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Cortical thickness and subcortical brain volumes in professional rugby league players

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ABSTRACT

Purpose: The purpose of this study was to examine cortical thickness and subcortical volumes in professional rugby players with an extensive history of concussions compared to control subjects.

Method: Participants included 24 active and former professional rugby league players [Age M(SD) = 33.3(6.3); Range = 21–44] with an extensive history of concussion and 18 age- and education-matched controls with no history of neurotrauma or participation in contact sports. Participants underwent T1-weighted imaging and completed a neuropsychological battery, including two tests of memory. Whole brain cortical thickness analysis and structural volume analysis was performed using FreeSurfer version 6.0.

Results: Professional rugby league players reported greater alcohol consumption (p < .001) and had significantly worse delayed recall of a visually complex design (p = .04). They did not differ from controls on other clinical outcome measures. There were no differences in cortical thickness between the groups. Professional players had smaller whole brain (p = .003), bilateral hippocampi (p = .03), and left amygdala volumes (p = .01) compared to healthy controls. Within the players group, there were significant associations between greater alcohol use and smaller bilateral hippocampi and left amygdala volumes. There were no associations between structural volumes and history of concussions or memory performance.

Conclusions: The literature examining cortical thickness in athletes with a history of multiple concussions is mixed. We did not observe differences in cortical thickness in professional rugby league players compared to controls. However, smaller subcortical volumes were found in players that were, in part, associated with greater alcohol consumption.

1. Introduction

Concussion is a common injury in athletes, with about 2 to 3 concussions occurring for every 10,000 player-exposures at the high school and collegiate levels (Marar et al., 2012). By high school, approximately half of student athletes will have sustained a concussion and by college, a third will have multiple concussions (Field et al., 2003). There is considerable interest in better understanding the possible long-term sequela of multiple concussions.

There have been a small number of studies examining cortical morphometry in athletes with a history of concussion. In retired university athletes, greater ventricle size as well as increased cortical thinning associated with age has been observed in the frontal, temporal, and parietal lobes (i.e., older retired athletes had greater thinning in these areas compared to controls of the same age) (Tremblay et al., 2013). Retired Canadian Football League (CFL) players had cortical...
thinning in the left anterior temporal lobe compared to healthy controls (Goswami et al., 2016). In retired soccer players, cortical thickness within the temporal, parietal, and occipital lobes has been observed to decrease with age, and a lifetime estimate of “ball headings” was found to negatively correlate with cortical thickness in the right parietal and occipital lobes (Koerte et al., 2016). Collegiate football players with a history of concussion have been observed to have thinner areas of cortex in the left anterior cingulate, orbital frontal cortex, and medial superior frontal cortex compared with healthy controls (Meier et al., 2016). Furthermore, those with a history of concussion had significantly thinner cortex in the right central sulcus and precentral gyrus compared to football players without a history of concussion (Meier et al., 2016). In contrast, two studies examining collegiate and preparatory school athletes did not find an association between concussion history and cortical thickness (Albaugh et al., 2015; Tremblay et al., 2014).

There have also been few studies examining subcortical structures in athletes with a history of concussion. In retired professional football players, former athletes with at least one grade 3 concussion had lower mean hippocampal volumes bilaterally compared to control participants (Strain et al., 2015). Coughlin and colleagues (Coughlin et al., 2015) examined volumes in hippocampal regions and amygdala, as well as total gray matter and brain parenchymal volumes, in former National Football League (NFL) players. After adjusting for multiple comparisons, former NFL players had smaller right amygdala volumes.

The present study examines cortical and subcortical morphometry in active and former professional rugby league players and healthy matched controls. Rugby league is a full contact sport that is associated with numerous collisions and tackles throughout the match (Cummins & Orr, 2015). The objectives are to examine (1) potential differences in cortical thickness between groups, and (2) whole brain, hippocampal, and amygdala volumes between groups. We hypothesized that there would be significant clusters of cortical thinning in professional rugby players compared to healthy controls and that the players would have smaller hippocampal and amygdala regions. Furthermore, we examined associations between subcortical morphometry and clinical measures.

2. Method

2.1. Participants

Professional rugby league players (n = 24) were recruited to the current study through communication with the club alumni. Our sample included both active and former players. Exclusion criteria included any medical history of neurosurgery, major psychiatric disturbance, or medical contraindications to MRI. Healthy community control subjects similar in age and education were recruited through a research participant registry (n = 18). All participants underwent a clinical interview to document their concussion history. Participants were provided with a definition of concussion based on the 2012 Zurich consensus statement on sport concussion guidelines (McCrory et al., 2013). All control subjects reported no previous history of concussion. All participants provided informed, written consent. The study was approved by the University of Newcastle Human Ethics Committee (Ref: H-2011-0081).

2.2. Measures

The following patient-reported measures and cognitive tests were used in this study: (1) The Depression, Anxiety, Stress Scale 21-item, which is a 21-item measure that is an abbreviated version of the original 42-item DASS. It is comprised of three 7-item subscales measuring symptoms of depression, anxiety, and stress (Lovibond & Lovibond, 1995). (2) The Alcohol Use Disorders Identification Test which is a 10-item alcohol screen that is used to help identify persons who are hazardous drinkers or have active alcohol use disorders (Bohn et al., 1995). (3) The Rey Auditory Verbal Learning Test (Rey, 1964) which is a neuropsychological test that evaluates auditory-verbal learning and recall of a word list. The Rey Complex Figure Test (Meyers & Meyers, 1995) which is a neuropsychological test that requires an individual to reproduce and recall a complex geometric figure. (5) Trail Making Test (Reitan, 1958) which is a neuropsychological test of visual attention, processing speed, and task switching. Part-A requires individuals to quickly connect circles in numerical order, whereas Part-B requires individuals to switch between connecting circles in numerical and alphabetical order. Mitrusinha et al. (Mitrushina et al., 2005) meta-norms were used to convert raw data to standard scores for the cognitive tests.

2.3. Neuroimaging and statistical analysis

Imaging was performed on a 3 T Siemens Skyra scanner with a 20-channel head coil. T1-weighted images were acquired with a 3D MP-RAGE sequence (TR/TE:2300/3.03 ms; flip angle: 90; 192 sagittal slices with 1 mm3 voxel size). MRI datasets were examined for image quality. Cortical thickness analysis and structural volume analysis were performed using FreeSurfer version 6.0 (Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA). A z-distribution Monte Carlo simulation with 10,000 repeats was then applied to correct for multiple comparisons using a cluster-forming threshold set at p < .05. In addition, to examine cortical thickness in the frontal cortex specifically, a mask of the frontal cortex was created from Freesurfer cortical parcelation labels that were merged into one mask. Surface-based permutation testing was performed to correct for multiple comparisons using 10,000 permutations and a cluster-forming threshold of p < .05. Structural volumes were corrected for intracranial volume (ICV) using a proportion method. Non-parametric tests (Mann-Whitney tests) and/or bootstrapping were used (for ANCOVA and regression) because of violations to normality. Data was analyzed using IBM SPSS Statistics® version 22.

3. Results

Rugby league players reported greater alcohol consumption in the past year compared to controls (U(1) = 49.5; p = <.001; Cohen's d = 1.63). Rugby league players performed worse on long-delay recall on the Rey Complex Figure Test (U(1) = 137.0; p = .04; d = 0.71). A trend towards significantly lower short-delay recall Complex Figure scores was also observed (U(1) = 145.5; p = .07; d = 0.66). No significant differences were observed between rugby league players and controls on other clinical characteristics or cognitive performance. The results are summarized in Table 1.

There were no differences between groups in whole brain cortical thickness. To follow-up on past findings of frontal cortical thinning in collegiate athletes (Meier et al., 2016), cortical thickness was examined specifically in the frontal lobe. No significant clusters were observed between groups. Rugby league players had smaller whole brain volume, corrected for intracranial volume (U(1) = 99.0; p = .003; d = 1.00). The rugby league players had larger intracranial volumes compared to controls, though these differences did not meet a statistical significant criterion of p < .05 (U(1) = 140; p = .053). Rugby league players also had smaller bilateral hippocampi (right U(1) = 131.0; p = .03; d = 0.82; left U(1) = 130; p = .03; d = 0.90) and left amygdala (U(1) = 114.0; p = .01; d = 1.24) compared to controls. A moderately large difference was observed in the right amygdala, but this finding was not statistically significant (U(1) = 142.0; p = .06; d = 0.70; see Fig. 1). No significant correlations were observed between subcortical volumes and number of concussions; depression, anxiety, and stress scales; or memory scores (ps > .05).

To examine the potential relationship between alcohol consumption and subcortical volumes in our two groups, we first examined differences in subcortical volumes between groups while controlling for alcohol use (AUDIT) using a series of ANCOVAs, bootstrapped for 1000
We found smaller whole brain volumes in professional rugby league players compared to control subjects. To our knowledge, we are the first to report whole brain volume differences in professional athletes. There is some evidence of reduced hippocampal and amygdala volumes in retired professional athletes (Strain et al., 2015; Coughlin et al., 2015). In the present study, professional rugby league players had smaller bilateral hippocampi and left amygdala volumes, with large effect sizes. Rugby league players reported significantly greater alcohol consumption in the past year compared to controls and demonstrated worse visual memory performance. Researchers have reported smaller subcortical volumes in individuals with alcohol misuse (Fein & Fein, 2013; Durazzo et al., 2011; Lee et al., 2016). For example, smaller total hippocampal volumes in the left presubiculum, fimbria, and bilateral subiculum were observed in men meeting clinical criteria (i.e., Diagnostic Statistical Manual-IV-TR) for alcohol dependence compared to social drinkers (Lee et al., 2016). Smaller bilateral amygdala and hippocampal volumes have been reported in alcohol dependent relapers and abstainers compared to healthy controls (Durazzo et al., 2011). Furthermore, hippocampal volumetric recovery in some regions (i.e., cornu ammonis regions 1 and 2) has been reported after two weeks of alcohol abstinence (Kühn et al., 2014). In our study, we found that within the players group, greater alcohol use was associated with smaller bilateral hippocampi and left amygdala volumes. No other significant associations were observed between subcortical volumes and memory performance, psychological distress, or number of past concussions. These findings highlight the importance of examining broad clinical characteristics (e.g., alcohol use) when investigating the potential effects of concussion exposure on brain structure and function in athletes.

In conclusion, there were large statistically significant differences in whole brain and subcortical structure volumes in retired professional rugby league players compared to controls. Alcohol abuse is a risk factor for volumetric changes in the brain (Fein & Fein, 2013; Durazzo et al., 2011; Lee et al., 2016) and that likely was contributory in this sample. We suspect that the structural changes observed in this study are associated with a combination of alcohol use and repetitive neurotrauma associated with participation in this high contact sport. But, it is notable that there were no significant correlations between structural volumes and number of concussions. More research is needed to determine if these structural changes are associated with accelerated cognitive aging or specific neurodegenerative diseases.

### Author disclosures

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### Table 1

| Clinical characteristics | Rugby players (n = 24) | Healthy controls (n = 18) | p     | Cohen’s d |
|-------------------------|------------------------|--------------------------|-------|-----------|
| Age [M (SD)]            | 33.3 (6.3)             | 33.7 (7.5)               | 0.75  | 0.06      |
| Education in years [M (SD)] | 12.1 (1.9)           | 12.7 (22.4)              | 0.56  | 0.06      |
| Number of concussions [Md (Range)] | 20 (1–125)          | –                        | –     | –         |
| Number of concussions with LOC [Md (Range)] | 3 (0–30)             | –                       | –     | –         |
| Depression Scale [M (SD)] | 4.3 (8.8)             | 1.9 (2.3)                | 0.77  | 0.40      |
| Anxiety Scale M ([SD])  | 3.2 (4.4)              | 2.0 (2.7)                | 0.55  | 0.32      |
| Stress Scale M ([SD])   | 8.3 (8.9)              | 7.0 (5.3)                | 0.86  | 0.18      |
| AUDIT score (alcohol use, M (SD)) | 10.3 (4.4)         | 3.9 (3.3)                | 0.001 | 1.63      |

| Cognitive tests\(^a\) | RAVLT Learning [M (SD)] | 43.0 (9.6) | 44.4 (9.8) | 0.83 | 0.14 |
|------------------------|-------------------------|------------|------------|------|------|
| RAVLT Short-Delay [M (SD)] | 44.2 (13.8)        | 48.9 (9.8) | 0.32 | 0.39 |
| RAVLT Long-Delay [M (SD)] | 45.1 (12.7)        | 46.9 (12.7) | 0.74 | 0.14 |
| RCFT Short-Delay Recall [M (SD)] | 43.3 (9.9)    | 49.1 (7.3) | 0.07 | 0.66 |
| RCFT Long Delay Recall [M (SD)] | 43.4 (9.6)       | 49.4 (7.0) | 0.04 | 0.71 |
| TMT A [M (SD)]         | 45.6 (6.8)          | 46.9 (8.9) | 0.67 | 0.16 |
| TMT B [M (SD)]         | 56.8 (10.1)         | 57.3 (10.9) | 0.76 | 0.05 |
| Stroop Interference [M (SD)] | 51.5 (11.7)     | 51.6 (13.9) | 0.80 | 0.01 |

| Structural regional volumes\(^b\) | Whole Brain \[^c\] | 751.4 (82.7) | 863.2 (150.3) | 0.003 | 1.00 |
|-----------------------------------|-------------------|-------------|---------------|-------|------|
| Right Hippocampus                  | 2.7 (0.4)         | 3.1 (0.6)  | 0.03 | 0.82 |
| Left Hippocampus                   | 2.6 (0.4)         | 3.0 (0.5)  | 0.03 | 0.98 |
| Right Amygdala                     | 1.0 (0.1)         | 1.1 (0.2)  | 0.06 | 0.70 |
| Left Amygdala                      | 0.9 (0.2)         | 1.2 (0.3)  | 0.01 | 1.24 |

Notes: M = mean, SD = standard deviation, Md = median, AUDIT = Alcohol Use Disorders Identification Test, RAVLT = Rey Auditory Verbal Learning Test, RCFT = Rey Complex Figure Test, LOC = loss of consciousness, and TMT = Trail Making Test. The data highlighted in bold is statistically significant p < .05.

\(^a\) All cognitive scores are T-scores that have been normed using Mitrushina et al. (2005) except for RAVLT scores which were normed using Schmidt et al. (1996).

\(^b\) Structural comparisons of regional volumes (RV) corrected for intracranial volume (ICV; RV/ICV) and multiplied by 1000.

\(^c\) Excluding ventricles, cerebrospinal fluid, and choroid plexus.
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Fig. 1. Cortical and subcortical volumes for professional rugby league players and controls.
Note: structural comparisons of regional volumes (RV) corrected for intracranial volume (ICV; RV/ICV) and multiplied by 1000; whole brain excludes ventricles, cerebrospinal fluid, and choroid plexus.

Table 2
Regression results predicting subcortical structure volumes.

|                         | B      | S.E.  | Standardized beta | 95% CI          | p     |
|-------------------------|--------|-------|-------------------|-----------------|-------|
| Right hippocampus       |        |       |                   |                 |       |
| Group                   | 0.25   | 0.28  | 0.25              | −0.41 to 1.03   | .41   |
| AUDIT                   | 0.08   | 0.03  | 0.80              | 0.003 to 0.22   | .03   |
| Group × AUDIT           | −0.11  | 0.04  | −1.34             | −0.21 to −0.06  | .01   |
| R², %                   | 29.6   |       |                   |                 |       |
| Left hippocampus        |        |       |                   |                 |       |
| Group                   | 0.33   | 0.27  | 0.34              | −0.23 to 1.05   | .24   |
| AUDIT                   | 0.09   | 0.03  | 0.90              | 0.01 to 0.28    | .01   |
| Group × AUDIT           | −0.12  | 0.04  | −1.51             | −0.21 to −0.08  | .008  |
| R², %                   | 33.0   |       |                   |                 |       |
| Right amygdala          |        |       |                   |                 |       |
| Group                   | 0.10   | 0.12  | 0.24              | −0.16 to 0.34   | .37   |
| AUDIT                   | 0.02   | 0.01  | 0.44              | −0.02 to 0.14   | .19   |
| Group × AUDIT           | −0.03  | 0.02  | −0.97             | −0.06 to 0.02   | .05   |
| R², %                   | 18.4   |       |                   |                 |       |
| Left amygdala           |        |       |                   |                 |       |
| Group                   | 0.14   | 0.13  | 0.30              | −0.12 to 0.45   | .31   |
| AUDIT                   | 0.04   | 0.02  | 0.74              | 0.004 to 0.13   | .01   |
| Group × AUDIT           | −0.05  | 0.02  | −1.36             | −0.09 to −0.03  | .005  |
| R², %                   | 30.8   |       |                   |                 |       |
| Whole brain             |        |       |                   |                 |       |
| Group                   | 0.31   | 73.78 | .001              | −165.50 to 194.91 | .99 |
| AUDIT                   | 9.93   | 8.34  | .393              | −8.25 to 68.88  | .29   |
| Group × AUDIT           | −17.04 | 9.95  | −.814             | −46.32 to 4.37  | .15   |
| R², %                   | 25.3   |       |                   |                 |       |

Note: group: rugby players = 1; controls = 0.

* Bootstrapped results based on 1000 bootstrap samples.
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