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Modifications neurométaboliques et microstructurales à la suite d'une commotion cérébrale chez les athlètes féminines

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RÉSUMÉ

L'utilisation de méthodes d'investigation cérébrale avancées a permis de mettre en évidence la présence d'altérations à court et à long terme à la suite d'une commotion cérébrale. Plus spécifiquement, des altérations affectant l'intégrité de la matière blanche et le métabolisme cellulaire ont récemment été révélées par l'utilisation de l'imagerie du tenseur de diffusion (DTI) et la spectroscopie par résonance magnétique (SRM), respectivement. Ces atteintes cérébrales ont été observées chez des athlètes masculins quelques jours après la blessure à la tête et demeuraient détectables lorsque les athlètes étaient à nouveau évalués six mois post-commotion. En revanche, aucune étude n'a évalué les effets neurométaboliques et microstructuraux dans la phase aigüe et chronique d'une commotion cérébrale chez les athlètes féminines, malgré le fait qu'elles présentent une susceptibilité accrue de subir ce type de blessure, ainsi qu'un nombre plus élevé de symptômes post-commotionnels et un temps de réhabilitation plus long. Ainsi, les études composant le présent ouvrage visent globalement à établir le profil d'atteintes microstructurales et neurométaboliques chez des athlètes féminines par l'utilisation du DTI et de la SRM.

La première étude visait à évaluer les changements neurométaboliques au sein du corps calleux chez des joueurs et joueuses de hockey au cours d'une saison universitaire. Les athlètes ayant subi une commotion cérébrale pendant la saison ont été évalués 72 heures, 2 semaines et 2 mois après la blessure à la tête en plus des évaluations pré et post-saison. Les résultats démontrent une absence de différences entre les athlètes ayant subi une commotion cérébrale et les athlètes qui n'en ont pas subie. De plus, aucune différence entre les données pré et post-saison a été observée chez les athlètes masculins alors qu'une diminution du taux de N-acetyl aspartate (NAA) n'a été mise en évidence chez les athlètes féminines, suggérant ainsi un impact des coups d'intensité sous-clinique à la tête.

La deuxième étude, qui utilisait le DTI et la SRM, a révélé des atteintes chez des athlètes féminines commotionnées asymptomatiques en moyenne 18 mois post-commotion. Plus spécifiquement, la SRM a révélé une diminution du taux de myo-inositol (mI) au sein de l'hippocampe et du cortex moteur primaire (M1) alors que le DTI a mis en évidence une augmentation de la diffusivité moyenne (DM) dans plusieurs faisceaux de matière blanche. De

plus, une approche par région d'intérêt a mis en évidence une diminution de la fraction d'anisotropie (FA) dans la partie du corps calleux projetant vers l'aire motrice primaire.

Le troisième article évaluait des athlètes ayant subi une commotion cérébrale dans les jours suivant la blessure à la tête (7-10 jours) ainsi que six mois post-commotion avec la SRM. Dans la phase aigüe, des altérations neuropsychologiques combinées à un nombre significativement plus élevé de symptômes post-commotionnels et dépressifs ont été trouvés chez les athlètes féminines commotionnées, qui se résorbaient en phase chronique. En revanche, aucune différence sur le plan neurométabolique n'a été mise en évidence entre les deux groupes dans la phase aigüe. Dans la phase chronique, les athlètes commotionnées démontraient des altérations neurométaboliques au sein du cortex préfrontal dorsolatéral (CPDL) et M1, marquées par une augmentation du taux de glutamate/glutamine (Glx). De plus, une diminution du taux de NAA entre les deux temps de mesure était présente chez les athlètes contrôles.

Finalement, le quatrième article documentait les atteintes microstructurales au sein de la voie corticospinale et du corps calleux six mois suivant une commotion cérébrale. Les analyses n'ont démontré aucune différence au sein de la voie corticospinale alors que des différences ont été relevées par segmentation du corps calleux selon les projections des fibres calleuses. En effet, les athlètes commotionnées présentaient une diminution de la DM et de la diffusivité radiale (DR) au sein de la région projetant vers le cortex préfrontal, un volume moindre des fibres de matière blanche dans la région projetant vers l'aire prémotrice et l'aire motrice supplémentaire, ainsi qu'une diminution de la diffusivité axiale (DA) dans la région projetant vers l'aire pariétale et temporale.

En somme, les études incluses dans le présent ouvrage ont permis d'approfondir les connaissances sur les effets métaboliques et microstructuraux des commotions cérébrales et démontrent des effets délétères persistants chez des athlètes féminines. Ces données vont de pair avec la littérature scientifique qui suggère que les commotions cérébrales n'entraînent pas seulement des symptômes temporaires.

Mots-clés : commotions cérébrales, imagerie de diffusion, imagerie par résonance magnétique spectroscopique, traumatisme craniocérébral, athlètes féminines

ABSTRACT

The presence of short and long-term alterations following a sports-related concussion has been detected using advanced neuroimaging methods. Using Diffusion Tensor Imaging (DTI) and Magnetic Resonance Spectroscopy (MRS), alterations of white matter integrity and cellular metabolism have been revealed, respectively. These brain anomalies were detectable in male athletes a few days after a head injury and persisted when athletes were re-evaluated six months post-concussion. However, no study has evaluated the neurometabolic and microstructural effects in the acute and chronic phases of a concussion in female athletes, despite increased susceptibility in women to suffer this type of injury, and a higher number of post-concussion symptoms and rehabilitation time when this injury occurs. Thus, the studies comprising the present thesis aim to document the neurometabolic and microstructural profiles of female concussed athletes using DTI and MRS.

The first study evaluated neurometabolic changes in the corpus callosum of male and female hockey players during a university season. Athletes who suffered a concussion were also assessed 72 hours, 2 weeks and 2 months after the head injury in addition to pre- and post-season evaluations. Results showed no difference between athletes who suffered a concussion and control athletes. Furthermore, no difference between pre- and post-season was observed in male athletes, while a decrease in NAA was found in female athletes, suggesting an impact of subconcussive hits to the head.

The second study, which used DTI and MRS, revealed alterations in asymptomatic female concussed athletes evaluated an average of 18 months post-concussion. More specifically, MRS revealed a decrease in myo-inositol (mI) levels in the hippocampus and the primary motor cortices (M1) while DTI showed an increase in mean diffusivity (MD) in several white matter tracts. In addition, a region of interest approach of the corpus callosum showed decreased fractional anisotropy (FA) in the segment containing fibers projecting to M1.

The third article evaluated athletes who suffered a concussion in the days following head injury (7-10 days) and six months post-concussion using MRS. In the acute phase, neuropsychological alterations and a higher severity of post-concussion and depressive

symptoms were found in concussed athletes relative to controls, but showed recovery in the chronic phase. In contrast, no neurometabolic differences were found between the two groups in the acute phase. In the chronic phase, concussed athletes showed neurometabolic impairments in prefrontal and motor cortices, characterized by a pathological increase of glutamate/glutamine (Glx). Also, a significant decrease in NAA was observed in control athletes at the second time point.

Finally, the fourth study aimed to document microstructural alterations within the corticospinal tract and the corpus callosum (CC) of athletes suffering a sport-related concussion six months prior to testing. The analysis showed no difference in the corticospinal tract while several differences were found when segmenting the corpus callosum based on the projections of the callosal fibers. The concussed group had lower MD and lower radial diffusivity (RD) in the region of the CC projecting to the prefrontal cortex, a lower volume of white matter fibers was found in the region projecting to the premotor and supplementary motor areas and a decrease in axial diffusivity (AD) in the region projecting to the parietal and temporal areas was detected.

In conclusion, the studies included in this thesis have helped increase knowledge about the neurometabolic and microstructural alterations following a sport-related concussion and showed persistent effects in female athletes. These data are consistent with the literature that suggests concussions are not only causing temporary symptoms.

Keywords: Sport concussion, traumatic brain injury, female athletes, magnetic resonance spectroscopy, diffusion tensor imaging.

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CDC	Center for Disease Control and Prevention
LNH	Ligue Nationale de Hockey
NCAA	National Collegiate Athletic Association
NFL	Ligue Nationale de Football
OMS	Organisation Mondiale de la Santé

LISTE DES ABBREVIATIONS

ATP	Adénosine triphosphate
Ca^{2+}	Calcium
CPDL	Cortex préfrontal dorsolatéral
Cr	Créatine
CST	Voie corticospinale
CT	Tomodensitométrie
DA	Diffusivité axiale
DM	Diffusivité moyenne
DTI	Imagerie du tenseur de diffusion
FA	Fraction d'anisotropie
ÉCG	Échelle de coma de Glasgow
ECT	Encéphalopathie traumatique chronique
GABA	Acide gamma-aminobutyrique
Glx	Glutamine + glutamate
H^{+}	Hydrogène
IRM	Imagerie par résonance magnétique
IRMf	Imagerie par résonance magnétique fonctionnelle
K^{+}	Potassium
LAT	Lésions axonales traumatiques
M1	Cortex moteur primaire
Mg^{2+}	Magnésium
mI	Myo-inositol

Na^+	Sodium
NAA	N-acetyl-aspartate
NMDA	N-methyl-D-aspartate
PCr	Phosphocréatine
SPC	Syndrome post-commotionnel
SMT	Stimulation magnétique transcrânienne
SRM	Spectroscopie par résonance magnétique
TCC	Traumatisme craniocérébral
TCCl	Traumatisme craniocérébral léger
tCr	créatine + phosphocréatine

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CHAPITRE 1 INTRODUCTION GÉNÉRALE

1.1 Traumatisme craniocérébral (TCC): Définition et prévalence

Un traumatisme craniocérébral (TCC) se définit comme une atteinte cérébrale caractérisée par une destruction ou un dysfonctionnement du système nerveux central (SNC) provoquée par le contact brusque entre le tissu cérébral et la boîte crânienne (Menon, Schwab, Wright, & Maas, 2010). Un TCC pourrait résulter d'une blessure ouverte à la tête par un objet pénétrant (e.g. un projectile d'arme à feu). Ce type de TCC entraine des risques importants d'infections ou de contaminations du SNC et est responsable de près de 40 % des décès des suites d'un TCC aux États-Unis (Coronado et al., 2011). D'un autre côté, un TCC peut être engendré par une blessure fermée résultant d'un transfert d'énergie cinétique à la tête n'occasionnant pas de fracture du crâne. Dans cette situation, les séquelles qui en découlent sont directement liées à la force avec laquelle le cerveau se heurte à la boite crânienne (Menon et al., 2010).

Ce type de blessure représente un problème de santé sociétal important. Les estimations indiquent qu'annuellement, 1,7 million d'individus subissent un TCC aux États-Unis seulement (Faul, Xu, Wald, & Coronado, 2010). De ce nombre, 1,365 millions (80 %) nécessitent des traitements dans les urgences, 275 000 doivent se faire hospitaliser et 50 000 décèdent des suites de cette blessure (Faul et al., 2010). Toutefois, ces chiffres tendent à sous-estimer le nombre réel d'incidents, car ils ne prennent pas en considération les personnes qui consultent dans des cliniques externes ou d'autres ressources communautaires de santé (Coronado et al., 2012). Les dernières estimations utilisant les données de la *National Hospital Ambulatory Medical Care Survey* et du *National Ambulatory Medical Care Survey* indiquent que 84 000 patients avec un TCC sont vus annuellement dans les cliniques externes des hôpitaux et qu'environ 1,080 million d'individus sont vus dans des bureaux de médecins ou d'autres ressources communautaires de santé. Ainsi, le nombre total de TCC subis annuellement aux États-Unis seulement approcherait les 3,5 millions (Coronado et al., 2012). Malgré tout, ce nombre alarmant ne comprend pas les vétérans, les individus qui n'ont pas recours à une aide médicale ou les hôpitaux militaires.

De manière plus globale, le TCC est actuellement la principale cause d'invalidité et de mortalité dans le monde chez les individus âgés de moins de 45 ans. L'Organisation mondiale de la santé (OMS) rapporte qu'approximativement 10 millions d'individus souffrent d'un TCC annuellement et prévoit que le TCC sera le troisième plus important contributeur d'invalidité et de mortalité dans le monde d'ici 2020 (World Health Organization, 2006). Dans le plus récent rapport du *Center for Disease Control and Prevention,* le phénomène entourant les TCC est décrit comme étant une « épidémie silencieuse » de par l'ampleur des séquelles encourues qui sont la plupart du temps peu détectables (Faul et al., 2010). Avec une prévalence aussi importante, le TCC est un facteur contributif aux décès dans le tiers (30,5 %) des décès par blessure recensés aux États-Unis (Faul et al., 2010). De plus, ce type de blessure est la cause la plus répandue d'invalidité chronique chez la population adulte nord-américaine et une des atteintes neurologiques affichant la plus haute incidence chez les jeunes adultes occidentaux (Hirtz et al., 2007). Chez ces derniers, le TCC constitue la première cause de déficits cognitifs sévères et la première cause de décès (Hirtz et al., 2007). La plupart des TCC qui surviennent annuellement sont des TCC légers (TCCl; 75 %) (Centers for Disease Control and Prevention, 2003) alors que deux fois plus d'hommes que de femmes en sont victimes (Langlois, Rutland-Brown, & Wald, 2006). Les principales causes sont les chutes (28 %), les accidents de véhicules motorisés (20 %), les collisions (20 %) et les agressions (11 %) (Langlois et al., 2006). Finalement, au moins 5,3 millions d'Américains vivent à ce jour avec des handicaps permanents conséquents à un TCC, ce qui engendre des dépenses annuelles moyennes de près de 60 milliards de dollars (Langlois et al., 2006).

1.2 Sévérité des traumatismes craniocérébraux

La sévérité des TCC s'étend sur une échelle allant de « léger », soit une brève altération du statut mental, à « sévère », c'est-à-dire une période prolongée d'inconscience ou d'amnésie suivant le coup à la tête (Centers for Disease Control and Prevention, 2003). L'échelle de Coma de Glasgow (ECG) permet de classifier la sévérité de l'atteinte neurologique en mesurant l'amélioration ou la dégradation de l'état d'un patient dans la phase aigüe d'apparition des dommages cérébraux en plus de prédire le pronostic du patient (Teasdale &

Jennett, 1974). En observant les mouvements d'ouverture des yeux, la réponse aux commandes motrices et aux commandes verbales, un résultat global issu de ces trois catégories fournit un indice de la sévérité du TCC. Cette atteinte neurologique est qualifiée de sévère lorsque le résultat à l'ECG est inférieur à 8, modérée entre 9 et 12 et légère entre 13 et 15. Un TCC léger est ce qui est retrouvé dans la majorité des cas lorsque la blessure survient pendant la pratique d'un sport.

1.3 Commotions cérébrales du sport: Définition, symptomatologie et prévalence

Le terme commotion cérébrale est réservé aux TCC survenant dans un contexte sportif et se définit comme un processus pathophysiologique complexe affectant le cerveau et résultant d'un impact direct ou indirect à la tête pouvant être induit par un mouvement d'accélération/décélération linéaire ou rotationnelle (McCrory et al., 2013). Toutefois, les termes commotion cérébrale et TCCl sont parfois utilisés de manière interchangeable (Dimou & Lagopoulos, 2014), bien que plusieurs auteurs considèrent ces deux phénomènes comme étant distincts (McCrory et al., 2013). Pour ces auteurs, une commotion cérébrale serait un sous-type de traumatismes crâniens (McCrory et al., 2013) et cette distinction terminologique a été récemment établie. Ainsi, dans la présente thèse, le terme TCC léger est utilisé lorsque la blessure survient dans un contexte non sportif alors que le terme commotion cérébrale est utilisé pour qualifier les atteintes cérébrales survenant dans un contexte sportif.

Lors du quatrième *Consensus Statement on Concussion in Sport*, les composantes cliniques et biomécaniques établies lors des précédents regroupements (Aubry et al., 2002; McCrory et al., 2005; McCrory et al., 2009), ont été débattues afin de préciser la définition d'une commotion cérébrale et comprennent les éléments suivants :

1. Une commotion cérébrale peut être causée par un impact direct à la tête, le visage, le nez ou indirectement par un transfert cinétique d'énergie à la tête.
2. Une commotion cérébrale se traduit généralement par l'apparition rapide et de courte durée d'une altération du statut mental et des fonctions neurologiques qui se résorbent

spontanément. Toutefois, dans certains cas, l'altération du statut mental et des fonctions neurologiques peut durer de quelques minutes à quelques heures.

3. Une commotion cérébrale peut engendrer des changements neuropathologiques bien que les symptômes aigus reflètent davantage un dysfonctionnement fonctionnel plutôt que structurel. De fait, aucune anomalie n'est détectable dans les études utilisant les méthodes d'imagerie structurelle standards (tomodensitométrie cérébrale ou imagerie par résonance magnétique standard).
4. Une commotion cérébrale provoque un ensemble de symptômes cliniques pouvant impliquer une perte de conscience sans que ce symptôme ne soit nécessaire. La résorption des symptômes cognitifs et cliniques s'effectue graduellement. Cependant, il est important de noter que dans certains cas, la résorption des symptômes peut être prolongée.

Cette blessure engendre donc une variété de symptômes cognitifs (sensation d'être au ralenti, avoir les idées embrouillées, difficulté de concentration, amnésie rétrograde et/ou antérograde), émotionnels (tristesse, irritabilité, anxiété, labilité émotionnelle) et physiques (fatigue, difficulté d'endormissement, changement dans les habitudes de sommeil, perte d'énergie, nausée, vomissement, problème d'équilibre, engourdissement et/ou picotement, étourdissement, maux de tête, sensation de pression à la tête, sensibilité à la lumière et/ou au bruit) (McCrory, et al., 2013). Par ailleurs, bien que la commotion cérébrale ait été auparavant associée à une perte de conscience et que celle-ci ait longtemps été nécessaire au diagnostic, les études actuelles suggèrent que seulement 10 % des individus souffrant d'une commotion cérébrale vont avoir une période plus ou moins prolongée de perte de conscience (Ellemberg, Henry, Macciocchi, Guskiewicz, & Broglio, 2009). Cette brève perte de conscience serait le résultat d'une force rotationnelle appliquée à la jonction du cerveau moyen supérieur (*upper mid-brain*) et du thalamus, causant ainsi une perturbation transitoire du fonctionnement du système réticulaire responsable du maintien du niveau d'alerte (Dimou & Lagopoulos, 2014). Les symptômes les plus fréquents d'une commotion cérébrale seraient la présence de maux de tête, de fatigue, d'un ralentissement psychomoteur, d'irritabilité, de troubles de l'équilibre, de difficultés de concentration et de déficits mnésiques (Cantu, 1996). Cependant, les symptômes qui caractérisent le plus la commotion cérébrale sont la présence de confusion, ainsi qu'une amnésie pour l'incident et/ou pour les évènements qui le précèdent ou le suivent (McCrory et

al., 2013). Ces symptômes se résorbent habituellement au cours d'une période de sept à dix jours chez les adultes, bien que cette période puisse être plus longue chez les enfants et les adolescents (McCrory et al., 2013). Toutefois, chez environ 10 à 15 % des athlètes, les symptômes post-commotionnels vont perdurer au-delà de la fenêtre normale d'environ 7 à 10 jours, bien que la prévalence exacte demeure ambigüe. Lorsque les symptômes persistent au-delà de trois mois, il est alors question d'un syndrome post-commotionnel (SPC) (Bigler, 2008; Williams, Potter, & Ryland, 2010). Finalement, chez approximativement 10 à 20 % des athlètes ayant un diagnostic de SPC, les symptômes vont persister pour plusieurs mois, voire un an après la commotion (Broshek, De Marco, & Freeman, 2015; Lovell, 2008). Il est alors question d'un syndrome post-commotionnel persistant qui suggère la présence possible d'altérations fonctionnelles permanentes (Bigler, 2008). La nature des mécanismes pathologiques menant à une persistance des symptômes est encore inconnue, démontrant ainsi l'importance de mieux comprendre l'étiologie et les mécanismes neuronaux impliqués afin de prévenir une chronicisation des symptômes.

La présence d'une symptomatologie variée et parfois persistante chez ces athlètes contraste avec l'absence d'anomalies anatomiques observées avec les méthodes traditionnelles d'imagerie cérébrale (McCrory et al., 2013). Cette divergence fait en sorte que la décision de retourner un athlète au jeu constitue un défi considérable pour les équipes médicales traitantes. Cette décision est d'autant plus complexe qu'elle doit prendre en considération la susceptibilité accrue de ces athlètes de subir d'autres commotions cérébrales (Guskiewicz et al., 2003) ainsi que l'augmentation de la sévérité des symptômes post-commotionnels et du temps de récupération si un nouvel impact survient (Collins et al., 2002; Guskiewicz et al., 2003). Plus inquiétant encore est le risque de conséquences sévères pouvant résulter d'une nouvelle commotion alors que l'athlète est encore symptomatique, pouvant même entraîner la mort de l'athlète (Cantu, 1998). Ce grave, mais rare, incident, plus communément appelé le syndrome du second impact (Cantu, 1998), représente sans contredit le phénomène le plus parlant de la sévérité des conséquences d'un traumatisme crânien dans le cadre d'un évènement sportif, bien que ce phénomène demeure controversé. Lorsque l'athlète subit un nouvel impact alors qu'il est encore symptomatique, pouvant même être de moins grande intensité que le premier, une série de réactions cellulaires potentiellement catastrophiques pour l'athlète est provoquée (Wetjen, Pichelmann, & Atkinson, 2010). En effet, après le premier

épisode traumatique, le cerveau serait dans un état de vulnérabilité métabolique, qui dans l'éventualité d'un second choc à la tête, précipiterait une chaîne de réactions chimiques pouvant mener à un œdème cérébral soudain et fatal. Les autopsies suggèrent par ailleurs que le second impact produit un effet synergétique sur la pathologie initiale, qui elle-même prédispose le cerveau à une réponse accentuée. L'enflement cérébral diffus qui s'en suit peut ultimement mener à la mort de l'athlète, car cette condition se prête peu aux interventions neurochirurgicales (Toledo et al., 2012).

Les commotions cérébrales du sport représentent la cause la plus prévalente de traumatisme crânien léger avec une prévalence annuelle estimée entre 1,6 et 3,8 millions aux États-Unis seulement (Langlois et al., 2006) bien qu'il semble que ce nombre soit encore grandement sous-estimé (Bailes & Cantu, 2001; Langlois et al., 2006). À ce chapitre, une étude menée par McCrea et collaborateurs (2004) montre que seulement 47,3 % des athlètes de niveau secondaire ayant subi une commotion cérébrale ont rapporté leur blessure. Les athlètes n'ayant pas rapporté leur commotion considéraient leurs symptômes comme n'étant pas assez sévères. Au niveau professionnel (Ligue Canadienne de Football), une étude de Delaney et collaborateurs (2000) a montré que seulement 18,8 % des 44,8 % des joueurs de football qui ont subi une commotion ont rapporté leur blessure. Ainsi, la prévalence importante ainsi que les conséquences délétères qui peuvent survenir font ressortir l'importance de mieux comprendre la biomécanique d'une commotion cérébrale et les mécanismes impliqués pour assurer une meilleure compréhension du phénomène et une prise en charge adaptée.

1.4 Biomécanique d'une commotion cérébrale

Une commotion cérébrale implique un transfert instantané d'énergie cinétique et résulte des mouvements du cerveau à l'intérieur de la boîte crânienne (Echemendia, 2006; Shaw, 2002). La compréhension de la biomécanique d'une commotion cérébrale implique nécessairement une compréhension de la composition physiologique du cerveau et de sa position à l'intérieur du crâne. Anatomiquement, le cerveau baigne à l'intérieur de la boîte crânienne dans l'espace sous-arachnoïdien qui protège le cerveau et qui est rempli de liquide

céphalo-rachidien (LCR) permettant d'empêcher le cerveau d'entrer en collision contre les parois du crâne lors des déplacements de la tête (Bear, Connors, & Paradiso, 2007; Kandel, Schwartz, & Jessell, 2000). Cependant, lorsque l'énergie cinétique appliquée à la tête excède les propriétés gélatineuses du LCR, le cerveau va entrer en contact avec les os du crâne, ce qui va entraîner une distorsion, une compression et/ou une déformation des tissus nerveux (Shaw, 2002). L'énergie cinétique tend à excéder les capacités protectrices du LCR lorsque la vitesse du cerveau est moindre que celle du crâne (accélération) ou lorsque la boîte crânienne ralentit abruptement alors que le cerveau continue de se déplacer à la même vitesse (décélération) (Shaw, 2002). Le cerveau heurte alors violemment les parois crâniennes et différents principes biomécaniques peuvent induire un traumatisme crânien.

Coup et contre-coup: Les mouvements d'accélération et de décélération entraînent le phénomène du coup/contre-coup (Ommaya, Goldsmith, & Thibault, 2002). Au moment de l'impact, le cerveau s'écrase au point de collision (coup) en s'arrachant diamétralement au point opposé. Lors du retour à l'équilibre, le cerveau va s'écraser du côté opposé au site de l'impact (contre-coup) en s'éloignant du point de choc (Shaw, 2002). L'action de tendre les muscles du cou avant un impact a ainsi pour avantage de limiter l'ampleur du mouvement de la tête et de permettre une dispersion de l'énergie cinétique à travers l'ensemble du corps au lieu d'être totalement absorbée par le cerveau, ce qui évite un grand nombre de commotions au football (Cantu, 1992; Ropper & Gorson, 2007). Le coup/contre-coup peut également survenir en l'absence d'impact direct à la tête par un changement abrupt d'inertie (Shaw, 2002), pouvant provoquer une commotion cérébrale tout aussi sévère que celles résultant d'un impact direct (Barth, Freeman, Broshek, & Varney, 2001).

Vecteurs de force linéaire et rotationnelle: Les commotions cérébrales surviennent selon l'un des deux vecteurs de forces: linéaire (translationnelle) ou angulaire (rotationnelle). Un vecteur de force linéaire est transféré à travers le cerveau selon une ligne droite passant par le centre de la tête et peut provoquer la compression ou l'étirement des tissus neuronaux (Shaw, 2002). Cette situation survient lorsque deux athlètes entrent en collisions de front ce qui crée un déséquilibre entre les forces d'inertie linéaire transportées par chaque adversaire (Broglio et al., 2009; Greenwald, Gwin, Chu, & Crisco, 2008). En revanche, un transfert d'énergie cinétique angulaire peut provoquer une rotation du cerveau autour de son axe central

(Echemendia, 2006), par exemple, lorsqu'un athlète est frappé par un adversaire de biais (Broglio et al., 2009). L'application de ce vecteur de force latérale est plus à risque de provoquer une commotion cérébrale compte tenu de l'inter-connectivité des os, des muscles et des tissus connectant la tête, le nez ainsi que la partie supérieure du torse (Echemendia, 2006). Il peut s'en suivre des déchirures, des compressions et des étirements des tissus neuronaux (Echemendia, 2006).

Lésions axonales diffuses (LAD): La compréhension des effets des commotions cérébrales ne peut se limiter aux mouvements de déformations du cerveau et doit s'élargir aux conséquences qui s'en suivent, notamment les LAD. Ces lésions touchent particulièrement les axones situés de manière perpendiculaire aux vecteurs de force en jeu et sont plus susceptibles de survenir lorsque le cerveau subit une accélération angulaire autour de son axe central (Johnson, Stewart, & Smith, 2013; Ommaya et al., 2002) bien que la pathophysiologie responsable des LAD soit encore méconnue (Ducreux, Huynh, et al., 2005). La présence d'une gaine de myéline autour des tissus de MB entraîne une disparité dans la rigidité des tissus de MB et de MG, et bien que la myéline permette d'augmenter la vitesse de conduction à l'intérieur de la MB, elle rend également ces tissus plus rigides, et donc plus vulnérables aux LAD (Ducreux, Huynh, et al., 2005; Ducreux, Nasser, Lacroix, Adams, & Lasjaunias, 2005). Les LAD reflèteraient donc la vulnérabilité sélective des faisceaux de matière blanche aux mécanismes biomécaniques impliqués dans une commotion cérébrale (Johnson et al., 2013). Ces atteintes ont été documentées pour les différentes sévérités d'un traumatisme crânien, mais pourraient représenter un substrat pathologique clé du TCC léger et de la commotion cérébrale. Pathologiquement, les LAD peuvent sous-tendre plusieurs anomalies, telles qu'une rupture mécanique du cytosquelette axonal, une interruption du transport axonal, ou un enflement des axones (Johnson et al., 2013). La dégénérescence axonale qui en résulte semble être chronique et de récentes études ont suggéré que les traumatismes crâniens peuvent précipiter un processus neurodégénératif, en partie dû à cette dégénérescence des axones (Chen, Johnson, Uryu, Trojanowski, & Smith, 2009). Bien que des examens histopathologiques post-mortem soient nécessaires afin de confirmer la présence de LAD, de plus en plus d'études démontrent l'utilité de l'imagerie du tenseur de diffusion (DTI) dans l'évaluation de l'intégrité de la matière blanche *in vivo* (Henry, 2014). Le fonctionnement et

l'utilité du DTI dans l'investigation des effets des commotions cérébrales sont discutés plus loin.

1.5 Cascade neurométabolique

Les travaux de Giza et Hovda (2001) ont fortement contribué au développement d'une compréhension des changements neurométaboliques qui sous-tendent les processus pathophysiologiques d'une commotion cérébrale et continuent de faire l'objet d'investigations (Barkhoudarian, Hovda, & Giza, 2011). Immédiatement après que l'athlète ait subi un coup à la tête d'intensité suffisante afin de provoquer une commotion cérébrale, une cascade neurométabolique s'enclenche dans le cerveau de l'athlète. Cette série d'évènements débute avec des dépolarisations non spécifiques massives et l'enclenchement de plusieurs potentiels d'action. Il s'en suit une libération accrue et incontrôlée de neurotransmetteurs excitateurs (glutamate), et ce immédiatement après la commotion. La liaison des neurotransmetteurs excitateurs aux récepteurs N-Methyl-D-aspartate (NMDA) entraine à son tour une plus grande dépolarisation neuronale impliquant les ions potassium (K^+) et calcium (Ca^{2+}). Étant donné cette perturbation des gradients ioniques, les pompes ioniques du sodium (Na^+) et du K^+ sont activées dans une tentative de restaurer le potentiel de la membrane au repos, ce qui nécessite environ deux tiers des ressources énergétiques du cerveau dans des conditions normales (Yoshino, Hovda, Kawamata, Katayama, & Becker, 1991). Les pompes Na^+ et K^+ utilisent d'importantes quantités d'adénosine triphosphate (ATP), une molécule essentielle qui fournit par hydrolyse l'énergie nécessaire aux réactions chimiques du métabolisme. Ces évènements ont pour conséquence d'augmenter drastiquement la consommation de glucose, le système entre alors dans une phase d'hypermétabolisme dans une tentative de répondre à la forte demande d'ATP. Cet hypermétabolisme survient conjointement à une diminution du flux cérébral sanguin et cette disparité enclenche une crise énergétique cellulaire menant inévitablement à un hypométabolisme chez l'athlète. Cette série d'évènements pourrait contribuer à la vulnérabilité accrue d'un athlète commotionné en phase aigüe d'être victime d'une nouvelle commotion compte tenu de l'épuisement des ressources disponibles. Cette période de dépression neurométabolique tend à retourner graduellement à la normale à

l'intérieur de 7 à 10 jours post-commotion. Cette fenêtre temporelle concorde généralement avec la période de rétablissement des symptômes (McCrea et al., 2003; McCrory et al., 2013), ce qui suggère un rôle de la perturbation métabolique dans la symptomatologie aigüe.

Bien que cette hypothèse explicative soit pertinente, la cascade neurométabolique ne permet pas d'expliquer les différences entre les athlètes masculins et les athlètes féminines quant aux symptômes post-commotionnels ou encore la présence de symptômes chroniques dans certains cas. La prochaine section traite des différences relevées dans la littérature en traumatologie sportive entre les deux sexes.

1.6 Commotions cérébrales du sport : Différence entre les hommes et les femmes

La participation féminine dans les sports individuels et collectifs a connu une forte augmentation dans les dernières années. Il y a maintenant plus de 186 000 athlètes féminines dans les équipes du *National Collegiate Athletic Association* (NCAA) (Zgonc, 2010) et plus de 3 millions au sein des équipes sportives des écoles secondaires américaines (National Federation of State High School Associations, 2011). Des études épidémiologiques ont démontré qu'autant au niveau universitaire (Covassin, Swanik, & Sachs, 2003a, 2003b; Gessel, Fields, Collins, Dick, & Comstock, 2007; Hootman, Dick, & Agel, 2007) que secondaire (Gessel et al., 2007; Lincoln et al., 2011; Marar, McIlvain, Fields, & Comstock, 2012), les athlètes féminines sont plus à risque de subir une commotion que leurs confrères masculins (voir Dick, 2009 pour une revue de la littérature). Ce risque plus élevé chez les athlètes féminines demeure présent même en comparant des sports équivalents en terme de règles et de pratiques entre les deux sexes, par exemple le soccer ou le basketball (Gessel et al., 2007; Lincoln et al., 2011; Marar et al., 2012). Par ailleurs, ces données épidémiologiques diffèrent de celles de la population générale où les hommes sont deux fois plus à risque (Langlois et al., 2006).

Plusieurs hypothèses explicatives ont été élaborées afin de clarifier ces incidences différentes entre les hommes et les femmes dans le domaine du sport. Au niveau

physiologique, les athlètes féminines, contrairement aux athlètes masculins, présentent une diminution de la circonvolution du cou qui pourrait entrainer une augmentation de l'accélération angulaire lors de l'impact (Barth et al., 2001; Tierney et al., 2008; Tierney et al., 2005), augmentant ainsi les chances de provoquer une commotion cérébrale (Echemendia, 2006). Les femmes présentent également une force cervicale nettement moindre que celle des hommes, ce qui entraînerait une moins grande capacité d'absorber les coups (Garces, Medina, Milutinovic, Garavote, & Guerado, 2002; Tierney et al., 2005). Une récente méta-analyse a également démontré que les femmes ont un moins grand volume de liquide céphalo-rachidien dans le cerveau comparativement aux hommes (Ruigrok et al., 2014), ce qui offrirait une protection moins efficace afin d'absorber les chocs à la tête et empêcher le cerveau d'entrer en contact avec la boîte crânienne. Finalement, une autre hypothèse explicative, plus spécifique au soccer, stipule que les joueuses de soccer ont une différence de ratio ballon-tête plus grande qui pourrait les prédisposer davantage aux commotions cérébrales (Barnes et al., 1998).

Au plan hormonal, il existe des contradictions dans la littérature scientifique quant à l'effet néfaste ou protecteur de l'estrogène, l'hormone féminine primaire. Les recherches animales ont démontré que des traitements d'estrogène avant l'induction d'un TCC ont un effet protecteur chez les rats mâles (Chen et al., 2009; Emerson, Headrick, & Vink, 1993) alors qu'ils ont des effets néfastes chez les femelles (Emerson, et al., 1993). L'effet délétère de l'estrogène pourrait être causé par les récepteurs impliqués dans l'altération du métabolisme énergétique (Emerson, et al., 1993) ou encore en raison de la réponse de potentialisation de l'estrogène aux acides aminés excitateurs (Smith, 1989). D'autres études n'ont trouvé aucun effet délétère à l'estrogène suivant un TCC chez l'animal (Bruce-Keller et al., 2007). De nouvelles recherches demeurent nécessaires afin d'établir s'il existe un lien entre les hormones et les commotions cérébrales.

En plus d'une incidence différente, les deux genres diffèrent également quant aux conséquences suivant une commotion cérébrale, nécessitant ainsi une prise en charge différente (Covassin, Elbin, Crutcher, & Burkhart, 2013). Sur le plan neuropsychologique, les athlètes féminines sont davantage affectées que les athlètes masculins aux tâches de temps de réaction simples et complexes (Broshek et al., 2005; Colvin et al., 2009) ainsi qu'aux tâches mnésiques visuelles (Covassin, Elbin, Larson, & Kontos, 2012; Covassin, Schatz, & Swanik,

2007). Cependant, d'autres études ont démontré que les deux sexes diffèrent lors des évaluations pré-saison (Barr, 2003; Covassin et al., 2006; Shehata et al., 2009) démontrant ainsi l'importance d'acquérir des données propres à chaque sexe afin d'assurer un suivi approprié des athlètes.

Sur le plan symptomatologique, des études suggèrent que les athlètes féminines présentent un plus grand nombre de symptômes post-commotionnels dans la phase aigüe et qu'elles nécessitent plus de temps afin de se rétablir d'une commotion cérébrale (Baker et al., 2015; Bazarian, Blyth, Mookerjee, He, & McDermott, 2010; Berz et al., 2013; Broshek et al., 2005; Colvin et al., 2009; Covassin et al., 2012; Preiss-Farzanegan, Chapman, Wong, Wu, & Bazarian, 2009). À ce propos, une méta-analyse réalisée par Farace et Alves (2000) a démontré que les femmes qui subissent un TCC présentent des conséquences plus néfastes que les hommes sur 85 % des variables mesurées, notamment les symptômes post-commotionnels incluant les maux de tête, les étourdissements, l'anxiété, la fatigue ainsi que les troubles de concentration et de mémoire. Une autre revue de la littérature a identifié le sexe féminin comme étant un facteur de vulnérabilité significatif au développement de symptômes post-commotionnels persistants (King, 2014). Plusieurs raisons peuvent expliquer ce nombre plus élevé de symptômes chez les athlètes féminines. Des facteurs neurobiologiques tels qu'un taux de circulation cérébrale sanguine et un métabolisme du glucose plus élevés (Esposito, Van Horn, Weinberger, & Berman, 1996; Ruigrok et al., 2014) pourraient expliquer cette symptomatologie plus sévère en exacerbant la cascade neurométabolique (Covassin & Elbin, 2011). La diminution du flux cérébral sanguin et l'augmentation de la demande métabolique à la suite d'un TCC (Giza & Hovda, 2001) entreraient en interaction avec une demande métabolique à la base plus élevée chez les femmes qui conduirait à une exacerbation des symptômes (Broshek et al., 2005). Toutefois, ces résultats doivent être interprétés avec prudence compte tenu des différences dans les symptômes auto-rapportés lors des évaluations pré-saison pour lesquels les athlètes féminines rapportent un plus grand nombre de symptômes (Covassin et al., 2006; Shehata et al., 2009). En effet, elles sont davantage portées à rapporter des symptômes associés à une commotion cérébrale lors de l'évaluation pré-saison que les athlètes masculins (voir Brown et collaborateurs (2015) pour une revue de la littérature). Ces incohérences dans la divulgation des symptômes et le manque de consensus quant au rôle du

sexe dans la gestion des commotions cérébrales démontrent l'importance d'investiguer les conséquences post-commotionnelles spécifiques à chacun des sexes.

1.7 Effets à long terme des commotions cérébrales

Au cours de la dernière décennie, de nombreuses études se sont intéressées aux effets à long terme des commotions cérébrales multiples. En plus d'augmenter la susceptibilité de subir une nouvelle commotion cérébrale chez un joueur ayant un historique de commotions cérébrales (Broshek & Freeman, 2005), de récentes données suggèrent une association entre un historique de commotions cérébrales multiples et le développement de troubles cognitifs chroniques et/ou de maladies neurodégénératives (McCrea, Broshek, & Barth, 2015). Ainsi, il a été postulé que les commotions cérébrales ou même le fait de subir des coups répétés d'intensité sous-cliniques à la tête épuiseraient la capacité fonctionnelle du cerveau à faire face au vieillissement et diminuerait le seuil de développement de troubles neurodégénératifs et de démence (Bigler, 2013; Lehman, Hein, Baron, & Gersic, 2012; Smith, 2013; Smith, Johnson, & Stewart, 2013). Un syndrome ayant particulièrement attiré l'attention de la communauté scientifique est l'encéphalopathie traumatique chronique (ECT), décrite pour la première fois en 1928 chez des boxeurs professionnels (Martland, 1928). L'ECT est un désordre neurodégénératif qui serait causé par une accumulation de dommages pathophysiologiques au cerveau causés par des traumatismes crâniens subis à répétition (Cantu, 2007; Omalu et al., 2006; Omalu et al., 2005). Les premières manifestations cliniques sont caractérisées par une détérioration marquée de l'attention, la concentration et la mémoire et sont accompagnées d'une désorientation, de vertiges, de maux de tête et des troubles de l'humeur (Sundman, Doraiswamy, & Morey, 2015). Les stades plus avancés sont marqués par des troubles moteurs qui peuvent s'apparenter aux symptômes retrouvés dans la maladie de Parkinson, tels que de la bradykinésie, des troubles de stabilité posturale, ainsi que des symptômes de démence (McKee et al., 2009; Stein, Alvarez, & McKee, 2015; Stern et al., 2011; Sundman et al., 2015). Sur le plan neuropathologique, l'ECT serait caractérisée par la présence d'enchevêtrements neurofibrillaires et l'accumulation de la protéine Tau dans des régions du cerveau qui sont davantage susceptibles d'être endommagées lors d'un TCC (Stein, Alvarez,

et al., 2015). Une autopsie s'avère nécessaire afin de confirmer le diagnostic (Gardner, Iverson, & McCrory, 2014). Bien que la plupart des cas diagnostiqués par des analyses post-mortem des tissus cérébraux aient été répertoriés chez des athlètes professionnels plus âgés (McKee et al., 2009), les symptômes tendent à se manifester plus tôt que les autres troubles neurodégénératifs, avec un âge d'apparition variant entre 30 et 50 ans et le plus jeune cas confirmé d'ECT à 18 ans (Baugh et al., 2012; McKee et al., 2010). L'ECT partage des similitudes avec d'autres maladies neurodégénératives, telles que la maladie d'Alzheimer et la maladie de Parkinson, mais également des différences autant sur le plan de la présentation clinique que des marqueurs neuropathologiques (Bailes, Turner, Lucke-Wold, Patel, & Lee, 2015). Ceci rend le diagnostic différentiel d'autant plus difficile entre l'ETC et les autres troubles neurocognitifs qui ont également une prévalence plus élevée chez les athlètes multi-commotionnés. En effet, des études épidémiologiques ont démontré une prévalence de 20 % plus élevée chez des joueurs de la Ligue Nationale de Football (NFL) en ce qui concerne le développement de troubles cognitifs, de démence et de troubles affectifs incluant l'anxiété et la dépression comparativement à la population générale (Amen, Wu, Taylor, & Willeumier, 2011). De plus, il a été démontré que des athlètes retraités ayant souffert de commotions cérébrales multiples (trois ou plus) ont cinq fois plus de chances de développer un trouble cognitif léger que des athlètes n'ayant jamais subi de commotion cérébrale (Guskiewicz, Marshall, & Bailes, 2005). Un historique de commotions cérébrales multiples est un facteur de risque au développement de la maladie d'Alzheimer (Jordan, 2013) et augmenterait de près de onze fois les chances de développer la sclérose latérale amyotrophique caractérisée par une dégénérescence des motoneurones supérieurs et inférieurs (Chen, Richard, Sandler, Umbach, & Kamel, 2007; Piazza, Sirén, & Ehrenreich, 2004). Il importe ainsi de poursuivre les recherches avec des méthodes d'investigation cérébrale novatrices afin d'identifier les marqueurs neuropathologiques pouvant être à même d'augmenter la susceptibilité d'un athlète à développer ultérieurement ces troubles.

1.8 Méthodes d'investigation des commotions cérébrales

Bien que les méthodes traditionnelles d'imagerie cérébrale telles que l'imagerie par résonance magnétique (IRM) et la tomodensitométrie (CT Scan) puissent être fort utiles dans un contexte clinique (Yuh, Hawryluk, & Manley, 2014), plusieurs limites à ces méthodes persistent. En effet, la tomodensitométrie se montre particulièrement sensible à la présence d'hémorragies intracrâniennes nécessitant une intervention chirurgicale immédiate, ce qui est davantage le cas pour les TCC modérés et sévères, alors que ce type de situations survient très rarement à la suite d'une commotion cérébrale (Yuh et al., 2014). En ce qui touche l'IRM, bien que cette méthode présente une sensibilité supérieure à la tomodensitométrie afin d'identifier des hémorragies ou de petites contusions, l'IRM n'est actuellement pas recommandée dans les lignes directrices quant à la gestion des commotions cérébrales et TCC léger en phase aigüe (Yuh et al., 2014). Cette méthode est davantage recommandée dans le cas de patients qui présentent des TCC légers avec des symptômes ou des déficits persistants (Yuh et al., 2014). De plus, considérant qu'une commotion cérébrale reflète particulièrement une atteinte fonctionnelle et non pas structurelle, la tomodensitométrie et l'IRM sont d'une utilité limitée (Dimou & Lagopoulos, 2014; Yuh et al., 2014). Pour ces raisons, il importe d'utiliser de nouvelles méthodes d'imagerie cérébrale plus sensibles aux perturbations microscopiques à court et à long terme que peut entrainer une commotion cérébrale. Dans cette optique, la spectroscopie par résonance magnétique (SRM) et l'imagerie du tenseur de diffusion (DTI) s'avèrent des méthodes d'investigation cérébrale novatrices permettant de mieux comprendre la pathophysiologie aigüe et chronique d'une commotion cérébrale.

1.8.1 Spectroscopie par résonance magnétique (SRM)

1.8.1.1 Principe de fonctionnement

La SRM permet de quantifier les concentrations des différents métabolites dans les tissus nerveux et s'avère particulièrement utile pour corroborer la présence de dommages axonaux diffus qui peuvent se manifester autant dans la structure physique du neurone que dans sa composition à la suite d'un TCC (Maudsley, 2002; Toga & Mazziotta, 2002). La SRM est une méthode *in vivo* qui fonctionne selon les principes de la résonance magnétique nucléaire

(RMN), c'est-à-dire qu'elle utilise les propriétés des noyaux atomiques afin d'absorber le rayonnement électromagnétique et les radio-fréquences du champ magnétique pour évaluer les propriétés physiques et chimiques des différentes structures (Maudsley, 2002). Avec la SRM, le proton le plus utilisé afin d'obtenir une quantification des métabolites est l'hydrogène (^{1}H) étant donné la grande disponibilité de ce proton dans l'environnement et sa forte sensibilité pour la RMN (Gujar, Maheskwari, Björkman-Burtscher, & Sundgren, 2005). D'un autre côté, l'utilisation de cette méthode d'investigation cérébrale doit être utilisée de manière complémentaire avec l'imagerie par résonance magnétique (IRM) afin d'obtenir un portrait plus précis et global que si la SRM était utilisée seule (Callicott, 2001). L'IRM permet de localiser précisément une structure alors que la SRM permet l'obtention d'un spectre des concentrations des métabolites dont les principaux sont le N-acetyl aspartate (NAA), la choline (Cho), le myo-inositol (mI), la créatine (Cr) et finalement le glutamate et la glutamine (Glx) (Burtscher & Holtas, 2001; Castillo, Kwock, & Mukherji, 1996; Novotny, Fulbright, Pearl, Gibson, & Rothman, 2003). Ces deux méthodes non-invasives permettent donc d'obtenir une cartographie de la concentration des métabolites dans le cerveau. Dans la SRM, les variations chimiques entre les métabolites sont le principal mécanisme qui permet d'obtenir une discrimination spectroscopique entre ces composantes (Maudsley, 2002). En d'autres mots, l'identification des métabolites se fait à partir des caractéristiques de résonance qui leur sont propres, notamment la fréquence sur le spectre. Sur une figure démontrant un spectre métabolique, la fréquence est exprimée en particules par millions (ppm) et se situe sur l'axe des abscisses alors que l'axe des ordonnées représente l'amplitude de chaque métabolite. Il est donc possible d'observer, par exemple, la présence du NAA à une fréquence d'environ 2,0 ppm, la créatine a une fréquence près de 3,03 ppm alors que la choline est visible à une fréquence approximative de 3,2 ppm (Gujar et al., 2005). En exprimant les fréquences de manière normalisée sur une échelle en ppm, il est alors possible d'effectuer des comparaisons de différents spectres malgré l'utilisation d'un champ magnétique de force différente.

1.8.1.2 Mesures et marqueurs

Étant donné les caractéristiques de cette méthode d'imagerie, la SRM permet de mieux comprendre les altérations biochimiques suivant une commotion cérébrale. Au niveau théorique, chaque métabolite sur le spectre est présenté à un endroit précis sur l'axe des

abscisses et fournit des informations spécifiques sur l'activité neuronale du cerveau (Maudsley, 2002). En effet, le NAA, qui est le métabolite le plus saillant, est considéré comme un marqueur de l'intégrité neuronale (Castillo et al., 1996). Une diminution du NAA peut donc être interprétée comme étant le signe d'une perte ou d'un dommage neuronal. Le myo-inositol représente un marqueur de l'état des cellules gliales et est un osmolyte important (Burtscher & Holtas, 2001), alors que le glutamate/glutamine donne des informations sur l'état de la neurotransmission excitatrice (Maudsley, 2002). Finalement, la créatine est un marqueur du niveau d'énergie du métabolisme cérébral (Castillo et al., 1996; Maheshwari, Fatterpekar, Castillo, & Mukherji, 2000). Ce métabolite demeure très stable même pour les populations présentant différentes pathologies, ce qui fait en sorte que la créatine est souvent utilisée comme un standard afin d'établir des ratios avec les autres métabolites (Burtscher & Holtas, 2001; Castillo et al., 1996; Maheshwari et al., 2000; Rubaek Danielson & Ross, 1999).

1.8.1.3 SRM et commotions cérébrales

Avec la venue de cette méthode d'investigation, quelques études ont évalué l'impact spécifique des commotions cérébrales sur le métabolisme cérébral des athlètes à court et à long terme. L'étude d'Henry et collaborateurs (2010) a mis en évidence des changements à la suite d'une commotion cérébrale chez des joueurs de football américain, soit une diminution du taux de NAA dans le cortex préfrontal dorsolatéral (CPDL) et le cortex moteur primaire (M1) ainsi qu'une diminution du taux de Glx dans M1, lesquels étaient corrélés avec la sévérité des symptômes subjectifs rapportés par les athlètes commotionnés en phase aigüe. D'autres études ont observé des réductions de la concentration de NAA à l'intérieur d'un mois suivant la commotion cérébrale (Cimatti, 2006; Johnson et al., 2012; Vagnozzi et al., 2010; Vagnozzi et al., 2008). Par ailleurs, une étude a démontré que le rétablissement des concentrations des métabolites tend à différer selon le métabolite en question alors que certaines anomalies neurométaboliques émergent en phase post-aigüe (Henry, Tremblay, Leclerc, et al., 2011). Ces altérations chroniques du métabolisme sont en contradiction avec d'autres études qui démontrent que le rétablissement du taux de NAA suite à une commotion cérébrale semble être complet après une période 30 jours suivant la blessure à la tête, cette période pouvant s'étendre jusqu'à 45 jours avec la survenue d'un nouvel impact (Vagnozzi et al., 2010; Vagnozzi et al., 2008). Cependant, il apparait prématuré de statuer sur le possible

rétablissement neurométabolique complet après seulement 30 à 45 jours, notamment en considérant les atteintes neurophysiologiques présentes plusieurs années après la commotion cérébrale (De Beaumont et al., 2009; Theriault, De Beaumont, Tremblay, Lassonde, & Jolicoeur, 2011). Ces quelques études suggèrent que les commotions cérébrales entraînent des altérations touchant la structure chimique neuronale sensible à la SRM.

1.8.2 Imagerie du tenseur de diffusion (DTI)

1.8.2.1 Principes de fonctionnement

L'imagerie de diffusion est une méthode d'imagerie par résonance magnétique non-invasive permettant d'établir l'intégrité de la matière blanche par l'entremise des propriétés de diffusion de l'eau dans le cerveau (Dimou & Lagopoulos, 2014; Johnson et al., 2013). Le signal de résonance magnétique provient le plus souvent des noyaux d'hydrogène (protons). De fait, comme les tissus biologiques sont notamment constitués d'eau, les protons contenus dans les molécules d'eau contribuent majoritairement au signal obtenu dans l'imagerie de diffusion. Par exemple, les mouvements du liquide céphalorachidien ne sont pas restreints, et donc libres de diffuser dans toutes les directions (diffusion isotropique). En revanche, la mobilité des molécules d'eau dans les tissus biologiques est influencée par la microstructure des tissus. Ainsi, les fibres de matière blanche sont encapsulées dans la myéline, les neurofilaments, les microtubules et la membrane axonale qui restreint la diffusion des molécules d'eau dans la direction de l'orientation de l'axone (diffusion anisotropique) (Sundman et al., 2015). Cette diffusion étant contrainte par les tissus environnants et les obstacles physiques qui limitent et contraignent la mobilité des molécules d'eau, le DTI permet d'obtenir indirectement la position, l'orientation et l'anisotropie des structures fibreuses, notamment de matière blanche du cerveau.

1.8.2.2 Mesures et marqueurs

La principale mesure d'anisotropie, la fraction d'anisotropie (FA), dérive des trois valeurs propres de diffusion des tenseurs ($\lambda_i, i = 1,2,3$) et s'exprime comme suit:

$$FA(D) = \frac{\sqrt{3}}{\sqrt{2}} \frac{\sqrt{(\lambda_1 - \langle\lambda\rangle)^2 + (\lambda_2 - \langle\lambda\rangle)^2 + (\lambda_3 - \langle\lambda\rangle)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

avec

$$\langle\lambda\rangle = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$

Cette mesure représente la forme de l'ellipsoïde de diffusion correspondant au degré de diffusion anisotropique (Amyot et al., 2015) et fournit de l'information sur la direction que prennent les fibres de MB (Toga & Mazziotta, 2002). Ainsi, la FA représente un indice de la cohérence directionnelle, du degré de myélinisation des fibres et du degré de dommages axonaux (Yang, Nucifora, & Melhem, 2011).

La diffusivité moyenne (DM) est une mesure globale des déplacements des molécules d'eau dans un voxel et a l'avantage d'être indépendante de l'orientation donnée au cadre de référence. La DM se définit comme suit:

$$DM = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$

Cet indice mesure la magnitude de la diffusion et une diminution de FA combinée à une augmentation de la DM seraient des indicateurs d'une altération de la matière blanche (Sundman et al., 2015).

D'un autre côté, la diffusion axiale (DA) est simplement λ_1, la valeur propre de diffusion parallèle à l'axone alors que la diffusion radiale (DR) représente la moyenne des deux valeurs propres de diffusion perpendiculaires à l'axone et s'exprime ainsi:

$$DR = \frac{\lambda_2 + \lambda_3}{2}$$

La DA et la DR seraient respectivement des indicateurs de l'intégrité de l'axone et de la myéline (Wheeler-Kingshott & Cercignani, 2009).

1.8.2.3 DTI et commotions cérébrales

L'imagerie du tenseur de diffusion a été utilisée dans un nombre important d'études en traumatologie sportive qui ont démontré des altérations microstructurales autant à court terme

qu'à long terme à la suite d'une commotion cérébrale (Sundman et al., 2015). Contrairement aux sujets contrôles, une diminution de la FA dans le corps calleux et la capsule interne ainsi qu'une augmentation du coefficient de diffusion apparent (CDA), une des mesures globales de diffusion semblable à la diffusivité moyenne, chez des boxeurs révèlent des atteintes dans les réseaux de MB (Zhang, Heier, Zimmerman, Jordan, & Ulug, 2006). Une étude ultérieure a également répliqué l'augmentation du CDA chez un groupe de boxeurs multi-commotionnés et la diminution de la FA dans la MB en plus d'observer une diminution du CDA dans la MG corticale (Chappell et al., 2006). Ces changements microstructuraux se manifestent par des écarts entre les groupes de 6 à 23 % selon les régions cérébrales (Chappell et al., 2006), suggérant ainsi un patron variable d'altérations des fibres neuronales en fonction des régions étudiées. Récemment, l'utilisation combinée du DTI et de l'IRMf dans une tâche de mémoire de travail a permis d'observer des hyperactivations dans le CPDL gauche pendant une tâche cognitive qui corrèle avec une diminution de la diffusion exprimée par le CDA dans cette même région chez les athlètes commotionnés (Zhang et al., 2010). Par ailleurs, une étude de tractographie a démontré une absence de différence au niveau de la FA et une augmentation de la DM dans plusieurs réseaux de fibres situés dans l'hémisphère gauche, notamment les faisceaux longitudinaux inférieur et supérieur, le faisceau fronto-occipital, la capsule interne, les radiations thalamiques postérieures et les radiations auditives (Cubon, Putukian, Boyer, & Dettwiler, 2011). De plus, les altérations microstructurales reflétées par des variations de la FA et de la DM dans le corps calleux et la voie corticospinale chez des athlètes évalués en phase aigüe sont toujours présentes six mois post-commotion (Henry, Tremblay, Tremblay, et al., 2011), suggérant une persistance des altérations microstructurelles à la suite d'une commotion cérébrale.

1.9 Objectifs expérimentaux et hypothèses

L'objectif principal de cette thèse est d'évaluer les effets à court et à long terme d'une commotion cérébrale avec la spectroscopie par résonance magnétique et l'imagerie du tenseur de diffusion chez des athlètes féminines. Bien que ces méthodes d'imagerie soient de plus en plus utilisées afin de comprendre la pathophysiologie d'une commotion cérébrale, aucune

étude, à notre connaissance, n'a porté spécifiquement sur les athlètes féminines malgré l'augmentation draconienne de la participation féminine dans les sports (National Federation of State High School Associations, 2011; Zgonc, 2010). D'autres facteurs importants viennent renforcer la nécessité d'évaluer les effets des commotions cérébrales chez les athlètes féminines. Ceux-ci incluent notamment le risque accru de souffrir de la maladie d'Alzheimer chez les femmes (Li & Singh, 2014), l'association récente entre un historique de commotions cérébrales et le développement de troubles cognitifs et de maladies neurodégénératives (Guskiewicz et al., 2005, Stein et al., 2015) ainsi que la mise en évidence de conséquences post-commotionnelles plus importantes chez les athlètes féminines (Bazarian et al., 2010; Broshek et al., 2005; Dick, 2009). Ainsi, ces facteurs qui mettent les athlètes féminines à risque de conséquences délétères démontrent clairement l'importance d'acquérir des données sur les spécificités des atteintes chez cette sous-population.

1.9.1 Article 1 : Étude prospective des effets des commotions cérébrales chez des joueurs et des joueuses de hockey au cours d'une saison universitaire

Dans l'article 1, la spécificité des altérations neurométaboliques engendrées par des commotions cérébrales ou des coups d'intensité sous-cliniques à la tête est étudiée chez un groupe de joueurs et joueuses de hockey au cours d'une saison universitaire. Une séance d'imagerie cérébrale comprenant la SRM est réalisée au début et à la fin de la saison universitaire. Dans le cas des athlètes subissant une commotion cérébrale pendant la saison, des séances d'imagerie cérébrale ont également été réalisées 72 heures, 2 semaines et 2 mois post-commotion afin de documenter les changements aigus et sous-aigus. Considérant les études antérieures effectuées auprès d'athlètes commotionnés (Henry et al., 2010; Johnson et al., 2012), les hypothèses suivantes ont été formulées:

1) Des changements dans le métabolisme cérébral des athlètes commotionnés seront observés aux différents temps de mesure et tendront à revenir vers les concentrations pré-saison sans toutefois atteindre ces niveaux.

2) Des patrons neurométaboliques différents seront observés entre les athlètes féminines et les athlètes masculins, démontrant la spécificité des changements métaboliques entre les deux sexes.
3) Les athlètes n'ayant pas subi de commotion cérébrale présenteront également des changements dans leur métabolisme cellulaire compte tenu de l'accumulation de coups d'intensité sous-clinique à la tête au cours d'une saison universitaire.

1.9.2 Article 2 : Effets persistants des commotions cérébrales sur le métabolisme cellulaire et l'intégrité de la matière blanche chez les athlètes féminines

Dans l'article 2, les effets à long terme des commotions cérébrales sur le métabolisme cellulaire et l'intégrité de la matière blanche sont étudiés chez des athlètes féminines asymptomatiques ayant subi une commotion cérébrale il y a plus de 7 mois par l'entremise de la SRM et du DTI. Compte tenu de la présence d'altérations persistantes sur les plans neurophysiologique (De Beaumont et al., 2009; Tremblay, de Beaumont, Lassonde, & Theoret, 2011), neurométabolique (Henry, Tremblay, Leclerc, et al., 2011) et microstructurel (Henry, Tremblay, Tremblay, et al., 2011), les hypothèses suivantes ont été émises

1) Les athlètes commotionnées vont présenter des altérations neurométaboliques persistantes contrairement aux athlètes contrôles.
2) Des altérations microstructurales chez les athlètes commotionnées seront retrouvées dans plusieurs faisceaux de matière blanche.

1.9.3 Article 3 : Spécificité des altérations neurométaboliques, neuropsychologiques et symptomatologiques à court terme et à long terme chez des athlètes féminines commotionnées

Dans l'article 3, la spécificité des atteintes neurométaboliques, neuropsychologiques et symptomatologiques est investiguée chez des athlètes féminines dans les 7 à 10 jours ainsi que six mois suivant une commotion cérébrale. Afin de statuer sur les différences sur le plan du

métabolisme cérébral entre la phase aigüe et chronique, le cortex moteur primaire, le cortex préfrontal dorsolatéral et l'hippocampe des hémisphères gauche et droit ont été identifiés comme régions d'intérêt selon les résultats d'une étude similaire auprès d'athlètes masculins (Henry, Tremblay, Leclerc, et al., 2011). Selon les résultats de cette précédente étude, les hypothèses suivantes ont été émises :

1) Un rétablissement des altérations cognitives et des symptômes post-commotionnels sera observé entre la phase aigüe et chronique chez les athlètes commotionnées.
2) Une persistance des altérations neurométaboliques est attendue six mois post-commotion.

1.9.4 Article 4 : Investigation des altérations microstructurales chroniques d'une commotion cérébrale par l'utilisation de paramètres de diffusion variés.

Dans l'article 4, les altérations microstructurales de la voie corticospinale et du corps calleux sont investiguées par l'entremise de paramètres de diffusion variés comprenant les paramètres traditionnels (FA, DM, DA, DR), mais aussi d'autres paramètres de diffusion (mode, volume). Ces deux faisceaux d'intérêt ont été sélectionnés selon les résultats d'études antérieures (Caeyenberghs et al., 2011; Henry, Tremblay, Tremblay, et al., 2011; Johnson et al., 2012; Rutgers et al., 2008). De plus, une subdivision du corps calleux a été réalisée afin de déterminer s'il existe une vulnérabilité prononcée de certaines régions calleuses aux commotions cérébrales. Les hypothèses suivantes ont été émises :

1) Des altérations microstructurales sont attendues chez les athlètes féminines commotionnées au niveau de la voie corticospinale et du corps calleux.

CHAPITRE 2 ARTICLE 1: A PROSPECTIVE STUDY OF PHYSICIAN-OBSERVED CONCUSSION DURING A VARSITY UNIVERSITY HOCKEY SEASON: METABOLIC CHANGES IN ICE HOCKEY PLAYERS. PART 4 OF 4

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2.1 Abstract

Object. Despite negative neuroimaging findings using traditional neuroimaging methods such as MRI and CT, sports-related concussions have been shown to cause neurometabolic changes in both the acute and subacute phases of head injury. However, no prospective clinical study has used an independent physician-observer design in the monitoring of these changes. The objective of this study was to evaluate the effects of repetitive concussive and sub-concussive head impacts on neurometabolic concentrations in a prospective study of two Canadian Interuniversity Sports (CIS) ice hockey team using MR spectroscopy (MRS).

Methods. Forty-five ice hockey players (25 men and 20 women) participated in this study. All participants underwent pre- and postseason MRI, including spectroscopy imaging, using a 3-T MRI machine. The linear combination model was used to quantify the following ratios: glutamate/creatine-phosphocreatine (Cr), myoinositol/Cr, and N-acetylaspartate (NAA)/Cr. Individuals sustaining a medically diagnosed concussion were sent for MRI at 72 hours, 2 weeks, and 2 months after injury.

Results. No statistically significant differences were observed between athletes who were diagnosed with a concussion and athletes who were not clinically diagnosed as sustaining a concussion. Although no statistically significant longitudinal metabolic changes were observed among athletes who were diagnosed with a concussion, the results demonstrated a predictable pattern of initial impairment, followed by a gradual return to ratios that were similar to, but lower than, baseline ratios. No significant pre- to postseason changes were demonstrated among men who were not observed to sustain a concussion. However, a substantively significant decrease in the NAA/Cr ratio was noted among the female hockey players (t (13) = 2.58, p = 0.02, η (2) = 0.34).

Conclusions. A key finding in this study, from the standpoint of future research design, is the demonstration of substantively significant metabolic changes among the players who were not diagnosed with a concussion. In addition, it may explain why there are few statistically significant differences demonstrated between players who were diagnosed with a concussion and players who were not diagnosed with a concussion (that is, the potency of the independent variable was diminished by the fact that the group of players not diagnosed with a concussion

might be better described as a subgroup of the players who may have sustained a concussion but were not observed and diagnosed with a concussion). This result suggests that definitions of concussion may need to be revisited within sports with high levels of repetitive subconcussive head impacts. Future analysis of these data will examine the relationships between the modes of MRI (diffusion tensor imaging, MRS, and susceptibility-weighted MR imaging) used in this study, along with other more sensitive evaluative techniques. This type of intermodal comparison may improve the identification of concussions that were previously dependent on the unreliable self-reporting of recognized concussion symptomatology by the athlete or on poorly validated neuropsychological tests.

Keywords: Concussion, ice hockey, magnetic resonance imaging, magnetic resonance spectroscopy, sex, Canada

Abbreviations used in this paper: CIS=Canadian Interuniversity Sports; Cr=creatine/phosphocreatine; DTI=diffusion tensor imaging; Glu=glutamate; HCEP=Hockey Concussion Education Project; mI=myoinositol; MRS=magnetic resonance spectroscopy; NAA-*N*-acetylaspartate; SWI=susceptibility-weighted MR imaging

2.2 Introduction

Sports-related concussion is defined as a complex pathophysiological process affecting the brain induced by traumatic biomechanical forces.[22] This injury represents a major public health concern, as the annual prevalence of concussion is estimated to be between 1.6 and 3.8 million individuals in the US alone.[18] However, concussion incidence appears to vary depending on the sport, patient sex, patient age, level of play, and type of exposure (such as time played per athlete, or number of games played per athlete).[19]

Ice hockey is a contact sport that has several inherent features that predispose players to brain injury. Typically, a greater proportion of concussions in ice hockey are reported in men than in women,[19] with incidence rates reported to be as high as 21.5 concussions per 1000 athlete exposures.[10] The results of the Injury Surveillance Study reported by the NCAA demonstrate that women's ice hockey has the second highest rate of concussions of all sports surveyed and the highest rate of concussions among the sports played by both sexes.[1,15]

Interestingly, although female ice hockey players report higher incidence rates of concussion than male players,[1] the impact exposures in women are less frequent and of a lower magnitude.[3] Note that although incidence rate may be useful for the description of player risk, its utility is heavily dependent on factors such as diagnosis criteria for concussion, observation method (whether the games are directly observed or whether the concussions are self-reported), and even observer type (physician vs nonphysician, or independent observer vs team-affiliated observer).[8] Improved concussion screening—ideally in the form of an objectively scored, easily administered physiological measure—would provide a critical source of diagnostic evidence to the first responder that would be useful for medical specialists who are involved in the diagnosis and treatment of sport concussion. Such a screening test would also be useful for determining the most appropriate timeline for return to play, if it were sensitive to important individual differences in sensitivity to brain injury. However, such a test has not yet been validated for this purpose.

The physical, emotional, and cognitive symptoms following a concussion typically resolve after a period of 7–10 days in adults,[20–22] a time window that closely coincides with

the resolution of the neurometabolic cascade following a concussion.[11] These symptoms are transient in the majority of observed cases, but appear in conjunction with the absence of the tissue damage that is visible using standard neuroimaging techniques such as CT and MRI. Studies of individuals who have sustained multiple sport concussions in their past have demonstrated objective evidence of chronic cognitive deficits and disorders.[6,12,24,29] These data emphasize the importance of using the full spectrum of neuroimaging techniques to assess the potential brain alterations following a sport-related concussion.

Magnetic resonance spectroscopy is a neuroimaging technique that could be helpful in the investigation of brain alterations following a concussion, providing insight into the subtle neurophysiological alterations that accompany injury among concussed athletes.[5] Magnetic resonance spectroscopy is a noninvasive technique that allows the detection and quantification of brain metabolites in the brain. Thus, it is a useful tool for detecting neuronal damage and diffuse axonal injury because damage-related changes to neurons are manifest not only in their physical structure, but also in their composition.[28] The principal metabolites are NAA, a marker of neuronal and axonal integrity; Cr, a fairly stable energy marker commonly used as an internal standard; mI, an osmolyte and astrolyte marker; and Glu, a marker of excitatory neurotransmission.

An increasing number of studies of sports-related concussions have focused on brain metabolism changes in the acute phase following a concussion. Studies that assess the acute phase are particularly important[13,14] because the athletes remain symptomatic during this time and experience a period of metabolic vulnerability within the brain tissue known as the "neurometabolic cascade" following a concussion.[11] In the sports trauma literature, decreased levels of NAA have been found in the acute and subacute phases of concussion.[13,14,16,17,30,31] However, the rate of recovery for this metabolite is still equivocal, with some studies findings NAA recovery to baseline levels within a period of 30–45 days after a concussion,[31] and others demonstrating persistent decreases for at least 6 months after concussion.[14] Moreover, the corpus callosum appears particularly vulnerable to neurometabolic disruptions and is a major predictor of predilection to concussion,[26,27] being highly susceptible to the biomechanical forces induced by mild traumatic brain injury.[25] A

recent study has demonstrated lower NAA ratios in the genu and splenium of the corpus callosum in the subacute postinjury phase of concussed athletes.[17] However, another recent study[16] found a significant NAA decrease in the genu of the corpus callosum, but not in the splenium, in combination with a surprisingly greater alteration of the NAA ratio among patients recovering from their first concussion, as compared with athletes sustaining multiple concussions.

Despite recent studies assessing the neurometabolic profile of concussed athletes, few studies have examined the recovery pattern of metabolites following a concussion. Vagnozzi and colleagues[30,31] evaluated athletes at a few time points after injury (3, 15, 22, and 30 days) and determined that concussions open a temporal window of metabolic imbalance. However, the control group was not composed of athletes, and the study population of the 2008 study contained both men and women with a sizeable age range, with no statistical treatment of sex differences. Moreover, this study[31] focused exclusively on NAA recovery. The current literature suggests that there is a need to assess the neurometabolic recovery of multiple metabolites in regions particularly vulnerable to brain injury, notably the corpus callosum, and to take into account possible sex differences for this recovery. Furthermore, it may be important to assess the extent to which there are metabolic changes among individuals with subclinical concussions or those who may have sustained multiple subconcussive blows to the head.

In this study, we sought to investigate the neurometabolic profiles of male and female ice hockey players following a sport-related concussion. To assess changes on the chemical structure of the corpus callosum over time, this study evaluated the concentration of NAA, mI, and Glu relative to Cr during the acute (72 hours) and subacute (2 weeks and 2 months) phases following a concussion. While no differences between groups are suspected at baseline, a significant decrease in NAA/Cr and Glu/Cr, as well as a significant increase in mI/Cr, was hypothesized to occur when athletes sustained clinically diagnosed concussions. Furthermore, a sequential recovery of the 3 metabolites was expected for group of individuals diagnosed with a concussion for each postinjury time point, with ratios approaching (but not reaching) baseline levels. Finally, it was expected that athletes who had not been diagnosed as sustaining

a clinical concussion would demonstrate changes in their metabolite ratios over the course of the season due to multiple nonobserved injuries to the brain occurring as a result of regular play.

2.3 Methods

2.3.1 Participants and Study Protocol

Forty-five ice hockey players (25 men and 20 women) were included in this study. The male players were between 20 and 26 years of age (mean 22.24 years) and the female players were between 18.5 and 37.2 years of age (mean 20.21 years). All participants were part of the HCEP, a cohort study performed during a CIS ice hockey season (2011–2012). The clinical data for this study are described in detail by Echlin et al.[9]

Individuals were excluded from participation in this study if they had a history of central neurological conditions other than head injury, severe cognitive impairment (and/or an inability to consent), a history of pacemaker usage, previous eye surgery, or if they had worked in an environment that exposed them to a risk of having metal fragments embedded in their eyes. Each participant provided written informed consent and a release of medical information at the outset of the study. This study was approved by a university research ethics board.

This study focuses on the MRS analyses, whereas the detailed description and interpretation of concussion incidence and neuropsychological testing, as well as DTI results are presented in other papers within this issue of *Neurosurgical Focus*. Susceptibility-weighted MR imaging results from this study will be published in the near future.

2.3.2 Magnetic Resonance Imaging Protocol and Data Acquisition

Data acquisition was performed using a 3-T MRI machine (Achieva, Phillips) equipped with an 8-channel SENSE head coil array. Each player involved in this study

received a baseline MRI evaluation. Athletes sustaining a concussion underwent further imaging at 72 hours, 2 weeks, and 2 months postinjury.

2.3.3 Magnetic Resonance Spectroscopy

The corpus callosum was chosen as the MRS region of interest because it forms the largest and highest-density commissural white matter bundle in the brain. It also provides interhemispheric connections that project to all cerebral lobes. The corpus callosum is suspected to be highly vulnerable to the biomechanical forces involved with concussion.[7,16,17,26,27,32] The placement of the voxel within the corpus callosum attempted to ensure an adequate distance from the ventricles, fatty tissue, and bone for all patients.

The cognitive demands of playing ice hockey include rapid and effective information transmission in the brain to allow adequate decision-making and execution of complex motor sequences. The examination of metabolite profiles within the corpus callosum may provide evidence of the effects of microstructural alterations within this structure and on transmission processes between the cerebral lobes.

Each patient was placed in the MRI machine and underwent a standard localizer and SENSE calibration scan. Voxels were then applied for the corpus callosum (10 × 20 × 30 mm). Spectroscopic examination was carried out using a PRESS (Point RESolved Spectroscopy) sequence pulse with the following settings: TE 35 msec, TR 2000 msec, 128 acquisitions, and 1024 points, on an 8-channel head coil.

The linear combination model[23] was used for metabolite quantification (see Fig.1 for a reference figure of metabolic analysis). This operator-independent spectral analysis software estimates metabolite concentrations and their ratios relative to Cr using a set of basis reference spectra acquired from individual metabolites on the MR instrument. Concentrations are derived from the areas under the corresponding peaks. *N*-acetylaspartate/Cr, Glu/Cr, and mI/Cr were only analyzed if the estimated uncertainty calculated as Cramer Ratio lower bounds (% SD) was less than 20%. The linear combination model operator was blind to group membership.

2.3.4 Statistical Analysis

Statistical analyses of metabolite ratios (Glu/Cr, mI/Cr, and NAA/Cr) were conducted using SPSS version 20. Due to the small number of concussed individuals in whom we had complete data across the postconcussion time periods, data analysis was performed graphically rather than statistically. Accordingly, the average metabolite ratios were plotted at each time point (baseline, 72 hours, 2 weeks, and 2 months), with error bars representing ± 1 standard error. Individuals who were not diagnosed as having sustained a concussion were evaluated separately for each sex using a series of paired t-tests. Adjustments to the comparison α were performed within each sex using a Bonferroni adjustment; to maintain an overall experiment-wise α of 0.05, each of the 3 comparisons conducted within each sex was made against an α of 0.017 (0.05/3). Finally, a split-plot ANOVA was used to determine the extent to which group membership (individuals diagnosed with a concussion vs those not diagnosed with a concussion) interacted with time course (preseason vs postseason) in predicting each of the 3 metabolite ratios.

2.4 Results

Descriptive statistics for each metabolite ratio at baseline assessment and at each of the 3 postinjury evaluations are presented in Table 1 and depicted graphically in Fig. 2.

Descriptive statistics for the individuals within the sample who were not clinically identified as sustaining a concussion are presented in Table 2 along with the results of the paired t-test calculations. Although none of the t-tests were statistically significant after adjusting for potential inflation of a Type I error due to multiple comparison bias, women appeared to demonstrate a substantively significant decrease in their NAA/Cr ratios over the course of the season ($t_{(13)} = 2.58$, $p = 0.02$, $\eta^2 = 0.34$) that suggests that 34% of the postseason variability on this metabolite was due to subconcussive impacts sustained over the course of the season.

No statistically significant effects were demonstrated for the interaction between group and time for Glu/Cr ($F_{(1,31)} = 2.945$, $p = 0.096$), mI/Cr ($F_{(1,31)} = 0.820$, $p = 0.372$), or NAA/Cr

($F_{(1,31)} = 0.214$, $p = 0.646$), suggesting that seasonal changes did not differ significantly between individuals who were diagnosed with a concussion and individuals who were not diagnosed with a concussion.

2.5 Discussion

The present study is unique in that it is a part of a multidimensional prospective effort (the HCEP) to independently and directly evaluate sport concussion incidence as well as the neuropsychological and multimodal MRI changes in the participant group over one season of CIS varsity hockey. The aim of the present study was to investigate the neurometabolic alterations in the corpus callosum of male and female ice hockey players following a concussion. A second aim of this study was to investigate the metabolite changes of athletes who had not been diagnosed with a concussion over the pre- to postseason time interval. Using MRS, no statistically significant differences were found for any metabolite ratios when comparing athletes diagnosed with a concussion to control athletes.

The most interesting findings within this study were found in female athletes within the group of individuals who were not diagnosed with a concussion. This group demonstrated a decrease in their NAA/Cr ratio over the course of the season. The ratio of each metabolite remained stable in the sample of male athletes who were not diagnosed with a concussion.

The results of the present study do not corroborate the findings of previous researchers, who demonstrated a decrease in the NAA ratio within the acute phase of a concussion.[13,14,31] Several factors could explain the different metabolic profiles found in this study. First, previous studies investigated different regions of interest, notably the frontal regions, the primary motor cortices, and different regions within the corpus callosum where neurometabolic changes were different depending on the regions observed.[13,14] The different metabolites in any given voxel are, in principle, unrelated and uncorrelated.[4] Based on this assumption, it is possible that the neurometabolic alterations observed in previous studies were specific to the cerebral regions examined in those studies and the corpus callosum may not be affected in the acute phase of a concussion, as demonstrated in the current study. It is possible

that there were no effects of concussions on metabolite concentration in the present sample because of the anatomical variation of voxel location. Future studies should examine cortical and subcortical regions following a brain injury to determine the pattern of changes in neurochemistry specific to each region.

Second, the sample in the present study differed from samples used in previous studies. The sample in the study of Vagnozzi et al.[31] was composed of a large age range of men and women from different sports (kickboxing, boxing, soccer, alpine skiing, and rugby), while the studies of Henry et al.[13,14] included only male football players. The heterogeneity of the group who was diagnosed with a concussion combined with a control group composed of nonathletes in the study of Vagnozzi et al.[31] makes it difficult to compare their findings with the results of the present study. Furthermore, the present study found that there were substantively significant differences between preseason and postseason NAA/Cr ratios among the female players. These data suggest that the primary independent variable—the group who was diagnosed with a concussion versus the group who was not diagnosed with a concussion—was of reduced potency.

An interesting finding in the present study is the difference between male and female athletes over the course of the season, and a key variable appears to be NAA/Cr. While relative quantification of metabolite ratios remained stable over the course of one season in male athletes, female athletes showed a decrease in NAA ratios. A recent study demonstrated that female hockey players sustain fewer impacts and suggested that the impacts in which they are involved result in lower head acceleration compared with male athletes.[3] However, female athletes have a higher incidence of concussion than their male counterparts,[1] possibly reflecting a higher sensitivity to head impacts and subconcussive blows sustained during practices and games over the course of one season. This provisional hypothesis is corroborated by a recent DTI study examining multiple subconcussive blows.[2] The sex differences shown in the present research emphasize the importance of assessing the cerebral alterations specific to each sex following a brain injury, as this will allow us to better understand the pathological mechanisms involved in this injury, and ultimately, to ensure a safe return to play for these athletes.

An important limitation of this study, common to most neuroimaging studies, is the small sample size. The small number of participants of both sexes in each group limits the extent to which the current findings can be generalized to all sports practiced by both sexes. The study also lacks a control group of matched participant athletes from a collegiate varsity sport with a low probability of head contact (such as swimming). The latter change is likely to result in an independent variable (group difference) of higher potency and would increase the power of the study.

2.6 Conclusions

Physician observation and diagnosis using current international diagnostic criteria offers a unique design to assess neurochemical changes in the acute and subacute phases of concussion in both men and women ice hockey players.

The nonsignificant differences in metabolic ratios between those players who were clinically diagnosed with a concussion and those individuals who were not identified as sustaining a concussion may be interpreted as evidence of nondiagnosed (and nonobserved) subconcussive neural injuries sustained over a regular season of play. Future analysis of these data will examine the relationships between the modes of MRI (DTI, MRS, and SWI) used in this study, along with other more sensitive evaluative techniques. This type of intermodal comparison may improve the identification of concussions that were previously dependent upon unreliable self-reported concussion symptoms by the athlete, supplemented by poorly validated neuropsychological tests.

This unique and multidimensional prospective study demonstrates a pressing need for follow-up studies using a similar design, involving independent physician and nonphysican observers, within simultaneous multimodal objective investigation.

The potential consequences of sustaining both clinically diagnosed concussions and nondiagnosed recurrent subconcussive blows should be explored temporally. Follow-up studies should also consider further investigation of sex differences in neurochemistry. In

future publications a comparison of the neurochemical changes among subjects should be made to the other objective investigations (such as DTI and SWI) that were simultaneously used. The involvement of larger and more diverse sample groups will allow for a greater generalizability of the findings.

2.7 Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Echlin, Forwell. Analysis and interpretation of data: all authors. Drafting the article: Echlin, Chamard, Skopelja, Forwell, Johnson. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Echlin. Statistical analysis: Echlin, Chamard, Johnson. Administrative/technical/material support: Echlin, Skopelja, Forwell. Study supervision: Theoret, Forwell.

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2.10 Figures

Figure 2.1. Example of a metabolite spectrum

Legend: An example of a metabolite spectrum produced by the linear combination model that was used for metabolite quantification. This operator-independent spectral analysis software estimates metabolite concentrations and their ratios relative to Cr, using a set of basis reference spectra acquired from individual metabolites on the MR instrument. Concentrations are derived from the areas under the corresponding peaks. NAA/Cr, Glu/Cr, and mI/Cr were only analyzed if the estimated uncertainty calculated as Cramer Ratio lower bounds (% SD) was less than 20%. The linear combination model operator was blind to group membership.

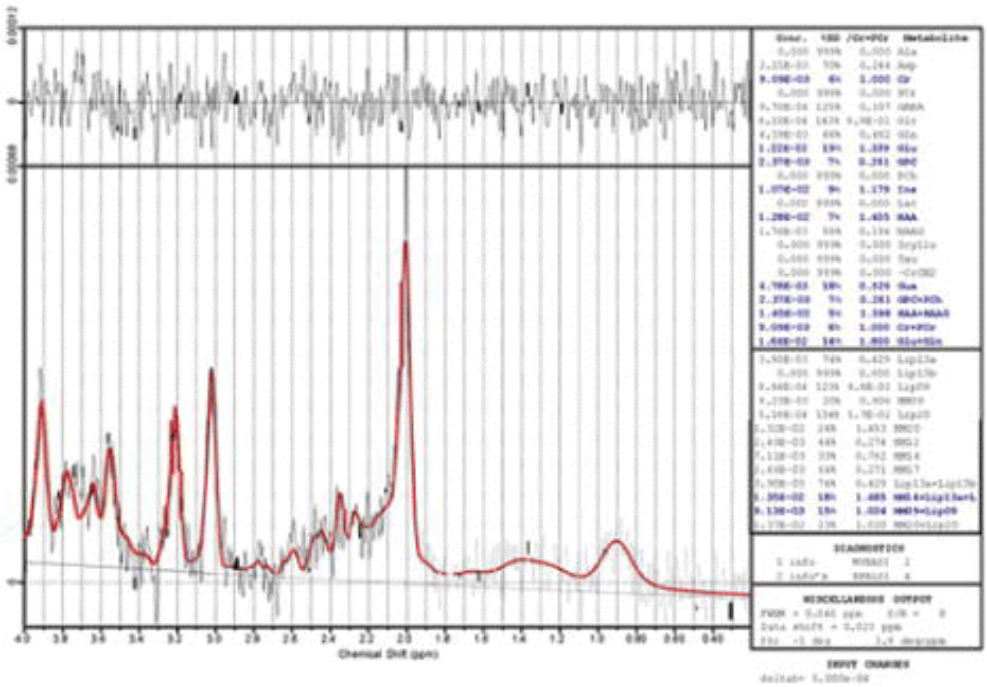
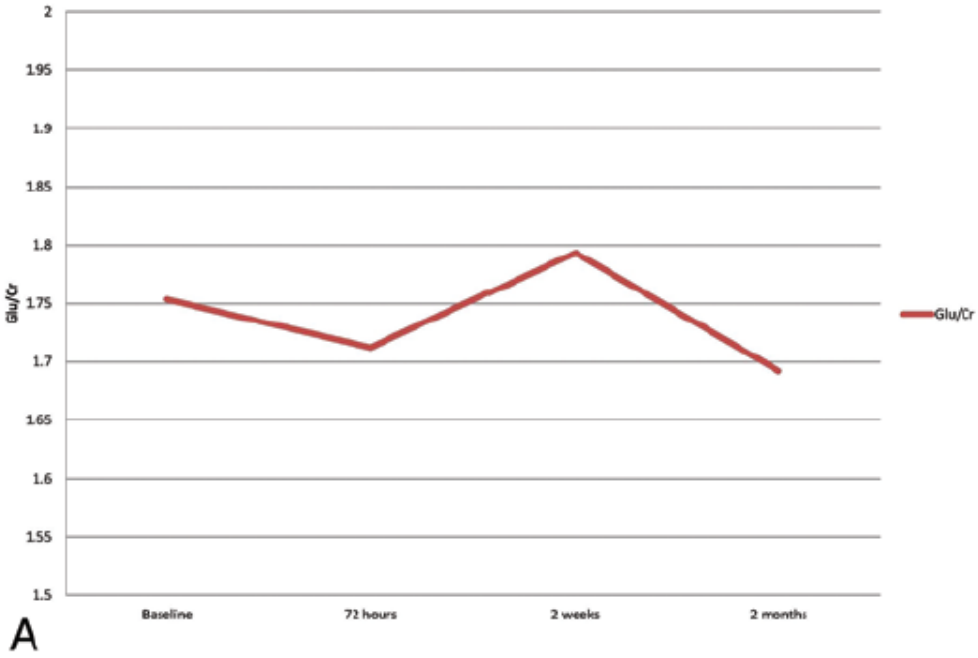


Figure 2-1. Example of metabolite spectrum

Figure 2.2. Temporal concentration relative to Cr

Legend : The temporal concentration of Glu relative to Cr (A), mI relative to Cr (B), and NAA relative to Cr (C) during the acute (72 hours) and subacute (2 weeks and 2 months) phases following a concussion.



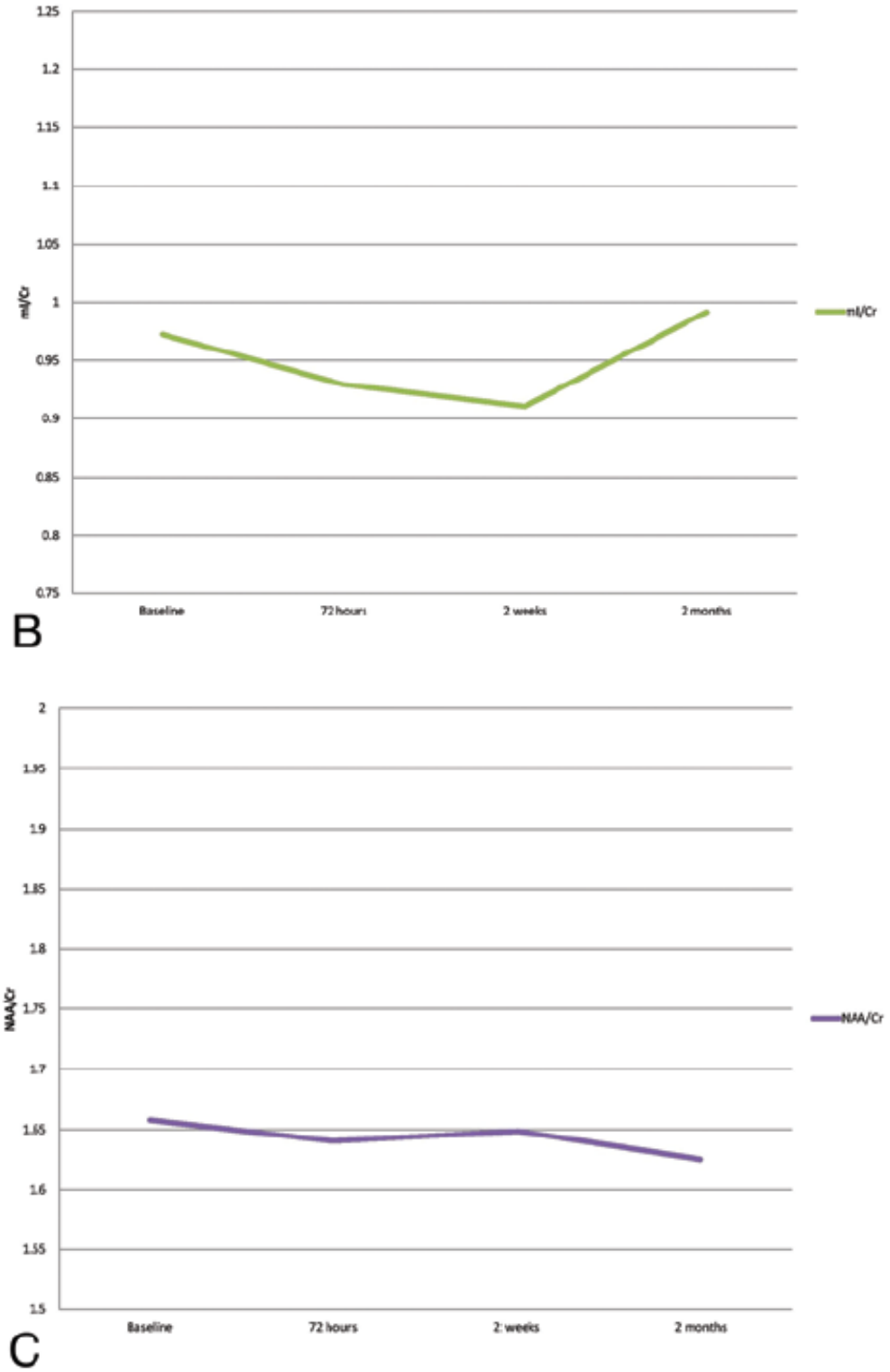


Figure 2-2. Temporal concentration relative to Cr

2.11 Tables

Tableau 2-1. Descriptive statistics for individuals sustaining a clinically diagnosed concussion at baseline and 3 time points after injury

	Glu/Cr			mI/Cr			NAA/Cr		
Evaluation Period	Mean	SD	No. of Patients	Mean	SD	No. of Patients	Mean	SD	No. of Patients
baseline	1.75	0.23	11	0.97	0.28	11	1.66	0.30	11
72 hrs postinjury	1.71	0.10	7	0.93	0.18	8	1.64	0.19	8
2 wks postinjury	1.79	0.20	10	0.91	0.13	10	1.65	0.36	10
2 months postinjury	1.69	0.26	9	0.99	0.11	9	1.63	0.14	9

Tableau 2-2. Descriptive statistics for individuals not clinically identified as sustaining a concussion over the course of the ice hockey season*

			t-Test		
Variable	Baseline	End of Season	$t_{(df)}$ Value	p Value	η^2†
men					
Glu/Cr			$t_{(10)} = 0.56$	0.59	0.03
mean	1.81	1.76			
SD	0.30	0.24			
no. of patients	11	11			
mI/Cr			$t_{(13)} = 0.027$	0.98	0.00
mean	0.98	0.97			
SD	0.23	0.26			
no. of patients	14	14			
NAA/Cr			$t_{(15)} = 0.44$	0.97	0.01
mean	1.62	1.63			
SD	0.23	0.26			
no. of patients	16	16			
women					
Glu/Cr			$t_{(13)} = 0.46$	0.66	0.02
mean	1.93	1.90			
SD	0.20	0.26			
no. of patients	14	14			
mI/Cr			$t_{(12)} = 0.28$	0.79	0.01

mean	0.97	0.98			
SD	0.13	0.17			
no. of patients	13	13			
NAA/Cr			$t_{(13)} = 2.58$	0.02	0.34
mean	1.90	1.69			
SD	0.32	0.27			
no. of patients	14	14			

* df = degrees of freedom

†Measure of effect size, interpreted as the percentage of variance within the dependent variable that is accounted for by independent variable.

CHAPITRE 3 ARTICLE 2: NEUROMETABOLIC AND MICROSTRUCTURAL ALTERATIONS FOLLOWING A CONCUSSION IN FEMALE ATHLETES

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3.1 Abstract

Background: Sports-related concussions are a major public health concern affecting millions of individuals annually. Neurometabolic and microstructural alterations have been reported in the chronic phase following a concussion in male athletes, while no study has investigated these alterations in female athletes.

Methods: Neurometabolic and microstructural alterations following a concussion were investigated by comparing 10 female athletes with a concussion and 10 control female athletes, using magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI). Athletes with concussion were scanned at least 7 months post-concussion (mean.18.9 months).

Results: MRS revealed a significant lower level of myo-inositol in the hippocampus and the primary motor cortices (M1) bilaterally. DTI analysis using Tract-Based Spatial Statistics (TBSS) showed no difference in fractional anisotropy (FA) while higher level of mean diffusivity (MD) in athletes with concussion was detected in large white matter tracts including the forceps minors, inferior/superior longitudinal fasciculi, inferior fronto-occipital fasciculus, cingulum, uncinate fasciculus, anterior thalamic radiations and corticospinal tract. Moreover, a region of interest approach for the corpus callosum revealed a significant lower level of FA in the segment containing fibres projecting to M1.

Conclusions: This study demonstrates persistent neurometabolic and microstructural alterations in female athletes suffering a sports-related concussion.

Keywords: Diffusion tensor imaging, magnetic resonance spectroscopy, traumatic brain injury

3.2 Introduction

Sports-related concussions are a major public health concern that annually effect between 1.6–3.8 million individuals in the US alone [1]. This mild traumatic brain injury (mTBI) is defined as a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces [2]. More precisely, sports concussions are closed head injuries due to either a direct blow to or shaking of the head by an impulsive force resulting in a transient alteration in mental status and brain processes that may include loss of consciousness, memory dysfunction (amnesia), impairment of reflex activity and/or disorientation [3]. The physical, emotional and cognitive symptoms following a concussion seem to typically resolve after a period of 7–10 days in adults [4, 5], a time window that closely coincides with the resolution of the neurometabolic cascade following a concussion [6]. While concussion effects are well studied in male athletes, the effects of a concussion on female athletes are relatively unknown despite worst outcomes. Epidemiological studies have shown a greater risk of sustaining a concussion in female athletes relative to male athletes at both university [7–10] and high school levels [9]. A decreased head–neck segment mass resulting in greater angular acceleration of the head [11–13], decreased neck strength and neck girth [13, 14] and a larger ball-to-head size ratio in female soccer players [15] have been proposed as potential explanations for the higher concussion risk in female athletes. Also, female athletes exhibit a higher number of symptoms in the acute phase and typically require a longer time to recover from injury [16–18] (see also [19] for a meta-analysis), although it should be understood within the context that females tend to report a higher number of symptoms at baseline [20]. A greater cerebral blood flow rate coupled with a higher basal rate of glucose metabolism in females [21] may interact with an increased neurometabolic demand following a concussion [6] and thereby exacerbate the severity of post-concussive symptoms [16].

Given a resolution of symptoms in the majority of cases after 7–10 days in conjunction with the absence of tissue damage using standard neuroimaging techniques such as CT scan or MRI, the effects of concussions have typically been considered transient. However, the reported association between a history of multiple concussions in former retired athletes and the development of dementia pugilistica [22] or Alzheimer's disease [23] has increased

awareness of the possible long-term effects of sports concussions. Also, the chronic traumatic encephalopathy (CTE), characterized by an atrophy of the cerebral hemispheres, which was previously diagnosed in boxers, has recently been documented in athletes playing sports with a lower risk of sustaining head injury [24, 25]. In healthy former retired athletes with a history of concussions, evidence for the abnormal enlargement of the lateral ventricles, cortical thinning, neurometabolic anomalies and neuropsychological alterations has been reported [26]. Furthermore, it has been shown that former retired athletes who sustained their last concussions more than three decades prior to testing experience neurophysiological (e.g. electrophysiological anomalies of P3a and P3b components; abnormal intracortical inhibition over the primary motor cortex using TMS) as well as functional alterations (e.g. cognitive decline on neuropsychological tests assessing memory and executive functions; bradykinesia (slowed motor execution) symptoms) relative to their unconcussed counterparts [27]. These data highlight the fact that while there appears to be little or no functional impact of sports concussions in most athletes after the acute period, persistent sub-clinical alterations of brain function and structure may significantly compromise healthy ageing. In addition to the higher risk of developing neurodegenerative disease with a history of multiple concussions, studies have shown a greater incidence of Alzheimer's disease in women compared to men [28]. This highlights the importance of assessing the pathophysiological process underlying persistent alterations in female athletes suffering a concussion given the multiple risk factors of late-life diseases in this population.

Magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) are useful techniques in the investigation of functional abnormalities that occur following a concussive injury that could help explain the presence of persistent neurophysiological anomalies despite negative neuroradiological findings in athletes suffering a concussion. At the neurochemical level, studies using MRS in mTBI related to sports practice have shown a decrease in N-acetyl aspartate (NAA) [29–31], which is thought to reflect axonal injury or neuronal loss [32]. The NAA returns to baseline levels within 30–45 days after concussion, suggesting that the alterations affecting the chemical structure of the neurons from targeted regions of interest are transient [30]. However, a recent study showed a pathological decrease in NAA in the acute phase that persisted for at least 6 months postconcussion [29], supporting

the notion that sports-related concussions may induce persistent alterations. Chronic elevations of myo-inositol levels have also been found in athletes suffering a concussion [29], which is consistent with enduring glial proliferation [33]. To date, decreased mI levels have only been evidenced in animal studies during the acute postconcussion phase [34]. The level of this metabolite is also decreased in stroke, tumours, lymphoma and low-grade malignancies [35]. Taken together, these studies suggest that the recovery of metabolite levels tend to differ depending on the metabolite, with some abnormalities emerging in the post-acute phase [29], further demonstrating the complex pathophysiological process following a concussion.

Traumatic axonal injury following a concussion can be assessed by the main DTI indices, which are fractional anisotropy (FA), a measure of microstructural integrity and mean diffusivity (MD), an overall average diffusion reflecting white matter integrity [32]. In the sports trauma literature, a recent study using DTI showed white matter alterations affecting the corticospinal tract (CST) and the corpus callosum in the acute phase (1–6 days post-injury) that persisted in the chronic phase (6 months post-injury) in male athletes suffering a concussion [36]. Another study by Cubon et al. [37] revealed alterations in diffusivity in several large tracts of the left hemisphere, notably the inferior/superior longitudinal and fronto-occipital fasciculi, the internal capsule and the posterior thalamic and acoustic radiations. Moreover, alterations in the diffusion measures seem to correlate with functional alterations on a working memory task in athletes with a concussion using functional magnetic resonance imaging (fMRI), suggesting an association between the microstructural and functional deficits following a sports-related concussion [38]. Also, the corpus callosum (CC) is particularly vulnerable to mTBI where a decrease in FA is frequently observed [39]. Globally, these studies suggest the presence of persistent cerebral alterations in mTBI athletes that could be assessed by MRS and DTI.

In the present study, MRS and DTI were used to evaluate metabolic impairments and white matter integrity following a concussion in a sample consisting solely of female athletes. The choice to evaluate female athletes was driven by the fact that, to the authors' knowledge, no neuroimaging study has assessed the specific alterations associated with a sports-related concussion in a group of female athletes, despite a higher risk of sustaining a concussion, a higher number of post-concussion symptoms and a longer rehabilitation time compared to

male athletes [16–19]. In MRS, the primary motor cortex (M1) was chosen as a region of interest (ROI) because of recent evidence suggesting a higher vulnerability to concussion of this region [29]. Likewise, the dorsolateral prefrontal cortex (DLPC) was selected based on both ERP [40, 41] and fMRI studies [42–46] suggesting concussion-related disruptions of mediated functions. Finally, the hippocampus was chosen because of its susceptibility to damage [47, 48]. It was hypothesized that all ROIs would show lower levels of NAA and glutamate and higher levels of mI. Using a whole-brain voxel-based method, it was also hypothesized that athletes suffering a concussion would demonstrate a lower level of FA as well as a higher level of MD relative to controls in the major white matter (WM) tracts of the brain. It was further hypothesized that the corpus callosum would demonstrate particular vulnerability as consistent with the extant literature [49, 50] (see also [39] for a review) and a ROI approach was chosen for this brain area.

3.3 Methods

3.3.1 Participants

Participants in this study were all active female players in university varsity sports teams or Canadian national teams. They were recruited with the help of team physicians and physiotherapists. The following exclusion criteria were applied to select the athletes who took part in the study: history of alcohol and/or substance abuse, psychiatric illness, learning disability, neurological disorders (seizure disorder, central nervous system neoplasm or brain tumour) and TBI unrelated to contact sports. None of the participants were taking psychotropic medications at the time of testing. The experimental group (mTBI group) consisted of 10 female athletes who suffered a sports-related concussion 7 months or more before testing (mean. 18.9 months, SD. 15.2 months; Table I). The control group consisted of 10 female athletes who never sustained a concussion. Control and concussed athletes were equivalent with regards to age ($t(18) = 0.90$, $p = 0.38$) and level of education ($t(18) = 1.24$, $p = 0.23$) and all head injuries were classified as mild. In addition, the two groups were similar in terms of sports played. A standardized concussion history form was administered to obtain

detailed information about the number of previous concussions (if any), approximate date(s) of each concussion, description of the injury(ies) and nature and duration of relevant postconcussion symptoms (confusion and/or disorientation, retrograde and/or anterograde amnesia and loss of consciousness). Finally, participants had to report any subjective symptoms at the time of the evaluation using the Post Concussion Symptom Scale (PCSS). Reported symptom scores were similar between groups ($t(18) = 0.25$, $p = 0.81$).

3.3.2 Neuroimaging

3.3.2.1 MR imaging

The experiment was conducted at the Unité de Neuroimagerie Fonctionelle (UNF) of the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal (CRIUGM), using a Siemens 3 Tesla whole-body MRI system (Siemens, Erlangen, Germany). The study was approved by the Research and Community Ethics Boards of the UNF and Université de Montréal and was done in compliance with the code of ethics as stated in the Declaration of Helsinki. All subjects gave written informed consent following careful screening for MRI compatibility and were financially compensated for their participation.

3.3.2.2 MR spectroscopy

The regions of interest (ROIs) were positioned using a rigorous anatomical localization protocol. Subjects were placed in the scanner and underwent a localizing scan parallel to the hippocampus (anterior commissure-posterior commissure). Voxels were then applied for the hippocampus (20 mm X 40mm X 16 mm), DLPC (16 mm X 16mm X 16 mm) and M1 (16 mm X 20mm X 32 mm) bilaterally (see Figure 1). All voxels were placed on an AC-PC-oriented oblique axial slice corresponding to the ROI first on a sagittal view and were then confirmed with coronal and axial views to ensure an adequate distance from the ventricles, fatty tissue and bone. Single-voxel ^{1}H-MRS spectroscopic measurements were performed using a PRESS (Point RESolved Spectroscopy) sequence (TE (echo time) = 30 ms, TR (repetition time) = 1500 ms, 256 acquisitions, 1200 Hz bandwidth, 1024 points, duration 6.5 minutes) on a 12-channel head coil. To ensure that all ROIs could be captured within a

reasonable scan duration and to ensure the comfort of the participants in the scanner, this study opted for a moderate TR and a shorter TE to balance T1-associated and T2-associated signal losses and scan times. Outer-volume suppression bands contiguous with the PRESS-selected volume were automatically placed in all three dimensions based on the voxel size of each ROI.

The Linear Combination (LC) model [51] was used for metabolite quantification. It is an operator-independent spectral analysis software that estimates metabolite concentrations and their ratios relative to creatine/phosphocreatine (Cr) using a set of basis reference spectra acquired from individual metabolites on the MR instrument. NAA/Cr, Glu/Cr and mI/Cr were only analyzed if the estimated uncertainty calculated as Cramer Ratio lower bounds (%SD) was less than 20%. The LCModel operator was blind to group membership. Statistical analyses were done using SPSS version 16.0. Coefficients of variance (CV) were calculated for each metabolite. All subsequent statistical analyses were performed only for metabolite ratios that had overall CV values <20% (i.e. NAA/Cr, Glu/Cr and mI/Cr). Values from left and right hemispheres were averaged for all three ROIs. The rationale for averaging the ROIs across the hemispheres was 2-fold. First, the literature suggests that there are no lateralization effects in the regions examined in this study [52–55]. Furthermore, it is not known if the effects of a concussion are greater at the site of impact or if any resulting changes are distributed diffusely regardless of impact location. As such, it was decided to combine the spectra from both hemispheres within each ROI. The absence of lateralization was confirmed in the control group across regions of interest and metabolite ratios (hippocampi: Glu/Cr, $t(9) = 0.79$, $p = 0.45$; mI/Cr, $t(9) = 0.60$, $p = 0.57$; NAA/Cr, $t(9) = 1.36$, $p = 0.21$; DLPC: Glu/Cr, $t(9) = 0.95$, $p = 0.37$; NAA/Cr, $t(9) = 0.13$, $p = 0.90$; M1: Glu/Cr, $t(9) = 0.84$, $p = 0.42$; mI/Cr, $t(9) = 1.55$, $p = 0.16$; NAA/Cr, $t(9) = 0.34$, $p = 0.74$). There was one significant lateralization difference in DLPC (mI/Cr: $t(9) = 2.43$, $p = 0.04$), but this effect seemed to be driven by a control participant whose result differed more than 2 SD from the mean value. After excluding this participant from the analysis of the mI/Cr ratio in the DLPC, the lateralization effect was no longer significant ($t(8) = 1.99$, $p = 0.08$). The different metabolites in any given voxel are unrelated in principle and are not correlated [56]. As such, the metabolite ratios of the two groups were compared using Student's independent T-tests.

3.3.2.3 Diffusion tensor imaging

The imaging parameters were as follow: diffusion weighting gradients applied in 64 directions with b values of 0 and 700 s mm^{-2} and four averages in each direction, repetition time of 12 800 ms, echo time of 101 ms, field of view of 256 x 256mm^2, matrix size of 128 x 128 with partial Fourier reconstructed to 6/8, slice thickness of 2 mm with 0.6-mm gaps and 75 slices. 3D T1-weighted images of corresponding subjects were also acquired with an inversion recovery rapid gradient echo sequence using a 3T Trio Siemens MRI scanner. Acquisition parameters were as follows: TI/TR/TE = 1500/2500/3.83 ms; flip angle = 15°; slice thickness = 0.9 mm, with an acquisition matrix of 256 x 256 x 256. Total scan time was 28 minutes (4 minutes localizers, 9 minutes MPRage and 15 minutes DTI). The most common univariate anisotropy measure, FA, is defined in terms of the eigenvalues, λ_i, i = 1,2,3, of the diffusion tensor as:

$$FA(D) = \frac{\sqrt{3}}{\sqrt{2}} \frac{\sqrt{(\lambda_1 - \langle\lambda\rangle)^2 + (\lambda_2 - \langle\lambda\rangle)^2 + (\lambda_3 - \langle\lambda\rangle)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

where

$$\langle\lambda\rangle = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$

It is widely accepted as an index of WM integrity and it is sensitive to the effects of ageing, cognition, trauma and neurodegenerative disease [32]. MD is a rotationally invariant trace of the diffusion tensor and provides valuable information about the overall diffusion in a voxel or region where MD = $< \lambda > = (\lambda_1 + \lambda_2 + \lambda_3) / 3$. Voxel-wise statistical analysis of the FA and MD data was carried out using TBSS (Tract-Based Spatial Statistics [57]), part of FSL software [58]. First, the effects of head movement and eddy currents were corrected. Then, the FA images were created by fitting a tensor model to the raw diffusion data using FDT and then they were brain-extracted using BET [59]. All subjects' data was then aligned into a common space (FMRIB58_FA standard image) using the non-linear registration tool FNIRT [60, 61], which uses a b-spline representation of the registration warp field [62]. Next, the mean FA images were created and thinned to create a mean FA skeleton, which represents the centres of all tracts common to the group. Each subject's aligned data was then projected onto

this skeleton and the resulting data fed into voxel-wise cross-subject statistics. For MD images, the FA transformation matrices were utilized to achieve the same nonlinear registration. Finally, a voxel-wise Student T -test to the derived scalar images was applied, using a permutation method with a significance threshold of $p < 0.05$, family-wise error rate (FWE) corrected, which is a conservative procedure that enables high control of Type 1 error, being the probability of one or more false positives the same as the significance level. The Threshold-Free Cluster Enhancement (TFCE) method was used to define the cluster. Finally, areas corresponding to significant clusters were identified using the JHU white-matter tractography atlas.

Concerning the ROI approach used for the CC, a common partitioning approach was used to sub-divide the callosum into five sub-regions. Parcellation of the CC by introducing vertical sub-divisions was done with respect to the outcome of the fibre tractography of the study of Hofer and Frahm [63] which proposed a novel classification of the CC. An illustration of the partitioning schemes for regional analysis used in this study is presented in Figure 2. A student T –test between the two groups was then performed on the derived scalar images to assess if there were any differences between the groups across the sub-divisions of the CC.

Finally, Pearson correlations were performed on significant neurometabolic findings and significant microstructural findings of the corresponding region (if any).

3.4 Results

3.4.1 MR Spectroscopy

There were no significant differences between control and mTBI subjects in the DLPC. Glu/Cr was statistically equivalent between the two groups ($t(18) = 0.97$, $p = 0.34$), as were NAA/Cr ($t(18) = 0.75$, $p = 0.46$) and mI/Cr ratios ($t(17) = 0.59$, $p = 0.56$). Because of a near significant effect between the left and right hemispheres for mI/Cr in control subjects during the assessment of lateralization, a Student T-test was also carried out for the left and right mI/Cr ratio between the two groups to verify if there was a difference after excluding the data

of the control participant who was driving the lateralization effect. Results revealed no significant difference between the two groups relative to the ratio of mI/Cr in the left ($t(17) = 0.67$, $p = 0.51$), as well as in the right hemisphere ($t(18) = 0.16$, $p = 0.88$). Results from the hippocampi revealed a significantly lower level of mI/Cr in the mTBI group ($t(18) = 2.14$, $p = 0.05$), while there were no differences in Glu/Cr ($t(18) = 1.09$, $p = 0.29$) and NAA/Cr ratios ($t(18) = 0.38$, $p = 0.71$). M1 revealed a similar pattern of metabolic alterations: mI/Cr levels were significantly lower in the mTBI group ($t(18) = 2.33$, $p = 0.05$), while Glu/Cr ($t(18) = 1.22$, $p = 0.24$) and NAA/Cr ($t(18) = 0.65$, $p = 0.52$) ratios remained unaffected. Graphics illustrating neurometabolite concentrations are presented in Figure 3.

3.4.2 Diffusion tensor imaging

FA and MD were recorded. Because each cluster is composed of several voxels—each with its own *T*-value—significant clusters are reported as $p < 0.05$, FWE corrected, along with the maximum *T*-value in the cluster.

First, no significant cluster differences were found between the two groups relative to FA. For MD, all significant clusters showed a higher level in the mTBI group. Significant clusters were found in the left forceps minor ($t(18) = 3.64$, $p < 0.05$ corr), the left inferior fronto-occipital fasciculus ($t(18) = 3.45$, $p < 0.05$ corr), the left cingulum ($t(18) = 5.02$, $p < 0.05$ corr), the left uncinate fasciculus ($t(18) = 3.27$, $p < 0.05$ corr), the left inferior longitudinal fasciculus ($t(18) = 4.28$, $p < 0.05$ corr), as well as the anterior thalamic radiations bilaterally (left: $t(18) = 3.75$, $p < 0.05$ corr; right: $t(18) = 5.13$, $p < 0.05$ corr), the superior longitudinal fasciculus bilaterally (left: $t(18) = 4.45$, $p < 0.05$ corr; right: $t(18) = 3.27$, $p < 0.05$ corr) and the corticospinal tract bilaterally (left: $t(18) = 4.65$, $p < 0.05$ corr; right: $t(18) = 3.92$, $p < 0.05$ corr) (Figure 4).

Partitioning the CC in five sub-divisions revealed a significantly lower level of FA in region 3, also corresponding to the motor segment of the CC [64] (see Figure 2) in the mTBI group compared to controls ($t(18) = 2.60$, $p < 0.05$ corr). No difference was found for MD in this ROI.

Finally, no correlations were found between a decrease of mI/Cr in M1 and an increase in MD in the corticospinal tract of concussed athletes.

3.5 Discussion

The aim of this study was to evaluate specific long-term neurometabolic and microstructural alterations following a concussion in a sample of female athletes. Using MRS, chronic alterations were found following a concussion in female athletes' hippocampi and primary motor cortices, reflected by a lower level of myo-inositol. The other major finding of the present study is the microstructural alterations in female athletes with concussion, reflected by a higher level of MD in major white matter tracts as well as a lower level of FA in the corpus callosum.

While previous studies in sports-related mTBI report an increase in mI [29], diminished levels of mI have been found in animal models of brain injury [34] as well as in stroke, tumours, lymphoma and low-grade malignancies [35]. In female athletes, lower levels of myo-inositol could be related to focal ischemia, as is the case in stroke [65]. Despite the variability in the direction of changes in myo-inositol in the clinical population, there is still a disruption of the level of this metabolite following a brain injury. It is possible that the level of this metabolite fluctuated across time, with higher levels in the acute phase and lower levels in the years following the concussion. The present study demonstrated higher levels following the concussion, which could reflect different pathological mechanisms in the long time course of the injury. It is surprising that no difference was found in the NAA/Cr ratio in athletes suffering a concussion relative to controls because previous studies have demonstrated lower levels in the acute [29], sub-acute [30, 31] and chronic [29] phases. Several factors could explain the different metabolic profiles found in this study. Time elapsed since the injury is expected to play a role in neurometabolite balance and this could account for Glu/Cr and NAA/Cr ratio inconsistencies with those reported by Henry et al. [29]. Athletes were assessed on average 18 months post-injury, as opposed to the study by Henry et al. [29], in which the athletes were evaluated 6 months post-concussion. It is possible that, if there were alterations in NAA/Cr and Glu/Cr 6 months post-injury, these effects were not present at 18 months post-injury. In the present study athletes were tested at a single time point, making it impossible to determine if there is metabolic recovery in the chronic phase. Nevertheless, this remains a distinct possibility and future studies will need to address the time course of the neurometabolic profile of female athletes. Another explanation could be that the

neurochemical changes following a brain injury differ between women and men. However, comparisons with a sample composed solely of male athletes were not included in this study and future studies should consider gender differences in the assessment of brain injury.

DTI analyses revealed microstructural alterations in female athletes suffering a concussion. First, no difference between groups was found in FA whole-brain analysis while differences were only found relative to MD. These results are in agreement with recent TBSS studies by Messé et al. [66] in mTBI patients with persistent neurobehavioural impairment and by Cubon et al. [37] in athletes who reported increased MD and no FA changes. However, using a ROI approach, a lower level of FA was found in the mid-region of the corpus callosum, which is thought to reflect a loss of white matter integrity, which may in turn reflect damage to the myelin or the axon membrane or reduced axonal packing density or axonal coherence [39]. In the chronic stage following mTBI, these changes in anisotropy may also represent axonal degeneration [68]. This result is interesting since this section of the CC mainly projects to the primary motor cortices and is involved in motor command and coordination [47]. Since metabolic alterations were also found in the primary motor cortices, it is possible that these two processes could partly explain neurophysiological and functional alterations in M1. Also, these alterations are present, despite the absence of self-reported symptoms in concussed athletes.

MD, the average molecular diffusion measure is thought to be affected by cellular size and integrity [32, 68]. In this study, higher levels of MD were found in the left forceps minor, the left inferior fronto-occipital fasciculus, the left cingulum, the left uncinate fasciculus, the left inferior longitudinal fasciculus as well as the anterior thalamic radiations bilaterally, the superior longitudinal fasciculus bilaterally and the corticospinal tract bilaterally. These alterations in some of the major white matter tracts are in line with a recent study using TBSS in symptomatic athletes. While they found no changes in FA, they reported increased MD in the left hemisphere (specifically to parts of the inferior-superior longitudinal and fronto-occipital fasciculi, the retrolenticular part of the internal capsule and the posterior thalamic and acoustic radiations) [37]. Consistent with this notion, a study assessing WM fibre tract integrity months post-injury in individuals with persistent cognitive impairment reported increased MD [69]. These higher levels in MD could reflect cytotoxic oedema and

inflammation, homeostatic membrane dysfunction, fibre reorganization, increased membrane permeability, destruction of intracellular compartments or glial alterations [32, 68, 70, 71]. Despite the non-specificity of these measures, the present data provide evidence of persistent microstructural alterations phase in the WM skeleton of female athletes suffering a concussion. The present study also points to the unmatched sensitivity of MD to detect subtle structural damages, such as those caused by concussions. Taken together, the changes observed suggest chronic alterations in brain anisotropy that could contribute to overt concussion related symptomatology as former athletes age [27]. While all athletes were asymptomatic months after their last concussion, they still demonstrated microstructural alterations that can be a contributing factor to the longer rehabilitation time following brain injury in women. It raises the intriguing possibility that these persistent metabolic and microstructural anomalies may be related to post-concussion recovery. Despite the absence of clear functional impact, these disruptions in cellular metabolism and WM integrity may have important long-term consequences. This is especially important in female athletes, considering the higher risk of developing Alzheimer's disease in women [28] and the increased risk of developing neurodegenerative diseases in athletes with a history of multiple concussions [22–25]. The persistent neurometabolic and microstructural alterations seen in female athletes could, thus, be a contributing factor to late-life difficulties observed in this population.

While changes in diffusivity affect a large number of tracts, some may be particularly vulnerable to the effects of sports-related concussions. Notably, the superior longitudinal fasciculus and the corticospinal tract are characterized by higher levels of MD bilaterally. The superior longitudinal fasciculus is an important associative WM tract in the brain, since it connects the frontal, parietal, temporal and occipital lobes together [64]. Playing sports demands rapid and effective information transmission in the brain to allow adequate decision-making and execution of complex motor sequences. Therefore, the microstructural alterations observed in this WM tract are particularly problematic given its importance in the transmission process between the cerebral lobes. Similarly, microstructural alterations affecting the corticospinal tract are particularly problematic in athletes, since this WM tract primarily underlies the primary motor cortex and is responsible for the transfer of motor information [64]. The abnormalities observed across DTI measures in this WM tract may

explain the reduced effectiveness of transmission of motor commands, which could put the athlete at greater risk of sustaining another head injury. Moreover, neurometabolic alterations affecting M1 in female athletes suffering a concussion emphasize the presence of residual abnormalities affecting this brain area. Previous biomechanical studies of mTBI highlight the vulnerability of M1 to shear strain with rotational forces applied in the event of a concussive injury [72–74]. In female athletes, the neurometabolic and microstructural alterations to this brain area persist months following the injury and are in line with the biomechanical studies that demonstrated a higher vulnerability of the primary motor cortex following the effects of a concussion. Moreover, these effects in M1 could be exacerbated by the decrease in muscle resistance [11–13] and decrease in head–neck segment mass in female athletes compared to male athletes, resulting in greater angular acceleration to the head and a greater risk to sustain a concussion for the same impact [11–13].

An important limitation of the present study is common to neuroimaging studies and is related to the small sample size with a large variance in terms of time since injury. The small number of subjects in each group limits the extent to which the current findings may be generalized to all sports practiced by female athletes. The large variance in the time elapsed since the last injury emphasizes the importance of cautious interpretation of the results since time elapsed since the injury is expected to play an important role in the reported effects. Moreover, the sample was composed exclusively of female athletes, thus it is not possible to generalize the results obtained with MRS and DTI to mTBI sustained in the general population. It is also not possible to know if the neurochemical and microstructural profiles observed in this study are specific to female athletes since they were not directly compared to male athletes. Also, while the sample allowed control over demographic factors such as age and education level, the subjects were recruited from different sports, which show a variation in the levels of risk of sustaining sub-concussive blows to the head. This aspect could have influenced the results since the effects of sub-concussive blows are still elusive, particularly amongst control athletes. Indeed, a study from Bazarian et al. [75] recently reported changes in anisotropy that were intermediate for the sub-concussive group compared to a control group and a group of athletes with a single concussion. Future studies should consider these aspects in the recruitment of athletes.

To conclude, even though concussive injuries do not typically result in observable brain trauma through traditional neuroimaging techniques and while athletes with concussion typically recover from self-reported post-concussion symptoms within weeks after the injury, there is evidence of persistent effects in the WM and in the cellular metabolism of female athletes. These brain abnormalities are still present months after the last concussion, despite the absence of self-reported symptoms. However, further studies are needed to confirm the robustness of these findings. Future research should investigate the neurometabolic and microstructural profiles of female athletes suffering a concussion at several time points between the acute and the chronic phase. Also, future investigations should compare female and male athletes using these two techniques to better understand potential gender differences in anatomical and metabolic alterations and recovery timelines.

3.6 Declaration of interest

The authors report no declaration of interest. The authors alone are responsible for the content and writing of the paper.

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3.8 Figures

Figure 1. Regions of interest (ROI) for magnetic resonance spectroscopy (MRS) data acquisition depicted in the sagittal, coronal, and axial planes, in the hippocampus (top ; 20 x 40 x 16 mm), primary motor cortex (M1, middle ; 16 x 20 x 32 mm), and dorsolateral prefrotal cortex (DLPC, bottom; 16 x 16 x 16 mm). Spectra were recorded in both the left and right hemispheres.

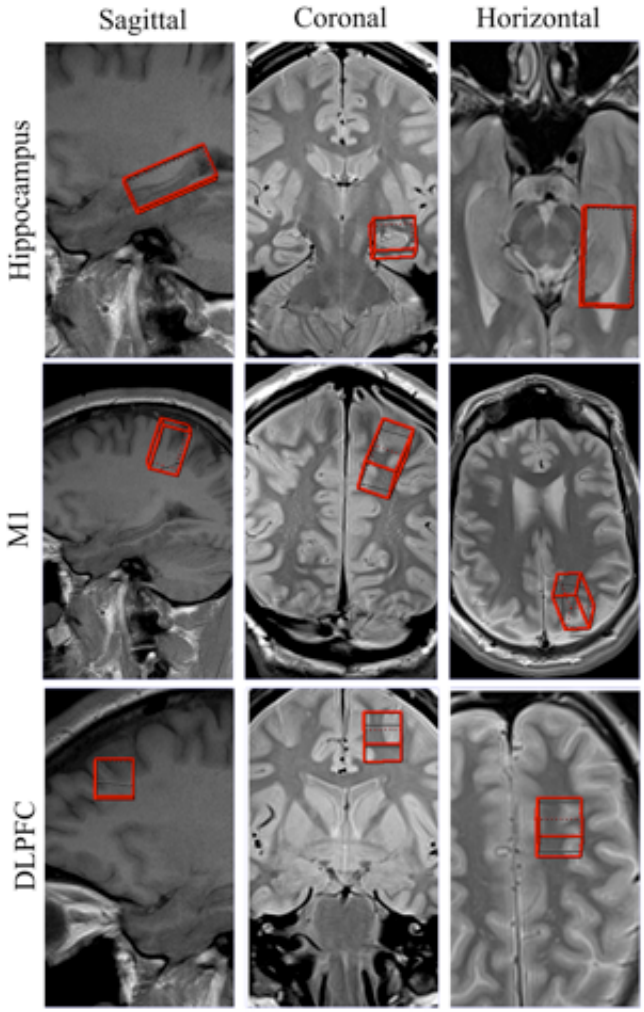


Figure 3-1. Regions of interest (ROI) for magnetic resonance spectroscopy (MRS)

Figure 2. Parcellation approach of the corpus callosum (CC) into five subdivisions. (From Hofer S., & Frahm, J. (2006) Topography of the human corpus callosum revisited - Comprehensive fiber tractography using diffusion tensor magnetic resonance imaging, NeuroImage, 32, 989-994)

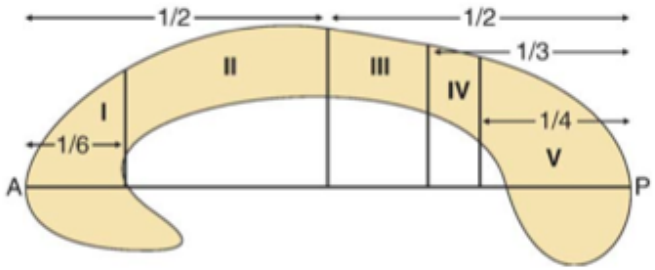
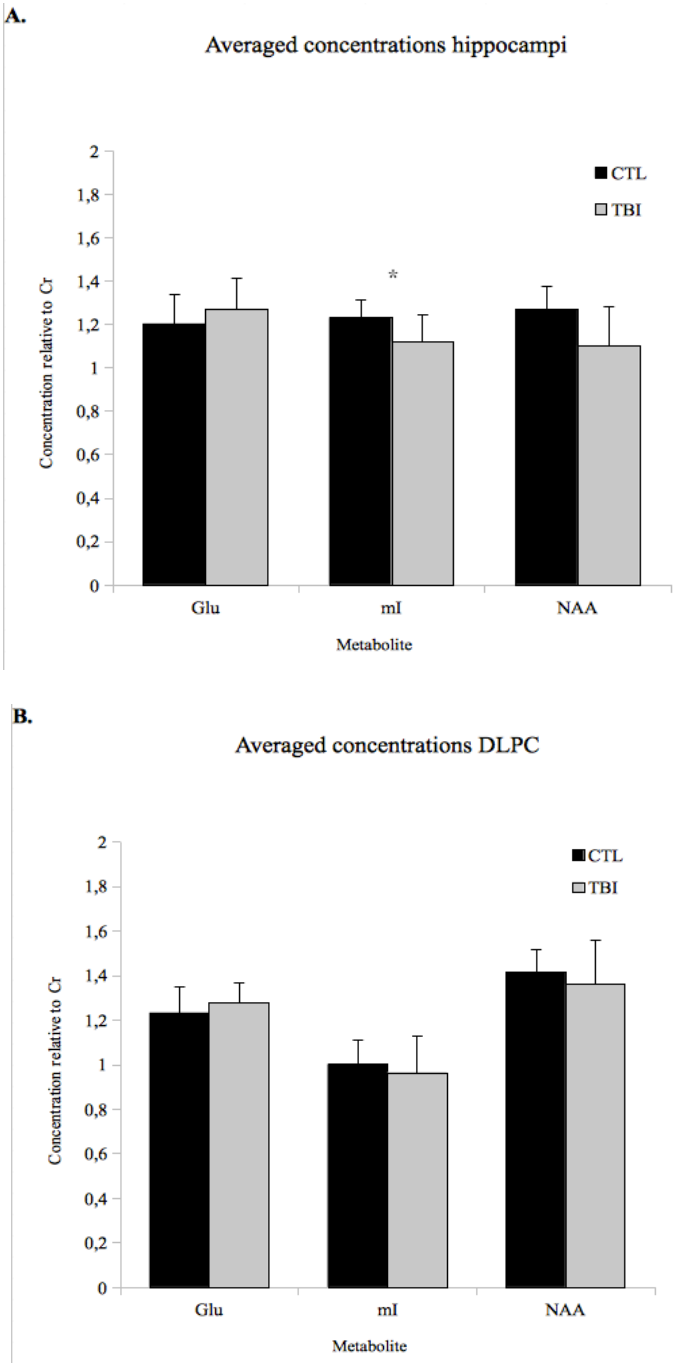


Figure 3-2. Parcellation approach of the corpus callosum (CC) into five subdivisions

Figure 3. Bar graphs of the mean Glu/Cr, mI/Cr, and NAA/Cr metabolite ratios for control (black bars) and concussed (gray bars) athletes for the hippocampus (A), dorsolateral prefrontal cortex (DLPC - B) and primary motor cortex (M1 - C). Standard errors of the means are represented by vertical bars. An asterisk indicates a statistically significant difference relative to controls ($p < .05$).



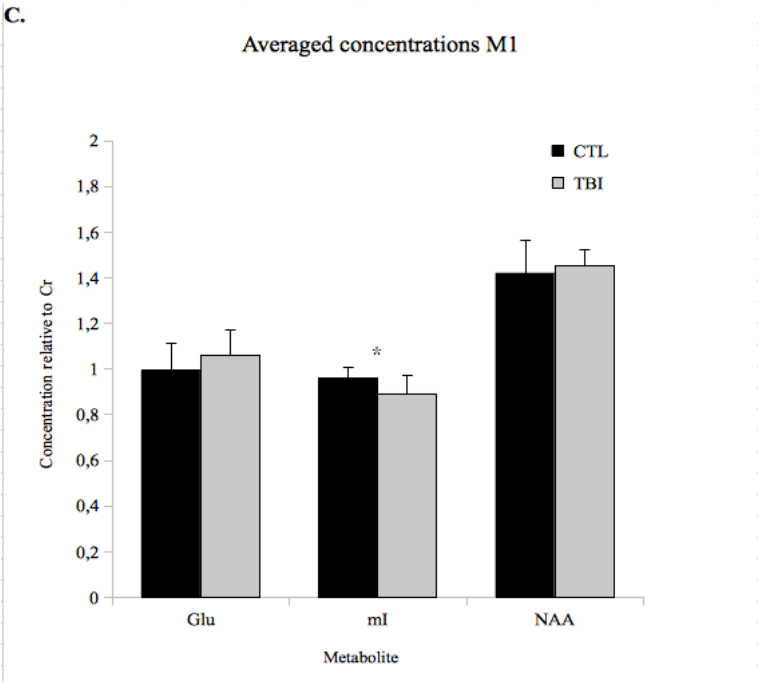


Figure 3-3. Metabolic ratios relative to Cr

Figure 4. Differences in mean diffusivity (MD) between control and concussed athletes in the left (A) and right corticospinal tract (B).

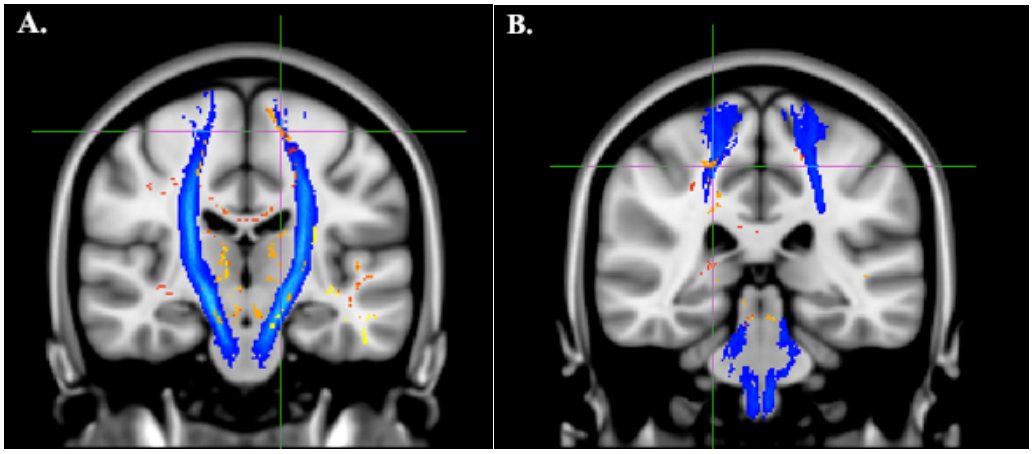


Figure 3-4. Differences in mean diffusivity (MD) between control and concussed athletes in the left and right corticospinal tract

3.9 Tables

Tableau 3-1. Demographic table describing the two groups of the study

Group	Age	Education (years)	Number of concussions	Time post-concussion (months)	Mean PCSS
mTBI (*n*=10)	21.70 (2.06)	15.70 (1.64)	2.60 (2.3)	19.5 (15.0)	6.70 (4.14)
Control (*n*=10)	21.00 (1.33)	14.90 (1.20)	0	0	6 (4.97)

PCSS: Post-Concussion Sympton Scale.

CHAPITRE 4 ARTICLE 3: A FOLLOW-UP STUDY OF NEUROMETABOLIC ALTERATIONS IN FEMALE CONCUSSED ATHLETES

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4.1 Abstract

Athletes who sustain a concussion demonstrate a variety of symptoms and neuropsychological alterations that could be brought on by neurometabolic abnormalities. However, no study has yet investigated these aspects in female athletes using magnetic resonance spectroscopy. The present study investigated the neurometabolic and -psychological effects of a concussion in the acute (7–10 days postinjury) and chronic (6 months postinjury) phases after injury. Eleven female concussed athletes and 10 female control athletes were scanned at both time points in a 3T magnetic resonance imaging scanner. Neuropsychological and symptomatic evaluations were completed at each time point. Neuropsychological alterations and a higher severity of symptoms were found in the acute phase in concussed athletes, relative to controls, but showed recovery in the chronic phase. Concussed athletes showed neurometabolic impairment in prefrontal and motor cortices characterized by a pathological increase of glutamine/glutamate (Glx/Cr) only in the chronic phase. Also, a significant decrease in N-acetyl-aspartate/Cr ratio was observed in control athletes at the second time point. Concussed female athletes showed acute cognitive alterations and higher severity of symptoms that do not appear to be underlied by neurometabolic abnormalities, which are only present in the chronic postinjury phase.

Keywords: female athletes; magnetic resonance spectroscopy; sport; traumatic brain injury

4.2 Introduction

Female participation in individual and collective sports has drastically increased in the last few years. Currently, there are more than 186,000 female athletes in the National Collegiate Athletic Association[1] and more than 3 million female athletes in U.S. high schools.[2] Sports-related concussions are closed-head injuries caused by either a direct blow to the head or shaking of the head by an impulsive force resulting in a transient alteration in mental status and brain processes that may include loss of consciousness (LOC), memory dysfunction (amnesia), impairment of reflex activity, and/or disorientation.[3] In the majority of cases, postconcussion symptoms experienced in the acute phase tend to disappear after a period of 7–10 days,[4] a time window that closely coincides with resolution of the neurometabolic cascade that occurs after concussion.[5] However, the recovery process differs between gender, and female athletes tend to exhibit a higher number of symptoms in the acute phase and typically require a longer time to recover from injury than their male counterparts.[6–8] Also, a recent study showed that concussion rates vary by sport, gender, and type of exposure, where girls had a higher concussion rate than boys in gender-comparable sports.[9] Epidemiological studies have also shown a greater risk of sustaining a concussion in female athletes, relative to male athletes, at both university[10–13] and high school levels,[12] despite lower head impact strength in women.[14] However, the specific effects of a sports-related concussion in female athletes are relatively unknown, and neurometabolic disruptions in the acute post-injury phase could be related to the higher severity of postconcussion symptoms and neuropsychological alterations after injury.[6,7,15,16]

The association between neurochemical alterations and severity of self-reported symptoms has previously been demonstrated in American football players.[17] Using magnetic resonance spectroscopy (MRS) in the acute phase of a concussion, concussed athletes showed decreases in N-acetyl-aspartate (NAA)[16–20] that have been associated with axonal injury or neuronal loss.[21] Decreases in NAA levels, which are thought to be key contributors in myelin lipid formation as well as osmoregulation,[22] were found in primary motor cortices,[17,18] frontal regions,[17–20] and the corpus callosum.[16] Moreover, whereas a study demonstrated that NAA levels return to baseline levels within 30–45 days after concussion,[19,20] recent studies reported pathological decreases in NAA in the subacute phase[16] as well as 6 months postconcussion.[18]

Alterations in levels of myo-inositol (mI), a precursor molecule for inositol lipid synthesis and an important osmolyte in the brain, and glutamate/glutamine (Glx), a marker of excitatory neurotransmission,[21] were also found in athletes after sports-related concussions at different time points postinjury.[17,18] A temporary decrease of Glx was found in male concussed athletes, where levels were lower in the days after a concussion but returned to control levels 6 months postinjury.[18] However, higher levels of Glx in the general population suffering a mild traumatic brain injury (mTBI)[23,24] and in professional athletes[25] were also found in the acute and chronic post-injury phases. Finally, alterations of mI levels were found after a sports-related concussion, but the direction of these changes is still debated because some studies found a decrease in female athletes and animals with brain injury,[26,27] whereas others reported increased mI levels in male athletes.[18]

Taken together, these studies suggest that neurometabolic recovery tends to differ depending on the metabolite, reflecting the complex pathophysiological process that follows a concussion. This also suggests the clinical value of assessing athletes in both the acute phase, when the athletes are still symptomatic, and chronic phase because previous studies demonstrated persistent neurophysiological, neurometabolic, and microstructural alterations months to years post-injury. Additionally, the reported association between a history of multiple concussions in former retired athletes and development of neurodegenerative diseases, such as Alzheimer's disease (AD) and chronic traumatic encephalopathy, emphasizes the importance of assessing the long-term course of injury.[28–30] Finally, the risk of suffering from dementia and AD is higher in women[31] and reinforces the need to better understand the pathophysiological process that accompanies head injury, specifically in female athletes.

In addition to the aforementioned effects of sports concussion, depressed mood is also frequently reported by concussed athletes.[4] A functional magnetic resonance imaging (fMRI) study demonstrated that concussed athletes with symptoms of depression presented alterations in activation and deactivation patterns in a working memory task, compared to controls.[32] Severity of depressed symptoms in athletes correlated with neural response in brain areas that are implicated in major depression.[32] These data emphasize the need to evaluate depression symptoms in both acute and chronic postinjury phases in the assessment of sports-related concussion, which has never been specifically studied in a sample of female athletes.

The aim of the present study was to investigate the neurometabolic, symptomatic, and neuropsychological profiles specific to concussed female athletes in the acute and chronic postinjury phases. At the neurochemical level, the hippocampus, dorsolateral prefrontal cortex (DLPFC), and primary motor cortex (M1) were chosen as regions of interest (ROIs). The hippocampus was chosen because of research suggesting that hippocampal atrophy is related to memory deficits after TBI.[33,34] Likewise, the DLPFC was selected based on event-related potential[35–37] and fMRI studies, [32,38–41] suggesting concussion-related disruptions in functions mediated by this region. Finally, the M1 was chosen as a ROI because of evidence suggesting its high vulnerability to concussion. [17,18,42–44] In accord with previous studies, a decrease of NAA-Cr (creatine) and Glx-Cr ratios as well as an increase in mI-Cr was hypothesized in the acute postinjury phase. A persistence of neurometabolic abnormalities was hypothesized at 6 months postconcussion. Relative to neuropsychological profiles, it was expected that concussed athletes would perform worse than control athletes in the acute phase, but would show similar performance in the chronic phase, suggesting cognitive recovery. Finally, it was expected that concussed athletes would experience more postconcussion and depressive symptoms in the acute phase, but a similar level to controls in the chronic postinjury phase.

4.3 Methods

4.3.1 Participants

Participants in this study were all active female athletes in university varsity sports teams or Canadian national teams. They were recruited with the help of team physicians and physiotherapists. The following exclusion criteria were applied: history of alcohol and/or substance abuse; psychiatric illness; learning disability; neurological disorders (seizure disorder, central nervous system neoplasm, or brain tumor); and TBI unrelated to contact sports. None of the participants were taking psychotropic medication at the time of testing. The experimental group consisted of 11 female athletes, and the control group was composed of 10 female athletes with no history of head injury, sports-related or otherwise. One concussed athlete sustained a back injury after the first time point and had to abandon the

study, and 1 control athlete sustained a concussion after the first time point and was included in the experimental group and did the two scans postinjury. Baseline data of these 2 participants were excluded from analysis. The experimental group was first scanned, on average, 9 days after injury (mean, 9.4; standard deviation [SD], 4.3). The second scan took place 6 months after the head injury for the concussed group (mean, 178.3 days; SD, 36.4 days) and 6 months after the initial scan for controls (mean, 181.9 days; SD, 14.6 days). All concussed athletes followed a step-by-step return-to-play protocol supervised by their team physicians or physiotherapists to ensure a safe return to play. Also, all athletes were scanned during the afternoon at each time point to control for intraindividual variations that occur in the course of a day.[45] However, the menstrual cycle has not been assessed in this study because concussed athletes had to be tested within a narrow temporal window during the acute phase, which does not allow for control of this variable. Control and concussed athletes were equivalent with regard to age (concussed, 21.4; controls, 21.1; $t(17) = 0.403$; $p = 0.692$) and level of education (mean, 14.7 years; $t(17) = 0.487$; $p = 0.633$), and all head injuries were classified as mild (Glasgow Coma Scale > 13 at time of injury). A standardized concussion history form based on athlete recollection was administered in an interview setting to obtain detailed information about the number of previous concussions (if any), approximate date(s) of each concussion, description of the injury(ies), and nature and duration of relevant postconcussion symptoms (confusion and/or disorientation, retrograde and/or anterograde amnesia, and LOC). The group of concussed athletes ($N = 10$) was composed of cases of single-concussed athletes ($N = 5$), and multiple-concussed athletes suffering two ($N = 1$), three ($N = 3$), and four concussions ($N = 1$). Time elapsed since last injury varied from 1 month to 8 years. Finally, participants had to report any subjective symptom at each time point of the evaluation using the Post-Concussion Symptom Scale (PCSS; see Table 1).

4.3.2 Neuropsychological Testing

Neuropsychological assessments were done at each time point. Neuropsychological tests from the National Hockey League neuropsychological testing program were used to assess multiple aspects of cognitive function.[46] This battery includes classic neuropsychological tests[47,48] selected to evaluate attention (Pennsylvania State University [PSU] cancellation task), visual scanning and mental flexibility (Color Trails A [CTA] and B

[CTB] and Symbol Digit Modality Test [SDMT]), visual memory (Brief Test of Visual Memory; BVMT), verbal memory (Hopkins Verbal Learning Test; HVLT), and speech fluency (Verbal Fluency Test; phonemic component). The Beck Depression Inventory (BDI-II) was also administrated.

4.3.3 Magnetic Resonance Spectroscopy

The experiment was conducted at the Unité de Neuroimagerie Fonctionelle (UNF) of the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, using a Siemens 3T whole-body magnetic resonance imaging (MRI) system (Siemens, Erlangen, Germany). This study was approved by the research and community ethics boards of the UNF and the Université de Montréal (Montreal, Quebec, Canada). All subjects gave written informed consent subsequent to careful screening for MRI compatibility and were financially compensated for their participation. ROIs were positioned using a rigorous anatomical localization protocol. Subjects were placed in the scanner and underwent a localizing scan parallel to the hippocampus (anterior commissure/posterior commissure; AC-PC). Voxels were then positioned for the hippocampus (20 x 40 x 16 mm), DLPFC (16 x 16 x 16 mm), and M1 (16 x 20 x 32 mm) bilaterally. All voxels were placed on an AC-PC-oriented oblique axial slice corresponding to the ROI first on a sagittal view and were then confirmed with coronal and axial views to ensure an adequate distance from the ventricles, fatty tissue, and bone. Single-voxel 1H-MRS measurements were performed using a PRESS (Point RESolved Spectroscopy) sequence (TE [echo time] = 30 ms; TR [repetition time] = 1500 ms; 256 acquisitions; 1200-Hz bandwidth; 1024 points; duration, 6.5 minutes) on a 12-channel head coil. To ensure that all ROIs could be captured within reasonable scan duration and to ensure the comfort of participants in the scanner, a moderate TR and a shorter TE to balance T1-associated and T2-associated signal losses and scan times were chosen. Outer-volume suppression bands contiguous with the PRESS-selected volume were automatically placed in all three dimensions based on the voxel size of each ROI.

The linear combination model[49] was used for metabolite quantification. It is an operator-independent spectral analysis software that estimates metabolite concentrations and their ratios, relative to Cr/phosphocreatine, using a set of basis reference spectra acquired from

individual metabolites on the magnetic resonance instrument. This software uses complete model spectra, rather than individual resonances, to incorporate maximum information and uniqueness into the analysis. A constrained regularization method accounts for differences in phase, baseline, and line shapes between the in vitro and in vivo spectra and estimates the metabolite concentrations and their uncertainties. Finally, the analysis is fully automatic in that the only input is the time-domain in vivo data and is useful in clinical studies because the results are user independent, with no subjective interaction.[49] NAA/Cr, Glx/Cr, and mI/Cr were only analyzed if the estimated uncertainty, calculated as Cramer ratio lower bounds (%SD), was less than 20%.

4.3.4 Statistical Analysis

Statistical analyses were done using SPSS statistical software (version 16.0; SPSS, Inc., Chicago, IL). Coefficients of variance (CVs) were calculated for each metabolite. All subsequent statistical analyses were performed only for metabolite ratios that had overall CV values < 20% (i.e., NAA/Cr, Glx/Cr, and mI/Cr). Spectra from both hemispheres within each ROI were combined because it was not possible to determine exactly which side of the brain received the impact in concussed athletes without the use of sensor-equipped helmets. However, the literature suggests that there are no lateralization effects in the regions examined in the present study.[50–53] The different metabolites in any given voxel are unrelated in principle and are not correlated.[50] As such, metabolite ratios of the two groups were compared using two-way group x time repeated-measures analysis of variance (ANOVA) for each metabolite in each ROI. Tests of simple effects were carried out on metabolites that differed between concussed and control athletes. Neuropsychological results of the two groups as well as postconcussion and depressive self-reported symptoms were also compared using two-way group x time repeated-measures ANOVA. Tests of simple effects were carried out on results that differed between concussed and control athletes. Finally, Pearson's correlations were performed on significant neurometabolic findings and other variables of interest (number of previous concussions as well as postconcussion and depressive self-reported symptoms).

4.4 Results

4.4.1 Postconcussion and depressive symptoms

Total symptom scores from the PCSS revealed a significant main effect of group (F(1, 17) = 8.694; p = 0.009) and a main effect of time (F(1, 17) = 14.188; $p < 0.05$). Analysis also revealed a significant interaction (F(1, 17) = 19.558; $p < 0.05$), where concussed athletes were significantly more symptomatic than controls in the acute postinjury phase ($p < 0.05$), but were statistically equivalent to controls in the chronic postinjury phase (p = 0.368). The same pattern of results was observed for the total BDI symptom scores. A significant main effect of group (F (1, 17) = 8.566; p = 0.009), a main effect of time (F(1, 17) = 12.325; $p < 0.05$), and a significant interaction (F(1, 17) = 21.995; $p < 0.05$) were found, where concussed athletes reported more depressive symptoms in the acute phase ($p < 0.05$) and were statistically equivalent to controls in the chronic phase (p = 0.603). Because some items in this questionnaire overlap with the symptoms of a concussion, notably, fatigue, reduced concentration, irritability, changes in sleep patterns, lack of energy, indecisiveness, agitation, and crying, a supplementary analysis was carried out to see whether the differences between groups were still significant after separating these symptoms (BDI - concussion) from the rest of the items specific to depression (BDI - depression). Results revealed that the interaction was still present (F 1, 17) = 21.995; $p < 0.05$). During the acute phase, concussed athletes differed from control athletes in the BDI-concussion ($p < 0.05$) and the BDI-depression symptoms ($p < 0.05$), whereas the two groups were equivalent in the chronic postinjury stage.

4.4.2 Neuropsychological Assessment

HVLT results revealed a main effect of time (F(1, 17) = 14.425; $p < 0.05$), no main effect of group (F(1, 17) = 1.604; p = 0.222), and a significant interaction (F(1, 17) = 4.723; $p < 0.05$), where the concussed group had lower performance than the control group in the acute phase ($p < 0.05$), and performance returned to control levels in the chronic phase (p = 0.921). Results for SDMT, Verbal Fluency, and CTB revealed a similar pattern of results: a significant main effect of time (SDMT: F(1, 17) = 4.588, $p < 0.05$; Verbal Fluency: F(1, 17) = 11.433, $p < 0.05$; CTB: F(1, 17) = 8.918, $p < 0.05$), for which performance was higher in the chronic

postinjury phase, and no significant main effect of group or interaction between factors ($p > 0.05$). CTA results revealed a main effect of group ($F(1, 17) = 5.459$; $p < 0.05$), where the concussed group had lower performance, and no main effect of time ($F(1, 17) = 3.141$; $p = 0.094$) or interaction between factors ($F(1, 17) = 0.334$; $p = 0.571$). Finally, results for BVMT and PSU tests revealed no main effect or interaction between factors ($p > 0.05$).

4.4.3 Magnetic Resonance Spectroscopy

Analysis of the hippocampus (Fig. 1) revealed no significant main effect or interaction for all three metabolites ($p > 0.05$).

Within DLPFC (Fig. 2), Glx-Cr concentrations showed no main effect of group ($F(1, 17) = 0.544$; p = 0.471) and no main effect of time ($F(1, 17) = 0.577$; $p = 0.458$). However, there was a trend toward a significant time x group interaction ($F(1, 17) = 3.508$; $p = 0.078$), where concentrations were equivalent between groups in the acute phase ($p = 0.389$), whereas the concussed group showed higher levels than controls in the chronic phase ($p = 0.062$). With regard to NAA/Cr and mI/Cr, no main effect or interaction was found ($p > 0.05$).

Analysis of Glx/Cr in M1 revealed no main effect of group ($F(1, 17) = 0.782$; $p = 0.389$) and no main effect of time ($F(1, 17) = 0.980$; $p = 0.336$). However, there was a significant interaction between factors ($F(1, 17) = 5.076$; $p < 0.05$), where the concussed group showed higher Glx-Cr levels in the chronic phase ($p < 0.05$) that were not present in the acute phase ($p > 0.05$). NAA-Cr analysis revealed no main effect of time ($F(1, 17) = 0.854$; $p = 0.368$), no main effect of group ($F(1, 17) = 0.160$; $p = 0.694$), and a significant interaction between factors ($F(1, 17) = 5.575$; $p < 0.05$). The concussed group showed equivalent NAA/Cr levels at both time points ($p > 0.05$), whereas the control group showed lower concentrations in the chronic postinjury phase, compared to baseline ($p < 0.05$). No main effect or interaction between factors was found with regard to mI/Cr concentrations ($p > 0.05$). Results in M1 are presented in Figure 3. Finally, no correlation was found between neurometabolic changes in M1 as well as number of previous concussions or severity of self-reported symptoms.

4.5 Discussion

The present study investigated the effects of a sports-related concussion on the neurometabolic, neuropsychological, and symptomatic profiles of female athletes. Globally, concussed athletes showed acute neuropsychological alterations and symptoms that resolved within 6 months. Concussed athletes also displayed metabolic alterations that seemed to predominantly target Glx levels, most notably reflected by its increase in prefrontal and motor areas in the chronic postinjury phase. Finally, control athletes showed NAA decreases in M1 in the follow-up scan that were not present in the baseline scan.

Concussed athletes experienced a higher number of postconcussive and depressive symptoms in the acute phase than control athletes, which disappeared when the athletes were evaluated 6 months later. These results are consistent with previous studies showing clinical recovery within the first week postinjury in the majority of cases.[4,54] Depressive symptoms after brain injury in athletes have previously been shown using the BDI-II.[32] However, the overlapping of postconcussion and depressive symptoms has not been taken into account. The results from the present study show that concussed athletes present depressive symptoms even after controlling for concussive symptoms in the acute phase, but not in the chronic phase. In some cases, concussed athletes may have to refrain from physical activity or even temporarily abandon the practice of their sport. Concussions can also lead to academic difficulties as well as changes in athletic career. This could be a mitigating factor explaining the presence of depressive symptoms in the acute phase. Also, depressive symptoms could be related to the perturbation of the neural substrates underlying these symptoms,[32] and future studies should assess directly these possibilities in female athletes.

At the neuropsychological level, different profiles were obtained depending on the evaluated function. In general, concussed athletes were equivalent to control athletes at both time points in tests assessing visual selective attention, visual memory, mental flexibility, and speech fluency. This absence of neuropsychological abnormalities is common to many concussion studies[55,56] and may point to the limited sensitivity of neuropsychological tools to detect subtle brain dysfunction associated with brain injury or lack thereof. However, two neuropsychological tests revealed significant differences between groups. Concussed athletes

displayed impaired verbal learning in the acute phase, which returned to the level of control athletes in the postinjury phase. Further, concussed athletes had lower scores across time in a test assessing visual scanning and processing speed. This persistent effect could be more problematic considering that sports demand rapid, effective information processing to allow adequate decision making and execution of complex motor sequences. Previous studies have shown that the risk of sustaining a concussion is higher in concussed athletes,[57] and female athletes who had sustained multiple concussions are particularly vulnerable.[7] Reduced processing speed could be one of the factors underlying this susceptibility to brain trauma. Alterations in processing speed could also reflect persistent alterations in brain regions or neuronal pathways underlying these specific cognitive functions.

The present study suggests the presence of neurometabolic changes occurring at later stages after a concussion. These changes were characterized by increased levels of Glx in the prefrontal and motors areas in the chronic phase, which were not present in the acute phase. Consistent with previous studies, increased Glx levels could indicate alterations in the excitatory neurotransmission process, which have been reported in the chronic phase after concussions in professional athletes,[25] but also in the days post-TBI in the general population.[23,24] Glx is the primary excitatory neurotransmitter in the brain, and studies have shown that Glx resonance is a predictor of outcome after severe TBI.[23] A blow to the skull causes immediate biomechanical injury to the brain, resulting in a pathophysiological cascade of disruptions that include abrupt neuronal depolarization, release of excitatory neurotransmitters, ionic shifts, changes in glucose metabolism, altered cerebral blood flow, and impairments in axonal function.[5,58] This cascade of disturbances in cellular metabolism generally recovers after a period of 7 days in humans,[5] possibly explaining the absence of differences between the subject groups in the present study, because concussed athletes were scanned, on average, 9 days postinjury. However, this increase in Glx was observed 6 months postconcussion in female athletes, which points to a secondary mechanism that could be related to glutamatergic dysfunction.[59] Increases in Glx levels in the chronic phase could be related to higher concentrations of Glx at the glutamate receptors. This opens the ion channels, allowing calcium to enter the cell, causing delayed excitoxicity,[60] and, ultimately, causing cell death by turning on the N-methyl-D-aspartate receptors.[61] This neurotoxicity caused by higher

Glx concentrations points to different mechanisms of injury, depending on the time elapsed since the insult to the brain. Finally, hormonal changes may partly explain abnormal Glx levels, especially in female athletes, as well as compensatory plastic changes that may mediate acute and long-term response to TBI. The Glx signal combines glutamate and glutamine peaks and it is not possible to distinguish the two components with a 3.0T MRI system. Glutamate release during neurotransmission leads to astrocytic uptake and conversion of glutamate to glutamine by the enzyme, glutamine synthase.[62] In the study of Lin and colleagues,[59] glutamine was increased, suggesting increased astrocyte oxidative metabolism, and glutamate was decreased, suggesting reduced neuronal oxidative metabolism. Thus, concussions may induce glutamatergic dysfunction by changes in the Glx cycle. Because it is possible to separate glutamate from glutamine signals with higher field scanners, future studies should investigate the pattern of changes of these two metabolites separately to assess the hypothesis of glutamatergic pathway disruptions after brain injury.

Finally, the present data suggest that the brain may still be vulnerable in asymptomatic athletes and could be more sensitive to further subconcussive and concussive blows to the head several months after the last brain trauma. However, these dysfunctions cannot readily explain the neuropsychological deficits and symptoms present in the acute phase because no neurometabolic alterations were found in the weeks after brain trauma.

Decreases in NAA (marker of neuronal integrity) levels in M1 were found in control athletes when they were tested 6 months after their first scan. This is in line with a previous prospective study that reported a similar decrease in NAA levels in female hockey players who never sustained a concussion and were scanned three times in a season (72 hours, 2 weeks, and 2 months). This effect was found only in female athletes and was not present in male hockey players, suggesting a higher sensitivity of female athletes to subconcussive blows to the head over the course of a season.[63] Abnormal NAA levels at the second time point could thus reflect increased exposure to subconcussive blows in a brain region particularly vulnerable to shear strain and rotational forces.[64] Subconcussive head blows were, however, not directly assessed in the present study, and, as such, no conclusion can be drawn with regard to their effect on neurometabolism. Future studies are needed to directly test this hypothesis by carefully documenting any impact to the head sustained by athletes.

To conclude, even though concussive injuries do not typically result in observable brain trauma using conventional imaging techniques, female concussed athletes demonstrated postconcussion symptoms and neuropsychological alterations in the acute phase that seem to resolve in the chronic postinjury phase. These symptomatic and neuropsychological profiles do not appear to be related to alterations in cellular metabolism, because neurometabolic abnormalities are only present in the chronic postinjury phase. Alterations in cellular metabolism in prefrontal and motor regions are present months after injury in female athletes, highlighting the need to assess acute and long-term effects of injury. Finally, future investigations should directly compare female and male athletes to better understand potential gender differences in anatomical and metabolic alterations as well as recovery timelines.

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4.7 Author Disclosure Statement

No competing financial interests exist.

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4.9 Figures

Figure 1. Spectra in hippocampi. Left. Line graphs of the Glx/Cr ratios; Center. Line graphs of the mI/Cr ratios; Right. Line graphs of the NAA/Cr ratios. Standard errors are representing by vertical bars.

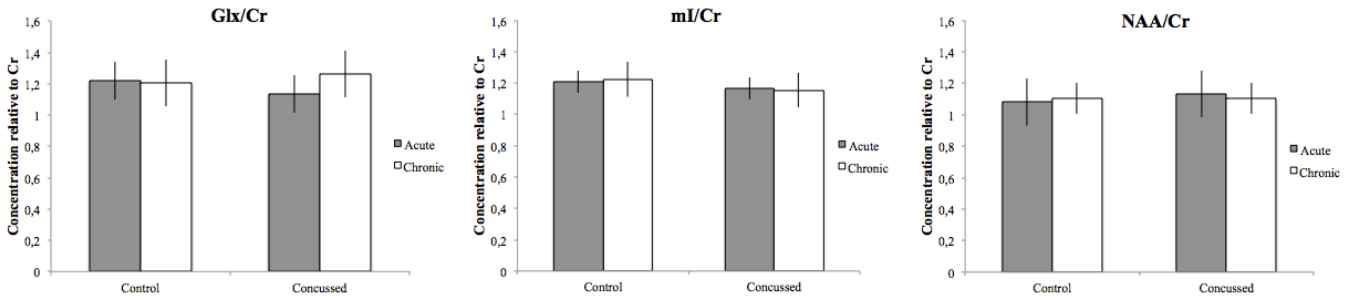

Figure 4-1. Spectra in hippocampi

Figure 2. Spectra in DLPFC. Left. Line graphs of the Glx/Cr ratios; Center. Line graphs of the mI/Cr ratios; Right. Line graphs of the NAA/Cr ratios. Standard errors are representing by vertical bars.

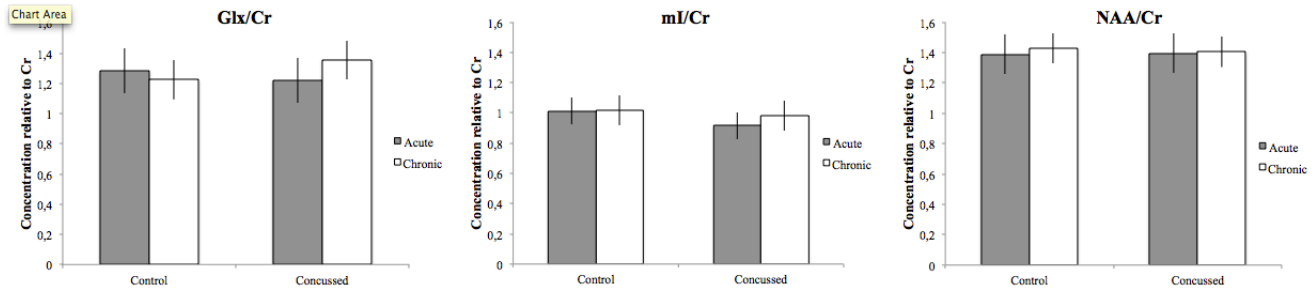

Figure 4-2. Spectra in DLPFC

Figure 3. Spectra in M1. Left. Line graphs of the Glx/Cr ratios; Center. Line graphs of the mI/Cr ratios; Right. Line graphs of the NAA/Cr ratios. Standard errors are representing by vertical bars. An asterisk indicates a significant difference of $p < .05$.

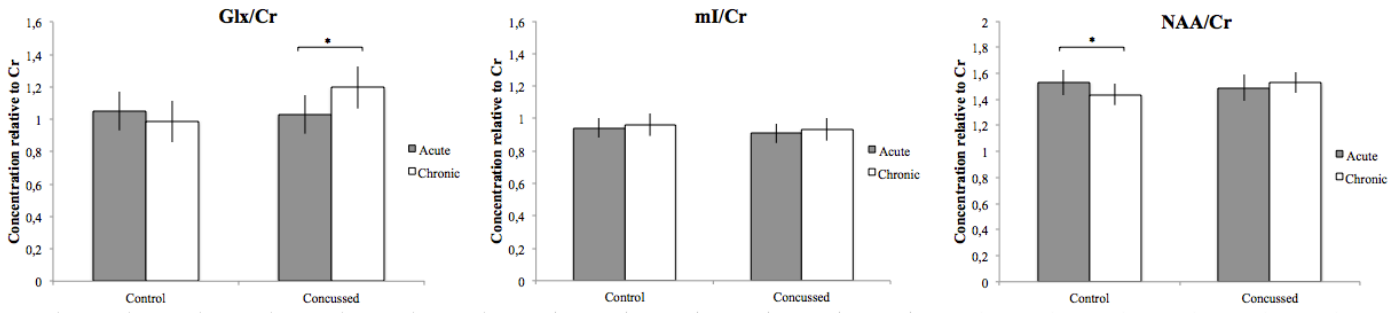

Figure 4-3. Spectra in M1

4.10 Tables

Tableau 4-1. Demographic data, number of concussions and symptoms score for control and concussed groups

Group	*Age*	*Education (years)*	*Number of concussions (mean)*	*PCSS Score*		*BDI symptom score*	
				Time 1	*Time 2*	*Time 1*	*Time 2*
Control	21.11 (1.36)	15.0 (1.22)	0	4.0 (3.81)	5.76 (8.30)	1.33 (1.80)	2.56 (4.03)
Concussed	21.4 (1.71)	14.6 (2.17)	2 (1-4)[a]	25.10 (14.25)	2.90 (5.02)	10.30 (5.77)	1.80 (1.93)

Numbers in parentheses represent the standard deviation.

[a]Numbers in parentheses represent the range.

PCSS, Post-Concussion Symptoms Scale; BDI, Beck Depression Inventory.

CHAPITRE 5 ARTICLE 4: LONG-TERM ABNORMALITIES IN THE CORPUS CALLOSUM OF FEMALE CONCUSSED ATHLETES

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5.1 Abstract

Concussion is an injury affecting millions of individuals annually that can be associated with long-term sequelae. Recent studies have reported long-term abnormalities in the white matter (WM) tracts of male athletes. The corpus callosum (CC) and corticospinal tract (CST) have been shown to be particularly vulnerable to concussion, which may be related to abnormal interhemispheric functional connectivity and motor impairments. These anatomical pathways, however, have not been investigated in female athletes despite the functional significance of the CC and CST to adequate sports performance. In the present study, 8 healthy, unconcussed female athletes (soccer, hockey) were compared with 10 female athletes (soccer, hockey, water polo) 6 months post-concussion. Diffusion tensor imaging (DTI) of the CC and CST was conducted in a 3T magnetic resonance imaging (MRI) scanner. DTI analysis showed no significant differences between groups within the CST but revealed differences between groups in the CC. The concussed group had lower mean diffusivity ($t = 2.14$; $p = 0.048$) and lower radial diffusivity ($t = 2.91$; $p = 0.010$) in the region of the CC projecting to the prefrontal cortex. A lower volume of WM fibers was found in the region projecting to the premotor and supplementary motor areas ($t = 2.14$; $p = 0.048$). Finally, lower axial diffusivity (AD) was observed in the CC area projecting mainly to the parietal and temporal area ($t = 2.23$; $p = 0.041$). Long-term alterations in the CC of female athletes appear to affect mostly the anterior part of the CC projecting to the prefrontal and premotor areas. Further studies are needed to determine whether these alterations are associated with a higher risk of sustaining a subsequent concussive injury.

Keywords: athletes; corpus callosum; diffusion tensor imaging; female; sports concussion

5.2 Introduction

Sports-related concussion is recognized as a worldwide problem affecting millions of athletes every year.[1] Concussion is generally defined as a closed traumatic brain injury (TBI) due to either a direct blow to or a shaking of the head by an impulsive force, resulting in a transient alteration in mental status and brain function.[2,3] This sudden change in mental status appears to be temporary, but recent studies have demonstrated long-term alterations following injury, suggesting that concussions may be more severe than previously thought. These alterations can be found months after a concussion and affect many aspects of an athlete's life because of cognitive impairments and affect depreciation.[4] Structural and functional brain changes have also been observed using various methods of investigation (for a review, see Henry, 2014).[5] For example, microstructural alterations affecting white matter (WM) integrity have been found in football players 1 week post-concussion. These alterations were still present 6 months post-concussion despite the absence of self-reported symptoms.[6] Another study has found diffuse axonal injury of the WM skeleton following a concussion in a group of male and female athletes[7] using diffusion tensor imaging (DTI).

Diffusion magnetic resonance imaging has proven to be an effective method to investigate the anatomical consequences of concussion because of its sensitivity to WM changes. This method allows the mapping of water diffusion in the brain using the main indices that are fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). These measurements are based on the fact that the network of fibers within the brain is composed of a distinct microstructure that constrains the flow of water molecules.[8] In traumatology studies, opposite variations have been reported in various brain regions. Some studies have found reduced FA combined with increasedMD,[9–14] whereas other studies have found increased FA and decreased MD.[6,15–17] Microstructural alterations have been demonstrated in various regions of the brain; however, the corpus callosum(CC) and the corticospinal tract (CST) appear to be particularly vulnerable to long-term abnormalities both in female[18] and male concussed athletes.[6,19]

In the present study, WM integrity of the CST and the CC was assessed in a population of female concussed athletes. The CC is the principal commissure connecting the two

hemispheres and has been shown to be particularly affected by concussive injury due to its vulnerability to the rotational accelerations/decelerations that usually accompany concussions.[20,21] Indeed, CC abnormalities have been repeatedly demonstrated using metabolic[20] and anatomical measures.[22] Functionally, the CC is heavily involved in bimanual coordination, [23] which has been shown to be impaired in patients with moderate to severe TBI.[24] Further, the same study reported that bimanual coordination test scores were correlated with the level of structural damage affecting the CC.[24] The CST also appears to be vulnerable to concussions. For example, Henry and colleagues[6] reported abnormal FA, AD, and MD values in the acute and chronic phases of concussion. Numerous studies have also shown abnormalities in the neurophysiology of primary motor cortex (for a review, see Major and co-workers[25]), which appear to be associated with deficits in motor performance.[26–28] As a result, damage to the CST (and CC) following concussion may have important functional impacts, particularly in a sports context where complex and fast motor responses are required.

The aim of the present study was to investigate long-term WM abnormalities in female concussed athletes. Compared with their male counterparts, female athletes appear to be at greater risk of sustaining a concussion and they exhibit a higher number of symptoms in the acute phase and typically require a longer recovery time.[29–31] Comparing equivalent sports in terms of rules, Gessel and collaborators[32] reported a higher risk in female soccer players to sustain a concussion compared with male soccer players. However, these results have to be taken with caution considering differences in self-reported symptoms at baseline, where female athletes are more likely to report any symptom associated with a concussion than male athletes (see Brown and colleagues,[33] for a review and meta-analysis). These inconsistencies in reporting symptoms and the lack of consensus on the role of sex in concussion management highlight the need to assess gender-specific brain responses to injury.

In accordance with previous studies assessing male athletes, it was hypothesized that female concussed athletes would demonstrate WM alterations 6 months post-injury in the CST and CC. Exploratory analyses were also performed on the six subdivisions of the CC described by Hofer and collaborators[34] to determine whether specific interhemispheric projections are more vulnerable to the effects of concussion. In addition to parameters normally used (FA, MD, AD, RD), other indices were calculated to assess diffusion changes

in the brain. The mode, which specifies the type of anisotropy as a continuous measure reflecting differences in shape of the tensor ranging from planar to linear in which one fiber population orientation predominates,[35] was also computed. Finally, the volume was assessed to characterize the number of WM fibers in the regions of interest.

5.3 Methods

5.3.1 Participants

Participants in this study were all female athletes involved in hockey, soccer, or water polo university sports teams. They were recruited with the help of team physicians and physiotherapists. The following exclusion criteria were applied: history of alcohol and/or substance abuse, psychiatric illness, learning disability, neurological disorder, and TBI unrelated to contact sports. None of the participants were taking psychotropic medication at the time of testing. The control group was composed of 8 female athletes with no history of TBI, sports-related or otherwise. The experimental group consisted of 10 female athletes who suffered a sports-related concussion 6 months prior to testing. All concussed athletes followed a strict return-to-play protocol after their injury. Control and concussed athletes were equivalent with regards to age ($t(16) = 0.348$; $p = 0.563$), and level of education ($t(16) = 0.168$; $p = 0.687$), and all TBIs were classified as mild (Glasgow Coma Scale score >13 at the time of injury). A standardized concussion history form based on athlete recollection was administered in an interview setting to obtain detailed information about the number of previous concussions (if any), approximate date(s) of each concussion, description of injury(ies), and nature and duration of relevant post-concussion symptoms (confusion and/or disorientation, retrograde and/or anterograde amnesia, and loss of consciousness). Demographic information and injury data are presented in Tables 1 and 2.

5.3.2 Neuroimaging

5.3.2.1 MR Imaging

The experiment was conducted at the Unité de Neuroimagerie Fonctionelle (UNF) of

the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal (CRIUGM), using a Siemens 3T whole-bodyMRI system (Siemens, Erlangen, Germany). The study was approved by the Research and Community Ethics Boards of the UNF and Université de Montréal. All subjects gave written informed consent following careful screening for MRI compatibility and were financially compensated for their participation.

5.3.2.2 Diffusion Tensor Imaging

The imaging parameters were as follow: diffusion weighting gradients applied in 64 directions with b values of 0 and 700 sec/mm^2 and four averages in each direction, repetition time (TR) of 12/800 msec, echo time (TE) of 101 msec, field of view of 256 x 256 mm^2, matrix size of 128 x 128 with partial Fourier reconstructed to 6/8, slice thickness of 2 mm with 0.6-mm gaps and 75 slices. Three-dimensional (3D) T1-weighted images of corresponding subjects were also acquired with an inversion recovery rapid gradient echo sequence using a 3T Trio Siemens MRI scanner. Acquisition parameters were as follows: inversion time (TI)/TR/TE = 1500/2500/3.83 msec; flip angle = 15 degrees; slice thickness = 0.9 mm, with an acquisition matric of 256 x 256 x 255. Total scan time was 28 min (4 min localizers, 9 min magnetization-prepared rapid gradient-echo [MP-RAGE] and 15 min DTI).

The diffusion images were preprocessed using the Imeka pipeline (www.imeka.ca) following Whittingstall and associates.[36] Diffusion images were de-noised to correct for the Rician noise bias in the data using the NLMEANS tool.[37] The diffusion images were then upsampled to a 1-mm isotropic resolution; diffusion tensors and the corresponding FA maps were estimated using Diffusion in Python (Dipy).[38] From this, the single fiber response function was estimated from all FA values above a threshold of 0.7. This single fiber response was used as input to spherical deconvolution to compute the fiber orientation distribution function (fODF) with a maximal spherical harmonics order of 8. The T1 image was then nonlinearly registered to the diffusion data and a WM mask was computed using the ANTS software.[39] Streamline deterministic tractography was done on the field of fODF with 500,000 streamlines with the following tracking parameters: step size 0.5 mm, minimum/maximum streamline length 10/200 mm, minimum radius of curvature 1 mm, and fODF amplitude cutoff at 0.1, as provided by the MRtrix software (The Brain Research Institute, Melbourne,

Australia).[40] Tractography results were then reviewed and superimposed on the T1 image for quality control using the FiberNavigator (Sherbrooke Connectivity Imaging Lab, Quebec, Canada).[41]

Once the whole-brain tractography was computed, the six parts of the CC were extracted using regions of interest (ROIs) as defined by Hofer and colleagues.[34] This is done automatically using ROIs from Freesurfer (Laboratory for Computational Imaging, Charlestown, MA) and the novel TractQuerier software, as described by Wassermann and co-workers.[42] The CC was analyzed both as a whole and as segmented regions to better investigate possible microstructural alterations in specific regions. Hofer and colleagues[34] classified tracts according to their cortical projections, distinguishing between fibers associated with prefrontal (CC1), premotor and supplementary motor areas (CC2), primary motor cortex (CC3), primary sensory cortex (CC4), and primary parietal temporal and occipital cortical regions (CC5) (see Hofer and Frahm[34] for more information of the partitioning schemes of the CC). In the present study, the last region was subdivided into two distinct areas: one region corresponds to the area of the CC projecting mainly to the parietal and temporal cortex (CC5) and the most posterior region corresponds to the area of the CC projecting to the occipital lobe (CC6) for a total of six sub-regions. For each part of the WM CC bundle and the left and right CST, the diffusion metrics (FA, MD, AD, RD), the volume, and mode were calculated. Student's t tests between the two groups were performed on the derived scalar images to determine if there were any differences between the two groups. Figure 1 illustrates fibers of CC1 to CC6 regions in a control subject based on the partitioning approach. Figure 2 illustrates left and right CST in the same control subject.

5.4 Results

No significant differences between groups were found for both left and right CST on all diffusion measures. Also, there were no differences on all diffusion measures between groups when comparing the whole CC. As an exploratory analysis, individuals with a single concussion (n = 6) were directly compared with individuals with multiple concussions (n = 4) with regards to the whole CC. Significantly lower AD values were found in the multiple

concussion group (t = 2.49; p = 0.037). No differences were found for the CST between single concussion and multiple concussion groups. Partitioning the CC in six sub-divisions revealed significant differences between groups, notably in the anterior part of the WM tract.

In the CC1 region, corresponding to the region projecting to the prefrontal cortex, lower levels of MD (t(16) = 2.14; p = 0.048; Fig. 3A) were found in the concussed group as well as a lower RD (t(16) = 2.91; p = 0.010; Fig. 3B). A trend toward a higher mode (t(16) = 1.79; p = 0.09) and a lower volume (t(16) = 1.89; p = 0.08) in concussed athletes was also observed in this region. A significant lower volume in concussed athletes was found in the CC2 region (premotor and supplementary motor areas; t(16) = 2.14; p = 0.048; Fig. 3C), whereas all other measures were not significantly different. No significant difference on all anisotropic measures was found in CC3 and CC4 regions. A lower level of AD (t(16) = 2.23; p = 0.041; Fig. 3D) was found in concussed athletes in the region of the CC projecting to the parietal and temporal areas (CC5), whereas other anisotropy measures did not differ between groups. Finally, no significant difference between groups was found in region CC6 corresponding to the most posterior part of the CC.

5.5 Discussion

In the present study, the long-term impacts of sports concussions on the integrity of the CC and the CST were investigated in a sample of concussed female athletes 6 months after their last concussion. First, no microstructural alterations were found in the CST corresponding to motor fibers responsible for the expression of voluntary movement.[43,44] This result contrasts with another study from our group where increased MD in the CST bilaterally was found approximately 18 months following the last injury.[45] In this last study, however, female concussed athletes had a higher average number of concussions (average of 2.6 concussions; ranging from 1 to 8), and most had a history of multiple brain injuries in the context of sports, suggesting a cumulative effect of sports concussions on the microstructure of the CST. In the present study, the majority of athletes sustained only one concussion (6/10) and followed a safe return-to-play protocol supervised by team physicians and physiotherapists, suggesting that additional concussive events may further affect WM

integrity, and more specifically the CST. The possibility that WM damage may be more significant in multiple concussion athletes is supported by the fact that no difference was found between control and concussed athletes for the CC. However, when multiple concussion athletes were compared with single concussion athletes, lower AD values were observed in the multiple concussion group. This is in line with previous studies showing that concussions can have cumulative effects in a variety of domains including symptom severity and duration,[46] likelihood of subsequent injury,[46] cortical excitability,[47] and sleep.[48]

Significant differences affecting various measures of anisotropy, however, emerged when the CC was analyzed in sub-regions based on their projections to different parts of the cortex. This result is particularly important because it suggests differential sensitivity to subtle changes of anisotropy depending on the area, which is in line with previous studies that have show both metabolic[20] and anatomical[49,50] abnormalities limited to the genu of the CC. Similarly to these findings, segmented analysis revealed a lower level of MD in concussed athletes in the callosal region projecting to the prefrontal cortex (CC1). This measure represents the average molecular diffusion and is thought to be affected by cellular size and integrity.[8] A decrease in MD in female concussed athletes could point to cytotoxic edema and inflammation due to homeostatic membrane dysfunction.[51] Although cellular edema is thought to be an acute phenomenon,[15,17] the lower level of MD in the chronic phase of the injury suggests a chronicity of this process in female concussed athletes. This result is consistent with a previous study assessing male athletes, where lower levels of MD were also found in the chronic phase of the injury.[6] Axonal injury affecting the prefrontal cortex has been linked to impairments in executive function in mild traumatic brain injury (mTBI) patients.[52] Taken together, it is possible that the alterations affecting prefrontal regions are also related with anisotropy changes in callosal fibers projecting to the prefrontal cortex as it was demonstrated in the present study.

Analysis of CC1 also revealed lower RD in the concussed group. Lower levels of RD have been found in another study with concussed athletes[53] and in mTBI patients.[16] Sasaki and colleagues[53] attributed this abnormality to a restriction of diffusion in the extracellular space perpendicular to the main axis that could either be caused by axonal swelling or be due to more glial cells taking up the extracellular space. Mayer and colleagues[16] suggested that this

anisotropy change could be related to cytotoxic edema or changes in water content within the myelin sheath and that biomechanical force typically results in axonal stretching of supporting structures, resulting in decreased extracellular water and increased intracellular water. The decrease in extracellular water would then lead to a reduction in diffusivity perpendicular to the axon (radial diffusivity).[16] In the present study, a trend toward reduced volume of the WM tract was also found in this region, which means that a reduced number of WM fibers composed the tract projecting to the prefrontal areas. This lower volume could also be caused by axonal stretching,[54,55] leading to axon death and reduced numbers of WM fibers. In this region, a trend toward a higher mode was also found in athletes with a history of concussion. This suggests that mode tends to be more linear than planar when compared with control subjects.

In CC2, corresponding to the premotor and supplementary motor segments of the CC, a significantly lower volume was found in the concussed group. As for region CC1, lower volume could be related to a degradation of WM fibers caused by axonal swelling or degradation of glial cells. In concussed athletes, WM volume reduction in the premotor portion of the CC could be associated with decreases in speed of information propagation of motor information because this region mainly projects to the premotor cortex and is involved in motor command and coordination.[56] These abnormalities may be one of the factors responsible for the greater risk to sustain a subsequent concussion in athletes with a history of TBI.[57] Another significant difference was found in sub-region 5, projecting mainly to the parietal and temporal cortex, which exhibited lower AD values in the concussed group. AD quantifies the diffusion along the axon parallel to the predominant fiber orientation and a decrease of this measure is thought to reflect axonal degeneration.[58,59] Other studies have observed decreased AD with demyelination.[60] This change in AD could underlie axonal damage in the long-term course of a concussion in female athletes. Finally, the occipital region (CC6) exhibited no significant differences between concussed and control athletes. This suggests that more posterior areas of the CC are free from long-term damage following brain injury in female athletes, highlighting the differential vulnerability of specific regions of the CC to the biomechanical forces inducing a brain injury. Taken together, these data demonstrate long-term microstructural alterations in the CC of female concussed athletes that

are predominantly located in anterior areas.

It should be noted that some factors limit the generalization of the present results. An important limitation related to the small sample sizes is that the current findings may not generalize to all sports. It is also not possible to determine whether the present data can be extended to mTBI occurring in the general population or to male athletes. Future studies should consider these aspects to allow a better understanding of the long-term effects of a sports-related concussion. Despite these limitations, the present study demonstrates the effectiveness of DTI and anisotropy measures in the assessment of persistent WM alterations in female concussed athletes. These brain abnormalities affecting predominantly the CC are still present months after the last concussion despite the absence of self-reported symptoms and supervised return-to-play protocols.

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5.7 Author Disclosure Statement

No competing financial interests exist.

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5.9 Figures

Figure 1. Coronal view of the left and right corticospinal tracts from a control subject overlaid over her individual anatomical reference image.

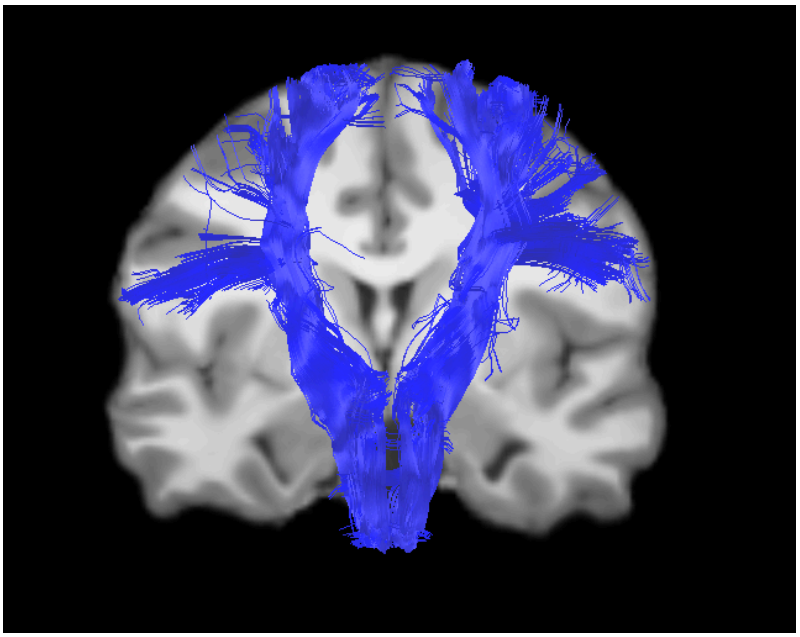


Figure 5-1. Coronal view of the left and right corticospinal tracts

Figure 2. Sagittal view of the callosal fiber tracts from a control subject overlaid over her individual reference image. Representation of the divisions of the corpus callosum comprising bundles projecting to the prefrontal lobe, premotor and supplementary motor areas, primary motor cortex, primary sensory cortex, parietal and temporal lobe, and occipital lobe.

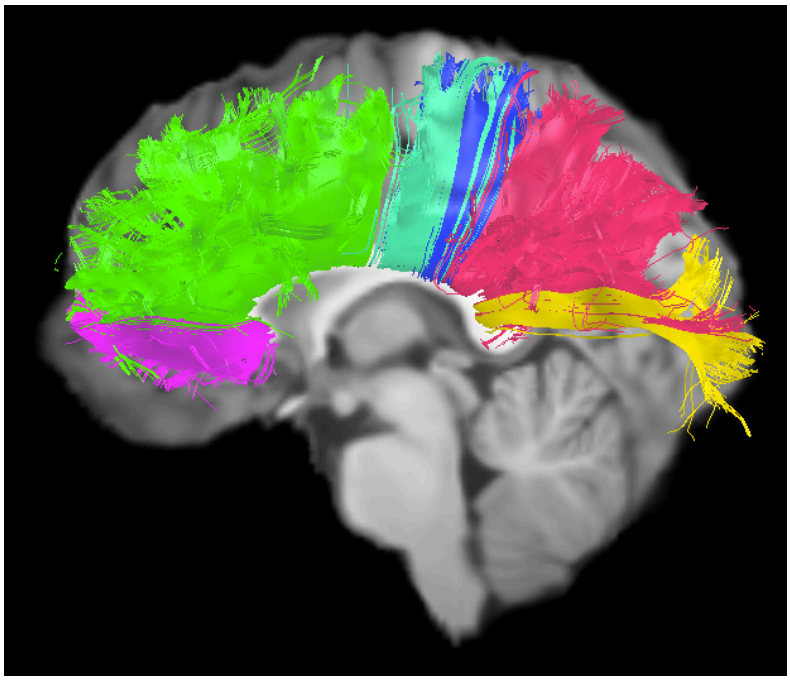
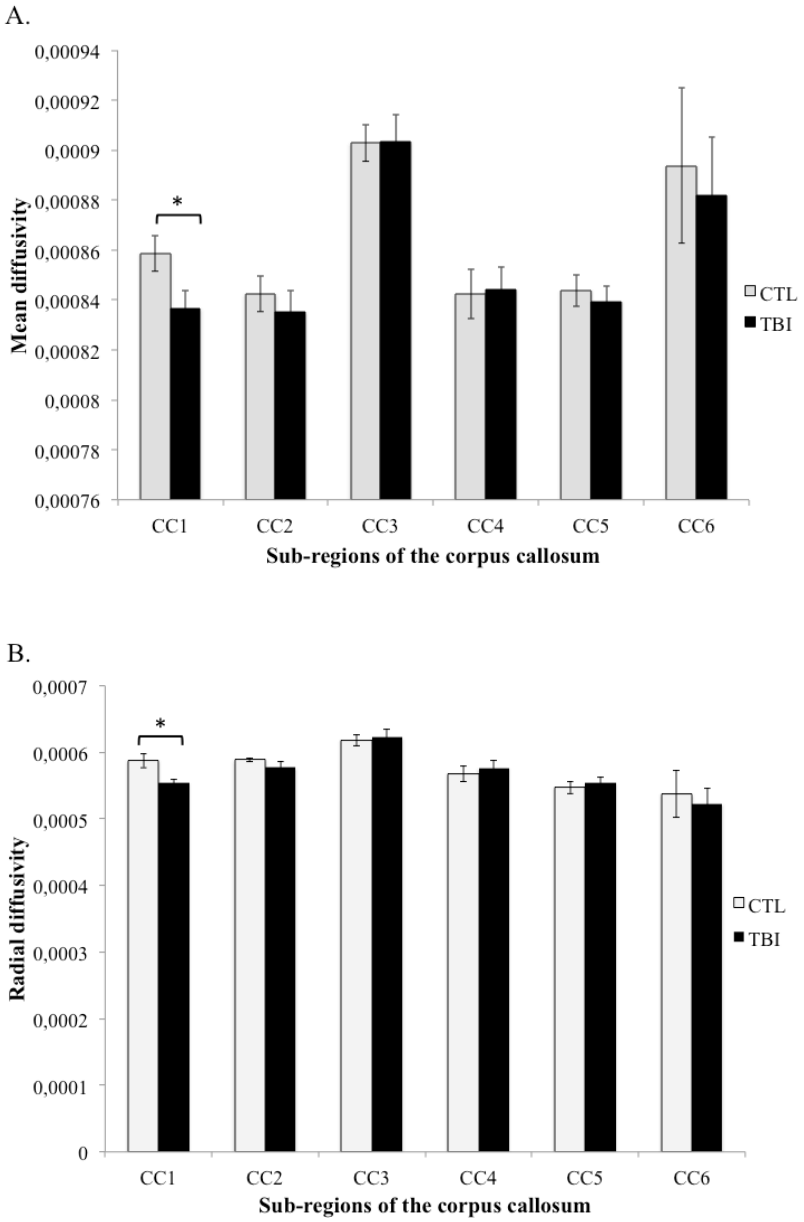


Figure 5-2. Sagittal view of the callosal fiber tracts

Figure 3. Bar graphs of the sub-regions of the corpus callosum for control (grey bars) and concussed (black bars) athletes showing differences in (A) mean diffusivity, (B) radial diffusivity, (C) volume, and (D) axial diffusivity. Standard errors of the mean are represented by vertical bars. An asterisk indicates a statistically significant difference relative to controls (p<,05).



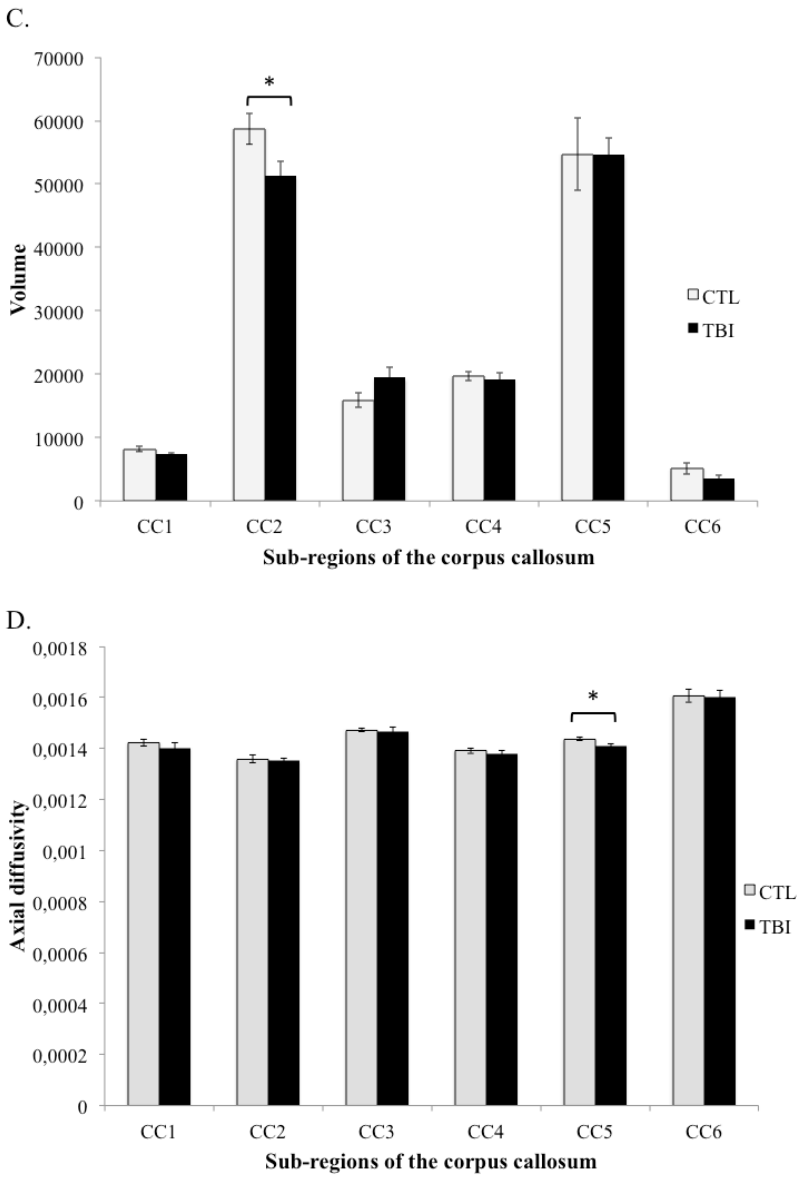


Figure 5-3. Bar graphs of the sub-regions of the corpus callosum for control (grey bars) and concussed (black bars) athletes showing differences in (A) mean diffusivity, (B) radial diffusivity, (C) volume, and (D) axial diffusivity

5.10 Tables

Tableau 5-1. Demographic table describing the two groups of the study

Group	*Age*	*Education (years)*	*Number of concussions*				*Sports*
			0	*1*	*2*	*3*	
Concussed (n= 10)	21.40 (1.71)	15.40 (1.35)	-	6	1	3	Soccer (n=4) Hockey (n=2) Waterpolo (n=4)
Control (n= 8)	21.00 (1.41)	14.88 (1.25)	8	-	-	-	Soccer (n=6) Hockey (n=2)

Tableau 5-2. Informations relative to the concussion sustained by the athletes

Athletes	*Mechanism of injury*	*Symptoms experienced (acute phase)*	*Duration of symptoms (days)*
TBI 1	Contact with opponent	Headache Fatigue Concentration problems Memory problems	25
TBI 2	Contact with ball	Confusion Headache Concentration problems	5

TBI 4	Contact with ball	Confusion Oversleeping	3
TBI 5	Contact with the ground	Confusion Memory loss Headache Fatigue	6
TBI 6	Contact with opponent	Dizziness Fatigue Headache	6
TBI 7	Contact with hockey puck	Confusion Headache Irritability	5
TBI 8	Contact with ball	Fatigue Headache	6
TBI 9	Contact with ball	Headache Sensitivity light	17
TBI 9	Contact with opponent	Fatigue Balance problems Headache	20
TBI 10	Contact with ball	Confusion Headache Fatigue	8

CHAPITRE 6 DISCUSSION GÉNÉRALE

6.1 Sommaire et implications

L'objectif de la présente thèse était d'évaluer le profil d'atteintes à court et à long terme d'une commotion cérébrale sur le plan neurométabolique et microstructurel chez des athlètes féminines. La décision d'orienter les recherches vers l'évaluation des athlètes féminines relevait de deux raisons principales. Premièrement, malgré l'effervescence dans la communauté scientifique sur le sujet des commotions cérébrales, très peu d'études se sont intéressées aux athlètes féminines. Le manque de connaissances sur la spécificité des atteintes post-commotionnelles chez les athlètes féminines est d'autant plus problématique lorsque l'on considère l'augmentation importante du nombre d'athlètes de sexe féminin dans les sports, et ce tant au niveau secondaire qu'universitaire (National Federation of State High School Associations, 2011; Zgonc, 2010). La seconde raison reposait sur les conclusions des quelques études disponibles chez les athlètes féminines. Ces études semblent démontrer des indices d'atteintes post-commotionnelles plus importantes chez les athlètes féminines comparativement aux athlètes masculins (Dick, 2009; Farace & Alves, 2000). En effet, les athlètes féminines seraient plus à risque de subir une commotion cérébrale, et ce même pour les sports présentant des règlements et pratiques similaires entre les deux sexes tels que le basketball et le soccer. À la suite d'une blessure à la tête, les femmes présenteraient également un plus grand nombre de symptômes post-commotionnels et nécessiteraient un temps de réhabilitation plus long pour se remettre de la commotion cérébrale. Il faut toutefois interpréter ces résultats avec prudence puisque certaines études suggèrent que les athlètes féminines auraient tendance à rapporter plus de symptômes lors des évaluations pré-saison. Également, les athlètes masculins auraient tendance à minimiser ou moins rapporter leurs symptômes et certains chercheurs suggèrent des raisons sociales et culturelles pour expliquer cette tendance (par exemple, la nécessité pour un athlète masculin de se montrer fort et endurant) (Brown et al., 2015). Malgré tout, il n'en demeure pas moins que plusieurs études ont relevé ces différences entre les athlètes masculins et féminines tant au niveau de l'incidence que du rétablissement post-commotionnel. Ainsi, il est fort possible que les protocoles de retour au jeu actuellement proposés ne soient pas adaptés aux athlètes féminines et ne prennent pas en

compte les spécificités propres à chaque sexe. Pour ces raisons, il s'avérait donc nécessaire d'entreprendre des études utilisant des méthodes objectives d'imagerie cérébrale afin d'évaluer spécifiquement les atteintes cérébrales associées à une commotion cérébrale dans cette population. En général, l'ensemble des résultats démontre des atteintes du métabolisme cellulaire et de l'intégrité de la matière blanche, notamment dans la phase chronique de la blessure à la tête. Afin de faire une synthèse des résultats, un tableau récapitulatif est présenté à la page suivante. Les différents résultats sont discutés dans les sections ultérieures.

Tableau 6-1. Tableau sommaire des quatre études.

	Nombre de sujets	*Âge moyen*	*Niveau éducation*	*Nb de commotions cérébrales*	*Temps post-commotion*	*Mesures prises*	*Régions d'intérêt*	*Direction de l'effet*
Article 1	CTL : 34 (20 H / 14F) AC : 11 (5H / 6F)	21	Non-disponible	Non-disponible	Pré- et post-saison 72 heures 2 semaines 2 mois	SRM Glu/Cr mI/Cr NAA/Cr	Corps calleux	Aucune différence entre CTL et AC Diminution NAA/Cr chez les CTL féminines entre pré- et post-saison
Article 2	CTL : 10 AC : 10	21	15	2.6 (2.3)	7 mois et + (moyenne de 18.9 mois)	SRM Glx/Cr mI/Cr NAA/Cr DTI	SRM CPDL M1 Hip DTI Ensemble du cerveau Corps calleux	SRM Taux plus faible de mI/Cr dans Hp et M1 DTI Augmentation DM dans CST, *forceps minor*, faisceaux longitudinaux inférieur et supérieur, cingulum, faisceau unciné et radiations thalamiques Diminution FA dans corps calleux (région projetant vers M1)
Article 3	CTL : 10 AC : 11	21	15	2 (1 à 4)	Temps 1 : 7 à 10 jours (moyenne de 9 jours) Temps 2 : 6 mois	SRM Glx/Cr mI/Cr NAA/Cr Évaluation	SRM CPDL M1 Hip	Altérations cognitives (apprentissage verbal et vitesse de traitement de l'information) au temps 1 Nombre plus élevé de symptômes dépressifs et SPC au temps 1 Augmentation du taux de Glx/Cr dans M1 et CPDL au temps 2

						cognitive et symptômes		Diminution de NAA/Cr dans M1 chez CTL
Article 4	CTL : 8 AC : 10	21	15	2 (1 à 4)	6 mois	DTI FA, DM, DR, DA, Mode, Volume	CST Corps calleux	Diminution DM et DR dans la région du corps calleux projetant vers cortex préfrontal Diminution volume dans la région du corps calleux projetant vers aire prémotrice et motrice supplémentaire Diminution DA dans la région du corps calleux projetant vers aire pariétale et temporale

Légende : CTL : Athlètes contrôles; AC : Athlètes commotionnées; CPDL : Cortex préfrontal dorsolatéral; M1 : Cortex moteur primaire; Hp : Hippocampe; DM : Diffusivité moyenne; CST : Voie corticospinale; FA : Fraction d'anisotropie; BDI : Échelle de dépression de Beck; SPC : Symptômes post-commotionnels; DR : Diffusivité radiale; DA; Diffusivité axiale

6.1.1 Effets à long terme des commotions cérébrales

Un premier constat qui ressort des études présentées dans cette thèse est la présence d'altérations post-commotionnelles affectant le métabolisme cellulaire ainsi que l'intégrité de la matière blanche, principalement dans la phase chronique. En effet, l'étude 2 fait état d'altérations neurométaboliques affectant l'hippocampe et le cortex moteur primaire combinées à des changements microstructuraux dans plusieurs faisceaux de matière blanche chez des athlètes ayant subi une commotion cérébrale en moyenne 18 mois avant l'expérimentation. L'article 4 démontre également la présence d'altérations microstructurales, notamment dans les régions antérieures du corps calleux, présentes six mois suivant la commotion cérébrale. Finalement, l'étude 3 rapporte des atteintes chroniques affectant le métabolisme cellulaire dans M1 et le CPDL alors qu'aucune altération métabolique n'était présente dans la phase aigüe (une semaine après la commotion cérébrale). Toutefois, les athlètes commotionnées présentaient des atteintes neuropsychologiques sur le plan de l'apprentissage verbal et de la vitesse de traitement de l'information ainsi qu'un nombre significativement plus élevé de symptômes post-commotionnels et dépressifs que les athlètes contrôles dans la phase aigüe.

Ces résultats suggèrent que les altérations cognitives et les symptômes commotionnels ne seraient pas sous-tendus par une altération du métabolisme cérébral dans les jours suivant la blessure à la tête. D'autres études sont nécessaires afin de mieux comprendre la pathophysiologie à court terme. Les altérations chroniques démontrées dans la présente thèse sont concordantes avec la littérature scientifique en traumatologie sportive et appuient l'idée que les commotions cérébrales ne sont pas une blessure transitoire et rendent d'autant plus difficile la décision de retourner une athlète au jeu. Dans les études présentées, toutes les athlètes ayant un historique de commotions cérébrales étaient asymptomatiques au moment des évaluations en phase chronique et ne présentaient pas de différences sur le plan symptomatologique comparativement aux athlètes contrôles. Ainsi, malgré une absence de symptômes auto-rapportés, les données objectives obtenues par la SRM et le DTI démontrent qu'il existe une vulnérabilité neurométabolique et microstructurale chez ces athlètes. Il est

possible que cette vulnérabilité cérébrale sous-tende le risque accru des athlètes commotionnées de subir une nouvelle blessure à la tête ou même d'enclencher les processus pathophysiologiques menant à un vieillissement pathologique. Il importe donc de poursuivre les études en phase chronique afin de mieux comprendre l'impact de ces altérations cérébrales.

6.1.2 Gradient de vulnérabilité des régions cérébrales

Un second constat qui ressort des études est la plus grande prédisposition des régions cérébrales antérieures aux effets des commotions cérébrales. Avec la SRM, les atteintes relevées dans les différentes études touchent principalement le cortex préfrontal dorsolatéral et le cortex moteur primaire. Le DTI a également mis en évidence des atteintes plus frontales, au niveau de la voie corticospinale et du corps calleux, plus spécifiquement dans les régions calleuses projetant vers les aires préfrontales, les aires prémotrices et motrices supplémentaires ainsi que les aires motrices primaires. Une récente méta-analyse a d'ailleurs soulevé la vulnérabilité plus grande des régions antérieures du cerveau à la suite d'un traumatisme crânien léger (Eierud et al., 2014). Par exemple, sur le plan fonctionnel, une vulnérabilité frontale a été démontrée par une diminution du signal dans le cortex préfrontal comparativement aux contrôles avec l'IRMf. Cette vulnérabilité semble accentuée par les changements anisotropiques observés avec le DTI, qui présentent un important gradient antérieur-postérieur dans lequel les régions antérieures sont plus fréquemment atteintes chez les gens ayant un historique de traumatismes crâniens légers (Eierud et al., 2014). Les études de la présente thèse s'ajoutent à ce postulat et soulèvent en plus l'apport des atteintes neurométaboliques sur la vulnérabilité des régions antérieures à la suite d'une commotion cérébrale. La présence d'une plus grande atteinte au niveau des régions du lobe frontal est particulièrement importante dans un contexte sportif où les athlètes doivent prendre rapidement des décisions afin d'effectuer des commandes motrices complexes, ces fonctions étant notamment sous-tendues par les régions préfrontales et motrices. Des activations fonctionnelles réduites et une altération du métabolisme cérébral, combinées à une altération de l'intégrité de la matière blanche pouvant réduire la vitesse de transmission de l'information dans le cerveau, pourraient être des facteurs contribuant à la plus grande vulnérabilité d'une

athlète commotionnée à subir une nouvelle commotion cérébrale (Guskiewicz et al., 2003).

6.1.3 Variabilité des changements anisotropiques et neurométaboliques

Toutefois, un troisième constat qui ressort des études présentées dans cette thèse est l'inconstance dans la direction des résultats d'une étude à l'autre. En effet, bien que des différences entre les athlètes commotionnées et les athlètes contrôles aient été mises en évidence dans les différentes études, il importe de soulever l'hétérogénéité observée quant aux variations des niveaux de métabolites et de la direction des changements anisotropiques. Sur le plan neurométabolique, l'article 1 évaluant des hockeyeurs et hockeyeuses au cours d'une saison ne relevait aucune différence entre les athlètes ayant subi une commotion cérébrale et ceux n'en ayant pas subie. En revanche, une diminution du taux de NAA chez les athlètes féminines non-commotionnées a été mise en évidence et l'hypothèse voulant que les impacts d'intensité sous-clinique répétés pouvaient altérer le métabolisme cérébral avait alors été soulevée. Cette même diminution du taux de NAA a été observée dans l'étude 3 chez les athlètes contrôles entre la phase aigüe (quelques jours post-commotion) et la phase chronique six mois post-commotion. Toutefois, ces résultats diffèrent de ce qui est retrouvé dans les autres études. Dans l'étude 2, une diminution du taux de mI/Cr a été observée dans l'hippocampe et M1 chez les athlètes commotionnées en moyenne 18 mois après la blessure à la tête. En revanche, la troisième étude ne rapporte aucune différence sur le plan métabolique dans les jours suivant la blessure à la tête alors qu'une augmentation du taux de Glx/Cr a été retrouvée chez les athlètes commotionnées dans le CPDL et M1 en phase chronique. Il est possible que ces différences entre les études soient sous-tendues par le fait que le nombre d'athlètes multi-commotionnées vs uni-commotionnées différait entre les études ou par la variété dans le temps post-commotionnel au moment de l'évaluation. Il n'en demeure pas moins que ces différences au sein de groupes relativement homogènes (athlètes féminines d'âge et de niveau d'éducation équivalent qui évoluent au sein d'équipes universitaires ou canadiennes), rendent d'autant plus complexe la compréhension de la pathophysiologie d'une commotion cérébrale et démontrent l'hétérogénéité interindividuelle de cette pathologie. Il importe toutefois de mentionner que cette disparité dans la direction des changements

neurométaboliques est retrouvée dans plusieurs autres études en traumatologie sportive (Dimou and Lagopoulos, 2014).

Des différences entre les études sont également retrouvées sur le plan des changements anisotropiques. Dans la première étude combinant la SRM et le DTI, aucune différence quant au FA n'est trouvée en faisant l'analyse globale du cerveau alors qu'une augmentation de la DM est retrouvée dans plusieurs faisceaux de matière blanche de l'hémisphère gauche, c'est-à-dire le *forceps minor*, le faisceau inférieur fronto-occipital, le cingulum, le faisceau unciné, le faisceau inférieur longitudinal, ainsi que certains faisceaux bilatéralement incluant les radiations thalamiques antérieures, le faisceau supérieur longitudinal ainsi que la voie corticospinale. Dans la même étude, une approche par région d'intérêt du corps calleux a révélé une diminution de la FA dans la région calleuse projetant dans la région motrice. En revanche, la dernière étude évaluant les changements anisotropiques six mois après la commotion cérébrale n'a démontré aucun changement à la suite d'une commotion cérébrale au niveau de la voie corticospinale. Une diminution du taux de DM et DR a été relevée dans les régions calleuses projetant vers le cortex préfrontal, une diminution du volume dans la région projetant vers les aires prémotrices et finalement, une diminution de la DA dans la région projetant vers le cortex pariétal/temporal. Ainsi, certaines inconstances dans les régions affectées ou dans les indices anisotropiques ont été mises en évidence malgré l'utilisation de groupes relativement homogènes. Ces différences ont également été soulignées dans une récente méta-analyse d'Eirud et collaborateurs (2014). Selon les résultats de cette méta-analyse, les inconstances retrouvées dans la littérature pourraient être expliquées, en partie, par une augmentation des mesures d'anisotropie dans la phase aigüe alors que les effets chroniques sur le plan microstructurel seraient caractérisées par une diminution de l'anisotropie (Eierud et al., 2014). En phase aigüe, l'inflammation et d'autres facteurs suivant la blessure à la tête (par exemple, ischémie ou hypoxie cérébrale) augmenteraient l'anisotropie, mais ces facteurs ne seraient pas contributifs dans la phase chronique. À long terme, les dommages résiduels de la matière blanche entraîneraient une diminution du signal anisotropique. D'autres études rapportent également cette élévation de l'anisotropie peu de temps après la commotion cérébrale en comparaison à une diminution de l'anisotropie en phase chronique (Niogi & Mukherjee, 2010), démontrant ainsi l'importance de l'intervalle

temporel suivant la blessure à la tête dans les mesures de diffusion (Mayer, Mannell, Ling, Gasparovic, & Yeo, 2011; Niogi & Mukherjee, 2010).

6.1.4 Effets des coups répétés d'intensité sous-clinique à la tête

Dans la présente thèse, certains effets neurométaboliques touchant les groupes contrôles ont été relevés dans deux études. Tout d'abord, une diminution du taux de NAA chez des joueuses de hockey a été observée entre les évaluations pré-saison et post-saison alors que cette diminution n'était pas présente chez les athlètes masculins (article 1). Cet effet suggère une plus grande susceptibilité des athlètes féminines aux coups d'intensité sous-clinique reçus pendant une saison. Cette même diminution du taux de NAA a été relevée au sein du cortex moteur primaire chez les athlètes du groupe contrôle six mois suivant le premier examen (article 3). L'hypothèse d'un effet des coups d'intensité sous-clinique à la tête avait alors été formulée, mais n'avait pas été directement évaluée dans ces études. Au cours des dernières années, l'intérêt des effets des coups d'intensité sous-clinique à la tête et la possibilité qu'ils entraînent des séquelles cognitives ou cérébrales a émergé. Plusieurs chercheurs ont tenté d'examiner dans quelle mesure des dommages neuronaux sont causés par des coups d'intensité sous-clinique, définis comme étant des coups à la tête générant assez de force pour perturber l'intégrité neuronale sans qu'il en résulte des symptômes cliniquement évidents chez les athlètes. En effet, des études ont par exemple démontré l'efficacité du DTI pour détecter des altérations microstructurales chez des athlètes commotionnés, mais également, à des degrés moindres, chez des athlètes subissant à répétition des coups d'intensité sous-clinique à la tête (Bazarian, Zhu, Blyth, Borrino, & Zhong, 2012). De plus, plusieurs études suggèrent que l'exposition fréquente aux coups d'intensité sous-clinique à la tête peut considérablement affecter l'intégrité neuronale, même chez les athlètes n'ayant jamais subi de commotion cérébrale (Dashnaw, Petraglia, & Bailes, 2012). Une autre étude utilisant le DTI rapporte une altération de l'intégrité de la matière blanche chez des joueurs de soccer comparativement à un groupe de nageurs n'ayant jamais subi de commotions cérébrales (Koerte, Ertl-Wagner, Reiser, Zafonte, & Shenton, 2012). Ces résultats sont compatibles avec une récente étude démontrant que le fait de frapper le ballon avec sa tête au soccer était

associé à la présence d'altérations microstructurelles et cognitives chez des joueurs de soccer non commotionnés (Lipton et al., 2013). Des différences microstructurelles affectant l'intégrité de la matière blanche auraient également été décelées au cours d'une saison chez des athlètes de hockey (Koerte, Kaufmann, et al., 2012). Ce même résultat a été retrouvé chez des athlètes de football où les atteintes microstructurelles étaient corrélées à des altérations cognitives, lesquelles n'étaient pas présentes au début de la saison (ou chez les athlètes ne prenant pas part à des sports de contact) (McAllister et al., 2014). D'autres études ont rapporté des différences entre les données pré-saison et post-saison (Koerte et al., 2015) qui étaient encore présentes après une période de repos de six mois sans contact (Bazarian et al., 2014). Les études évaluant le profil cognitif de joueurs de soccer après une période d'exposition à ces coups ont quant à elles rapporté des effets mitigés, certaines études relevant des déficits cognitifs (Witol & Webbe, 2003; Zhang, Red, Lin, Patel, & Sereno, 2013) alors que d'autres études n'ont observé aucune dysfonction (Belanger, Vanderploeg, & McAllister, 2015; Kontos, Dolese, Elbin, Covassin, & Warren, 2011; Rutherford, Stephens, & Potter, 2003).

Des changements sur le plan neurométabolique ont également été rapportés dans une étude chez des joueurs de soccer professionnels à la retraite n'ayant jamais subi de commotion cérébrales où une augmentation significative de la choline et du myo-inositol était présente comparativement à des athlètes ne pratiquant pas des sports de contact (Koerte et al., 2015). Les auteurs de cette étude ont suggéré une association entre l'accumulation de ces coups et des marqueurs de la SRM reliés à une neuroinflammation (Koerte et al., 2015). De nouvelles études vont plus loin et suggèrent même un lien entre le fait de subir des coups répétitifs à la tête n'entraînant pas de commotions cérébrales et le développement de troubles cognitifs avec l'avancement en âge. De récentes recensions de la littérature suggèrent d'ailleurs que le développement de l'ETC pourrait être causé par une accumulation de ces coups, même chez les athlètes ne présentant aucun historique de commotions cérébrales (Stein, Alvarez, et al., 2015; Sundman et al., 2015). L'accumulation des coups entraînerait ainsi le développement d'une cascade pathophysiologique résultant en une accumulation anormale de la protéine Tau dans le système nerveux central, menant ultimement au développement de l'ETC (Sundman et al., 2015). Par ailleurs, il a été démontré que les stades de taupathie de l'ECT chez des athlètes pouvaient être prédits par le nombre d'années que les joueurs ont pratiqué un sport de contact

et l'âge, mais non par le nombre de commotions cérébrales (Stein, Montenigro, et al., 2015). Ces résultats suggèrent qu'une période prolongée d'exposition à des coups d'intensité sous-clinique pourrait être associée au développement progressif de la taupathie de l'ECT (Stein, Alvarez, et al., 2015). Ainsi, le fait de subir des coups à répétition diminuerait la capacité fonctionnelle du cerveau de répondre au vieillissement et diminuerait le seuil de déclenchement de troubles neurodégénératifs ou de démence (Bigler, 2013; Lehman et al., 2012; Smith, 2013). Dans une récente recension de la littérature, les auteurs mentionnent toutefois que le fait de subir quelques commotions cérébrales bien gérées par les équipes médicales traitantes n'est pas suffisant pour développer l'ECT. Par contre, un historique de commotions cérébrales multiples au cours d'une carrière, particulièrement si ces dernières ne sont pas bien traitées ou identifiées, serait un facteur de risque considérable au développement de l'ECT. Le fait que les athlètes continuent de jouer après une commotion cérébrale expose alors leur cerveau aux coups à la tête d'intensité sous-clinique pendant une période de vulnérabilité cérébrale (Stein, Alvarez, et al., 2015).

6.2 Limites

Les études décrites dans cette thèse présentent quelques limites à prendre en compte dans l'interprétation des résultats ainsi que dans la mise en place de nouvelles études évaluant les effets des commotions cérébrales. Tout d'abord, un premier aspect à considérer est l'effet du cycle menstruel des participantes. Une recension de la littérature s'intéressant aux symptômes auto-rapportés entre les athlètes féminines et masculins démontrait que bien que les femmes aient eu une tendance plus grande à rapporter leurs symptômes lors des évaluations pré-saison, ces symptômes n'étaient pas nécessairement spécifiques aux commotions cérébrales et seraient associés à d'autres processus physiologiques, le plus probable étant le syndrome prémenstruel (Brown et al., 2015). Par ailleurs, une autre étude a démontré que les femmes qui subissent un TCC léger durant la phase prémenstruelle avaient des résultats significativement plus élevés sur les échelles de symptômes post-commotionels comparativement aux femmes qui subissaient cette blessure dans la phase folliculaire ou qui prenaient des contraceptifs oraux (Wunderle, Hoeger, Wasserman, & Bazarian, 2014).

L'impact du cycle menstruel sur la symptomatologie des athlètes est particulièrement important dans les décisions de retour au jeu des athlètes. Il est possible que le retour au jeu d'une athlète soit retardé pour ces raisons, ce qui vient fortement biaiser les différences entre les deux sexes quant au rétablissement post-commotionnel. Les évaluations pré-saison devraient être faites à deux reprises chez les athlètes féminines, soit une première fois lors de la phase folliculaire et une seconde fois lors de la phase prémenstruelle afin d'augmenter l'efficacité de la prise en charge post-commotionelle et le retour au jeu des athlètes. De plus, une étude en neuroimagerie a démontré des variations sur le plan du métabolisme cérébral dans les régions préfrontales selon la période menstruelle et la prise ou non de contraceptifs oraux (De Bondt, De Belder, Vanhevel, Jacquemyn, & Parizel, 2015). Cet aspect n'a pas été pris en compte dans la présente thèse étant donné l'accessibilité limitée à l'IRM. Plusieurs variables relatives au cycle menstruel doivent être prises en compte, par exemple le type de contraceptifs, la durée du cycle menstruel de l'athlète, la prise en continu ou non de contraceptifs oraux, la période du cycle menstruel au moment de l'expérimentation, etc., ce qui rend d'autant plus difficile l'analyse de l'effet du cycle menstruel chez des groupes aussi restreints d'athlètes féminines.

Une deuxième limite de cette thèse est l'absence de participantes dans les groupes contrôles qui ne pratiquaient pas de sports de contacts. En effet, les participantes des groupes contrôles des différentes études pratiquaient les mêmes sports que les athlètes commotionnées, notamment le soccer, le hockey et le rugby. Ces athlètes étaient donc soumises à des coups d'intensité sous-clinique à la tête dans la pratique de leur sport, par exemple, lorsqu'une athlète frappait un ballon de soccer avec sa tête. Ainsi, l'utilisation de groupes contrôles subissant à répétition des coups d'intensité sous-clinique pourrait avoir masqué ou minimisé les effets observés chez les athlètes commotionnées. Toutefois, une nouvelle étude de notre groupe de recherche a été menée récemment et visait à évaluer l'impact de coups d'intensité sous-clinique sur le plan cérébral et neuropsychologique chez des athlètes de niveau universitaire. Les séances de neuroimagerie comprenaient le DTI, la SRM, l'imagerie de susceptibilité magnétique (SWI) et l'évaluation de l'épaisseur corticale. Trois groupes ont pris part à l'étude, soit un groupe expérimental composé d'athlètes universitaires pratiquant des sports de contact tels que le rugby ou le soccer (n = 12 hommes, 12 femmes), un groupe

composé d'athlètes universitaires ne pratiquant pas un sport de contact (natation; *n* = 12 hommes, 12 femmes) et un groupe contrôle de non-athlètes (*n* = 12 hommes, 12 femmes) équivalent aux deux autres groupes en terme d'âge et de niveau d'éducation. Les résultats démontraient une absence de différence pour l'ensemble des mesures cognitives et d'imagerie cérébrale à une exception près. La seule différence a été retrouvée avec la SRM, où les athlètes du groupe expérimental démontraient une augmentation du myo-inositol dans M1 comparativement aux deux groupes contrôles. Ainsi, cette étude suggère un effet possiblement limité des coups d'intensité sous-clinique à la tête chez des athlètes de niveau universitaire sur le plan cognitif, symptomatologique, microstructural et neurométabolique (Lefebvre, Chamard, Proulx & Théoret, en préparation). Bien que d'autres études soient nécessaires afin de mieux comprendre les effets de ces coups répétitifs dans les sports de contacts, cet aspect fait toutefois ressortir l'importance d'utiliser des groupes contrôles adéquats ne pratiquant pas de sport de contacts, par exemple, des athlètes de natation. En utilisant ce type de groupes contrôles dans les études ultérieures, il sera ainsi possible d'augmenter la robustesse méthodologique des études en traumatologie sportive.

Finalement, une dernière limite est l'absence de groupes composés d'athlètes masculins dans trois des quatre études présentées. L'intégration d'athlètes masculins pratiquant les mêmes sports que les athlètes féminines, auraient ainsi permis non seulement d'évaluer les effets des commotions cérébrales chez les femmes, mais également de déterminer si les effets retrouvés sont différents de ceux observés chez les hommes. Une meilleure compréhension des similitudes et des différences entre les deux sexes permettrait ultimement d'implanter des protocoles de retour au jeu spécifique au sexe de l'athlète et ainsi, limiter l'impact de la blessure à la tête.

6.3 Conclusion et avenues de recherche futures

En somme, la présente thèse démontre que les commotions cérébrales sont associées à des altérations cérébrales affectant notamment l'intégrité de la matière blanche et le métabolisme cellulaire chez des athlètes féminines. Ces atteintes semblent davantage présentes dans la phase chronique alors que les athlètes ayant un historique de commotions cérébrales ne

semblent pas différer des athlètes contrôles sur le plan des symptômes auto-rapportés ou des tests neuropsychologiques. Ainsi, des effets délétères sont encore présents plusieurs mois après la blessure à la tête malgré le fait que ces athlètes soient pour la plupart de retour au jeu et ne démontrent plus de manifestations cliniques franches. Il est d'autant plus surprenant qu'aucune manifestation neurométabolique n'a été retrouvée quelques jours à la suite de la blessure à la tête alors que les athlètes présentaient des symptômes physiques, émotionnels et cognitifs ainsi que des perturbations sur le plan des facultés cognitives. Il serait ainsi intéressant de faire une étude longitudinale afin de mieux comprendre à quel moment surviennent ces altérations sous-cliniques en évaluant des athlètes dans les jours suivant la commotion cérébrale et à d'autres temps de mesure, tel qu'un mois, trois mois et six mois post-commotion. Il serait également pertinent, dans la phase aigüe, d'effectuer des études avec l'IRMf afin d'évaluer s'il existe un lien entre les atteintes cognitives retrouvées dans la phase aigüe, (apprentissage verbal et vitesse de traitement de l'information) et les patrons d'activation dans le cerveau. Ainsi, il serait possible de mieux comprendre le lien entre les altérations cérébrales et les manifestations cliniques en phase aigüe.

Le but de la présente thèse était d'explorer les altérations microstructurelles et neurométaboliques spécifiquement chez les athlètes féminines compte tenu du manque de littérature scientifique dans cette population. Il serait maintenant pertinent de faire des études avec des méthodes de neuroimagerie avancée qui viseraient à comparer directement les athlètes masculins et les athlètes féminines. Ces études permettraient ainsi de déterminer directement les différences sur le plan du rétablissement post-commotionnel entre les deux sexes et, ultimement, mettre en place des protocoles de retour au jeu adaptés aux spécificités propres à chaque sexe. Des études évaluant les athlètes masculins et les athlètes féminines à différents âges (par exemple, les athlètes du niveau secondaire ou universitaire) permettraient également d'étudier les effets de l'âge et du sexe sur les manifestations post-commotionnelles sur le plan symptomatologique, cognitif et des altérations cérébrales.

En ce qui se rapporte à l'effet de l'âge, les effets néfastes des commotions cérébrales multiples en lien avec le développement de troubles neurodégénératifs tels que l'encéphalopathie traumatique chronique ou la maladie d'Alzheimer ont été fortement suggérés (Stein et al., 2015). Cet aspect est particulièrement important chez les athlètes

féminines en considérant la susceptibilité accrue de ces dernières à développer la maladie d'Alzheimer (Li & Singh, 2014). Cependant, aucune étude n'a encore exploré cet aspect compte tenu de la récente émergence de la participation féminine dans les sports de contact au cours des deux dernières décennies. Dans les prochaines années, les études devraient évaluer le lien entre le vieillissement pathologique et un historique de commotions cérébrales chez des athlètes féminines en utilisant des méthodes variées d'investigation. L'augmentation des connaissances sur les atteintes cérébrales sous-tendant les commotions cérébrales et la pathophysiologie des troubles neurodégénératifs chez les athlètes féminines permettront ainsi d'identifier des facteurs de protection et de limiter l'expression des facteurs de risque menant au développement de ces troubles dans cette population.

Ainsi, la présente thèse est un effort de plus afin de comprendre cette blessure complexe qui était autrefois considérée comme transitoire et sans gravité. Il a maintenant été démontré à maintes reprises que les commotions cérébrales sont des blessures entraînant des conséquences immédiates, mais également chroniques sur le fonctionnement du système nerveux. Bien que les résultats soient hétérogènes et menés sur de petits groupes d'athlètes féminines, nous avons constaté la présence d'effets à long-terme des commotions cérébrales sur l'intégrité des faisceaux de matière blanche et du métabolisme cellulaire chez des athlètes féminines jeunes, actives et en bonne santé physique. Ces résultats démontrent l'importance de poursuivre les recherches en traumatologie sportive afin d'assurer à ces athlètes et aux générations futures une participation sécuritaire dans les sports de contact.

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