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ORIGINAL RESEARCH

A preliminary investigation of corpus callosum subregion white matter vulnerability and relation to chronic outcome in boxers

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Abstract

Microstructural neuropathology occurs in the corpus callosum (CC) after repetitive sports concussion in boxers and can be dose-dependent. However, the specificity and relation of CC changes to boxing exposure extent and post-career psychiatric and neuropsychological outcomes are largely unknown. Using deterministic diffusion tensor imaging (DTI) techniques, boxers and demographically-matched, noncontact sport athletes were compared to address literature gaps. Ten boxers and 9 comparison athletes between 26 and 59 years old ($M = 44.63$, $SD = 9.24$) completed neuropsychological testing and MRI. Quantitative DTI metrics were estimated for CC subregions. Group×Region interaction effects were observed on fractional anisotropy (FA; $\eta^2_p \geq .21$). Follow-up indicated large effects of group ($\eta^2_p \geq .26$) on splenium FA (boxers<comparisons) and genu mean diffusivity (MD; boxers>comparisons), but not radial diffusivity (RD). The group of boxers had moderately elevated number of psychiatric symptoms and reduced neuropsychological scores relative to the comparison group. In boxers, years sparring, professional bouts, and knockout history correlated strongly ($r > |.40|$) with DTI metrics and fine motor dexterity. In the comparison group, splenium FA correlated positively with psychiatric symptoms. In the boxer group, neuropsychological scores correlated with DTI metrics in all CC subregions. Results suggested relative vulnerability of the splenium and, to a lesser extent, the genu to chronic, repetitive head injury from boxing. Dose-dependent associations of professional boxing history extent with DTI white matter structure indices as well as fine motor dexterity were supported. Results indicated that symptoms of depression and executive dysfunction may provide the strongest indicators of global CC disruption from boxing.

Keywords Repetitive sports concussion · Boxing · DTI · Executive function · Depression · Corpus callosum

The repetitive concussive and sub-concussive blows to the head incurred by boxers can lead to chronic traumatic encephalopathy (CTE), a clinical syndrome involving neurological, neuropsychological, and neuropsychiatric symptoms (DeKosky et al. 2013; Roberts et al. 1990; Smith et al. 2013). This chronic and potentially progressive syndrome has also been linked to other forms of neurodegenerative disorder such as Alzheimer's and Parkinson's disease (Corsellis

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et al. 1973; Koerte et al. 2015; McKee et al. 2009; Smith et al. 2013). Gross and microstructural neuropathological findings of CTE have been commonly reported in boxers. However, neuroimaging modalities like computed tomography (CT) and conventional magnetic resonance imaging (MRI) sequences can lack sensitivity to detect presumed diffuse axonal injury (DAI) in sports-related concussion (Shenton et al. 2012). This is reflected in early neuroimaging studies of boxers, which predominantly utilized qualitative assessment of macrostructure to identify the most prevalent alterations of global cerebral atrophy, ventromegaly, and cavum septum pellucidum (Jordan et al. 1992; Levin et al. 1987). Characteristic structural abnormalities have since been extended to include gross markers of microstructural pathology such as dilated perivascular spaces and the presence of lesions indicative of shearing, or DAI (Orrison et al. 2009; Wilde et al. 2006; Lijuan Zhang et al. 2003).

Advances in diffusion tensor imaging (DTI) data acquisition and processing techniques have facilitated greater understanding of macro- and microstructure in boxing-related traumatic brain injury (TBI). DTI has proven to be more sensitive to the effects of DAI and repetitive head trauma than conventional structural MRI techniques (Koerte et al. 2015; Shenton et al. 2012; Zhang et al. 2006). Altered white matter integrity, as indexed by DTI-derived diffusivity metrics such as fractional anisotropy (FA), mean diffusivity (MD) and radial diffusivity (RD), has been previously reported in boxers relative to various comparison groups (Chappell et al. 2006; Herweh et al. 2016; Shin et al. 2014; L. Zhang et al. 2006; Lijuan Zhang et al. 2003). While white matter alterations can occur in diffuse brain regions (Orrison et al. 2009; Wilde et al. 2016; L. Zhang et al. 2006; Lijuan Zhang et al. 2003), heightened susceptibility of the white matter microstructure of the corpus callosum (CC) has been proposed, and has been shown to have dose-dependent relations with extent of boxing history (Herweh et al. 2016; Shin et al. 2014; Zhang et al. 2006).

Despite the mounting evidence for CC microstructural susceptibility to repetitive head injury from boxing, several gaps in the current literature remain. It is still unclear whether white matter disruption of the CC is regionally specific. Using tract-based spatial statistics in boxers, Herweh et al. (2016) provided emergent support for the relative sparing of medial aspects of the CC compared to more lateral regions that was particularly evident in the genu of the CC (CC_{Genu}). Further DTI results also suggested heightened vulnerability of anterior and posterior callosal regions, with findings indicating that CC_{Genu} and splenium ($CC_{Splenium}$) white matter may be differentially susceptible to the effects of repetitive boxing-related injuries (Herweh et al. 2016; Shin et al. 2014; Zhang et al. 2006). For example, extensive boxing involvement and other indices of boxing-related injury severity robustly relate to DTI metric alterations in these regions (Herweh et al. 2016; Shin et al. 2014). In amateur boxers, greater number of bouts corresponded with elevated FA and reduced MD in the CC, particularly in the medial CC_{Genu} (Herweh et al. 2016). Higher number of knockouts is also strongly related to disrupted white matter (i.e., reduced FA and increased MD) in the posterior CC in professional unarmed combatants, although to a considerably greater extent in boxers (Shin et al. 2014). There is also limited support that $CC_{Splenium}$ diffusion abnormalities relate to the extent of global brain changes from boxing (L. Zhang et al. 2006). Thus, directly assessing regional specificity of callosal white matter disruption using DTI techniques could provide a marker for identifying the extent of overall brain injury in boxers. However, no study to date has directly compared the white matter integrity of discrete CC regions to determine if such regional sensitivity exists.

Furthermore, the functional implications of CC white matter alterations in boxers are poorly understood. The CC is a major interhemispheric commissure with extensive cortical-subcortical connections linking widespread brain regions, and is, therefore, involved in motor, higher cognitive (e.g., attention and executive function), and emotional processes (Knyazeva 2013; Lischke et al. 2017; Marco et al. 2012; Voineskos et al. 2012). Although the neuropsychological sequelae of repetitive sports concussion in boxers remains largely unknown, identified impairments of CTE include motor, attention, and executive dysfunction as well as mood disturbance (e.g., depression and suicide) (Areza-Fegyveres et al. 2007; Corsellis et al. 1973; Heilbronner et al. 2009; McKee et al. 2015; Smith et al. 2013; Stern et al. 2013). However, with few exceptions, the neuropathology underlying cognitive and emotional dysfunction in boxers has not been studied (Banks et al. 2014; Levin et al. 1987; Wilde et al. 2016), and results have been limited to specific cognitive domains (i.e., impulsivity, implicit and declarative memory, and basic reaction time). It is noteworthy that impairments often ensue despite limited history of acute, repetitive concussive effects and lacking radiological evidence of frank TBI (Belanger et al. 2010; Jordan 2000; McKee et al. 2009, 2015). Similar to the relations with metrics of white matter integrity (i.e., diffusivity), greater extent of boxing exposure has also been related to increased risk of later neuropsychological complications (Heilbronner et al. 2009; Herweh et al. 2016; Stiller et al. 2014; Zhang et al. 2003). It is likely that the largely non-focal symptoms of repetitive head injury will be related to indices of CC connectivity alterations as indexed by DTI metrics.

Current study aims and hypotheses

Understanding the specificity of CC white matter disruption in chronic, repetitive boxing-related TBI and subconcussive head impacts may provide a biomarker of injury severity and aid in prognostic planning in boxers. To address gaps in the literature, the current study examined the following aims:

1. The primary aim of the current study was to determine the specificity of microstructural changes in subregions of the CC in chronic, repetitive boxing-related TBI relative to a comparison group of athletes who participated in noncontact sports. Deterministic tractography was used to examine diffusion characteristics of the CC_{Genu}, CC body (CC_{Body}) and $CC_{Splenium}$. Posterior regions were expected to show significantly greater diffusion abnormalities (i.e., reduced FA and increased RD and MD, respectively) in the group of boxers relative to the comparison athlete group. In addition, greater extent of boxing exposure, including number professional bouts, years sparring, and professional knockouts with and without loss of consciousness (LOC), was expected to be associated with increased alterations in white matter.
2. The second aim was to identify any group differences on commonly reported psychiatric and neuropsychological difficulties in patients with a history of boxing exposure versus other noncontact sport athletes (Areza-Fegyveres et al. 2007; Heilbronner et al. 2009; McKee et al. 2015; Smith et al. 2013). Specifically, groups were compared on anxiety and depression symptoms, as well as on standardized measures of executive function and fine motor dexterity. We expected that the boxers would generally exhibit greater psychiatric symptoms and perform more poorly on all neuropsychological measures compared to athletes in the comparison group. In addition, greater extent of boxing exposure was expected to be associated with more severe psychiatric and neurobehavioral difficulties in the boxers.
3. For the third aim, the clinical implications of white matter microstructural findings were examined. Specifically, relations of quantitative DTI metrics (i.e., FA, RD, and MD) with neuropsychiatric symptoms and neuropsychological performance were examined. Given increased risk for depression and cognitive impairment in patients with CTE (e.g., McKee et al. 2015), greater microstructural disruption was expected to correlate with increased symptoms of depression and poorer neuropsychological performance in the group of boxers.

Method

Participants

Nineteen male athletes between the ages of 26 and 59 years old ($M = 44.63$, $SD = 9.24$) completed neuropsychological testing and underwent diffusion MRI. A group of boxers ($n = 10$) with histories of amateur and/or professional boxing were recruited from local boxing gyms. To be included, boxers had to have at least 15 years of amateur and/or professional boxing, or at least 20 bouts and a regular schedule of sparring. Nine of the boxers had histories of fighting in amateur and professional bouts and one had only fought in amateur bouts. Except for 2 boxers who were still actively boxing, all had retired from boxing at the time of the study. For the comparison group, we recruited athletes ($n = 9$) with histories of noncontact sports involvement through the community via advertisement or referral. Individuals in the comparison group were matched to the boxers in terms of age (± 2 years) and education. In the comparison group, duration of sports involvement ranged between 3 to 50 years ($M = 30.89$ years, $Mdn = 31.0$) and was comparable to that of the group of boxers. As determined through a semi-structured sports history interview, none of the participants in the comparison group had sustained a concussion or other TBI (e.g., reported never experiencing loss or alteration of consciousness or post-traumatic amnesia). Inclusion criteria for both groups included (a) male, (b) fluency in English, (c) age between 25 and 60 years old, (d) no medical history of neurologic or psychiatric disorder (e.g., brain tumor, multiple sclerosis, schizophrenia, or bipolar disorder) that, for the boxers, was unrelated to boxing, (e) absence of any MRI contraindications, and (f) absence of diagnosed dementia or other severe cognitive impairment that precluded informed consent. Informed consent was obtained from all individual participants included in the study, and the study was approved and carried out by the ethical standards set forth by the Baylor College of Medicine Institutional Review Board. The current sample has also been described in Wilde et al. (2016), which examined a number of isolated white matter tracts in relation to declarative and implicit memory as well as basic reaction time performance. While the prior study included the CC, subregions were not examined in our previous analyses.

Materials and procedure

Participants completed a standardized neuropsychological test battery that included measures assessing psychiatric symptoms and neuropsychological function. A structured boxing history interview was also conducted with each boxer to ascertain both amateur and professional experience and TBI events, as summarized in Table 1.

Anxiety The Beck Anxiety Inventory (BAI) is a 21-item self-report measure used to assess symptoms of anxiety (Beck et al. 1988). Participants rated each item as follows: 0, not at all; 1, mildly - but it didn't bother me much; 2, moderately - it wasn't pleasant at times; or, 4 severely - it bothered me a lot. The sum of all items (i.e., total score) was used as an estimate of anxiety symptom severity. Scores of 0–21 are classified as low anxiety; scores between 22 and 35, moderate anxiety; with scores above 36 reflective of severe or potentially concerning levels of anxiety. The BAI has strong psychometric properties, including internal consistency and test-retest reliability.

Table 1 Demographic and respective boxing history data for the group of boxers and the group of comparison athletes (the control group)

	Group	
Variable	Boxers	Controls
Demographics		
Age (M ± SD Years)	45.70 ± 9.71	43.44 ± 9.11
Education (M ± SD)	13.00 ± 1.49	13.78 ± 1.92
Ethnicity (*n* [% Hispanic])	4 (40)	2 (22)
Socioeconomic status (M ± SD)	35.54 ± 11.46	42.09 ± 10.57
Handedness (*n* [% Right])	9 (90)	9 (100)
Boxing History		
Years Boxing (M ± SD [Range])	35.70 ± 9.15 (16–51)	–
Starting Age (M ± SD [Range])	10.00 ± 4.50 (6–22)	–
Years as Amateur (M ± SD [Range])	11.80 ± 8.46 (1–30)	–
Bouts as Amateur (M ± SD [Range])	139.50 ± 104.08 (20–357)	–
Years as Professional (M ± SD [Range])	6.70 ± 7.44 (0–26)	–
Professional Bouts (M ± SD [Range])	24.50 ± 31.26 (0–110)	–
Years Sparring (M ± SD [Range])	22.56 ± 13.46 (2–40)	–
Professional Knockouts (M ± SD [Range])	0.89 ± 0.60 (0–2)	–
Professional Knockouts with LOC (M ± SD [Range])	0.67 ± 0.71 (0–2)	–

Depression The Center for Epidemiological Studies-Depression (CES-D) is a 20-item report measure of depression (Radloff 1977). The CES-D rates the frequency with which participants experienced symptoms of depression, such as restless sleep, poor appetite, and feeling lonely, over the past week. Response options range from 0 to 3 for each item (0 = Rarely or None of the Time, 1 = Some or Little of the Time, 2 = Moderately or Much of the time, 3 = Most or Almost All the Time). Scores range from 0 to 60, with high scores indicating greater depressive symptoms. The CES-D provides cutoff scores (e.g., 16 or greater) for identifying individuals at risk for clinical depression, and has strong psychometric properties (Lewinsohn et al. 1997).

Executive function The Trail Making Test was utilized as a measure of visual attention and cognitive flexibility (Reitan and Wolfson 1985). The test is administered in two parts, Part A and Part B. Part A is thought to provide a robust measure of visual scanning and visuomotor tracking (attention), whereas Part B is considered to provide a measure of executive function, specifically divided attention and cognitive flexibility (set-shifting). For Part A, participants were asked to draw lines to connect 25 consecutively numbered circles, presented on a single page (i.e., 1–2-3…). Part B is similar, except that participants are asked to connect 25 circles marked with numbers and letters, alternating (in numeric and alphabetical order) between numbers and letters (i.e., 1-A-2-B-3…). For both parts, participants were instructed to go as fast as possible without lifting the pencil from the paper, and scores represented total time (in seconds) to complete each part. Prior to the administration of each part, participants completed practice sets that consisted of 8 circles.

Fine motor dexterity Fine motor dexterity was assessed using the Grooved Pegboard (Klove 1963; Lafayette Instruments 1989), which requires the placement of small, ridged pegs into a board containing a 5 × 5 set of slotted holes. Holes are angled in different directions, requiring rotation of each peg so that the ridged edge fits into a hole. The task was completed twice, initially with the dominant hand followed by the non-dominant hand. Raw scores reflect total time to completion (seconds to accurately place each peg in the board) for dominant and nondominant hands.

Magnetic resonance imaging

All participants underwent MRI without sedation on the same Siemens 3 T Trio scanner. Regular quality assurance testing was performed including American College of Radiology (ACR) phantom testing, and no concerns with quality assurance were noted throughout the study.

Image acquisition An anatomical series was used to assess neuropathology (reported in Wilde et al. 2016), including a 3D MPRAGE sequence (TR/TE/TI = 2600/3.02/900 ms, axial slices = 1 mm, no interslice gap, slices = 176, FOV = 256 mm, flip angle = 8 degree). Structural MRI findings for this sample are detailed in Wilde et al. (2016). A DTI diffusion scheme was used, and a 30-direction diffusion-weighted sequence, transverse multislice spin echo, single shot EPI sequence was used to calculate the diffusion tensor (TR/TE = 8000/92 ms, axial slices = 2.0 mm, gap = 0.6 mm, FOV = 256 mm^2, voxel = 2.67 × 2.67 × 2.6 mm^3, b_0-value = 1000 s/mm^2, collected twice; slices = 56; acquisition time = 4:44 min).

Clinical coding of anatomical imaging As detailed previously (Wilde et al. 2016), all MRI data were reviewed by a single board-certified neuroradiologist (JVH) for incidental and trauma-related abnormalities. Briefly, thinning of the corpus callosum was present in 2 boxers and 1 control athlete. A cavum septum pellucidum was a frequent finding (5 boxers, 2 controls). Evan's Index was significantly higher in the group of boxers compared to controls, controlling for age (Wilde et al. 2016).

Diffusion tensor imaging The diffusion tensor analysis was conducted using a deterministic fiber tracking algorithm in DSI Studio (http://dsi-studio.labsolver.org; Yeh et al. 2013). Using a whole brain seeding region, a multiple region of interest (ROI) approach was used to isolate each subregion of the CC, i.e., the CC_{Genu}, CC_{Body}, and $CC_{Splenium}$, by a single rater who was blind to participant group (ALW). Selected regions were based on a highly reliable (intra-class correlational coefficients ≥ .95), published tractography protocol in TBI (Levin et al. 2008; Shah et al. 2012; Wilde et al. 2009). Regions of the CC were specified according to a modified Witelson protocol (Wilde et al. 2006; Witelson et al. 2008). Examples of selected ROIs are shown in Fig. 1.

Fiber tracking was initiated using a step size of 0.5 mm. The anisotropy threshold was set to 0.2. Fibers that progressed with an angular threshold greater than 60 degrees, or that had a length less than 20 mm were discarded. The fiber trajectories were smoothed by averaging the propagation direction with 20% of the previous direction. A constrained, randomized seeding approach in which each voxel in the brain mask was given the probability of being seeded 25 times was used to account for individual brain mask differences. Thus, total number of seeds (N_{seeds}) was determined individually for each participant by multiplying the number of voxels in the brain mask (N_{brain}) by 25. For the current sample, the number of seeds ranged between 1,003,525 and 1,677,750 (M = 1,212,601.32, SD = 156,521.77) for the current sample, and did not differ between groups, $p = .812$. Average tract FA, MD and RD were obtained for the CC_{Genu}, CC_{Body}, and $CC_{Splenium}$. Results were considered highly reliable, intra-class correlation coefficient = .98. Tractography results for a participant from each group are shown in Fig. 1.

Statistical analysis

The statistical analyses for each aim were completed using general linear modeling procedures in SPSS 24.0 (Chicago, IL). For demographic data, univariate analyses were used to examine group differences on continuous variables and Pearson Chi-Square tests were used for categorical variables. Aim 1 was addressed using analysis of variance (ANOVA). Two (Group: boxers and comparison athletes) × 3 (Region: CC_{Genu}, CC_{Body}, $CC_{Splenium}$) mixed-model, repeated measures ANOVAs were used to examine differential effects of group on specific regions of the CC. For Aim 2, separate one-way ANOVAs were used to examine the effect of group on psychiatric symptoms and neuropsychological performance variables. Pearson correlations were utilized to examine associations among diffusion metrics (i.e., FA, MD and RD) with age and professional boxing history in the group of boxers (Aims 1and 2) as well as with psychiatric symptoms (i.e., anxiety and depression) and neuropsychological performance (Aim 3) within each group.

Given the exploratory nature of the present study, the statistical threshold of significance for all analyses was set to alpha $p < .05$, and no corrections for multiple comparisons

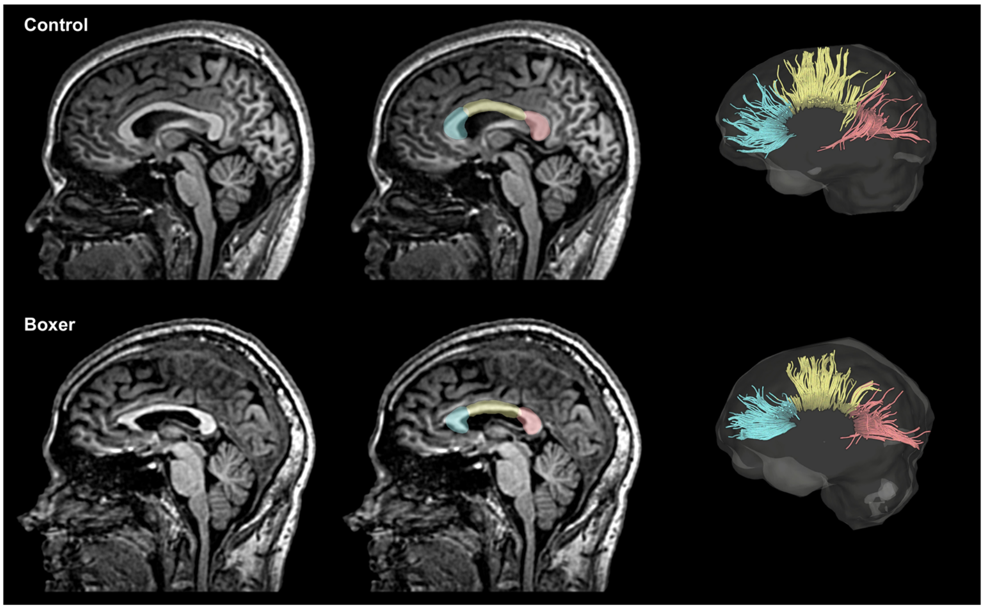

Fig. 1 A midsagittal view of the corpus callosum from the T_1-weighted anatomical scan (Left Column), and the regions of interest (Middle Column) and associated tractography results (Right Column) for the genu (blue), body (yellow), and splenium (red) of the corpus callosum of a participant in the comparison athlete control group (Top Row) and the boxer group (Bottom Row)

were applied. Instead, effect size was used to assess the strength of group differences and correlations. Specifically, measures of effect size magnitudes included η_p^2 and R^2 for group differences on Aim 1 and 2 outcome measures and the squared Pearson correlation coefficient for the structure-function correlations for Aim 3, respectively. Since criteria for interpreting effect sizes are somewhat arbitrary and vary depending on the context (Cohen 1988), the following set of criteria was used to assess effect size (i.e., η_p^2 and R^2) magnitudes in the current study: (a) values below .06 were considered weakly related (i.e., $r < |.25|$; small effect), (b) values between .06 and .16 were considered moderately related (i.e., $|.25| \leq r \leq |.40|$; moderate effect), and (c) values exceeding .16 being considered strongly related (i.e., $r > |.40|$; large effect). In the interest of space, only the findings of large effect size were considered statistically robust and are reported and discussed below. To control for the number of analyses, only results that had large effect sizes (i.e., $r > |.40|$) and that were also statistically significant (i.e., $p < .05$) were considered to be robust.

Preliminary analyses Preliminary analyses were conducted to ensure normality of distributions of the primary DTI metrics within and across groups. Significant outliers (2 boxers, 2 controls) were dropped from final analyses. Specifically, 2 of the boxers and athletes in the comparison control group had diffusion metrics in the $CC_{Splenium}$ that were > 2 SD from the group mean (before and after they were removed), and were removed from analyses examining group differences in DTI metrics of the CC subregions (Aim 1) and also between DTI metrics in the splenium and boxing history (Aim 1) as well as emotional and cognitive (Aim 3) functioning. Similarly, the same participants were excluded from respective analyses when scores were > 2 SD from the mean for CC_{Genu} MD and RD. Notably, the boxers with the lowest FA values and the highest MD/RD values, respectively, also had the greatest professional boxing history (e.g., 26 years of professional boxing; 110 professional bouts) compared to the other boxers (e.g., ≤ 10 years of professional boxing; ≤ 29 professional bouts).

For fine motor dexterity in the current analyses, 2 (Group: boxers and comparison athletes) × 2 (Hand: dominant and nondominant) repeated measures ANOVA indicated that while there was an expected main effect of hand across group, $F(1, 17) = 5.99$, $p = .026$, $\eta^2_p = .26$, the Group × Hand interaction effect was minimal, $F(1, 17) < 1.00$, $p = .569$, $\eta^2_p = .03$. Thus, groups showed a similar pattern whereby the dominant hand ($M = 80.26$, $SD = 22.61$) performance was better (faster) than the nondominant hand ($M = 91.53$, $SD = 26.48$). Given that lateralization was similar across the groups, scores for each hand were averaged to provide an estimate of an overall fine motor dexterity. As reported previously in the current sample (Wilde et al. 2016), age significantly correlated with boxing history variables as well as with DTI metrics. Therefore, age was entered as a covariate in initial models, and was trimmed from final models when appropriate. It is noteworthy, however, that overall results were similar with and without the covariate age.

Results

Demographic characteristics

Demographic information for each group is presented in Table 1 along with results from the structured boxing history interview for the group of boxers. Groups did not statistically differ in age, $F(1, 17) < 1.00$, $p = .609$, educational attainment, $F(1, 17) < 1.00$, $p = .271$, handedness, $\chi2\ (1) = 0.95$, $p = .330$, ethnicity, $\chi2\ (3) = 1.96$, $p = .580$, or socioeconomic status, $F(1, 12) = 1.24$, $p = .288$. All participants were living independently, and none had been diagnosed with dementia. One boxer had post-traumatic parkinsonism with slurred speech (i.e., dysarthria) and gross motor retardation (i.e., gait), but no known history of neurocognitive disorder diagnosis.

Aim 1: Diffusion characteristics of the Corpus callosum

Average diffusion metrics and pairwise statistics for between-group comparisons for the CC_{Genu}, CC_{Body}, and $CC_{Splenium}$ are reported in Table 2 and summarized in Fig. 2.

Fractional anisotropy As expected, the 2 (Group: boxers and comparison athletes) × 3 (Region: CC_{Genu}, CC_{Body}, $CC_{Splenium}$) repeated measures ANOVA indicated a large (i.e., $\eta^2_p > |.16|$) within-subjects effect of region, $F(2, 28) = 66.42$, $p < .001$, $\eta^2_p = .83$, and a large Group × Region interaction, $F(2, 28) = 3.\ 82$, $p = .034$, $\eta^2_p = .21$, on FA values. As shown in Fig. 2, FA values followed an anterior to posterior gradient in the CC subregions across groups, with the highest values observed in the $CC_{Splenium}$ ($M = 0.57$, $SD = 0.02$), followed by the CC_{Body} ($M = 0.53$, $SD = 0.02$) and then the CC_{Genu} ($M = .51$, $SD = .02$). There was a moderate between-subjects effect of group, $F(1, 14) = 1.90$, $p = .189$, $\eta^2_p = .12$, indicating that the group of boxers had reduced FA relative to the comparison group, across regions of the CC. As summarized in Table 2, pairwise comparisons indicated that the group of boxers had significantly reduced FA in the $CC_{Splenium}$ relative to the comparison group, $p = .003$, $\eta^2_p = .49$, but that CC_{Genu}, $p = .740$, $\eta^2_p < .01$, and CC_{Body}, $p = .203$, $\eta^2_p = .09$, FA was similar between the groups.

Mean diffusivity As expected, the 2 (Group) × 3 (Region) repeated measures ANOVA indicated a moderate within-subjects effect of region, $F(2, 26) = 2.14$, $p = .137$, $\eta^2_p = .14$,

Table 2 Summary of group averages and differences on white matter diffusion metrics, psychiatric symptoms, and neuropsychological performance for the group of boxers and the group of comparison athletes (the control group)

	Group (M ± SD)		Group difference	
	Boxers	Controls	Partial Eta Squared	*p* value
Diffusion Metrics				
Fractional Anisotropy (FA)				
CC_{Genu}	0.51 ± 0.02	0.50 ± 0.02	< .01	.740
CC_{Body}	0.53 ± 0.02	0.53 ± 0.02	.09	.203
$CC_{Splenium}$	0.56 ± 0.01	0.58 ± 0.02	**.49**	.003
Mean Diffusivity (MD)				
CC_{Genu}	0.82 ± 0.03	0.80 ± 0.01	**.26**	.038
CC_{Body}	0.83 ± 0.04	0.81 ± 0.04	.06	.329
$CC_{Splenium}$	0.86 ± 0.06	0.82 ± 0.05	.09	.242
Radial Diffusivity (RD)				
CC_{Genu}	0.57 ± 0.03	0.55 ± 0.02	.15	.151
CC_{Body}	0.56 ± 0.04	0.54 ± 0.04	.06	.333
$CC_{Splenium}$	0.58 ± 0.05	0.55 ± 0.05	.09	.249
Psychiatric Symptoms				
Anxiety	6.60 ± 8.80	1.89 ± 3.62	.12	.154
Depression	10.70 ± 10.16	5.56 ± 9.18	.07	.265
Neuropsychological Performance				
Visual Scanning/Visuomotor Tracking	32.00 ± 10.65	29.33 ± 6.96	.02	.532
Executive Function	103.20 ± 45.63	77.33 ± 33.49	.10	.181
Fine Motor Dexterity	92.85 ± 24.91	78.17 ± 18.01	.11	.163

Bolded = large effect size (partial eta squared >0.16); visual scanning and visuomotor tracking as measured by the Trail Making Test Part A; executive function as measured by the Trail Making Test Part B (Reitan and Wolfson 1985); fine motor dexterity as measured by the Grooved Pegboard (Klove 1963; Lafayette Instruments 1989)

but no Group × Region interaction effect, $F(2, 26) < 1.00$, $p = .820$, $\eta^2_p = .02$, on MD values. As shown in Fig. 2, MD values showed an anterior to posterior gradient in the CC across groups, with the highest values observed in the $CC_{Splenium}$ ($M = 0.84$, $SD = 0.06$), compared to the CC_{Body} ($M = 0.82$, $SD = 0.04$), and the CC_{Genu} ($M = 0.81$, $SD = 0.02$). There was also a large between-subjects, trend level effect of group, $F(1, 13) = 3.07$, $p =. 103$, $\eta^2_p = .19$. As shown in Fig. 2, the group of boxers tended to have elevated MD values relative to the comparison group, across CC subregions. As summarized in Table 2, pairwise comparisons indicated that the boxer group had significantly (large effect) higher MD values in the CC_{Genu}, $p = .038$, $\eta^2_p = .26$, although groups had similar MD values in the CC_{Body} and the $CC_{Splenium}$.

Radial diffusivity As shown in Fig. 2, the 2 (Group) × 3 (Region) repeated measures ANOVA results revealed a moderate effect of region, $F(2, 26) < 1.00$, $p = .618$, $\eta^2_p = .08$, but no Group × Region interaction effect, $F(2, 26) < 1.00$, $p = .918$, $\eta^2_p < .01$, on RD values. Thus, RD values were similar for the CC_{Genu} ($M = 0.56$, $SD = 0.02$), CC_{Body} ($M = 0.55$, $SD = 0.04$), and the $CC_{Splenium}$ ($M = 0.57$, $SD = 0.05$), across the groups. There was also a large between-subjects effect of group, $F(1, 13) = 3.08$, $p = .103$, $\eta^2_p = .19$; across regions of the CC, the group of boxers had trend-level elevations of RD relative to the comparison group. As shown in Fig. 2, the boxers tended to have higher RD compared to the controls, across CC subregions. However, this effect did not differ significantly between CC subregions (Table 2).

Correlations with boxing history Correlations between diffusion metrics and boxing history variables in the group of boxers are reported in Table 3 and shown in Fig. 3. Specifically, strong correlations (i.e., large effect sizes; $r > |.40|$) were observed between diffusion metrics in examined CC subregions and number of professional bouts, years of sparring, and number of professional knockouts with and without LOC. Specifically, number of professional bouts was strongly correlated with DTI metrics (i.e., FA, MD, RD) in the CC_{Genu} and CC_{Body}, with the exception of MD in the CC_{Genu}. Overall, greater number of professional bouts related to greater alteration (i.e., reduced FA; increased MD and RD) in the group of boxers. Greater number of years sparring was strongly associated with lower FA and higher RD values in the $CC_{Splenium}$, respectively. A similar pattern was observed

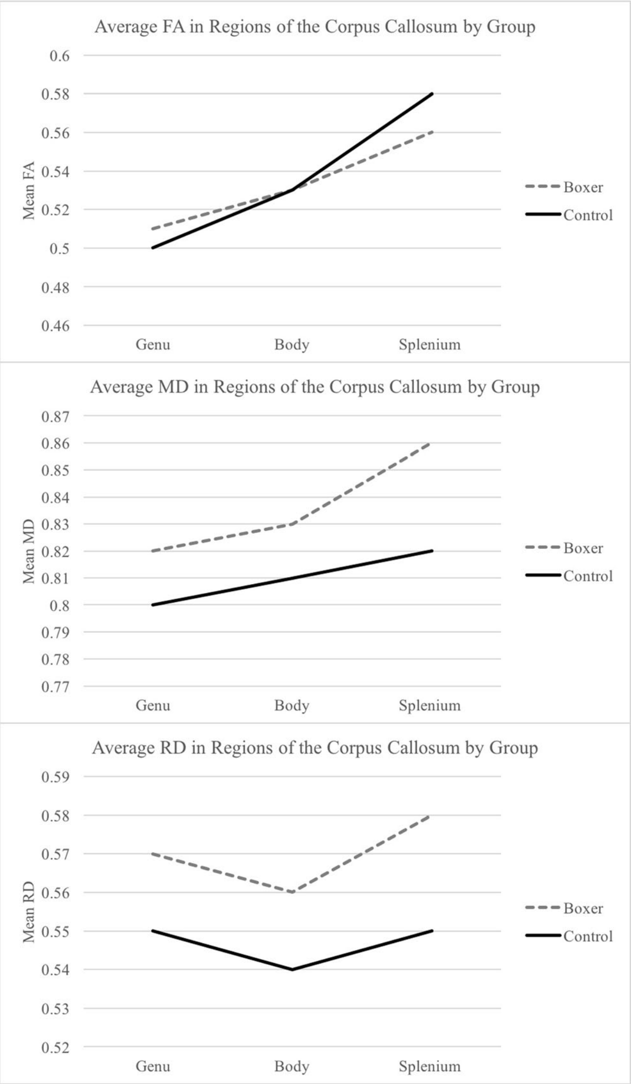

Fig. 2 Graphs illustrating the Group × Region interaction on fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD) of the corpus callosum subregions, respectively. Results generally indicated that the group of boxers had similar average diffusion metrics in the body of the corpus callosum, but had significantly altered metrics in the splenium and, to a lesser extent, the genu of the corpus callosum relative to the group of comparison athletes (the control group)

between total number of professional knockouts (with and without associated LOC) and diffusion metrics in the $\mathrm{CC}_{\mathrm{Body}}$; greater number of professional knockouts was strongly associated with lower FA and higher MD and RD values in the $\mathrm{CC}_{\mathrm{Body}}$, respectively. Number of professional knockouts with LOC was strongly, negatively correlated with FA in $\mathrm{CC}_{\mathrm{Splenium}}$; greater number of knockouts with LOC was strongly associated with lower FA values in the $\mathrm{CC}_{\mathrm{Splenium}}$.

Aim 2: Clinical outcomes

Average scores for psychiatric and neuropsychological measures for each group are provided in Table 2.

Psychiatric symptoms Results indicated that the group of boxers reported moderately greater number of symptoms related to anxiety, $F(1, 17) = 2.23$, $p = .154$, $\eta^2_p = .12$, and depression, $F(1, 17) = 1.33$, $p = .265$, $\eta^2_p = .07$, in relation to the comparison group.

Correlations with boxing history Correlations among scores on psychiatric measures and number of professional bouts, years of sparring, and number of professional knockouts with and without LOC in the group of boxers are shown in Table 3. Neither anxiety nor depression symptom scores were strongly associated with boxing history (i.e., small effect sizes; $r < |.40|$).

Neuropsychological performance As shown in Table 2, the group of boxers had similar performance on visual scanning visuomotor tracking, $F(1, 17) < 1.0$, $p = .532$, $\eta^2_p = .02$, but moderately reduced executive function, $F(1, 17) = 1.94$, $p = .181$ $\eta^2_p = .10$, and, fine motor dexterity (averaged across hands), $F(1, 17) = 2.12$, $p = .163$ $\eta^2_p = .11$, relative to the comparison control group, as measured by the Trail Making Test Part A and B, and the Grooved Pegboard, respectively (Klove 1963; Lafayette Instruments 1989; Reitan and Wolfson 1985).

Correlations with boxing history With the exception of a strong correlation between fine motor dexterity and number of professional knockouts with LOC, neuropsychological performance variables were not strongly (i.e., large effect sizes; $r > |.40|$) correlated with boxing history variables in the group of boxers. Greater number of professional knockouts with LOC was strongly associated with poorer (i.e., slower) fine motor dexterity in the boxers.

Aim 3: Relations among diffusion metrics of the Corpus callosum and clinical outcomes

Correlations among the diffusion metrics with psychiatric symptom and neuropsychological performance scores for each group are reported in Table 4 and shown in Fig. 4.

DTI metrics and psychiatric symptoms In the comparison group, symptoms of anxiety and depression were significantly (i.e., large effect sizes; $r > |.40|$), positively correlated with FA in the $\mathrm{CC}_{\mathrm{Splenium}}$. High FA was associated with high anxiety and depression symptoms, respectively.

As expected, in the group of boxers, number of depression symptoms significantly correlated with DTI metrics in all three CC subregions (Table 4). High symptoms of depression related to low FA and high MD and RD values in the $\mathrm{CC}_{\mathrm{Genu}}$ and $\mathrm{CC}_{\mathrm{Body}}$, respectively. In contrast, high symptoms related to high FA in the $\mathrm{CC}_{\mathrm{Splenium}}$.

Table 3 Correlation coefficients between diffusion metrics, psychiatric, and neuropsychological variables with age and boxing history in the group of boxers

	Professional bouts		Years sparring		Professional knockouts		Professional knockouts with LOC	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Diffusion metric								
Fractional anisotropy (FA)								
CC_{Genu}	**-.53**	.147	-.04	.915	-.04	.920	-.12	.769
CC_{Body}	**-.65**	.060	-.12	.758	**-.49**	.183	-.24	.529
$CC_{Splenium}$	.33	.432	**-.87**	.005	.23	.622	**-.42**	.345
Mean diffusivity (MD)								
CC_{Genu}	.37	.326	-.01	.980	.23	.554	.07	.855
CC_{Body}	**.52**	.152	-.20	.607	**.69**	.038	.37	.326
$CC_{Splenium}$	-.33	.425	.18	.672	-.35	.437	-.01	.978
Radial diffusivity (RD)								
CC_{Genu}	**.43**	.283	**-.46**	.251	.22	.634	-.21	.648
CC_{Body}	**.55**	.129	-.08	.847	**.65**	.057	.35	.363
$CC_{Splenium}$	-.28	.509	.21	.614	-.39	.382	.10	.825
Psychiatric symptoms								
Anxiety	.23	.555	-.16	.691	.19	.629	-.22	.578
Depression	.34	.344	-.02	.963	.09	.821	-.12	.765
Neuropsychological performance								
Visual scanning/Visuo motor tracking	.23	.550	-.30	.431	.24	.527	.29	.450
Executive function	.32	.398	.23	.554	-.15	.692	-.02	.954
Fine motor dexterity	.17	.666	.10	.806	.28	.460	**.61**	.080

LOC, loss of consciousness. **Bolded** = large effect size (i.e., $r > |.40|$); visual scanning and visuomotor tracking as measured by the Trail Making Test Part A; executive function as measured by the Trail Making Test Part B; fine motor dexterity as measured by the Grooved Pegboard (Klove 1963; Lafayette Instruments 1989)

DTI metrics and neuropsychological performance As shown in Table 4 and Fig. 4, none of the DTI metrics significantly correlated with neuropsychological performance on any measures in the comparison group.

However, in the group of boxers, visual scanning and visuomotor tracking scores signficantly correlated with RD in the CC_{Genu}; high RD values related to poor (i.e., slow) performance. Executive function scores significantly correlated with all of the DTI metrics in the CC_{Genu} and with FA in the CC_{Body}; poor (i.e., slow) performance related to low FA and high MD and RD values, respectively. Finally, fine motor dexterity speed significantly correlated with FA and MD in the CC_{Genu}; poor (i.e., slow) fine motor dexterity related to high FA and low MD values, respectively.

Discussion

Boxing has the highest risk for concussion in athletes of all ages and competitive levels (Koh et al. 2003). Although deleterious, dose-dependent effects of repetitive sports concussion from boxing on CC microstructure are documented in clinical (Herweh et al. 2016; Shin et al. 2014; L. Zhang et al. 2006) and preclinical (Mouzon et al. 2012) studies, this is the first known study to compare microstructural alterations between CC subregions and to determine the extent to which changes relate to clinical and functional outcomes. Specifically, the current study examined microstructural integrity of distinct CC regions in a group of boxers relative to noncontact sport athletes comparable in age and sex, and examined relations among diffusion characteristics of CC regions, boxing history, and psychiatric and neuropsychological symptoms to address gaps in the currently published research literature.

Microstructural alterations of reduced FA in the $CC_{Splenium}$ and increased MD in the CC_{Genu} were observed in the group of boxers compared to the demographically-matched group of noncontact sport athletes. Previous clinical findings have supported increased susceptibility of white matter in these regions in professional boxers (Chappell et al. 2006; Herweh et al. 2016; Shin et al. 2014; LZhang et al. 2006). For example, Zhang et al. (2006) reported differentially robust association between FA in the $CC_{Splenium}$ and global brain diffusion abnormalities in professional boxers that was thought to highlight the particular susceptibility of the $CC_{Splenium}$ to effects of chronic, repetitive boxing-related head injury. In addition, consistent with the literature (e.g., Chepuri et al. 2002), an anterior to posterior gradient of highest FA values in the $CC_{Splenium}$ and lowest FA in the CC_{Genu}, was observed across groups.

The mechanisms mediating altered DTI metrics in repetitive concussion from boxing are not entirely clear, and are difficult to infer from the current results. Preclinical studies of mild TBI and sports-related concussion typically implicate traumatic axonal injury as the major mechanism of increased MD during the first week after mTBI (reviewed in Shenton

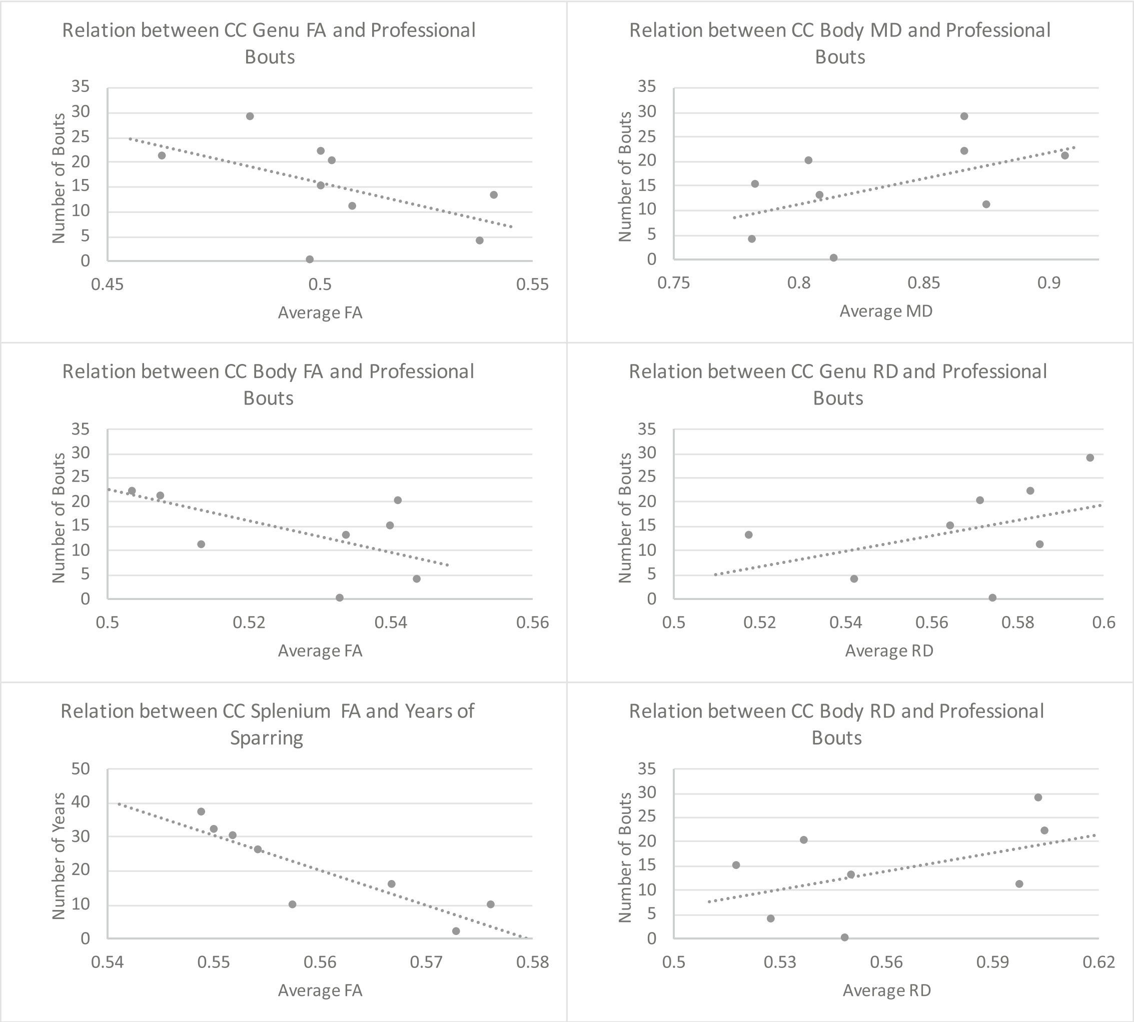

Fig. 3 Graphs illustrating the correlations between boxing history and fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD) of the corpus callosum subregions, respectively, in the group of boxers

et al. 2012). However, there has also been accumulating evidence for progressive neurodegenerative changes, including myelin degradation and neuroinflammation, as well as altered cerebral perfusion in boxers (Koerte et al. 2015). More relevant are findings from animal models and neuropathological studies of acute and sub-acute repetitive mild TBI, which have observed axonal injury, astrogliosis, as well as microgliosis in the CC (Mouzon et al. 2012; Xu et al. 2016). In terms of DTI metrics, these have often corresponded to reduced FA (demyelination) and elevated MD (edema) and RD (Budde et al. 2011; Shenton et al. 2012; Song et al. 2003). There is also evidence that the cumulative effects of repetitive, subconcussive head impacts can affect imaging findings in either mTBI or OI groups (Davenport et al. 2014; McAllister et al. 2014; Sollmann et al. 2018). It is also largely unclear how systemic responses to traumatic extracranial injury influence brain structure and function (Wilde et al. 2016), which is of concern in boxers. Needless to say, further investigations into the cascade of microstructural effects could advance our understanding of these mechanisms, among other potentially non-sports-related factors, and how they relate to DTI metrics, more specifically.

Greater microstructural alterations in the presence of longer and more involved professional boxing careers (i.e., professional bouts, years sparring, and professional knockouts) offers further support for dose-dependent effects of repetitive blows to the head and subconcussive impacts from boxing on white matter integrity (Herweh et al. 2016; McAllister et al. 2014; Shin et al. 2014; Sollmann et al. 2018; L. Zhang et al. 2006). Although groups did not significantly differ on all measures of microstructural integrity, boxing history accounted for a significant amount of the variance in diffusion characteristics of all three of the examined callosal subregions in the group of boxers. In particular, robust associations between years sparring and diffusion metrics in the CC_{Genu} and $CC_{Splenium}$ offers further support for the susceptibility of these regions to the effects of subconcussive blows to the head from boxing. It is possible that greater extent of callosal white matter disruption,

Table 4 Correlation coefficients between diffusion metrics with psychiatric and neuropsychological variables for the group of boxers and the group of comparison athletes (the control group)

	Fractional anisotropy (FA)						Mean diffusivity (MD)						Radial diffusivity (RD)					
	CC_{Genu}		CC_{Body}		$CC_{Splenium}$		CC_{Genu}		CC_{Body}		$CC_{Splenium}$		CC_{Genu}		CC_{Body}		$CC_{Splenium}$	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Boxers (*n* = 10)																		
Psychiatric symptoms																		
Anxiety	-.39	.262	-.52	.125	.51	.201	.43	.211	.37	.287	-.70	.052	.35	.399	.45	.188	-.70	.054
Depression	**-.69**	**.027**	**-.74**	**.016**	**.78**	**.022**	**.83**	**.003**	**.65**	**.044**	-.45	.261	.48	.227	**.73**	**.017**	-.49	.214
Neuropsychological performance																		
Visual scanning/Visuomotor tracking	**-.52**	.123	-.46	.182	.10	.806	.39	.271	.43	.220	-.16	.698	**.73**	**.041**	.43	.220	-.18	.671
Executive function	**-.91**	**< .001**	**-.67**	**.035**	.20	.635	**.83**	.003	.49	.150	-.66	.073	**.79**	**.019**	.56	.094	-.66	.075
Fine motor dexterity	**-.74**	**.014**	-.49	.154	-.22	.594	**.60**	.065	.48	.157	-.56	.149	.38	.354	.48	.161	-.49	.221
Controls (*n* = 9)																		
Psychiatric symptoms																		
Anxiety	.09	.819	.01	.985	**.72**	**.045**	.04	.941	.09	.813	-.23	.551	-.14	.761	.11	.785	-.32	.404
Depression	.06	.880	-.09	.819	**.75**	**.033**	-.01	.997	.10	.808	-.31	.413	-.19	.680	.13	.741	-.39	.297
Neuropsychological performance																		
Visual scanning/Visuomotor tracking	.64	.066	-.01	.985	.35	.402	-.12	.800	.02	.965	-.14	.711	-.54	.207	.03	.950	-.16	.674
Executive function	.45	.228	.17	.666	.54	.169	.06	.903	.04	.916	-.10	.807	-.16	.728	.02	.963	-.17	.670
Fine motor dexterity	.31	.421	-.26	.497	.64	.085	.06	.898	.18	.638	-.25	.517	-.31	.496	.23	.555	-.29	.442

Bolded = statistically significant and large effect size (i.e., $r > |.40|$); visual scanning and visuomotor tracking as measured by the Trail Making Test Part A; executive function as measured by the Trail Making Test Part B (Reitan and Wolfson 1985); fine motor dexterity as measured by the Grooved Pegboard (Klove 1963; Lafayette Instruments 1989)

particularly in posterior regions, may provide a marker for the degree of cumulative brain injury severity incurred as the result of boxing given that greater knockouts with LOC related to FA in the $CC_{Splenium}$ specifically. These results extend those of our previous study (i.e., Wilde et al. 2016), which examined associations among boxing history and the CC overall, to include greater susceptibility of posterior callosal regions to the repetitive head injury incurred from boxing. Importantly, however, is that other processes associated with white matter changes (e.g., genetic, sociodemographic) in this population were not directly examined and could shed light on the causality of white matter differences.

Psychiatric and neuropsychological outcomes were investigated given the clinical significance and high prevalence of mood disorders and cognitive dysfunction in professional boxers after retirement (Areza-Fegyveres et al. 2007; Heilbronner et al. 2009; McKee et al. 2015; Smith et al. 2013). Scores on the psychiatric symptom and neuropsychological measures were generally

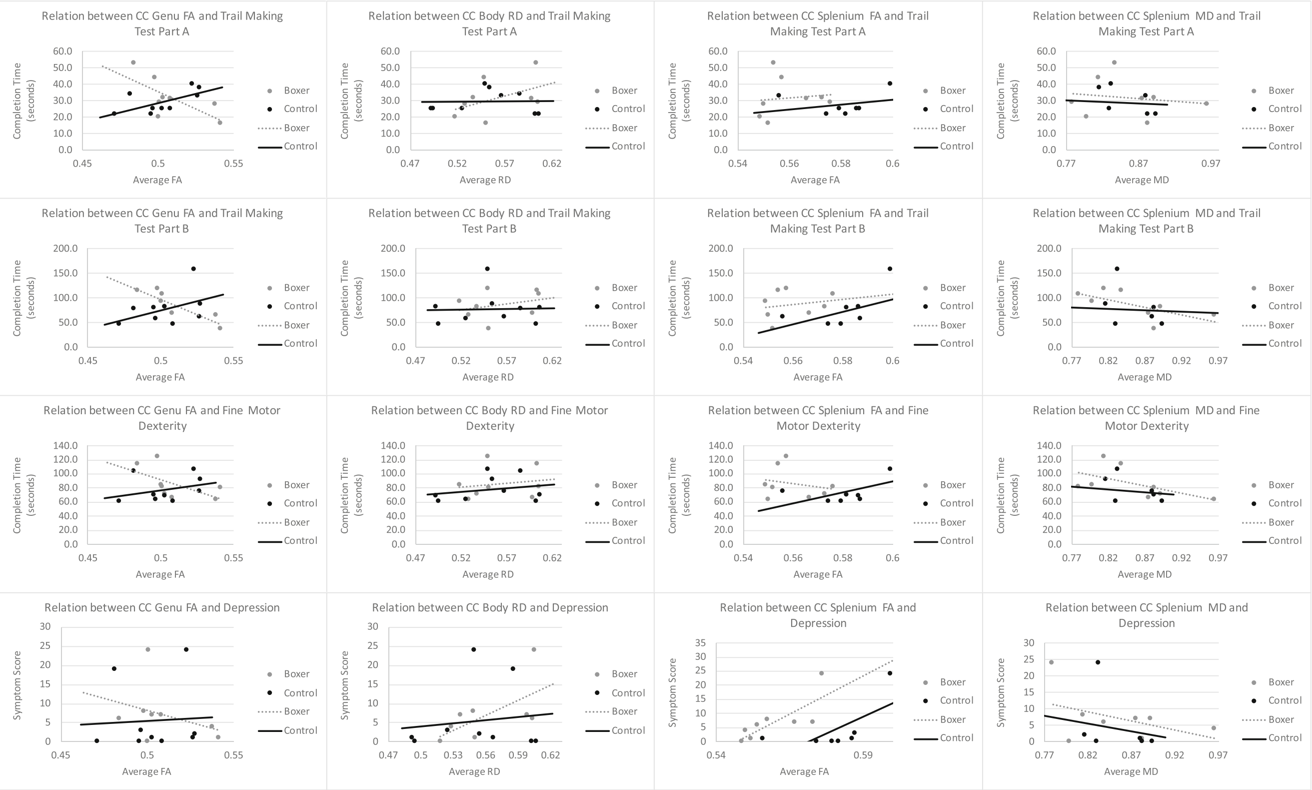

Fig. 4 Graphs illustrating the correlations between psychiatric and neuropsychological measures and fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD) of the corpus callosum subregions, respectively, in the group of boxers and the group of comparison athletes (the control group)

higher in the group of boxers relative to the athlete comparison group. Herweh et al. (2016) observed significantly reduced executive function performance in boxers relative age-matched controls on the same measure (Trail Making Test Part B), but not after groups were matched for age and IQ. Current results for the visual scanning and visuomotor tracking (Trail Making Test Part A) are also in line with their findings. Professional boxing involvement was previously associated with increased intra- and inter-individual variability during executive function tasks, and also with altered neural response during executive function tasks (Di Russo and Spinelli 2010). However, neither the mood nor cognitive scores related to extent of boxing involvement history, with one exception being between fine motor dexterity and number of knockouts with LOC. It is possible that our inclusion of professional boxers as well as a closely matched comparison group of athletes explains the differences between the current results between boxing history extent and neuropsychological outcomes and those reported in amateur boxers in Herweh et al. (2016).

Functional outcomes robustly correlated with diffusion metrics in all of the CC regions to a greater extent in the group of boxers relative to the comparison group. In particular, depression and executive cognitive processes (i.e., executive function) were the most robustly associated with indices of reduced white matter microstructure in the group of boxers compared to the group of noncontact sport athletes. These findings were expected given that depression, among other major mood disturbances such as suicidality, and executive dysfunction have been commonly reported in the literature on CTE and repetitive sports concussion (Areza-Fegyveres et al. 2007; Heilbronner et al. 2009; McKee et al. 2015; Smith et al. 2013). Unexpectedly, however, functional outcomes differentially related to DTI metrics in the $\mathrm{CC}_{\mathrm{Splenium}}$ compared to the $\mathrm{CC}_{\mathrm{Genu}}$ and $\mathrm{CC}_{\mathrm{Body}}$ in the group of boxers (Fig. 4). Results followed expected direction of better functional outcomes with high FA values in the $\mathrm{CC}_{\mathrm{Genu}}$ and $\mathrm{CC}_{\mathrm{Body}}$, except in the $\mathrm{CC}_{\mathrm{Splenium}}$, wherein high FA was unexpectedly associated with high symptoms of depression. Notably, a similar association was also observed in the comparison group. While the explanation for this is not clear, it could have reflected the more restricted sample size due to the loss of 2 boxers and two control athletes who were outliers in terms of both their DTI metrics, and for the boxers, boxing history as well. Further research with larger sample sizes would be beneficial in continuing to elucidate outcomes in professional boxers. The current results offer the first evidence that quantitative metrics derived using DTI are sensitive to psychiatric outcomes in boxers.

The current sample size is a study limitation. Future studies with greater number of participants should be used to substantiate the current findings and could possibly increase generalizability of current findings. This may be particularly important given the within-group variability on outcome measures that was evident in the group of boxers. Future research could also benefit from more within-group homogeneity (e.g., inclusion of only retired, professional boxers). However, our careful inclusion of participants in the noncontact sport athlete group who were matched to the boxers with regard to age (± 2 years) and educational attainment, and similar in terms of handedness, ethnicity, socioeconomic status, and sports involvement is considered a potential strength of the current study.

Methodological limitations of DTI should also be considered, including the resolution capabilities of diffusion data collected in 30 directions and sensitivity of this technique to motion artifact. Restricted tracking abilities, reflective of globally disrupted white matter in boxers compared to controls, also warrants some consideration, as discussed in detail in prior studies (Zhang et al. 2006). However, it is noteworthy that particular care was given to ensure reliability of current tractography data, and results were considered to be highly reliable. Future studies utilizing multi-shell and other advanced diffusion MRI approaches that show the potential for increasing resolution, including high angular resolution diffusion-weighted imaging and diffusion spectrum imaging techniques, is also warranted and could be beneficial.

Finally, the current preliminary study did not address causality of callosal microstructural differences or neuropsychiatric functioning of the current sample. The factors that can affect neurodegeneration with aging across the lifespan are likely highly complex, and were not specifically examined by these analyses. Therefore, we caution the assumption that the observed differences in the group of boxers relative to the comparison group are strictly the result of boxing. Furthermore, it is important to consider limitations of using a concurrent cross-sectional, cohort study design, which limited our understanding of how observed differences function over time, especially with increasing age. It is also not possible to infer from the current results whether these athletes are at risk for further neurodegeneration (e.g., pathology of CTE), or whether neurodegeneration has occurred as the result of their involvement in boxing.

Conclusions and future directions

Overall results support dose-dependent effects of chronic, repetitive exposure to brain trauma on brain parenchyma that is especially evident in more posterior regions of the CC. Results indicated that diffusion characteristics of the $CC_{Splenium}$ were particularly altered with repetitive boxing-related sports concussion and were worsened by more extensive professional boxing history. Boxers with longer professional boxing careers and with greater number of professional bouts also had more anomalous white matter in the CC overall than those with less professional involvement. The current results support that quantitative metrics as derived using DTI are sensitive to functional outcomes in boxers, with particularly promising support for understanding the neuropathological etiology of psychiatric difficulties in boxers after retirement. When taken together, these findings implicate the CC as a potential biomarker of injury severity and prognosis in professional boxers. Brain-behavior correlations indicated that depression symptom severity and executive dysfunction may provide the best indicators of global CC disruption following chronic, repetitive boxing-related concussion. Future prospective and longitudinal research with large samples would be beneficial in continuing to understand outcomes of repetitive blows to the head from boxing.

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Compliance with ethical standards

Conflict of interest None to report.

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