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Sex differences in white matter alterations following repetitive subconcussive head impacts in collegiate ice hockey players☆

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ABSTRACT

Objective: Repetitive subconcussive head impacts (RSHI) may lead to structural, functional, and metabolic alterations of the brain. While differences between males and females have already been suggested following a concussion, whether there are sex differences following exposure to RSHI remains unknown. The aim of this study was to identify and to characterize sex differences following exposure to RSHI.

Methods: Twenty-five collegiate ice hockey players (14 males and 11 females, 20.6 ± 2.0 years), all part of the Hockey Concussion Education Project (HCEP), underwent diffusion-weighted magnetic resonance imaging (dMRI) before and after the Canadian Interuniversity Sports (CIS) ice hockey season 2011–2012 and did not experience a concussion during the season. Whole-brain tract-based spatial statistics (TBSS) were used to compare pre- and postseason imaging in both sexes for fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). Pre- and postseason neurocognitive performance were assessed by

Abbreviations: AD, axial diffusivity; CIS, Canadian Interuniversity Sports; CR, corona radiata; dMRI, diffusion magnetic resonance imaging; EC, external capsule; FA, fractional anisotropy; HCEP, Hockey Concussion Education Project; IC, internal capsule; ImPACT, Immediate Post-Concussion Assessment and Cognitive Test; LH, left hemisphere; MD, mean diffusivity; MRI, magnetic resonance imaging; NCAA, National Collegiate Athletic Association; r_s, Spearman's rank correlation coefficient; RD, radial diffusivity; RH, right hemisphere; RSHI, repetitive subconcussive head impacts; SD, standard deviation; SLF, superior longitudinal fasciculus; TBI, traumatic brain injury; TBSS, tract-based spatial statistics; WM, white matter

☆ Previous presentation of data:
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the Immediate Post-Concussion Assessment and Cognitive Test (ImPACT).
Results: Significant differences between the sexes were primarily located within the superior longitudinal fasciculus (SLF), the internal capsule (IC), and the corona radiata (CR) of the right hemisphere (RH). In significant voxel clusters ($p < 0.05$), decreases in FA (absolute difference pre- vs. postseason: 0.0268) and increases in MD (0.0002), AD (0.00008), and RD (0.00005) were observed in females whereas males showed no significant changes. There was no significant correlation between the change in diffusion scalar measures over the course of the season and neurocognitive performance as evidenced from postseason ImPACT scores.
Conclusions: The results of this study suggest sex differences in structural alterations following exposure to RSHI. Future studies need to investigate further the underlying mechanisms and association with exposure and clinical outcomes.

1. Introduction

Concussion is a common injury in contact sports, with an incidence ranging between 1.6 and 3.1 per 1000 athlete exposures (Agel et al., 2007a, 2007b; Flik et al., 2005). Women are at higher risk than men for sustaining a sports-related concussion and they represent a large proportion of the athletic community in organized sports (Abrahams et al., 2014; Black et al., 2017; Covassin et al., 2003; Gessel et al., 2007). In fact, female participation in National Collegiate Athletic Association (NCAA) sanctioned sports is currently at an all-time high, where an estimated 43% (~210,000) of all collegiate student-athletes are women (Irick, 2015). However, despite the high number of female athletes, females remain an understudied population, as only a small number of studies have focused on female athletes. Moreover, evidence from these studies suggests that females have worse outcomes following concussion compared with males (Baker et al., 2016; Broshek et al., 2005; Colvin et al., 2009; Covassin et al., 2013, 2012, 2007; Majerske et al., 2008; Miller et al., 2016; Zuckerman et al., 2014). Specifically, women reported more post-concussive symptoms with greater symptom severity (Zuckerman et al., 2014), performed worse on neurocognitive tests (Broshek et al., 2005; Colvin et al., 2009; Covassin et al., 2013, 2012, 2007; Majerske et al., 2008), and demonstrated longer periods of recovery compared to males (Baker et al., 2016; Miller et al., 2016; Zuckerman et al., 2014).

Following a concussion, brain alterations have been detected using advanced neuroimaging techniques (for review see Shenton et al., 2012). One of these advanced techniques is diffusion magnetic resonance imaging (dMRI), which has been repeatedly used to detect and to characterize white matter (WM) alterations related to brain injury (Koerte et al., 2015; Shenton et al., 2012). However, to date, there is only one study using dMRI that has investigated sex differences in structural brain alterations following a concussion (Fakhran et al., 2014). This study included 47 male and 22 female individuals after a confirmed concussion (Fakhran et al., 2014). In this study, findings indicated that male concussed individuals demonstrated decreased fractional anisotropy (FA) in the uncinate fasciculus compared to concussed females or controls (Fakhran et al., 2014).

Even more common than concussions are subconcussive head impacts in contact sports. Evidence here suggests that repetitive subconcussive head impacts (RSHI) may also result in structural, functional, and metabolic alterations of the brain (for review see Koerte et al., 2015). Of note, dMRI has shown sensitivity to detect even subtle WM alterations related to RSHI (Koerte et al., 2015). Furthermore, dMRI parameters have predicted impairments in executive function, attention, memory, speed of processing, and learning following traumatic brain injury (TBI) (Caeyenberghs et al., 2011a, 2011b, 2014). Detection of sex-specific WM changes related to RSHI could facilitate an individualized clinical management at an early stage of potential brain injury. However, to date, there are no studies investigating sex differences in brain alterations following exposure to RSHI. Thus, the aim of this study is to evaluate potential sex differences in the brain's WM following exposure to RSHI in a sample of collegiate ice hockey players using dMRI.

2. Materials and methods

2.1. Participants and procedures

All study participants were part of the Hockey Concussion Education Project (HCEP), which was conducted during the Canadian Interuniversity Sports (CIS) ice hockey seasons of 2009–2010 and 2011–2012. The present study analyzed participants of the 2011–2012 HCEP, which used clinical examination, neurocognitive assessment, and pre- and postseason magnetic resonance imaging (MRI) as well as sequential testing and imaging at three time points after any concussion among ice hockey players (Echlin, 2012). Data from the HCEP have already been analyzed with respect to other specific research questions (Chamard et al., 2012; Echlin, 2010, 2012; Echlin et al., 2014, 2010a,

Table 1
Participant-related characteristics.

		Males	Females	p-Value
Number of players		14	11	–
Age (in years) (mean ± SD)		21.7 ± 1.3	19.2 ± 1.8	0.0005
Handedness (right/left/ambidextrous)		10/3/1	10/1/0	0.6040
ImPACT score (preseason testing) (mean ± SD)	Verbal memory	90.9 ± 4.5	91.0 ± 8.6	0.3615
	Visual memory	83.7 ± 8.6	85.4 ± 10.0	0.5358
	Visual motor speed	44.1 ± 4.2	42.7 ± 3.7	0.3712
	Reaction time	0.5 ± 0.1	0.6 ± 0.1	0.0862
ImPACT score (postseason testing) (mean ± SD)	Verbal memory	89.4 ± 7.7	94.7 ± 4.1	0.0608
	Visual memory	81.8 ± 11.9	79.2 ± 9.9	0.4623
	Visual motor speed	47.4 ± 5.3	42.9 ± 5.4	0.0344
	Reaction time	0.5 ± 0.1	0.5 ± 0.1	0.4613

This table gives an overview of participant-related characteristics, including the number of male and female participants, age, handedness, and pre- and postseason scores according to the four composite scores (verbal memory, visual memory, visual motor speed, and reaction time) derived from the results of the Immediate Post-Concussion Assessment and Cognitive Test (ImPACT). One female participant did not undergo neurocognitive assessment by the ImPACT.