestehen erhöhte

Risiken für neurologische und psychiatrische Symptome wie Demenz, Parkinson oder Depressionen, bis hin zur Neurodegeneration im Sinne einer chronisch-traumatischen Enzephalopathie (Baugh et al., 2012; Berthier, Kulisevsky, Gironell, & Lopez, 2001; De Beaumont, Tremblay, Poirier, Lassonde, & Theoret, 2012; Henry et al., 2011; Omalu, Fitzsimmons, Hammers, & Bailes, 2010; Stern et al., 2011).

Die diagnostische Abklärung des leichten SHT erfolgt nach gängigen Empfehlungen der Fachgesellschaften zunächst klinisch. Erst beim Vorhandensein von Risikofaktoren wie rezidivierendem Erbrechen oder längerer Amnesie wird eine CT Bildgebung empfohlen (**Abbildung 1**) (Vos et al., 2002). Eine ergänzende MRT Untersuchung wird nach unauffälliger CT nur bei Patienten mit anhaltenden neurologischen Störungen empfohlen (Firsching et al., 2001; Vos et al., 2002).

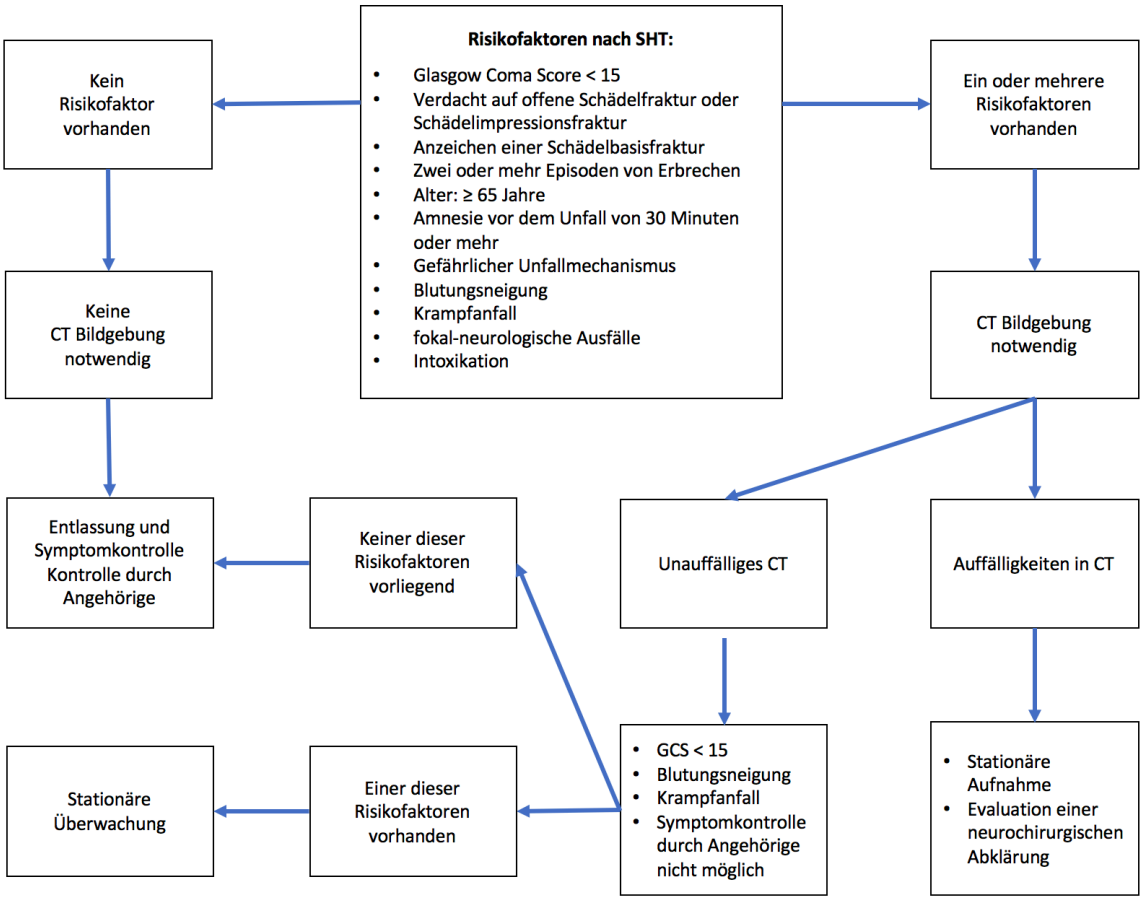

Abbildung 1: Akute Abklärung von Patienten mit leichtem SHT (gemäß Daten von Vos et al. (Vos et al., 2002)).

Es besteht außerdem die Möglichkeit einer kognitiven Testung mittels verschiedener Testbatterien wie beispielsweise dem Immediate Postconcussion Assessment and Cognitive Test (ImPACT) und Sport Concussion Assessment Tool-2 (SCAT2) (Covassin, Elbin, Stiller-Ostrowski, & Kontos, 2009).

4.1.2 Subklinische Schädelhirntraumata bei Kontaktsportathleten

Seit einigen Jahren werden über das klinisch symptomatische leichte SHT hinaus auch subklinische Traumata als mögliche Ursache für eine Schädigung des Gehirns diskutiert. Bei diesen regelmäßigen, leichten Traumata, die z.B. durch Zusammenstöße der mit Helm geschützten Köpfe beim American Football oder dem Kopfballspiel beim Fußball entstehen, führen möglicherweise zu ähnlichen Veränderungen des Gehirns wie ein klinisch symptomatisches Schädelhirntrauma. Diese Akzelerations-Dezelerations-Kräfte mit zusätzlichen Rotationskräften bewirken axonale und vaskuläre Scherkräfte (Gurdjian, Lissner, Evans, Patrick, & Hardy, 1961; Ropper & Gorson, 2007). Obwohl dieser Mechanismus subtil und nicht offensichtlich imponiert berichten neuropsychologische Studien jedoch von kognitiven Veränderungen, wie Gedächtnisstörungen, Aufmerksamkeitsdefiziten und einer verminderten mentalen Flexibilität nach Mitrotraumen (Koerte et al., 2017; Witol & Webbe, 2003). Die genauen Pathomechanismen, die zu den genannten Veränderungen der Hirnstruktur führen, bleiben noch unklar. Auch die Frage ob diese subklinischen Traumen einen noch längerfristigen Einfluss auf die Gehirnentwicklung haben und ob als Spätfolgen dieser Exposition neurologische und psychiatrische Erkrankungen wie Depression, Demenz und Parkinson auftreten können, ist noch weitestgehend unerforscht.

4.1.3 Bildgebung bei klinischem und subklinischem Schädelhirntrauma

Basierend auf den Empfehlungen der Fachgesellschaften ist bei leichtem SHT im Moment im Rahmen der klinischen Diagnostik keine Bildgebung durchzuführen (**Abbildung 1**) (Adelson et al., 2003; Brain Trauma et al., 2007), da auch bei temporär relevanter funktioneller Störungen des Gehirns mit den konventionellen, bildmorphologischen Verfahren (CT und MRT) meist keine Veränderungen detektiert werden können (Control, 2003; Jennett, 1996; Kibby & Long, 1996).

Die Forschung der letzten Jahre zeigte jedoch, dass neuere bildgebende Verfahren in der Lage sind signifikante Veränderungen des Gehirns bei Patienten nach leichtem SHT zu erfassen (Chu et al., 2010; Mayer et al., 2010; Slobounov et al., 2010; Wilde et al., 2010; Zhang et al., 2010b). Diese Veränderungen beinhalten beispielsweise multifokale axonale Schädigungsmuster, die zu verminderten Werten der FA (Arfanakis et al., 2002; Geary, Kraus, Pliskin, & Little, 2010; Inglese et al., 2005; Kraus et al., 2007; Little et al., 2010; Miles et al., 2008) und erhöhter Diffusivität (Miles et al., 2008; Niogi et al., 2008) in der Diffusions-Tensor Magnetresonanztomographie (diffusion tensor imaging – DTI) führen oder auch veränderte Aktivierungsmuster in der funktionellen Magnetresonanztomographie hervorrufen (Slobounov et al., 2011; Slobounov et al., 2010; Zhang et al., 2010a).

Aktuelle Studien liefern Hinweise, dass sich auch bei leichten repetitiven Traumata Veränderungen der mikrostrukturellen Integrität der weißen Substanz darstellen und quantifizieren lassen. Koerte et al. konnten erstmals auch bei jugendlichen Fußballspielern ohne diagnostiziertes SHT Veränderungen der weißen Substanz in der Diffusionsbildgebung im Vergleich mit einer Kontrollgruppe aus Schwimmern zeigen (**Abbildung 2**) (Koerte et al., 2012). Bazarian et al. untersuchten Kontaktsportathleten von denen einer ein leichtes SHT während des Spiels erlitten hatte, sowie acht weitere Sportler (Eishockey oder American Football Spieler) mit repetitiven (zwischen 26 und 399) subklinischen Traumata.

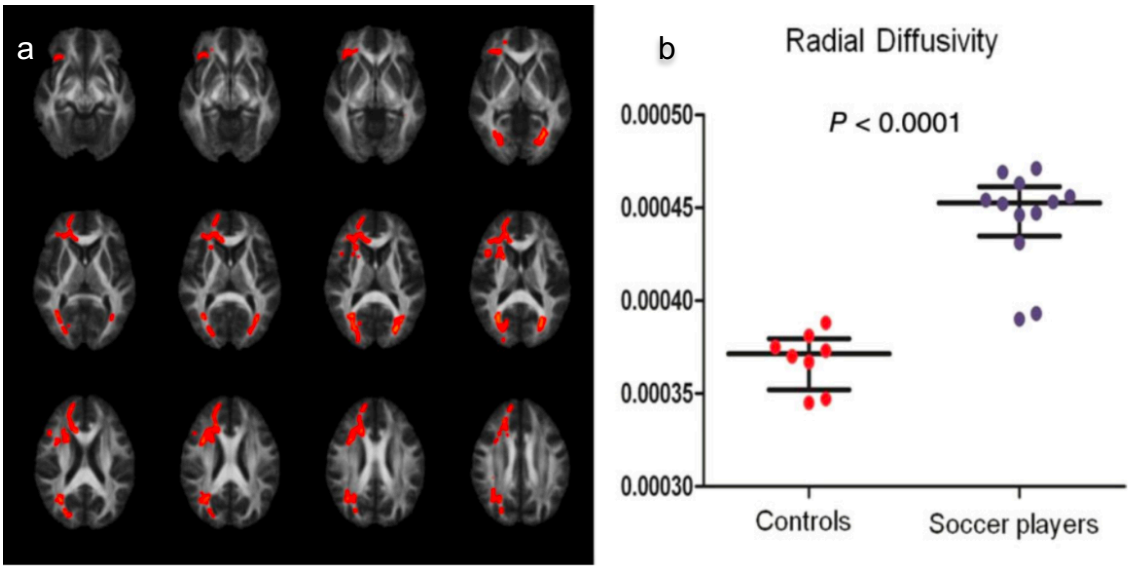

Abbildung 2: **Veränderungen in der Diffusionsbildgebung**
Regionen mit signifikant veränderter, radialer Diffusivität (RD) bei Fußballspielern im Vergleich mit Schwimmern (a). Die Mittelwerte der signifikant verändertern Regionen wurden für die einzelnen Athleten berechnet. (Koerte, Ertl-Wagner, Reiser, Zafonte, & Shenton, 2012)

Als Kontrollgruppe wurden 5 Athleten ohne SHT oder subklinische Traumata verwendet. Veränderungen der weißen Substanz wurden vor allem bei dem American Football Spieler, der ein symptomatisches SHT erlitten hatte, gefunden. Bei Athleten mit multiplen subklinischen Traumata wurden jedoch ebenso Veränderungen der MD und FA detektiert, während in der Kontrollgruppe keine Veränderungen erfasst werden konnten (Bazarian, Zhu, Blyth, Borrino, & Zhong, 2012).
Diese lässt vermuten, dass möglicherweisen bereits repetitive, subklinische SHT kumulativ zu Veränderungen der Gehirnstruktur führen können.

4.2 Methodische Grundlagen

4.2.1 Diffusionstensorbildgebung (DTI)

Die Diffusions-Tensor-Bildgebung (DTI von Englisch diffusion tensor imaging) ist ein bildgebendes Verfahren, welches auf der Magnetresonanztomographie basiert. Moseley et al. und Sotak et al. konnten zeigen, dass Wassermoleküle wesentlich stärker ausgeprägt entlang von Nervenfaserbündeln im Gehirn, als quer zu ihnen wandern (**Abbildung 3)** (Moseley, Wendland, & Kucharczyk, 1991; Sotak & Li, 1992). Dies ermöglicht die Fasern im Gehirn mittels DTI indirekt darzustellen und so Aussagen über die Ausrichtung und Beschaffenheit der Nervenfaserbündel zu treffen. DTI wird bereits seit ca. 30 Jahren zur Beurteilung intrakranieller Erkrankungen benutzt und hat sich im Vergleich zur konventionellen, morphologischen MRT-Bildgebung als deutlich sensitiver zur Diagnostik von Mikroverletzungen erwiesen (Basser, Mattiello, & LeBihan, 1994a, 1994b; Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996; Taylor & Bushell, 1985). Die aus der DTI errechnete DTI-Traktographie ermöglicht die Untersuchung einzelner Fasertrakte und kann klinisch zum Beispiel zur Planung von neurochirurgischen Operationen genutzt.

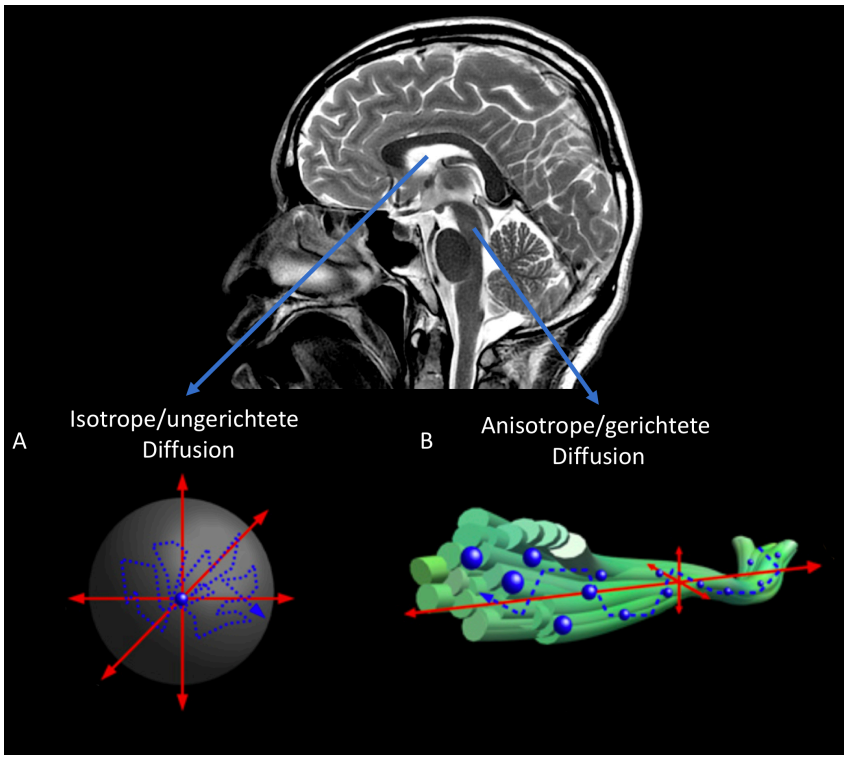

Abbildung 3: Cerebrale Diffusion im Liquor und entlang von Nervenfasern
In den Liquorräumen diffundieren Wassermoleküle ungerichtet (A). In der weißen Substanz erfolgt die Diffusion der Wassermoleküle hauptsächlich entlang der Hauptachse der Nervenfaserbahnen (B). (Abbildung modifiziert nach Phillips et al. (Phillips et al., 2012))

4.2.2 Analyse der DTI

Für jedes Voxel der MRT-Aufnahme wird die gemessen Verteilung der Diffusionsrichtungen von Wassermolekülen berechnet. Diese folgen der aus den Beobachtungen von Robert Brown stammenden und nach ihm benannten Brown'schen Molekularbewegung. 1905 beschrieb Albert Einstein mathematisch, wie diese zufällige, unregelmäßige Bewegung entsteht. Die von Einstein aufgestellte Formel zur Beschreibung dieses Phänomens wurde 1908 von Jean-Baptiste Perrin bewiesen.

Diese zufällige Verteilung der Wassermoleküle wird durch angrenzende Strukturen beschränkt. Damit lässt die DTI-Bildgebung indirekte Rückschlüsse auf die Position, Orientierung und Beschaffenheit von Faserstrukturen der umgebenden Gewebe, wie der weißen Substanz des Gehirns, zu (**Abbildung 3)**. Heute wird die Diffusion für jedes Voxel aus mindestens 6 Richtungen anhand der zeitabhängigen Signalintensität bestimmt und zur Auswertung ein Ellipsoid erstellt. Dieses ist je nach Ausprägung der Diffusion in bestimmte Richtungen eher gestaucht, kugelförmig oder gestreckt (**Abbildung 4**).

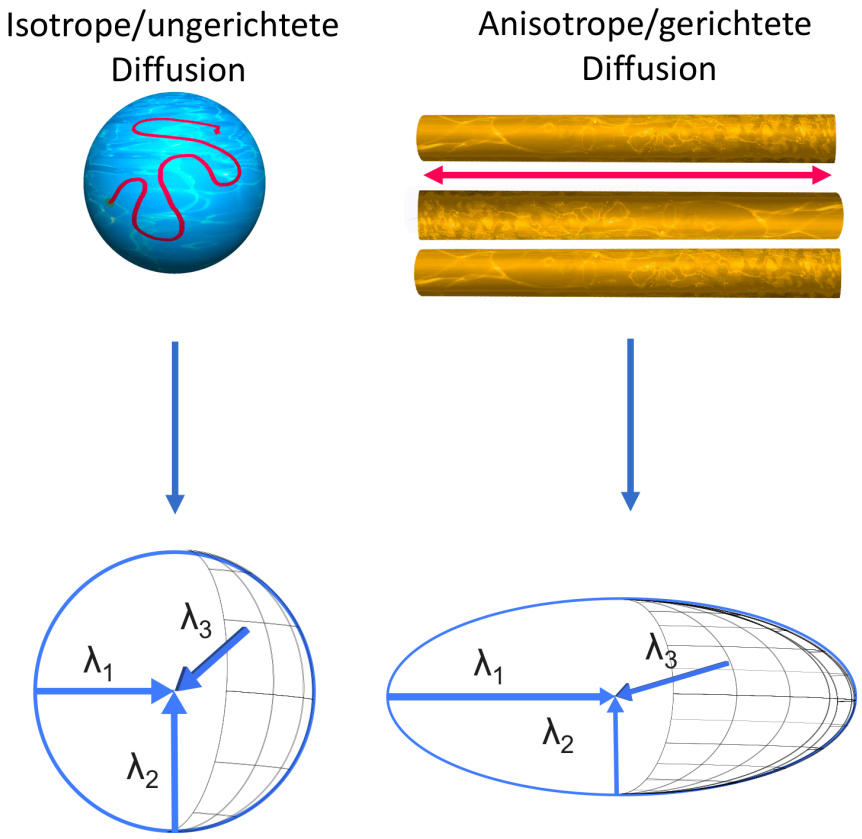

Abbildung 4 – Ungerichtete/isotrope und gerichtete/anisotrope Diffusion.
Ungehindert wie z.B. im Liquorraum diffundiert das Wassermolekül mit gleicher Wahrscheinlichkeit in jede Richtung (isotrope Diffusion).
Bei eingeschränkter Bewegungsfreiheit z.B. entlang von Nervenbündeln ist die Bewegungsrichtung nicht mehr Kugel- sondern Ellipsoidförmig (anisotrope Diffusion).

Bei einer Schädigung der Nervenfasern z.B. durch Entzündungen oder Scherverletzungen lässt sich eine Änderung der Diffusion messen.

Die 3 Achsen des Ellipsoids werden Eigenvalues (λ1, λ2 und λ3) genannt. Für sie gilt immer: λ1 > λ2 > λ3.
Aus den Eigenvalues lassen sich DTI Parameter berechnen, welche mit jeweils einer Zahl die Form des Ellipsoids beschreiben. Die nach Basser et al. 1996 vier geläufigen Parameter werden FA, Trace, AD und RD genannt (Basser & Pierpaoli, 1996). Diese werden im Folgenden näher erläutert:
FA beschreibt den Grad der Anisotropie. Ein FA Wert von 0 entspricht einer isotropen Diffusion und ein Wert von 1 einer kompletten Anisotropie nach λ1.
Trace ist die Summe der Einzelwerte von λ1, λ2 und λ3.
AD gibt mit λ1 den jeweils längsten Wert des Ellipsoids an und entspricht somit der Länge der Achse mit der Hauptrichtung der Diffusion.
RD ist der Durchschnitt der beiden kürzeren Achsen λ2 und λ3 (**Tabelle 1**). Da diese immer im 90 Grad Winkel zu λ1 liegen, quantifiziert RD die Diffusion in die Nebenrichtungen.

Eigenvalue	$= \lambda$
axiale Diffusivität (AD)	$= \lambda_1$
radiale Diffusivität (RD)	$= [(\lambda_2 + \lambda_3)/2]$
Trace	$= (\lambda_1 + \lambda_2 + \lambda_3])$
fraktionale Anisotropie (FA)	$= \sqrt{\frac{1}{2}} \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_1 - \lambda_3)^2 + (\lambda_2 - \lambda_3)^2}}{\sqrt{(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}$

Tabelle 1- Berechnung der Diffusionsparameter

Je nach Fragestellung werden sog. AD-, RD-, Trace und FA- Karten erstellt die voxelbasiert die Werte der individuellen Diffusionsparameter enthalten (erstes Bild in **Abbildung 5**).

Die so entstandenen Datensätze können, mit verschiedenen Methoden weiterverarbeitet und ausgewertet werden. Durch die Rekonstruktion von Faserbahnen (Traktographie) kann man Informationen über die Organisation und Struktur der weißen Substanz erhalten. Um bestimmte anatomische Regionen oder Strukturen zu vergleichen, kann eine *Region of Interest* (ROI) - Analyse durchgeführt werden. Zum Auswerten von Gruppenunterschieden in DTI Daten des Gehirns wird häufig die *Tract-Based-Spatial-Statistics (TBSS)* (Grabner et al., 2006) verwendet.

4.2.3 Tract-Based Spatial Statistics (TBSS)

TBSS erlaubt mittels voxelbasierter Statistik Gruppenvergleiche, longitudinale Verläufe und Effekte von Kovariaten aus DTI-Datensätzen zu berechnen. Dies geschieht durch einen nicht-perimetrischen Ansatz, der auf der Grundlage der Permutationstest-Theorie entstanden ist. Dafür werden zunächst alle individuellen DTI Daten auf eine Vorlage registriert und ausgerichtet (Grabner et al., 2006). Dieses sogenannte Grundskelett repräsentiert das Grundgerüst der weißen Substanz mit ihren wichtigsten Faserbahnen. Dies minimiert die Notwendigkeit der Datenglättung und führt daher zu weniger Partialvolumeneffekten und einer höheren statistischen Power als andere Voxel-basierte Ansätze (Bach et al., 2014). Da nun für jeden Bilddatensatz ein geometrisch identisches Grundskelett vorhanden ist, ist es möglich die Diffusionsparameter Voxel für Voxel miteinander zu vergleichen. Die Voxel des Grundgerüsts, die nach Korrektur für multiples Testen signifikant unterschiedliche Werte aufweisen, werden farblich markiert (**Abbildung 5**).
Der Nachteil der TBSS ist der Informationsverlust durch interindividuelle Variabilität oder durch Partialvolumeneffekte. Insbesondere bei neuroanatomisch sehr unterschiedlichen Gruppen ist die Methode deshalb weniger sensitiv und limitiert. Deshalb kann zusätzlich z.B. mittels Traktographie eine detailliertere Auswertung auf Ebene des Individuums folgen.

TBSS ist Teil der Softwaresammlung FSL 4.2 (FMRIB Software Library, The Oxford Centre for Functional MRI of the Brain – FMRIB) und wird auf der Internetseite des FMRIB detailliert beschrieben (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/tbss).

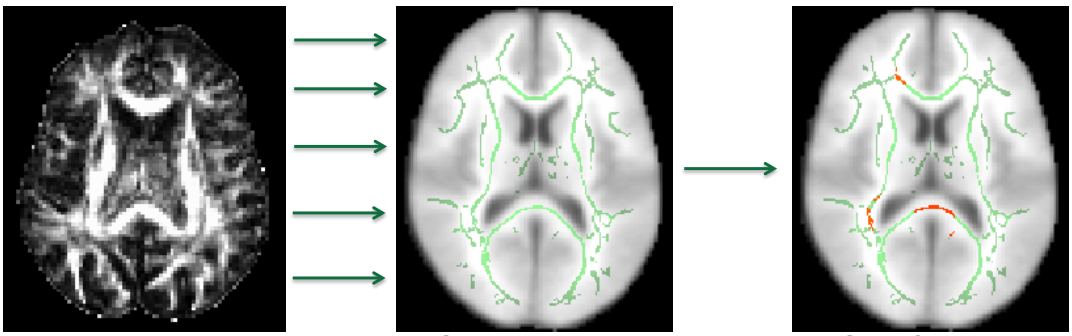

Abbildung 5: Ablauf der TBSS – Einzelne FA-Karte, die für jede Aufnahme erstellt wird (links). Diese wird auf das Grundgerüst angepasst (Mitte). Das grün dargestellte Grundskelett repräsentiert die wichtigsten Fasertrakte der weißen Substanz. Nach statistischer Analyse werden die Voxel mit signifikanten Gruppenunterschieden rot dargestellt (rechts).

4.3 Fragestellung und Eigenanteil

Das Ziel beider hier beschriebenen Studien war mittels Diffusionsbildgebung die Langzeiteffekte und das Ausmaß der Veränderungen des Gehirns bei Kontaktsportathleten zu untersuchen.

Arbeit 1: Die durch SHT verursachten Veränderungen bei Eishockeyspielern wurden bisher nur in wenigen Studien untersucht. Es wurde jedoch vermutet, dass die Untersuchung der Auswirkungen der SHT auf die Mikrostruktur des Gehirns zu einer früheren und genaueren Diagnose beiträgt, was wiederum zu einer verbesserten und spezifischeren Therapie und einer fundierten Entscheidung führen kann, ab wann es für den einzelnen Sportler wieder möglich ist am Sport teilzunehmen.

Ziel dieser Arbeit war es, die weiße Substanz des Gehirns unter Verwendung von DTI bei Eishockeyspielern nach klinisch symptomatischem SHT im Vergleich mit Spielern ohne SHT auf Unterschiede zu untersuchen.

Mein Beitrag bestand in der Datenweiterverarbeitung, der statistischen Analyse und der kritischen Durchsicht des Manuskriptes. Die Arbeit wurde im April 2014 im „Journal of Neurosurgery" veröffentlicht.

Arbeit 2: Die Hypothese dieser Arbeit war, dass wiederholte Erschütterungseffekte am Kopf, die keine SHT-typischen Symptome zur Folge haben, zu Gehirnveränderungen führen, welche denjenigen ähneln, die nach einem leichten SHT auftreten. Es wurde vermutet, dass sich durch DTI Bildgebung bei American Footballspielern auf College Ebene bereits nach einer gespielten Saison Veränderungen der weißen Substanz detektieren lassen. Das Ziel dieser Studie war es Veränderungen von American Footballspielern nach einer gespielten Saison ohne symptomatisches SHT zu detektieren und anschließend zu analysieren, wie sich diese Veränderungen nach einem Trainings- und spielfreiem Zeitraum von 6 Monaten entwickeln.

Mein Beitrag war das Erstellen des Manuskriptes, die Datenanalyse, die Datenweiterverarbeitung und die statistische Auswertung. Die Arbeit wurde im Januar 2017 als geteilte Erstautorenschaft im Fachjournal „Brain Imaging and Behavior" veröffentlicht.

5 Originalarbeiten und Ergebnisse

5.1 Arbeit 1: Hockey Concussion Education Project, Part 3. White matter microstructure in ice hockey players with a history of concussion: a diffusion tensor imaging study

Zielsetzung:

In dieser Arbeit wurden Eishockeyspielern mit Zustand nach klinisch symptomatischem SHT und Spieler ohne SHT mittels MR Diffusionsbildgebung untersucht. Das Ziel dieser Studie war festzustellen, ob sich die Mikrostruktur der weißen Substanz des Gehirns der Spieler mit Z.n. SHT von denen ohne SHT unterscheidet.

Methodik:

34 Eishockeyspieler wurden in einem 3-Tesla MR-Scanner (Achieva, Philips Medical Systems) mit DTI Sequenz zum Ende der 2011-2012 kanadischen Interuniversity Sport Eishockey Saison untersucht. 13 Spieler hatten bereits vor der Saison eine positive Anamnese für leichtes SHT (Durchschnittliche Anzahl: 1.46 ± 0.88) und 3 Spieler erlitten während der Saison erstmals ein leichtes SHT. Diese 16 Spieler mit Z.n. leichtem SHT (SHT Gruppe, Durchschnittsalter 21,7 ± 1,5 Jahre, 6 weiblich) wurden mit 18 Spielern ohne SHT in der Vorgeschichte (SHT-freie Gruppe, Durchschnittsalter 21,3 ± 1,8 Jahre, 10 weiblich) verglichen. Die DTI-Sequenz wurde mit den folgenden Parametern erhoben: 60 Diffusionsrichtungen, Repetitionszeit (repetition time, TR) 7015 ms, Echozeit (echo time, TE) 60 ms, b = 0, 700 s / mm^2 und 70 Schichten. Die Voxelgröße betrug 2,2 mm auf 2,2 mm auf 2,2 mm.

Mit Hilfe der TBSS Analyse wurden die Aufnahmen beider Gruppen auf einen signifikanten Gruppenunterschied untersucht.

Ergebnisse:

In der TBSS zeigte sich eine signifikant höhere FA und AD und eine signifikante niedrigere RD und Trace in mehreren Gehirnregionen in der Gruppe mit Z.n. SHT, verglichen mit der Gruppe ohne SHT ($p < 0,05$). Die Regionen mit erhöhtem FA und vermindertem RD und Trace beinhalteten das Crus posterius der Capsula interna, die rechte Corona radiata und den rechten Temporallappen (**Abbildung 6**). Eine erhöhte AD wurde in einem kleinen Bereich in der linken Corona radiata beobachtet. Es gab keinen signifikanten Gruppenunterschied bei den ImPACT- oder SCAT2-Scores. Innerhalb der Gruppe mit Z.n. SHT korrelierten die Ergebnisse der kognitiven Testung nicht mit den DTI-Parametern.

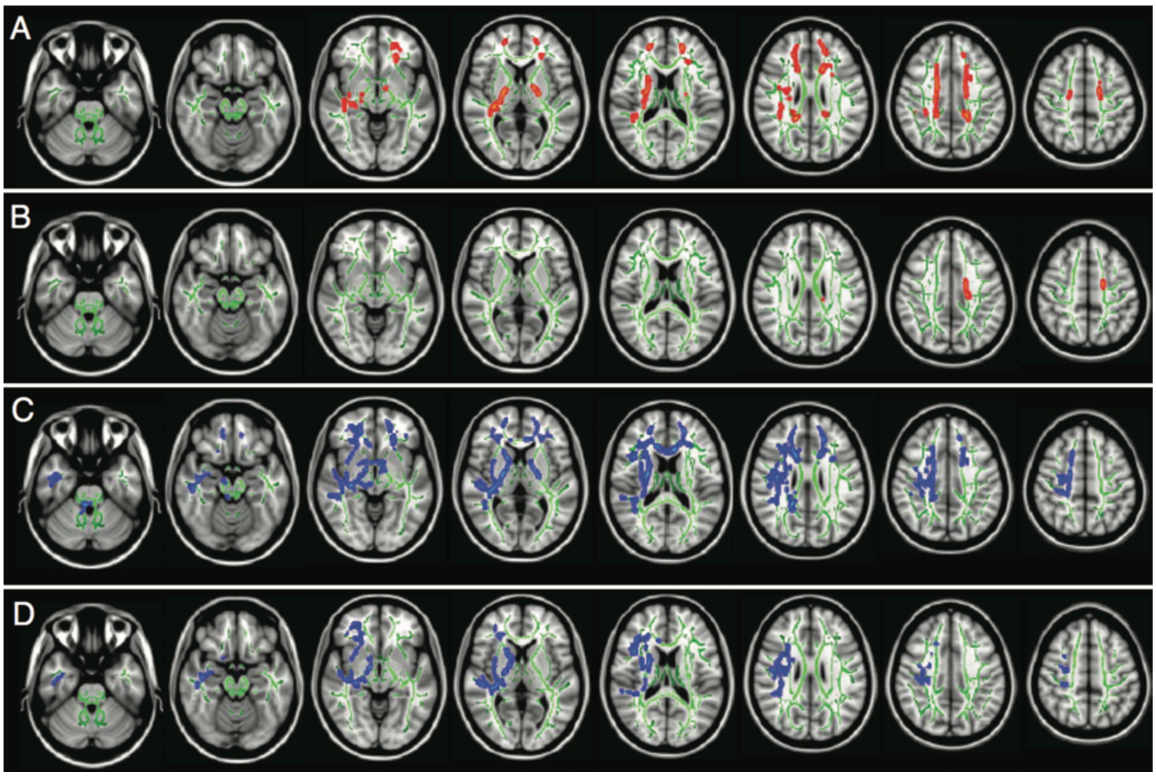

Abbildung 6: **Ergebnisse der TBSS-Analyse** zeigten alle Cluster mit signifikant erhöhtem FA (A) und AD (B) (rot) und verminderter RD (C) und Trace (D) (blau) für Spielern mit Z.n. SHT im Vergleich zu Spielern ohne SHT ($p < 0,05$).

Diskussion:

Die Ergebnisse von Arbeit 1 deuteten darauf hin, dass ein, teilweise mehrere Jahre zurückliegendes SHT bei Eishockeyspielern zu Veränderungen der Mikrostruktur der weißen Substanz des Gehirns führt. Ein erhöhter FA basierend auf einer verminderten RD kann neuroinflammatorische oder neuroplastische Prozesse des Gehirns widerspiegeln, die durch SHT verursacht wurden. Die gezeigten Ergebnisse stehen im Einklang mit Untersuchungen an American Football Spielern, Fußballspielern oder Athleten anderer Kontaktsportarten und sind am ehesten als Mikroläsionen der weißen Substanz, als Folge der SHT, zu deuten. Diese Arbeit zeigt auch die Notwendigkeit, einer longitudinalen Analyse der Strukturen und Funktionen des Gehirns nach einer SHT. Dies ermöglicht den komplexen zeitlichen Verlauf von DTI-Veränderungen und ihre klinische Bedeutung besser zu verstehen. Arbeit 2 untersucht deshalb ein anderes Kollektiv über einen Zeitraum von 18 Monaten zu verschiedenen Zeitpunkten.

See the corresponding articles in this issue, pp 864–872 and pp 873–881.

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Hockey Concussion Education Project, Part 3. White matter microstructure in ice hockey players with a history of concussion: a diffusion tensor imaging study

Clinical article

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Object. The aim of this study was to examine the brain's white matter microstructure by using MR diffusion tensor imaging (DTI) in ice hockey players with a history of clinically symptomatic concussion compared with players without a history of concussion.

Methods. Sixteen players with a history of concussion (concussed group; mean age 21.7 ± 1.5 years; 6 female) and 18 players without a history of concussion (nonconcussed group; mean age 21.3 ± 1.8 years, 10 female) underwent 3-T DTI at the end of the 2011–2012 Canadian Interuniversity Sports ice hockey season. Tract-based spatial statistics (TBSS) was used to test for group differences in fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and the measure "trace," or mean diffusivity. Cognitive evaluation was performed using the Immediate Postconcussion Assessment and Cognitive Test (ImPACT) and the Sport Concussion Assessment Tool–2 (SCAT2).

Results. TBSS revealed a significant increase in FA and AD, and a significant decrease in RD and trace in several brain regions in the concussed group, compared with the nonconcussed group ($p < 0.05$). The regions with increased FA and decreased RD and trace included the right posterior limb of the internal capsule, the right corona radiata, and the right temporal lobe. Increased AD was observed in a small area in the left corona radiata. The DTI measures correlated with neither the ImPACT nor the SCAT2 scores.

Conclusions. The results of the current study indicate that a history of concussion may result in alterations of the brain's white matter microstructure in ice hockey players. Increased FA based on decreased RD may reflect neuroinflammatory or neuroplastic processes of the brain responding to brain trauma. Future studies are needed that include a longitudinal analysis of the brain's structure and function following a concussion to elucidate further the complex time course of DTI changes and their clinical meaning.
(http://thejns.org/doi/abs/10.3171/2013.12.JNS132092)

Key Words • concussion • mild traumatic brain injury • diffusion tensor imaging • ice hockey • fractional anisotropy • white matter

Sports-related concussion is an important public health problem given the annual incidence of approximately 300,000 sports-related concussions in the US alone.[12,49] Concussion, a subset of mild traumatic brain injury (mTBI),[15] is caused by high-speed acceler-

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

Abbreviations used in this paper: AD = axial diffusivity; CIS = Canadian Interuniversity Sports; DTI = diffusion tensor imaging; FA = fractional anisotropy; HCEP = Hockey Concussion Education Project; ImPACT = Immediate Postconcussion Assessment and Cognitive Test; mTBI = mild traumatic brain injury; RD = radial diffusivity; SCAT2 = Sport Concussion Assessment Tool–2; SHB = subconcussive head blow; TBSS = tract-based spatial statistics.

* Drs. Echlin and Koerte share senior authorship of this work.

ation-deceleration head motions,[45] leading to complex pathophysiological processes affecting the brain's function and structure.[37,38] Common symptoms of concussion include confusion, dizziness, headache, nausea, and balance problems. These symptoms resolve in the majority (80%–90%) of individuals within the first 10 days.[37] However, in some individuals a concussion may result in symptoms lasting for more than 3 months, also known as prolonged postconcussive syndrome.[39] Moreover, repeated concussions have been associated with the development of chronic traumatic encephalopathy.[40]

To date, diagnosis and management of concussion are largely based on clinically observed or self-reported symptoms. However, this approach is both incomplete and inaccurate because symptoms may either not be reported by the athlete or not be associated with a concussion.[9,36] In addition, conventional neuroimaging such as CT and MRI fail to detect traumatic axonal injury, the underlying mechanism of mTBI.

Diffusion tensor imaging (DTI) is sensitive for detecting traumatic axonal injury and is therefore expected to improve the diagnosis of mTBI by providing objective parameters to quantify and to localize white matter alterations (see review by Shenton et al.[46]). DTI measures the movement of water in the brain. In white matter, water molecules move more in directions parallel to the fiber tracts than perpendicular to them. This characteristic, which is referred to as anisotropic diffusion, is most commonly measured by fractional anisotropy (FA), a measure derived from DTI that reflects the coherent microstructural organization of white matter.[50] In addition to FA, the measure "trace," or mean diffusivity, denotes the overall average of diffusion. Axial diffusivity (AD) and radial diffusivity (RD) denote the extent of diffusion parallel and perpendicular to the direction of maximal diffusivity, respectively; AD is purported to be sensitive to axonal damage, whereas RD is purported to be sensitive to myelin degeneration.[48]

Reports on alterations of diffusivity following TBI vary in the literature: FA has been shown to either decrease[2,19,24,26,27,32,41,42] or increase[17,18,25,30,33,50] after head trauma. Moreover, regions with increased and those with decreased FA have been reported within the same individual following mTBI.[3,28] It has been suggested that these diffusivity changes are determined by the severity and/or chronicity of the injury.[25,50]

Ice hockey is a high-speed collision sport[1] for which a high incidence rate of concussions is known.[8,10,11,34,44] A recent study by Echlin et al.[10] reported the number of concussions per 1000 athlete exposures to be as high as 11.67. To date, DTI studies have been performed in players of other contact sports such as American football,[16,18,31] boxing,[5,6,51,52] and soccer,[22,29] with only a small number of studies including ice hockey players.[3,7,23,35] However, evaluating the effects of sports-related concussion on the brain's microstructure among ice hockey players will probably contribute to earlier and more accurate diagnosis, which in turn may lead to improved and more specific therapeutic management and a more informed decision about when an athlete should return to play.

The aim of this study was to examine the brain's white matter microstructure using DTI in ice hockey players with a history of a clinically symptomatic concussion compared with players without a history of concussion.

Methods

Participants and Clinical Information

All participants were part of the Hockey Concussion Education Project (HCEP), a cohort study performed during a Canadian Interuniversity Sports (CIS) ice hockey season (2011–2012). Thirty-nine players underwent imaging at the end of the season. None of the included participants had a history of any neurological or psychiatric disorder other than concussion. Players with gross structural MRI abnormalities were excluded. The study protocol was approved by the ethics committees within the universities at which the CIS teams were based. All participants provided written informed consent prior to the beginning of the study.

Five players were excluded for the following reasons: severe motion artifacts (3 players); a large arachnoidal cyst (1 player); or an age more than 8 SDs from the mean (1 player). Therefore, 34 players (18 male and 16 female) were included in the statistical analyses.

A self-report of concussion history was obtained from the players prior to the beginning of the season by using a questionnaire. At the time the data were collected, concussion was defined according to the Zürich consensus statement on concussion from the 3rd International Conference on Concussion in Sport, which took place in 2009.[37] However, the definition used here also meets the concussion criteria from the 4th International Conference on Concussion in Sport, which took place in 2012.[38]

Prior to the current season, team members received physical examinations by the team physician (not study related). Thirteen of the 34 players reported that they had suffered at least 1 concussion prior to the start of the study (mean number of concussions 1.46 ± 0.88 [mean ± SD], range 1–4). Additionally, 8 of the 34 players experienced at least 1 clinically symptomatic concussion during the season. Concussions occurring during the season were directly observed and diagnosed by the independent designated specialist physician who attended the game.[10] The average concussion-to-scan interval was 95 ± 45 days (range 42–161 days) for those who suffered from concussion during the study. For those who sustained a concussion prior to the study, the concussion-to-scan interval was by definition more than 6 months. In total, 16 players had concussion(s) either prior to the study (n = 8), during the study (n = 3), or both (n = 5) (concussed group; mean age 21.7 ± 1.5 years), and 18 players reported no history of concussion (nonconcussed group; mean age 21.3 ± 1.8 years) (Fig. 1).

Cognitive Examination

At the end of the CIS season, cognitive testing was performed using the Immediate Postconcussion Assessment and Cognitive Test (ImPACT) examination (ImPACT Applications, Inc.) and the Sport Concussion Assessment Tool–2 (SCAT2). The ImPACT is a computer-based test battery consisting of a concussion symptom inventory

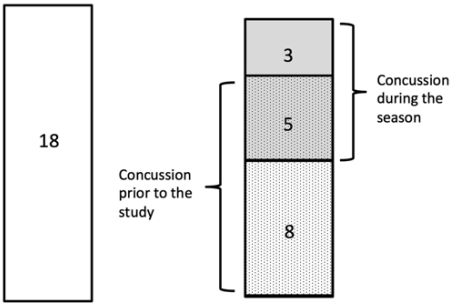

Fig. 1. The schematic illustration of grouping: nonconcussed (n = 18) and concussed (n = 16) groups. Within the concussed group, 8 players had a concussion during the season, and 13 players had a concussion prior to the start of the study. Five players had a concussion both during the season and prior to the start of the study.

and 6 modules measuring neurocognitive function. It is the most widely used system for evaluating sports-related concussion; however, to date it has not been independently evaluated. These modules were used to generate 4 composite scores: verbal memory, visual memory, visual motor speed, and reaction time. The SCAT2 is a test battery for the evaluation of concussion that consists of 8 component scores. These are designed to assess concussion symptoms, cognition, balance, Glasgow Coma Scale score, and other neurological symptoms.[14]

Protocol for MRI and Data Acquisition

Data were acquired using a 3-T MRI scanner (Achieva, Philips Medical Systems) with an 8-channel head coil array. A DTI sequence with 2 averages and the following parameters was performed: 60 noncolinear diffusion directions, TR 7015 msec, TE 60 msec, b = 0 and 700 sec/mm^2, and 70 slices. Data were acquired using a 2.2 mm isotropic voxel size and a 100 × 100 matrix reconstructed into a 112 × 112 matrix with a resolution of 2 × 2 × 2.2 mm^3.

Processing of DTI

Postprocessing and statistical analyses were performed by the first author (T.S.), who was not blinded to the groups. Blindness to group membership was not an issue, because the postprocessing measures are automated. The MRI data sets were examined for image quality. To remove intrascan misalignments due to eddy currents and head motion, an affine registration of the diffusion-weighted images to the baseline image was performed for each participant (FSL version 4.1, Functional MRI of the Brain [FMRIB] Software Library [FSL]). Gradient directions were adjusted using the rotational component of the affine transformations. Nonbrain tissue and background noise were then removed from the b0 image with the aid of 3D Slicer version 3.6.2 (Surgical Planning Laboratory, Brigham and Women's Hospital). The diffusion tensor for each voxel was estimated using a multivariate linear fitting algorithm, and the 3 pairs of eigenvalues and eigenvectors were obtained. From these tensor volumes, scalar measures including FA, AD, RD, and trace for each voxel were calculated as follows:

$$\mathrm{FA} = \frac{\sqrt{\left(\lambda_1 - \lambda_2\right)^2 + \left(\lambda_2 - \lambda_3\right)^2 \left(\lambda_3 - \lambda_1\right)^2}}{\sqrt{2}\sqrt{\left(\lambda_1^2 + \lambda_2^2 + \lambda_3^2\right)}}$$

$$\mathrm{AD} = \lambda_1$$

$$\mathrm{RD} = \left(\lambda_2 + \lambda_3\right)/2$$

$$\mathrm{trace} = \lambda_1 + \lambda_2 + \lambda_3,$$

where λ_1, λ_2, and λ_3 are the largest to smallest eigenvalues.

To avoid any bias due to head motion in the scanner, we computed a relative motion index. This parameter was then compared between groups by using a t-test. In addition, we included this index as a covariate in the statistical analysis (see below).

White Matter Analysis

Whole-brain tract-based spatial statistics (TBSS) version 1.2,[47] a voxel-based standard-space group statistical analysis (FSL version 4.1, Functional MRI of the Brain [FMRIB] Software Library [FSL]), was used for the investigation of white matter. The TBSS procedure is described in detail by Smith et al.[47] In short, FA images from all subjects were coregistered into a template and then linearly aligned into Montreal Neurological Institute 152 space. These aligned FA images were then averaged to generate a cross-participant mean FA image. The mean FA image was then thinned to create a mean FA skeleton, which represents the center of all white matter fiber tracts common to the group. The mean FA skeleton was thresholded to contain only voxels with FA > 0.3 to exclude peripheral voxels with significant intersubject variability and/or partial volume effects with gray matter. Each participant's aligned FA data were then projected onto the skeleton by searching the local maxima along the perpendicular direction from the skeleton to create a skeletonized FA map. Thus, without prior perfect coregistration, the central course of each subject's fiber tract is represented on the skeleton. To analyze group differences in the other scalar measures (AD, RD, and trace), we applied the nonlinear warps obtained from the FA registration, as well as the skeleton projection of the FA data, to the other diffusion scalar volumes.

Statistical Analyses

Group comparisons for each voxel on the skeleton were performed by a nonparametric permutations-based test (Randomise, Functional MRI of the Brain [FMRIB] Software Library [FSL]). Threshold-free cluster enhancement was used to avoid choosing an arbitrary initial cluster-forming threshold. The data were tested against an empirical null distribution generated by 5000 permutations for each contrast, thus providing statistical maps fully cor-

rected for multiple comparisons across space. A corrected value of $p < 0.05$ was considered significant. The test was linearly adjusted for age, handedness, sex, and motion, even though there was no significant difference in these variables between the groups (Table 1). Statistical maps plotting the corrected p values were visualized using FSL (TBSS_fill and FSLView). The Pearson linear analysis was used to assess the correlation between DTI parameters and measures of cognitive function. The Spearman rank correlation was used when normal distribution was not given. A p value < 0.05 was considered statistically significant.

Results

Demographic Characteristics and Neuropsychological Examination

Concussed and nonconcussed groups did not differ significantly with respect to age, sex, handedness, or head motion. There was also no significant difference in ImPACT score between the concussed and nonconcussed group (Table 1). For 1 player in the concussed group there were no ImPACT test results available. There was no significant difference between the groups for the SCAT2 score. For 4 players in the concussed group there were no SCAT2 results available.

Analyses Within the Concussed Group

The 8 subjects that suffered a concussion during the season did not differ within the group when a comparison was made regarding the number of concussions sustained, ImPACT scores, or SCAT2 scores (Table 2). A group comparison using TBSS did not show a significant difference (data not shown).

White Matter Analysis

The TBSS analysis revealed a significant increase in FA and AD and a significant decrease in RD and trace for the concussed group compared with the nonconcussed group ($p < 0.05$).

For FA, the concussed group showed significantly higher values in the bilateral corona radiata, the bilateral posterior limb of the internal capsule, the bilateral superior frontal white matter, and the right superior temporal white matter (Fig. 2A). For AD, the concussed group showed significantly higher values in the left corona radiata (Fig. 2B). For RD, the concussed group showed significantly lower values in the genu of the corpus callosum, bilateral corona radiata, bilateral posterior limb of the internal capsule, right anterior limb of the internal capsule, right cerebral peduncle, bilateral superior frontal and orbitofrontal white matter, right superior and inferior temporal white matter, and right external capsule (Fig. 2C). For trace, the concussed group showed significantly lower values in the right corona radiata, the right anterior and posterior limbs of the internal capsule, the right superior frontal white matter, and the right inferior temporal white matter (Fig. 2D). Diffusivity measures of the clusters with significant group differences are displayed in the respective scatterplots in Fig. 3. For those clusters, median value and interquartile range (median [interquartile range]) for the nonconcussed and concussed group were as follows: FA (0.547 [0.017] and 0.582 [0.022], respectively); AD (0.0013 [0.000037] and 0.0014 [0.000091] mm^2/second, respectively); RD (0.000560 [0.000037] and 0.000518 [0.000018] mm^2/second, respectively); and trace (0.00247 [0.00013] and 0.00235 [0.000049] mm^2/second, respectively).

There were no areas of significant decrease in FA or AD, nor were there any areas of significant increase in RD or trace. The DTI measures did not correlate with SCAT2 scores or with any of the composite scores of ImPACT (Table 3).

TABLE 1: Demographic characteristics and neuropsychological tests in 34 ice hockey players with and without concussion*

Characteristic	Nonconcussed Group	Concussed Group	Statistical Test, p Value
no. of players	18	16	
mean age in yrs	21.25 ± 1.84	21.68 ± 1.54	$t_{32} = 1.22$, p = 0.23
no. of females (%)	10 (56)	6 (38)	$\chi^2 = 1.11$, p = 0.29
handedness (no. rt/either/lt)	15/1/2	13/0/3	Fisher exact test, p = 0.82
mean head motion in mm	0.78 ± 0.09	0.79 ± 0.12	$t_{32} = -0.368$, p = 0.716
mean ImPACT score†			
verbal memory	92.3 ± 5.94	90.3 ± 9.26	$t_{31} = 0.78$, p = 0.44
visual memory	79.7 ± 11.1	80.9 ± 13.5	$t_{31} = 0.28$, p = 0.87
visual motor speed	45.7 ± 5.34	45.0 ± 6.95	$t_{31} = 0.33$, p = 0.74
reaction time	0.53 ± 0.06	0.54 ± 0.07	$t_{31} = 0.41$, p = 0.68
symptom scale	3.4 ± 4.7	5.3 ± 13.2	U = 114.0, p = 0.43
mean SCAT2 score‡			
total	94.4 ± 3.40	95.5 ± 1.62	$t_{28} = -1.05$, p = 0.30

* The mean values are expressed ± SD.
† One subject's data in the concussed group were not available.
‡ Four subjects' data in the concussed group were not available.

TABLE 2: Analysis within the concussed group of 16 ice hockey players

Characteristic	Concussed During (Season) Period of Study	Concussed Only Prior to (Season) Period of Study	Statistical Test, p Value
no. of players	8	8	
mean age in yrs	21.56 ± 1.5	22.16 ± 1.6	$t_{14} = 0.76$, p = 0.46
no. of females (%)	5 (63)	1 (13)	Fisher exact test, p = 0.12
handedness (rt/lt)	7/1	6/2	Fisher exact test, p = 1.00
mean no. w/ concussion	2.13 ± 1.4	1.25 ± 0.46	U = 18.0, p = 0.11
mean ImPACT score*			
verbal memory	89.9 ± 9.9	90.7 ± 9.2	$t_{13} = 0.17$, p = 0.87
visual memory	78.5 ± 16.3	83.7 ± 9.9	$t_{13} = 0.73$, p = 0.48
visual motor	44.8 ± 7.8	45.2 ± 6.5	$t_{13} = 0.1$, p = 0.92
reaction time	0.56 ± 0.08	0.51 ± 0.04	$t_{13} = 1.4$, p = 0.20
total symptom	8.00 ± 18.0	2.39 ± 3.1	U = 23.0, p = 0.56
mean SCAT2 score†			
total	96.4 ± 1.82	94.9 ± 1.22	$t_{10} = 1.78$, p = 0.11

* One subject's data were not available.
† Four subjects' data were not available.

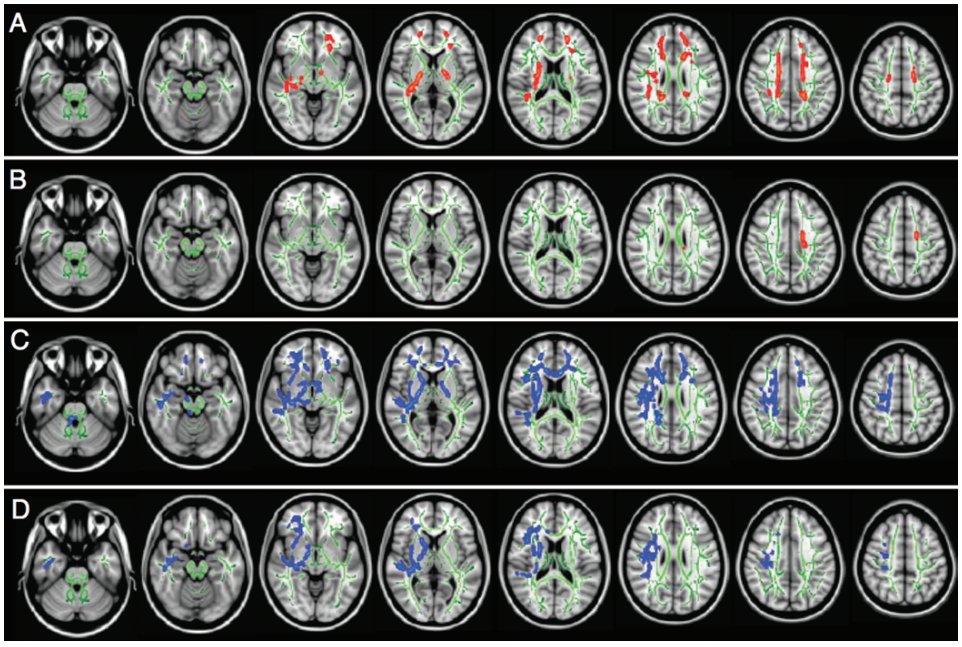

Fig. 2. Results of the TBSS analysis showing the clusters of significantly increased FA **(A)** and AD **(B)** *(red to yellow)*, and decreased RD **(C)** and trace **(D)** *(blue to light blue)* for concussed players compared with nonconcussed players ($p < 0.05$). Voxels are thickened into local tracts (TBSS_fill implemented in FSL) on the FA skeleton *(green)* and a T1-weighted template image. The left side in each image corresponds to the right hemisphere.

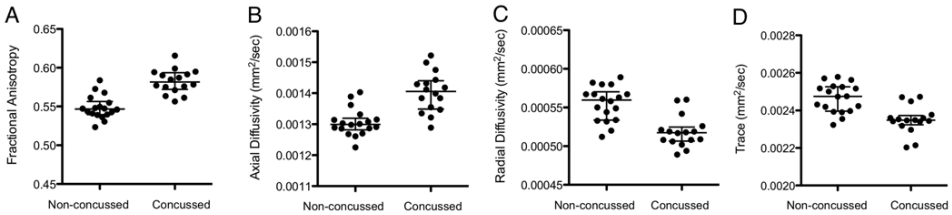

Fig. 3. The scatterplots of average values in the clusters with significant group differences are shown for each DTI parameter: FA **(A)**, AD **(B)**, RD **(C)**, and trace **(D)**. *Circles* represent individual values, and *horizontal bars* represent the median value and interquartile range.

Discussion

This study examined varsity-level ice hockey players and found a significant difference in DTI measures between the players with and without a history of concussion. We found a widespread increase in FA that overlapped with decreased trace and RD in the white matter of the brain in ice hockey players who had a history of concussion compared with players who did not report a history of concussion. These areas included the right corona radiata, the right posterior limb of the internal capsule, the right superior frontal white matter, and the right superior temporal white matter. Additionally, TBSS revealed a small cluster in the left corona radiata with increased FA and AD, but no changes in RD or trace. These results suggest possible alterations in white matter microstructure due to concussion. The lack of difference in the ImPACT and SCAT2 scores between the 2 groups suggests that DTI is highly sensitive for detecting brain alterations following a concussion, even in the absence of clinical symptoms, as evaluated using the ImPACT and SCAT2.

Other studies in which DTI was used to investigate the brain have reported either a decrease[2,19,24,26,27,32,41,42] or an increase[17,18,25,30,33,50] in FA following TBI. Moreover, and as noted previously, studies have suggested areas with increased and decreased FA within the same individual following mTBI.[3,28] Decreases in FA have been associated with demyelination and axonal degeneration disrupting the microstructural coherence.[4] As Wilde et al.[50] pointed out, the studies reporting decreased FA generally included patients with more severe cases (for example, with hemorrhages)[2,19,32,42] and/or cases with a rather long interval between injury and MRI scan.[24,26,42] On the other hand, most of the studies reporting an increase in FA have included patients in the acute and subacute phase following an mTBI.[18,33,50] In this context, an increase in FA has been explained in relation to the presence of an intracellular edema with consecutive restriction of diffusion in the extracellular space perpendicular to the main axis.[33]

However, increases in FA have been observed in the chronic phase following mTBI.[18,25,28,30,33] This is in line with the results of the present study, which revealed increased FA in large parts of the brain in participants who had a history of concussion. Mayer et al.[33] reported that increased FA persisted 3–5 months in some brain areas including the genu of the corpus callosum and the left internal capsule (left corona radiata) in patients with mTBI. Henry et al.[18] found increased FA in the corticospinal tracts and the corpus callosum of concussed athletes in

TABLE 3: Correlation analysis between DTI measures and cognitive tests in 34 ice hockey players*

DTI Measure	ImPACT Score					Total SCAT2 Score
	Verbal	Visual	Visual Motor	Reaction	Symptom	
FA						
correlation coefficient	−0.10	−0.11	0.02	0.02	0.026	0.00
p value	0.58	0.53	0.93	0.91	0.89	0.98
AD						
correlation coefficient	0.16	−0.03	0.08	0.11	−0.052	0.19
p value	0.36	0.88	0.65	0.55	0.77	0.31
RA						
correlation coefficient	0.13	0.00	0.09	0.00	−0.043	−0.03
p value	0.45	0.98	0.64	0.99	0.81	0.86
trace						
correlation coefficient	0.08	−0.05	0.12	0.00	−0.057	−0.12
p value	0.66	0.77	0.50	0.99	0.75	0.53

* Correlation coefficients represent the Pearson r value, except for the symptom subscore of the ImPACT scale, where it is the Spearman rho value.

the acute (1–6 days) and chronic (6 months) phases. Lo et al.[30] reported increased FA in the posterior limb of the internal capsule more than 2 years after the head trauma, although there were also areas with decreased FA. Additionally, Lipton et al.[28] reported areas with increased or decreased FA in the brains of individuals following an mTBI. The number of voxels with high FA initially increased between 2 weeks and 3 months, followed by a decrease in the number of voxels with high FA at 6 months.

Although the time course of FA changes following an mTBI is not fully understood, the existing literature and our current results suggest that increased FA may persist for months or even years following an mTBI. The underlying mechanism of increased FA is, however, not clear. Nonetheless, it is noteworthy that both the increase in FA and the decrease in trace are mathematically linked to the decrease in RD, which is probably due to restriction of diffusion in the extracellular space perpendicular to the main axis. This could either be caused by axonal swelling or it could be due to more glial cells taking up the extracellular space. Histological studies have reported long-lasting neuroinflammation with persistent microglial activation in the white matter tissue of patients with a history of TBI.[13,20] Increased FA has also been interpreted as neuroplastic processes of the brain responding to head trauma.[28] However, the evidence for such changes remains tenuous due to the lack of direct, quantitative comparisons between DTI results and histological preparations. Finally, in the current study there was a small area localized in the left corona radiata in which we found increased FA based on an increase in AD, indicating increased diffusivity parallel to the axon. This finding is not easy to explain in the context of a history of concussion. It may reflect axonal swelling due to acute and/or subacute neuroplastic processes.

Subconcussive head blows (SHBs) may have an additional effect on our results. Koerte et al.,[22] for example, found differences in white matter microstructure in soccer players without a history of concussion compared with swimmers. Additionally, Lipton et al.[29] reported an association between exposure to soccer heading and both abnormal white matter microstructure and impaired memory. Furthermore, comparing pre- and postseason head scans of football and ice hockey players, Bazarian et al.[3] reported increased FA and decreased mean diffusivity for the players who had SHBs in the absence of a clinically diagnosed concussion. The presence of SHBs was positively correlated with the degree of change in diffusivity, suggesting an association between white matter alterations and SHBs.[3] All athletes included in this study, both concussed and nonconcussed, probably experienced frequent SHBs during the ice hockey season in the months before the MRI scan. Players with a previous concussion may be more vulnerable to the additional effect of SHBs. The increase in FA and AD may therefore not only reflect the effects of concussions in the past, but also those of recently sustained SHBs resulting in ongoing repair mechanisms.

The lack of differences in cognition evaluated using ImPACT and SCAT2 measures between the groups indicates that there might be no clinically evident symptoms, despite alterations in white matter microstructure, or that these tests are not sufficiently sensitive to detect subtle differences in cognitive performance. The latter hypothesis is supported by a study by Mayer et al.[33] in which patients with a history of mTBI showed differences in DTI parameters but showed no differences in neuropsychological measures, compared with a control group. Further studies are nonetheless needed to determine whether changes in the microarchitecture of white matter in the brain in concussed players might precede symptoms and cognitive changes, or if other measures of cognitive and clinical function might be more sensitive and therefore more likely to be correlated to the observed DTI changes.

Limitations of this study include the small sample size and the lack of a control group consisting of athletes taking part in noncontact sports. A further limitation of the study is that information regarding the history of concussion before the season is based on the athlete's self-report. Self-reports of sports-related concussion may not be reliable.[21] Future studies should also include information on the frequency of SHBs. Furthermore, groupwise analysis by TBSS may not be sensitive to variable spatial location of abnormal DTI measures in heterogeneous conditions such as mTBI. Thus, future studies should include analysis of subject-specific changes such as tractography. Additionally, future studies should also include free-water corrected DTI measures. The free-water method as used by Pasternak et al. (Part 2 in this series[43]) estimates the extracellular portion of diffusion. Accordingly, free-water–corrected DTI parameters provide more specific information about the brain's tissue. Finally, subjects included in this study also underwent imaging before the start of the season. However, a gradient coil change occurred during the season and a possible bias could not be entirely ruled out, and so we refrained from comparing pre- and postseason scans in this sample.

Conclusions

The results of the current study indicate that a history of concussion may result in alterations of the brain's white matter microstructure in ice hockey players. The increase in FA due to a decrease in RD may reflect neuroinflammatory or neuroplastic processes of the brain responding to brain trauma. Future studies are needed that include longitudinal analyses of the brain's structure and function following a concussion, to elucidate the complex time course of DTI changes and their clinical meaning.

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5.2 Arbeit 2: White Matter Alterations in College Football Players: A Longitudinal Diffusion Tensor Imaging Study

Zielsetzung:

In Arbeit 2 wurde mit Diffusionsbildgebung untersucht, inwiefern sich die weiße Gehirnsubstanz im Verlauf einer Football-Saison und einer anschließenden Trainingspause ohne Kontaktsport verändert.

Methodik:

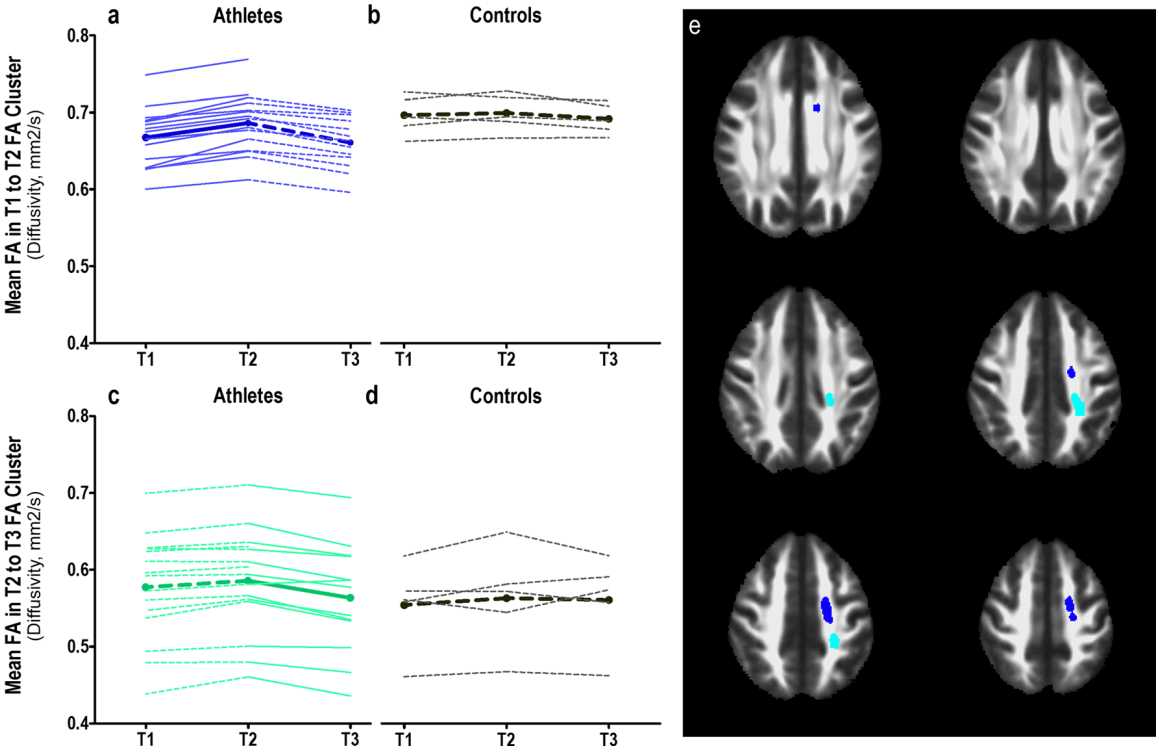
An dieser Studie nahmen 19 männliche Athleten (Durchschnittsalter 20,0 ± 1,0 Jahre) des „University of Rochester NCAA division III football team", die von 2011 bis 2012 und von 2012 bis 2013 als Spieler an der American Football Saison teilgenommen haben und 5 Kontrollen teil (Durchschnittsalter 20,9 ± 1,1 Jahre). Bei allen Probanden erfolgte zu 3 Zeitpunkten eine MRT (Siemens 3T Tim Trio System) u. a. auch mithilfe einer DTI-Sequenz:

1. Die erste Untersuchung wurde vor der Saison durchgeführt (T1).
2. Die zweite Untersuchung erfolgte nach der Saison, im Mittelwert 95 Tage (SD ± 7,5 Tage) nach der ersten Untersuchung (T2).
3. Die dritte Untersuchung erfolgte nach einem 176 ± 7.1 Tage andauerndem Intervall ohne Teilnahme an Footballspielen/-training und somit ohne durch Kontaktsport ausgelösten Erschütterungen des Gehirns (T3).

Die Voxelgröße der Diffusions MRT betrug 2 mm^3 und es wurden 60 Diffusionsrichtungen aufgenommen (TR = 10 s, TE= 89 ms, b = 1200 s / mm^2). Mit Hilfe der TBSS Analyse wurden die Diffusionswerte der drei Messzeitpunkte getrennt miteinander verglichen (T1-T2, T1-T3, T2-T3) und untersucht, ob sich zwischen den drei Zeitpunkten Gruppierungen von Voxeln (Cluster) finden, die einen signifikanten Gruppenunterschied in Diffusionswerten zeigen.
In Clustern mit signifikanten Veränderungen wurden die durchschnittlichen Diffusionswerte für jedes Individuum berechnet. Eine kognitive Testung wurde mit der Testbatterie ImPACT durchgeführt.

Ergebnisse:

Kein Athlet hat während des Studienzeitraums ein SHT erlitten. Nach einer Spielsaison (von T1 bis T2) beobachteten wir einen signifikanten Anstieg von Trace in einer Region im Hirnstamm und im linken Temporallappen und eine signifikante Zunahme der FA in einem Bereich des linken Parietallappens. Nach einer sechs-monatigen Trainingspause ohne Kontaktsport (T2 bis T3) wurde eine signifikante Abnahme von Trace und FA in Bereichen detektiert, welche teilweise überlappend oder in enger Nachbarschaft zu den ursprünglichen beobachteten Veränderungen lagen (von T1 bis T2). Der Vergleich von T1 und T3 ergab keine signifikanten Veränderungen (**Abbildung 7**). Bei der ImPACT Testung zeigte sich im Vergleich von T1 zu T3 eine signifikante Verbesserung bei der visuellen motorischen Geschwindigkeitstestung. Ansonsten gab es keinen signifikanten Gruppenunterschied.



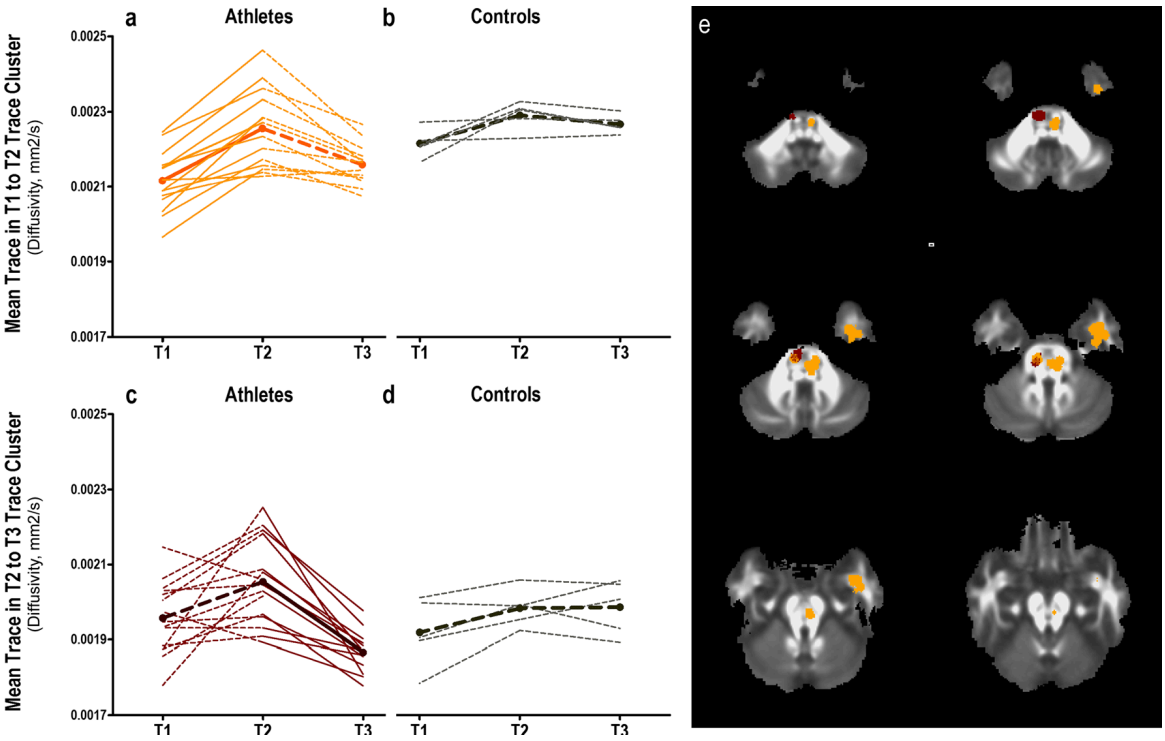


Abbildung 7: Signifikante FA-/ Trace-Änderungen von T1 bis T2 und von T2 bis T3. Durchschnittliche FA-/ Tracewerte (a-d) in den signifikanten Voxelregionen von T1 bis T2 und von T2 bis T3. Die Werte der einzelnen Probanden werden mit dünnen und die Gruppenmittelwerte mit dicken Linien dargestellt. Die Zeiträume, in denen statistisch signifikante Änderungen beobachtet wurden, werden mit durchgehenden Linien dargestellt (a und c). Die gepunkteten Linien stellen Werte im selben Voxelbereich zum jeweiligen dritten Zeitpunkt dar. Voxelregionen mit signifikant veränderten Bereich bei Kontaktsportlern wurden in der Kontrollgruppe dargestellt (b und d).

Diskussion:

Diese Studie zeigte, dass College Football Spieler bereits nach einer einzigen Saison mikrostrukturelle Veränderungen der weißen Gehirnsubstanz aufweisen. Diese Veränderungen schienen sich bei der Mehrzahl der Spieler nach einer Trainingspause von 6 Monaten ohne Kontaktsport wieder auf den Ausgangswert zurückgebildet zu haben. Dies könnte auf eine partielle Remission der Veränederungen bei diesen Sportlern hindeuten. Bei Spielern bei denen die Diffusionswerte nicht vollständig zurückgingen zeigten sich möglicherweise protrahierte mikrostrukturelle Veränderungen.

Um die Ursachen der mikrostrukturellen Veränderungen besser zu verstehen wurden zusätzlich die Trace Werte in der betroffenen Hirnstamm-/Temporallappenregion sowie die FA Werte der Parietallappenregion ausgewertet. In der betroffenen Hirnstamm-/Temporallappenregion zeigte sich die FA, analog zu TRACE, ebenfalls nach der Saison erhöht und bildete sich in der Zeit der Trainingspause zurück. In der Region im Parietallappen mit signifikanten Unterschieden in der FA zeigten sich die TRACE Werte konträr der Veränderungen in FA. Während der Saison nahmen sie bei den meisten Spielern ab und im Zeitraum nach der Saison zu. Die Veränderungen im Bereich des Hirnstamms und im linken Temporallappen waren auf Grund ihrer Lokalisation und dem Verhalten der Diffusionsparameter am ehesten als Folge der vielen wiederholten Erschütterungen des Gehirns während der Saison zu erklären. Bei der Region mit signifikanter Zunahme der FA im linken Parietallappen, über die Saison, war dies auch denkbar. Allerdings war hier auf Grund der Lokalisation, im prämotorischen/motorischen Cortex und der Entwicklung der DTI-Werte wahrscheinlicher, dass die Veränderungen als Folge einer gesteigerten neuronalen Plastizität durch eine erhöhte Stimulation dieser Bereiche während der Sportausübung entstanden sind.
Die Ergebnisse legen nahe, dass College Football Spieler von Trainingspausen, in der sie keinen wiederholten Traumata des Kopfes ausgesetzt sind, profitieren könnten. Es bedarf einer weiteren Fundierung dieser deskriptiven Daten um Rückschlüsse auf die zugrundeliegende Pathologie ziehen zu können.

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ORIGINAL RESEARCH

White matter alterations in college football players: a longitudinal diffusion tensor imaging study

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Abstract The aim of this study was to evaluate longitudinal changes in the diffusion characteristics of brain white matter (WM) in collegiate athletes at three time points: prior to the start of the football season (T1), after one season of football (T2), followed by six months of no-contact rest (T3). Fifteen male collegiate football players and 5 male non-athlete student controls underwent diffusion MR imaging and computerized cognitive testing at all three timepoints. Whole-brain tract-based spatial statistics (TBSS) were used to compare fractional anisotropy (FA), radial diffusivity (RD), axial diffusivity (AD), and trace between all timepoints. Average diffusion values were obtained from statistically significant clusters for each individual. No athlete suffered a concussion during the study period. After one season of play (T1 to T2), we observed a significant increase in trace in a cluster located in the brainstem and left temporal lobe, and a significant increase in FA in the left parietal lobe. After six months of no-contact rest (T2 to T3), there was a significant decrease in trace and FA in clusters that were partially overlapping or in close proximity with the initial clusters (T1 to T2), with no significant changes from T1 to T3. Repetitive head impacts (RHI) sustained during a single football season may result in alterations of the brain's WM in collegiate football players. These changes appear to return to baseline after 6 months of no-contact rest, suggesting remission of WM alterations. Our preliminary results suggest that collegiate football players might benefit from periods without exposure to RHI.

Key words TBSS · Diffusion tensor imaging · White matter · Longitudinal · High magnitude impact · Sports · Athletics · Subconcussive head trauma · Human studies · Football · Repetitive head impacts · Fractional anisotropy

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Introduction

American football is among the most popular sports in the United States with more than 8.9 million active players (Luker 2011; U.S.-Census-Bureau 2009). Football players are at high risk for repetitive concussive and subconcussive head impacts (RHI) (Jordan et al. 1996; Matser et al. 1999; Tysvaer and Lochen 1991). A study by Crisco et al., for example, reported a total number of impacts received by an individual player with a median of 420 head impacts (range 217–728) over the course of one season of college football (Crisco et al. 2011). Recent evidence also suggests a link between RHI and impaired cognitive performance (McAllister et al. 2012). Moreover, football players have been shown to be at increased risk for neurodegenerative diseases such as Alzheimer's disease, amyotrophic lateral sclerosis,

and chronic traumatic encephalopathy (CTE) later in life (Lehman et al. 2012; McKee et al. 2009; Stern et al. 2011). Further, recent work by both McAllister et al. and Bazarian et al. suggest that RHI may lead to structural alterations of brain white matter (WM) in college level football players over the course of one football season (Bazarian et al. 2014; McAllister et al. 2014). While the long-term clinical impact of these changes has yet to be determined, several studies suggest a link between RHI and impaired cognitive performance (Bailes 2013; Bazarian et al. 2012; Henry et al. 2011; Koerte et al. 2012a; Koerte et al. 2015a; Koerte et al. 2015c).

Diffusion Tensor Imaging (DTI) is an advanced magnetic resonance imaging (MRI) technique that measures the diffusion of water and has been shown to be sensitive for detecting changes in the brain following RHI (Bazarian et al. 2012; Davenport et al. 2016; Koerte et al. 2012a; Koerte et al. 2015b; McAllister et al. 2014). Diffusion parameters may provide information about how the brain's microstructure influences the motion of water molecules. Changes in diffusion parameters result when the diffusion of water molecules is restricted by, e.g., axonal membranes, filaments and/or myelin sheaths. A diffusion restriction perpendicular to the main axis leads to increased anisotropy. The most commonly used parameters are fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and trace. FA reflects the coherent linear organization of WM fibers (Basser and Pierpaoli 1996; Kubicki et al. 2007). Trace, which is the sum of the three eigenvalues, indicates the average of cumulative water diffusion (Basser and Pierpaoli 1996; Pierpaoli et al. 1996). AD and RD quantify the diffusion of water molecules parallel and perpendicular to maximal diffusivity, respectively (Budde et al. 2009; Song et al. 2003; Song et al. 2002). Demyelination and axon damage result in larger extracellular space and therefore decreased FA and increased trace (Budde et al. 2011; Sagi et al. 2012).

Only a small number of studies have investigated WM over the course of a sports season with exposure to RHI (Bazarian et al. 2014; Koerte et al. 2012b; McAllister et al. 2014). In these studies, changes in WM were reported to be associated with measures of head impact exposure in college level football (Bazarian et al. 2014; McAllister et al. 2014; Koerte et al. 2012b) and ice hockey players. However, very little is known about whether these WM changes persist once exposure to RHI has ceased. Further, only one study examined the effects of a period of no-contact rest following exposure to RHI. In a group of 10 collegiate athletes, Bazarian et al. found that whole brain WM changes following one season of football were still observed after a six-months period without exposure to RHI (Bazarian et al. 2014). This analysis utilized a wild boot strapping approach that identified the percent of white matter voxels with statistically significant change on an individual basis between time points. However, the study cohort was small (n = 10), WM changes were not further specified, and the location of the observed changes was not analyzed. Using a three dimensional statistical approach, tract-based spatial statistics (TBSS), addresses this limitation by identifying specific brain regions with changes in WM diffusion.

The objective of the current preliminary study was to examine longitudinal changes in brain white matter (WM) during one season of collegiate football and followed by six months of no-contact rest using TBSS.

Methods

Participants

Nineteen male athletes were recruited from the University of Rochester football team, which participates in Division III of the National College Athletic Association (NCAA). These athletes reflected a variety of positions and anticipated head impacts they would experience during the season. Of the 19 participating athletes, 10 were recruited during the 2011–12 season and were part of a previous publication (Bazarian et al. 2014). Additionally, 9 athletes were recruited during the 2012–13 season. Subjects were not eligible for participation if they were <18 years old or had sustained a clinically diagnosed TBI of any severity within 2 weeks of pre-season study activities. History of prior TBI was determined by self-report (Corrigan and Bogner 2007).

Five non-athlete controls were recruited from the University of Rochester general student body. Controls were selected based on responses to a campus-wide call for research volunteers. Of the 10 students who responded, 5 were not eligible (4 had contraindications to MRI scanning, and 1 played club rugby). The remaining 5 were enrolled as controls. All five controls were recruited during the 2011–12 season.

The University of Rochester Institutional Review Board approved this study and the process of informed consent. Written informed consent was obtained from all individual participants included in the study prior to any study activities.

Monitoring for concussion

Athletes were monitored for concussion at every game and practice by certified athletic trainers. Athletes were considered to have sustained a concussion if they had an injury meeting the definition of concussion defined by the Sport Concussion Assessment Tool 2 (SCAT2) (McCrory et al. 2009). This definition consists of an injury resulting in any one or more of the following: symptoms (such as headache), physical signs (such as unsteadiness), impaired brain function (such as confusion), or abnormal behavior.

Clinical outcome

All participating subjects underwent determination of cognition with the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) prior to the start of the football season (T1), at the end of the season (T2), and after 6 months of no-contact rest (T3). Physical activity between T2 and T3 was uniform across the athletes, and involved weekly weight training, and light cardiovascular activity. Athletes were not subject to subconcussive impacts during this period. ImPACT is a proprietary computer program that measures verbal memory, visual memory, reaction time, and visual motor speed (Collins et al. 2003). ImPACT also includes a post-concussive symptom inventory. The mean score among athletes in each domain was compared at T1 vs T2, at T2 vs T3, and at T1 vs T3. Given our sample size of athletes and an alpha level of 0.05, our study was powered (90%) to detect a pre-season to post-season decline of ≥4.3 points in verbal memory score, ≥9.8 in visual memory score, ≥5.5 in visual motor speed score, an increase of ≥0.08 s in reaction time, and an increase of ≥1.6 in total symptom score.

MR imaging data acquisition

All subjects underwent DTI at baseline/pre-season (T1), immediately post-season (T2), and six-months post-season (T3). All images were obtained on a Siemens 3 T Tim Trio system (Siemens Healthcare, Erlangen, Germany) running Numaris 4 software version B17. A 32-channel matrix head coil was used. DTI sequence parameters were: TR/TE =10 s/89 ms, voxel size 2x2x2 mm, 60 diffusion directions with b = 1200 s/mm2 and 10 averages of b = 0.

Post-processing of DTI

DTI data sets were visually inspected for image quality using 3D Slicer version 4.3.0 (http://www.slicer.org; Surgical Planning Laboratory, Brigham and Women's Hospital, Boston, MA) (Fedorov et al. 2012). An affine registration to the average of b = 0 images was applied for each scan to correct for head motion and eddy currents using the MCFLIRT and eddy tools of FMRIB Software Library (FSL 4.1, The Oxford Centre for Functional MRI of the Brain). An automated Otsu mask covering the entire brain was generated for each scan using 3D Slicer. Masks were visually inspected for quality and manually edited where necessary. Using a multivariate linear fitting algorithm, the diffusion tensor for each voxel was estimated, and the three pairs of eigenvalues and corresponding eigenvectors were obtained. From these tensor volumes, a diffusion tensor with associated ellipsoid was reconstructed. The scalar measures, which were calculated within each voxel, included FA, AD, RD and trace.

Analyses of DTI

WM diffusion characteristics were analyzed using TBSS. TBSS analysis was performed for each of the diffusion parameters: FA, trace, RD, and AD. The WM skeleton was created based on FA maps. Analyses for trace, RD, and AD were performed using the same skeleton that was derived from FA maps. This voxel-based standard-space statistical group analysis is part of FSL (http://fsl.fmrib.ox.ac.uk/fsl) (Jenkinson et al. 2012; Smith et al. 2004; Woolrich et al. 2009). This process is described in detail elsewhere (Smith et al. 2006). Briefly, all individual FA maps were registered and aligned to the standard FMRIB58_FA template, which is in MNI152 standard space (Grabner et al. 2006). The mean FA map was then projected and aligned to the FMRIB58_FA standard-space skeleton to generate the mean FA skeleton. The threshold for FA was set at >0.3 to include all major WM tracts and to exclude peripheral voxels with significant inter-subject variability as well as partial volume effects with gray matter. Trace, RD, and AD maps were registered into the FMRIB58_FA standard-space by applying the nonlinear transformation obtained from the FA registration. After FA, trace, RD, and AD mean skeletons were obtained, the 'skeleton-forming' voxels for each individual scan were extracted using FSL's fslsplit command. This allowed subtracting the individual-specific scans obtained at different time points from one another using the fslmaths command. This generated a skeletonized delta map that contains the change in diffusion between the different time points, resulting in three delta maps for each subject: T2-T1, T3-T2, and T3-T1. This process was repeated for FA, trace, RD and AD. Using the fslmerge command, delta maps were then merged across subjects into a single file for each comparison (T2-T1, T3-T2, and T3-T1), which contained the changes in diffusion metrics for each individual.

Statistical analyses

Clusters of voxels with significant changes in diffusivity were identified in the following manner. Merged delta maps were used to compare changes in diffusion parameters (FA, trace, RD, and AD) between time points across athletes. After aligning all of the scans, two-tailed one-sample t tests were performed using FSL randomise. This process is also described in detail at: http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/GLM. For all TBSS analyses, the random permutation number was set to the default of 5000. Threshold-free cluster enhancement was used to obtain differences between groups at a significance level of $p < 0.05$, after accounting for multiple comparisons using family-wise error rate.

Timepoint and individual specific diffusion values were obtained from the statistically significant voxel clusters. Average diffusivity values from significant voxels were plotted using GraphPad Prism (GraphPad Prism version 6.00, GraphPad Software, San Diego, California). Statistically

significant FA clusters were used to create a region of interest (ROI). which was applied to the FA map to obtain FA values in that same ROI. Significant clusters of voxels identified in the athlete group were then applied to the control group, and diffusion values in these clusters were measured using the fslstats command.

To confirm test retest reliability, the Intraclass Correlation Coefficient (ICC) was calculated within the control group (Matsushita et al. 2011; McGraw and Wong 1996). ICC values were calculated using a two-way mixed model with absolute agreement and a confidence interval of 95% using SPSS (IBM SPSS Statistics for Macintosh, Version 23.0, SPSS Inc., Chicago, Ill., USA). Changes in cognitive performance were determined using a paired t-test.

Results

None of the 19 athletes suffered a concussion during the study period, and three reported a concussion prior to the study, but all occurred more than 1 year prior to enrollment. Of the 19 athletes, 4 athletes displayed movement artifacts during the T1 scan, and thus were excluded from pre-season to post-season comparisons. Two athletes displayed significant movement artifact in their T3 scan, so both were included in T1 to T2 analysis but excluded from T1 to T3 and T2 to T3 analyses. Characteristics of the final study cohort are summarized in Table 1. Exposure among the final study cohort of athletes ranged from 48 to 1850 total impacts (mean ± SD = 800 ± 515), which were accrued over an average of 8.6 games and 41.3 practices over one season of football. Among athletes, there were no significant group mean declines in cognitive performance at any time point (Table 2).

Table 1 Demographics of football athletes (n = 15) and non-athlete controls (n = 5)

	Athletes (n = 15)	Controls (n = 5)
	Mean (SD)	Mean (SD)
Age	20.0 (1.0)	20.93 (1.1)
Height (cm)	184.4 (3.8)	181.9 (2.3)
Weight (kg)	106.7 (10.1)	72.6 (8.8)
BMI	31.4 (3.4)	22.0 (2.8)
	n (%)	n (%)
Race		
White	13 (87%)	5 (100%)
AA	2 (13%)	0 (0%)
Handedness		
Right	14 (93%)	4 (80%)
Left	1 (7%)	1 (20%)

Post-season (T2) DTI scans were performed on average 95 days ±7.5 days following the pre-season (T1) scan among athletes and 99 days ±7.7 days following the T1 scan among controls, reflecting the length of the collegiate football season. Six-months post-season (T3) DTI was performed on average 176 days ±7.1 days after the T2 scan among athletes, and 172 days ±7.0 days following the T2 scan among controls.

Diffusion changes between time points

FA Among athletes, TBSS identified a cluster of voxels with a significant T1 to T2 increase in FA in the left parietal lobe (dark blue regions in Fig. 1e). In this cluster, mean ± SD FA increased from 0.667 ± 0.038 at T1 to 0.686 ± 0.039 at T2 (solid line in Fig. 1a). After six months of rest (T2 to T3) there was a decrease in FA in this same cluster (hatched line in Fig. 1a). TBSS also identified a cluster of voxels with a significant T2 to T3 decrease in FA in a slightly different voxel cluster also located in the left parietal lobe (light blue regions Fig. 1e). In this cluster, FA decreased from 0.585 ± 0.068 at T2 to 0.563 ± 0.071 at T3 (solid line in Fig. 1c). There were no significant changes in FA from T1 to T3 for either cluster. However, three athletes (#2, 18, and 22) had T3 FA values in the significant T1 to T2 left parietal lobe cluster that were still 1.7–2.8% above their personal baseline at T1. The cluster with significant T1 to T2 increase in FA was accompanied by a decrease in trace, while the cluster with significant decrease in FA from T2 to T3 was accompanied by an increase in trace (data not shown).

Trace Among athletes, TBSS identified a cluster of voxels with a significant T1 to T2 increase in trace in the brainstem and in the left temporal lobe (orange regions in Fig. 2e). In this cluster, mean ± SD trace increased from 0.0021 ± 0.0001 at T1 to 0.0023 ± 0.0001 at T2 (solid line Fig. 2a). After six months of rest (T2 to T3), there was a decrease in trace in this cluster (hatched line in Fig. 2a). TBSS also identified a cluster of voxels with significant T2 to T3 decrease in trace in a slightly different but partially overlapping area of the brainstem (red regions in Fig. 2e). In this cluster, mean ± SD trace decreased from 0.0021 ± 0.0001 at T2 to 0.0019 ± 0.0001 at T3 (solid line in Fig. 2c). There were no significant changes in trace from T1 to T3 for either cluster. However, three athletes in the brainstem/left temporal lobe cluster (# 01, 14, and 16) and one athlete in the brainstem cluster (# 16) had T3 trace values that were still 4.8–8.5% above their personal baseline at T1. The trace cluster with significant T1 to T2 increase was accompanied by a decrease in FA, while the trace cluster with significant T2 to T3 decrease was accompanied by an increase in FA (data not shown).

Table 2 Longitudinal mean (SD) ImPACT scores of athletes (n = 15)

	T1		T2		T3		p - Value		
	Mean	SD	Mean	SD	Mean	SD	T1 to T2	T2 to T3	T1 to T3
Verbal memory score	91.5	5.7	90.0	7.5	88.5	10.3	0.4205	0.6098	0.1182
Visual memory score	75.0	12.9	80.1	13.6	75.0	12.6	0.1572	0.0519	0.6408
Visual motor speed score	42.9	7.3	44.0	7.1	44.3	7.1	0.3181	0.7068	0.0312
Reaction time	0.53	0.10	0.52	0.08	0.54	0.09	0.3246	0.3318	0.9678
Total symptom score	0.60	2.06	1.87	2.97	1.38	2.26	0.0805	0.7643	0.0510

Significant voxel clusters identified in athletes were applied to the control group (Fig. 1b, d, 2b, d,). No significant changes in AD or RD were found between any time points in any group.

Intraclass correlation coefficient

We used the control group in order to confirm that changes are within the range of normal variability of test-retest of the diffusion measures. More specifically, ICC of the white matter skeleton of the control group was 0.955 for FA and 0.983 for trace which reflects high test-retest reliability.

Discussion

It is well known that head hits resulting in concussion are associated with changes in diffusivity (for review see Shenton et al. 2012). However, it has not been until quite

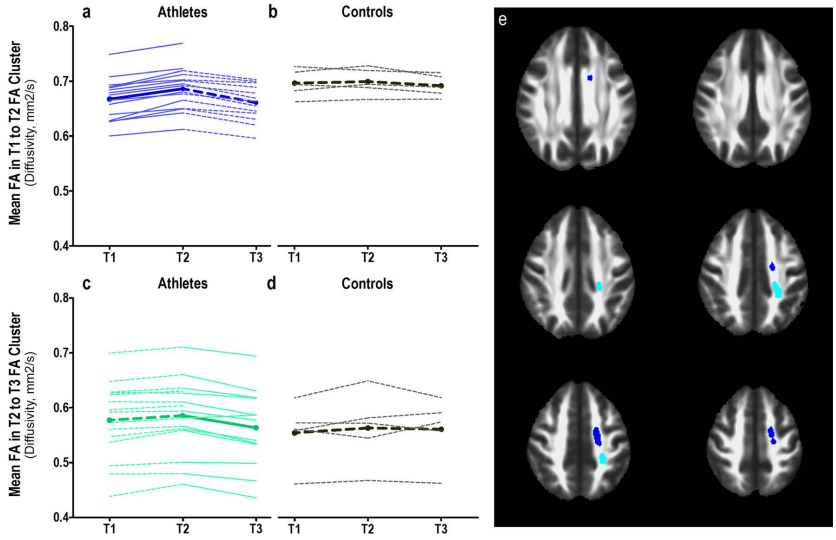

Fig. 1 Changes in FA from T1 to T2, and from T2 to T3. Mean FA (**a-d**) measured using TBSS in significant voxel clusters from T1 to T2 (MNI: X: 108; Y: 116; Z: 118) and from T2 to T3 (MNI: X: 115; Y: 90; Z: 119). *Thin lines* represent individual values; *bold lines* represent the group mean. *T1 to T2*: Clusters with statistically significant T1 to T2 changes in FA (**a**) are represented by *solid blue lines*; the *dotted lines* represent FA values in those same clusters from T2 to T3. *T2 to T3*: Clusters with statistically significant T2 to T3 changes in FA (**c**) are represented by *solid green lines*; the *dotted lines* represent FA values in those same clusters from T1 to T2. Significant voxel clusters for FA (**e**) are superimposed on the WM skeleton, and correspond to the respective graph with the same color. Significant clusters identified in athletes were applied to controls (**b** and **d**)

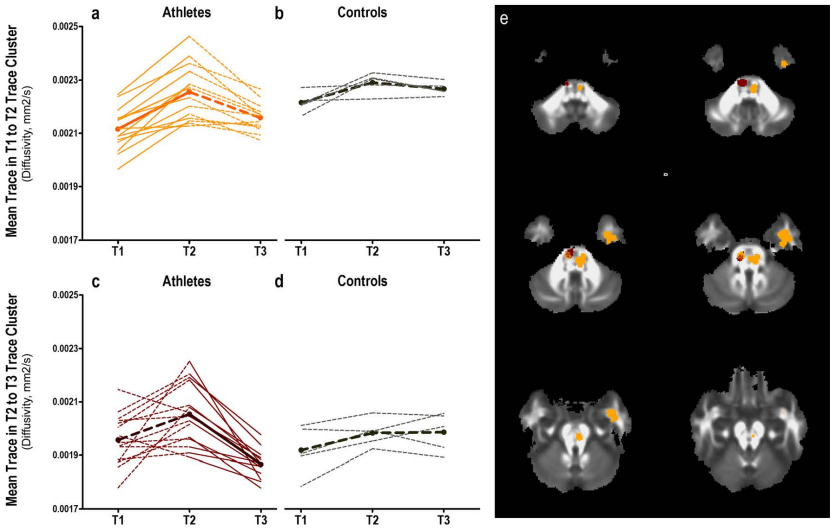

Fig. 2 Changes in trace from T1 to T2, and from T2 to T3. Mean trace (**a-d**) in significant voxel clusters from T1 to T2 and from T2 to T3. *Thin lines* represent individual values; *bold lines* represent the group mean. *T1 to T2*: Clusters with statistically significant T1 to T2 changes in trace (**a,** MNI: X: 83/125; Y: 103/121; Z: 42/36) are represented by *solid orange lines*; the *dotted lines* represent trace values in those same clusters from T2 to T3. *T2 to T3*: Clusters with statistically significant T2 to T3 changes in trace (**c,** MNI: X: 85; Y: 102; Z: 40) are represented by *solid red lines*; the *dotted lines* represent trace values in those same clusters from T1 to T2. Significant voxel clusters for trace (**e**) are superimposed on the WM skeleton, and correspond to the respective graph with the same color. Significant clusters identified in athletes were applied to controls(**b** and **d**).

recently that evidence has emerged suggesting that similar WM changes occur following exposure to repetitive subconcussive head impacts (for review see Koerte et al. 2015b). The extent to which these changes are temporary or may be reversible with rest is unknown. In the current preliminary study, we used TBSS to analyze longitudinally acquired DTI in collegiate football players before and immediately after a single season of football. To examine the effects of no-contact rest, we obtained a third set of scans after a six-months period of no-contact rest. From these data we present two main findings:

Our first main finding is that repetitive, non-concussive head impacts may be associated with changes in the WM microstructure. At the end of the three-months football season, we observed a cluster of voxels in the brainstem and in the left temporal lobe in which trace was significantly elevated compared to pre-season scans. This increase in trace was accompanied by decreased FA. This finding confirms the work of others who have described decreased FA, often accompanied by elevated trace, following concussion (Iverson et al. 2011; Lipton et al. 2013; Messe et al. 2011; Shin et al. 2014; Zhang et al. 2010), as well as after RHI (Chappell et al. 2006; Koerte et al. 2012b; McAllister et al. 2014; Shin et al. 2014). Koerte et al. described an increase in trace of 5.4% over a single season in ice hockey athletes in a voxel cluster involving the corpus callosum, the right corticospinal tract, the right internal capsule, and the right superior longitudinal fasciculus (Koerte et al. 2012b). Of note, three of the seventeen subjects included by Koerte et al. suffered a clinically diagnosed concussion during the season. Although the location is different, the magnitude of trace changes is similar to our findings, where we observed a cluster of voxels with a significant increase in trace in the brainstem and in the left temporal lobe from pre- to post-season. In this cluster, mean ± SD trace increased by 9.5% from 0.0021 ± 0.0001 to 0.0023 ± 0.0001, respectively.

Histopathologic studies of rodents subjected to experimentally-induced TBI reveal that this combination of diffusivity changes is due to demyelination and axonal degeneration (Budde et al. 2011; Mac Donald et al. 2007). This suggests that RHI may lead to similar WM injury in humans even in the absence of clinical symptoms. The location of these observed changes in the brainstem further supports this idea. The brainstem is known to be especially sensitive to head impacts, likely due to its close proximity to the bony skull base (Gale et al. 2005; Reeves 1981). This region experiences high shear stress due to

high-pressure gradients and triangulation of biomechanical forces in this region (Gurdjian et al. 1961; Ropper and Gorson 2007).

We also identified a cluster of voxels in the left frontal premotor area in which FA was significantly elevated at the end of the football season compared to scans acquired just prior to the start of the football season. This elevated FA was accompanied by decreased trace. FA increase has been observed following more severe head injury impacts acutely post-injury (Mayer et al. 2010), where it has been postulated to be associated with traumatic axonal swelling (Barzo et al. 1997; Mac Donald et al. 2007; Peled 2007). FA increase has also been observed after mild traumatic brain injury (mTBI) (Dodd et al. 2014), but not as frequently as decreased FA. Moreover, the location of the cluster in the corona radiata with proximity to the precentral gyrus and postcentral gyrus is common for neuroplasticity after motor tasks (Wang et al. 2013). Studies suggest that motor training leads to increases in FA due to increased myelination in the internal capsule, the corona radiata, and the corpus callosum (Hanggi et al. 2015; Wang et al. 2013). However, the aforementioned studies investigated shorter time periods. To our knowledge there are no studies investigating white matter changes for more than a few weeks following motor training. While traumatic axonal injury cannot be excluded, an alternative explanation for the increase in FA is increased myelination due to exertion-related stimulation of the premotor/motor area as well as sensory cortex during the course of the football season. The decreased trace observed in the same voxel clusters could also be due to axonal swelling, but increased trace is more commonly observed (McAllister et al. 2014; Shin et al. 2014). We speculate that decrease in trace in the clusters with proximity to the motor and sensory cortex may be due to neuronal plasticity. Decreased trace values may indicate changes of myelin thickness in white matter induced by activity-dependent modulation of axon number, axon diameter, or myelin thickness. A study by Wang et al. in 2013 reported a 2–3% decrease in trace in the right hemisphere, the posterior and anterior limbs of the internal capsule, the external capsule, the anterior and superior corona radiata, the body of the corpus callosum, and the superior longitudinal fasciculus following visuo-spatial motor training tasks over 9 sessions (2–3 weeks) (Wang et al. 2013). Triggered by increased stimulus, such as visual cortex stimulation by a flickering board, several studies have found a decrease in trace after stimulation of brain areas (Darquie et al. 2001). The high ICC for FA and trace among controls suggests that the contribution of normal variation in water motion toward the DTI changes observed among athletes was minimal.

Our second main finding was that possible WM changes apparent within one week after the end of the football season appeared to revert after six months of no-contact rest in some of the individuals. On a group level, FA and trace significantly increased between the pre-season and immediate post-season, and then significantly decreased 6 months later (Figs. 1 and 2). Further, there was no statistical difference in diffusion measures between T1 and T3. While recovery is one interpretation of this finding, small sample size might have obscured a difference between these DTI metrics at T1 and T3, which would imply non-recovery. This latter possibility is supported by the finding that five athletes had either FA or trace values at T3 that were higher than their personal baseline values and outside the range of variation observed among the controls (data not shown).

Nevertheless, the significant decrease in mean trace and FA from the elevated values observed immediately following the football season to values 6 months later suggests the possibility of remission of alterations in WM. The decrease in trace, which was associated with an increase in FA, could be due to the reparative effects of gliosis (Budde et al. 2011) or remyelination (Fox et al. 2011; Li et al. 2013) on RHI-induced axonal injury. The decrease in FA, associated with increased trace, could represent a reversal of the effects of physical exercise during a period of prolonged rest.

Our results have several implications. If RHI is associated with WM alterations similar to those observed after mTBI, these athletes may be at risk for long term cognitive or mood impairment. Limited available evidence, although not definitive, suggests that RHI-associated WM changes could pose a long term risk to the brain. DTI revealed decreased FA in the left temporal lobe in ten former NFL players (mean age 62 years) with impairments in cognition and/or mood (Hart et al. 2013). Interestingly, the left temporal lobe is the same anatomical location we detected FA changes in our athletes. Two recent studies lend additional support that RHI has long-term neurologic consequences, although these studies did not examine WM. In the first study, 11 former professional German soccer players (mean age 52 years) without a history of concussion demonstrated alterations in neurochemistry consistent with neuroinflammation on magnetic resonance spectroscopy (increase of choline and myo-inositol) compared to age and gender-matched no-contact athletes. Moreover, myo-inositol and glutathione correlated with lifetime estimates of heading (Koerte et al. 2015b). Another study on former professional soccer players found a greater decline in cortical thickness with age compared to a control group (Koerte et al. 2015c). Cortical thinning was associated with higher exposure to RHI and lower performance in a memory test. In another study, two years after participating in contact sports, nine college athletes without a history of concussion displayed impaired immediate and delayed memory on Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Killam et al. 2005). While not conclusive, these preliminary studies suggest the possibility that RHI may be detrimental to long-term brain health. If the observed changes resolve, this speaks to and might support the idea of a rest period for athletes following one season of play. If they do not

resolve, which several studies indicate, other strategies, such as longer rest periods or even taking a season off may be important to consider.

Future studies need to follow these athletes to determine if and when imaging findings normalize. Such information may also capture differences in vulnerability between those whose changes resolve versus those where reversal of brain changes is not observed, further leading to possible interventions. The effect of the large range of exposure that was observed should also be investigated further in future studies.

Finally, our preliminary finding of possible recovery of WM changes during a period of no-contact rest suggests that, if confirmed in future studies, contact athletes might benefit from an extended no-contact period prior to returning to play the following season. This is important given the current trend for many athletes to play their sport year round.

Limitations of this study include the small sample size, particularly for the control group. Its size limits our assurance of the normal degree of change. The sample size also decreases our level of sensitivity and specificity. However, this study is unique in that pre-season scans (in addition to two time points after exposure) were obtained. This study did not include covariates such as use of drugs or alcohol. While the NCAA mandates drug testing, this is not performed throughout the season and thus may be a confounding factor. No physics-based distortion correction was used to correct for EPI distortions. However, we performed a non-rigid alignment of the FA maps to a standard template. While some confounds in the temporal lobe potentially remain, we expect that the results are sufficiently robust. Given the small sample size, caution is needed in making inferences regarding the stability of the diffusion measures over time. Nonetheless, the test-retest variability over time in controls was very high (>0.983) and we therefore believe that the changes we see in the athlete group are related to true changes and not to test-retest variability in the diffusion measures over time. Further, group-wise analysis by TBSS may not be sensitive to the variable spatial location of abnormal diffusion measures in heterogeneous conditions such as brain alterations due to RHI. Spatial heterogeneity as well as small sample size may explain why no further areas of change could be identified. Thus, future studies should include an analysis of subject-specific changes such as those using an atlas based approach to determine subject-specific areas of change (Bouix et al. 2013). This is a preliminary study, thus future studies are needed to confirm the findings and to elucidate further the etiology and clinical meaning of brain WM changes in college football players.

Conclusion

Results of this study indicate that RHI during a single season may result in alterations of the brain's WM in college football players. Group-wise resolution of these alterations was observed after a six-months period without exposure to RHI following one season of play. However, on an individual-level, some of the athletes' diffusivity values did not return to baseline. These longitudinal changes suggest that athletes might benefit from periods without exposure to RHI.

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Compliance with ethical standards

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Conflict of interest Author Mayinger declares that he has no conflict of interest. Author Merchant-Borna declares that he has no conflict of interest. Author Hufschmidt declares that he has no conflict of interest. Author Muehlmann declares that he has no conflict of interest. Author Weir declares that she has no conflict of interest. Author Rauchmann declares that he has no conflict of interest. Author Shenton declares that she has no conflict of interest. Author Koerte declares that she has no conflict of interest. Author Bazarian declares that he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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