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Diffusion Measures Indicate Fight Exposure–Related Damage to Cerebral White Matter in Boxers and Mixed Martial Arts Fighters

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ABSTRACT

BACKGROUND AND PURPOSE: Traumatic brain injury is common in fighting athletes such as boxers, given the frequency of blows to the head. Because DTI is sensitive to microstructural changes in white matter, this technique is often used to investigate white matter integrity in patients with traumatic brain injury. We hypothesized that previous fight exposure would predict DTI abnormalities in fighting athletes after controlling for individual variation.

MATERIALS AND METHODS: A total of 74 boxers and 81 mixed martial arts fighters were included in the analysis and scanned by use of DTI. Individual information and data on fight exposures, including number of fights and knockouts, were collected. A multiple hierarchical linear regression model was used in region-of-interest analysis to test the hypothesis that fight-related exposure could predict DTI values separately in boxers and mixed martial arts fighters. Age, weight, and years of education were controlled to ensure that these factors would not account for the hypothesized effects.

RESULTS: We found that the number of knockouts among boxers predicted increased longitudinal diffusivity and transversal diffusivity in white matter and subcortical gray matter regions, including corpus callosum, isthmus cingulate, pericalcarine, precuneus, and amygdala, leading to increased mean diffusivity and decreased fractional anisotropy in the corresponding regions. The mixed martial arts fighters had increased transversal diffusivity in the posterior cingulate. The number of fights did not predict any DTI measures in either group.

CONCLUSIONS: These findings suggest that the history of fight exposure in a fighter population can be used to predict microstructural brain damage.

ABBREVIATIONS: TBI = traumatic brain injury; FA = fractional anisotropy; LD = longitudinal diffusivity; TD = transversal diffusivity; MD = mean diffusivity

Traumatic brain injury (TBI) has been reported in athletes involved in combat sports who are frequently exposed to repetitive blows to the head, such as boxers.^{1–8} This cumulative head trauma is thought to cause chronic traumatic encephalopathy as a result of chronic axonal injury.⁹ The clinical syndrome related to chronic traumatic encephalopathy in boxing is characterized by impulsive behavior, cognitive dysfunction, and in some cases, violence or suicide.¹⁰

Conventional MR imaging, such as T1-weighted and T2-weighted anatomic scans, cannot assess mild white matter disruption. Because DTI is sensitive to microstructural changes in white matter, this technique is often used to investigate white matter

integrity in patients with TBI.^{11–17} Previous studies have found that fractional anisotropy (FA) values in the corpus callosum,^{14,16,17} internal capsule,^{11,14,16,17} cingulum,¹⁴ and centrum semiovale^{11,14,16,17} are decreased in patients with TBI versus healthy control subjects. A longitudinal TBI study found that FA was decreased in the white matter of study participants because of decreased longitudinal diffusivity (LD) and increased transversal diffusivity (TD).¹³ Another study demonstrated that the peaks of whole-brain ADC histograms were significantly correlated with scores on the Glasgow Coma Scale in patients with TBI, indicating that a change in DTI values can predict functional deficit.¹⁸

A limited number of studies have investigated diffusion changes in the white matter of fighting athletes.^{7,8,19} These studies found that among fighting athletes, whole-brain diffusion is increased,⁸ FA is reduced in the genu and splenium of the corpus callosum and the posterior internal capsule,⁷ and FA is reduced and ADC increased in the lower brain, the splenium of the corpus callosum, and the lateral and dorsolateral cortical regions.¹⁹ Although these studies used age- and sex-matched control groups,

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Table 1: Pearson correlation between predictors

	Age	Years of Education	Weight	Number of Knockouts	Number of Fights	Years of Fighting
Age		0.288 ^b	0.268 ^a	0.321 ^b	0.092	0.511 ^b
Years of education			0.283 ^b	−0.009	0.013	0.055
Weight				0.061	0.025	0.010
Number of knockouts					0.057	0.250 ^a
Number of fights						0.520 ^b
Years of fighting						

^a Correlation is significant at the .01 level (2-tailed).

^b Correlation is significant at the .001 level (2-tailed).

variations among fighters in number of fights and number of knockouts have not been fully investigated. Zhang et al⁸ found that the number of hospitalizations for boxing injuries was positively correlated with the peak of the Gaussian-fitted brain tissue compartment in a whole-brain diffusion histogram in 24 professional boxers. However, this finding did not offer information regarding which regions were affected in hospitalized boxers.

In the present study, we sought to assess previous fight history and regional MR diffusion parameters to evaluate the relationship between microstructural brain damage and fight-related exposure. We hypothesized that previous fight exposure would predict DTI changes suggestive of microstructural damage in fighter populations.

MATERIALS AND METHODS

Fighter Population

The Professional Fighters' Brain Health Study was approved by the local institutional review board, and all participants provided informed consent. Participants in the Professional Fighters' Brain Health Study are athletes ages 18 and older who have achieved at least a fourth-grade reading level and are licensed in Nevada to fight professionally in one of the combat sports (boxing, mixed martial arts). In the Professional Fighters' Brain Health Study protocol, participants are scanned for a baseline evaluation and then annually over 4 years. Eligible participants in the current study had no MR-visible central nervous system disease or neurologic disorder.

Data from the first 199 professional fighters who visited for the baseline evaluation were used for this study. Information on sex, age, weight, years of education, type of fighting (boxing or mixed martial arts), years of fighting, number of fights, and number of knockouts was collected for each participant. Fifteen female fighters were excluded from the study to eliminate sex effects, and a 71-year-old male fighter was also excluded because his age made him an outlier. Missing data of individual information were deleted list-wise from 183 fighters in the analysis. A total of 155 male fighters (74 boxers and 81 mixed martial arts fighters) were included in the final analysis (Table 1).

MR Protocols

MR images were performed on a 3T Verio scanner with a 32-channel head coil (Siemens, Erlangen, Germany). 3D T1-weighted scans (voxel size = $1 \times 1 \times 1.2$ mm³; TR/TE/TI = 2300/2.98/900 ms; flip angle = 9°; scan time = 9:14), T2-weighted scans (voxel size = $0.8 \times 0.8 \times 4$ mm³; TR/TE = 5000/84 ms; 38 sections; scan time = 0:57), and FLAIR scans (voxel size = $0.8 \times 0.8 \times 4$ mm³; TR/TE/TI = 7000/81/2220 ms; 38 sections; scan time = 2:36) were performed. A single-shot EPI scan was used to

acquire diffusion tensor mapping (TR/TE = 7000/91 ms; FOV = 240×240 mm²; voxel size = $2.5 \times 2.5 \times 2.5$ mm³; 49 axial sections with no gap between sections; partial Fourier factor = 5/8; NEX = 1; 71 nonlinear diffusion-weighting gradients with b-value = 1000 seconds/mm² and eight $b = 0$ volumes for averaging; scan time = 8:24).

DTI Postprocessing

Field map–based distortion correction²⁰ was applied in the time-series diffusion images to unwarp EPI geometric distortion, and an iterative motion and eddy current artifact correction method was used²¹ before DTI parameter calculation. Subsequently, the diffusion tensor was calculated at each voxel with log-linear ordinary least squares.²² The tensors were diagonalized, yielding eigenvalues from which LD, TD, mean diffusivity (MD), and FA were calculated with the use of in-house software.²³ The detailed definition of DTI parameters is described with 3 eigenvectors ($\lambda_{1,2,3}$ and $\lambda_1 \geq \lambda_2 \geq \lambda_3$); LD = λ_1 , TD = $(\lambda_2 + \lambda_3)/2$, MD = $(\lambda_1 + \lambda_2 + \lambda_3)/3$, and FA = $\{[(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2]/(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)/2\}^{1/2}$.

ROI Analysis

Seventy-three ROIs in white matter (3 corpus callosum areas and 35 white matter regions in each hemisphere) and 7 subcortical gray matter regions in each hemisphere were defined in T1-weighted image space with the use of the FreeSurfer software package (<http://surfer.nmr.mgh.harvard.edu/>). The defined ROIs were aligned in DTI space by use of the Linear Image Registration Tool FLIRT (<http://www.fmrib.ox.ac.uk/>).²⁴ Average DTI values were calculated in each ROI. After a visual check, the caudal middle frontal, lateral orbitofrontal, medial orbitofrontal, parsorbitalis, rostral middle frontal, superior frontal, and frontal pole regions were excluded because of imperfect coregistration between the anatomic image and the unwrapped EPI image, caused by EPI geometric distortion in the frontal lobe area.

Statistical Analysis

Pearson correlation was calculated for fighter information (age, years of education, weight, number of knockouts, number of fights, and years of fighting). Years of fighting was highly correlated with age (correlation = 0.511; $P < .001$) and with number of fights (correlation = 0.520; $P < .001$); therefore, number of knockouts and number of fights were selected as fight-related predictors. Age, weight, years of education, number of knockouts, and number of fights were chosen as predictors to represent variance in independent measures (Table 1).

Multiple hierarchical linear regression analyses were performed to test the hypothesis that fight-related exposure (number

of knockouts and number of fights) could predict average DTI values in different regions. Age, weight, and years of education were controlled to ensure that they would not account for the hypothesized effects. Therefore, model 1 used age, weight, and years of education as predictors for DTI value ($DTI = \text{constant} + a_1 \times \text{age} + a_2 \times \text{weight} + a_3 \times \text{years of education}$). Model 2A used age, weight, years of education, and number of knockouts as predictors ($DTI = \text{constant} + b_1 \times \text{age} + b_2 \times \text{weight} + b_3 \times \text{years of education} + b_4 \times \text{number of knockouts}$), and model 2B

used age, weight, years of education, and number of fights as predictors ($DTI = \text{constant} + c_1 \times \text{age} + c_2 \times \text{weight} + c_3 \times \text{years of education} + c_4 \times \text{number of fights}$). Regions were defined as activated (ie, a fight-related exposure predicted DTI values) when the following criteria were met: 1) the significance change from model 1 to model 2A or 2B was significant, and 2) the linear regression result of model 2A or 2B was significant.

RESULTS

We found no significant ($P > .05$) differences between boxers and mixed martial arts fighters in age, weight, number of fights, or number of knockouts, but there was a significant difference between the groups in years of education ($P = .0045$; Table 2).

The number of knockouts among boxers predicted increased LD in the inferior parietal, isthmus cingulate, pericalcarine, precuneus, and amygdala areas and increased TD in the middle and posterior corpus callosum, isthmus cingulate, pericalcarine, pre-

cuneus, and amygdala regions after we controlled for individual variations in age, weight, and years of education (Table 3). There was increased MD and decreased FA in the corresponding areas. Interestingly, in mixed martial arts fighters, the number of knockouts predicted only decreased FA in the posterior corpus callosum and increased TD in the posterior cingulate. In the posterior corpus callosum of both boxers and mixed martial arts fighters, the number of knockouts predicted decreasing FA, but the decreasing tendency or the magnitude of coefficient of the number of knockouts over FA was larger in boxers than in mixed martial arts fighters ($-18.90 \times 10^{-6} \text{ mm}^2/\text{s}$ versus $-7.27 \times 10^{-6} \text{ mm}^2/\text{s}$; Table 4).

The number of knockouts predicted decreased LD in the pars triangularis, decreased LD and TD in the pallidum, and increased FA in the caudate and putamen regions. The number of fights did not predict DTI values in boxers or mixed martial arts fighters. The average DTI values for the regions in which the number of knockouts predicted DTI values are presented in Table 5.

DISCUSSION

We found that the number of knockouts in fighting athletes, most prominently in the boxing group, predicted DTI changes after we controlled for age, weight, and education effects. This finding suggests that the number of knockouts experienced by boxers can predict microstructural damage in the brain, as represented by increased LD and TD. In contrast, the number of fights did not account for microstructural injury.

Table 2: Demographic data

	Boxers	Mixed Martial Arts Fighters
Age, y	28.0 ± 6.3	28.2 ± 4.8
Years of education ^a	12.7 ± 3.0	14.0 ± 2.4
Weight, kg	74.5 ± 15.8	78.7 ± 10.9
Number of fights	13.2 ± 15.7	12.1 ± 14.1
Number of knockouts	1.1 ± 2.0	1.0 ± 2.1

^a Significantly different between groups ($P < .01$).

Table 3: Areas in which number of knockouts predicted DTI values after controlling for individual variation

ROI	Boxers				Mixed Martial Arts Fighters	
	LD	TD	MD	FA	TD	FA
Corpus callosum posterior		a		b		a
Corpus callosum central		a	a			
Cuneus				L ^a		
Inferior parietal	L ^a					
Isthmus cingulate	L ^c , R ^b	L ^c , R ^c	L ^c , R ^c			
Pars triangularis	L ^a					
Pericalcarine	L ^b , R ^a	L ^c , R ^b	L ^c , R ^b			
Posterior cingulate					R ^a	
Precuneus	R ^a	R ^a	L ^a , R ^a			
Caudate				L ^a		
Putamen				L ^a , R ^a		
Pallidum	L ^a , R ^b	L ^a , R ^a	L ^a , R ^b			
Amygdala	L ^a , R ^c	R ^b	L ^a , R ^c			

Note:—L and R represent the left and right hemispheres, respectively.

^a $P < .05$.

^b $P < .01$.

^c $P < .001$.

Table 4: Coefficients for number of knockouts for the areas in which number of knockouts predicted DTI values after controlling for individual variation

ROI	Boxers				Mixed Martial Arts Fighters	
	LD	TD	MD	FA	TD	FA
Corpus callosum posterior		26.48		−18.9		−7.27
Corpus callosum central		20.28	18.19			
Cuneus				(L) −4.60		
Inferior parietal	(L) 6.56					
Isthmus cingulate	(L) 24.24 (R) 16.73	(L) 19.25 (R) 22.61	(L) 20.91 (R) 20.65			
Pars triangularis	(L) −7.61					
Pericalcarine	(L) 15.80 (R) 10.05	(L) 24.26 (R) 15.92	(L) 21.44 (R) 13.96			
Posterior cingulate					(R) 5.49	
Precuneus	(R) 8.34	(R) 9.90	(L) 6.63 (R) 9.38			
Caudate				(L) 5.72 (L) 3.30 (R) 4.74		
Putamen						
Pallidum	(L) −14.60 (R) −19.30	(L) −10.10 (R) −18.20	(L) −11.60 (R) −18.60			
Amygdala	(L) 12.38 (R) 29.06	(R) 12.80	(L) 10.12 (R) 18.22			

Note:—L and R represent the left and right hemispheres, respectively.

A coefficient unit is $10^{-6} \text{ mm}^2/\text{s}$ for LD, TD, and MD, and 10^{-3} for FA.

Table 5: Average DTI values for the areas in which number of knockouts predicted DTI values

ROI	Boxers				Mixed Martial Arts Fighters	
	LD	TD	MD	FA	TD	FA
Corpus callosum posterior	1.617	0.689	0.998	0.525	0.656	0.546
Corpus callosum central	1.533	0.679	0.964	0.506	0.653	0.512
Cuneus	0.966	0.727	0.807	0.189	0.712	0.194
Inferior parietal	1.007	0.657	0.774	0.280	0.648	0.284
Isthmus cingulate	1.292	0.569	0.810	0.481	0.540	0.498
Pars triangularis	0.956	0.650	0.752	0.266	0.635	0.270
Pericalcarine	1.128	0.787	0.901	0.238	0.769	0.250
Posterior cingulate	1.209	0.570	0.783	0.448	0.543	0.463
Precuneus	1.086	0.647	0.793	0.326	0.631	0.337
Caudate	1.235	0.966	1.056	0.170	0.949	0.168
Putamen	0.879	0.610	0.700	0.240	0.602	0.246
Pallidum	0.808	0.515	0.613	0.323	0.518	0.315
Amygdala	1.125	0.864	0.951	0.181	0.854	0.184

Note:—A coefficient unit is 10^{-3} mm²/s for LD, TD, and MD and 0–1 for FA.

We found that increased TD resulted in increased MD and decreased FA in the corpus callosum among boxers. The corpus callosum is an area known to be involved in TBI.^{7,16,17,25–30} Several studies have demonstrated increased MD and/or decreased FA in various white matter regions among patients with mild TBI versus matched control subjects.^{7,17,31} Inglese et al¹⁷ found a significant reduction in FA in the corpus callosum, internal capsule, and centrum semiovale and a significant increase in MD in the corpus callosum and internal capsule in 46 patients with mild TBI. In a study of 49 professional boxers who had been exposed to repeated blows to the head, Zhang et al⁷ observed a significant decrease in FA in the anterior and posterior corpus callosum, as well as a significant decrease in FA and an increase in MD in the internal capsule. In a study of 24 boxers, Zhang et al⁸ also found that the mean diffusion constant of the brain tissue was significantly correlated with the times of hospitalization for boxing injuries ($P < .05$) but not with age when boxing was started, total rounds, years of fighting, or number of wins and losses. Cubon et al³¹ reported that college athletes with mild TBI (5 men and 5 women) who had concussion showed significantly increased MD in the left hemisphere, spanning the sagittal striatum, retrolenticular section of the internal capsule, and the posterior thalamic radiation (by use of tract-based spatial statistics), but there was no significant change in FA. In a recent study, Zhang et al³² found no significant differences in fMRI and DTI results among patients with mild TBI versus control subjects; the authors suggested that these regional variations in FA and MD changes in patients with mild TBI might be the result of differing timeframes, technological issues involved in DTI, and different methodologic approaches.

Besides the corpus callosum, the areas in which increased LD was predicted by the number of knockouts among boxers were identical to the regions in which increased TD was predicted by the number of knockouts with the exception of the inferior parietal region. Our results of increased LD and TD among boxers suggests that knockouts could induce irreversible myelin damage, as has been discussed previously.³⁰ Kraus et al³⁰ found that patients with mild to severe TBI showed increased TD and LD in all white matter regions; patients with mild TBI also showed increased LD in the sagittal striatum and superior longitudinal fasciculus but not TD in any regions versus control subjects. This

study also found that moderate to severe TBI groups showed severe impairment of neuropsychological assessment, compared with mild TBI and control groups. We have performed cognitive testing for the participants in our study, and further analyses will be conducted to assess whether our DTI findings are correlated with individual cognitive assessments.

In our study, decreased LD and/or TD in the pars triangularis and pallidum were predicted by the number of knockouts. In a previous study, Bazarian et al³³ found decreased median MD and increased median FA in the posterior corpus callosum in 6 patients with mild TBI when scans were performed within 4 hours after the injury; MD was also decreased in the left anterior internal capsule in ROI analysis. Wilde et al³⁴ found increased FA in adolescents with mild TBI who were scanned within an average of 2.7 days (1–6 days) after the injury. McAllister et al³⁵ showed that strain rate positively predicted FA changes before and 10 days after head injury in the corpus callosum in 10 athletes. Mayer et al³⁶ also found increased FA in patients with mild TBI during the semi-acute injury period (average of 12 days after injury) and confirmed this finding in a replicate experiment (average of 15.6 days after injury).³⁷ This increased FA in semi-acute mild TBI may be induced by inflammation and/or cytotoxic edema and could be transient. A recent study by Wilde et al³⁸ assessed FA values in patients with mild TBI over time during the semi-acute period (from day 1 to days 7–8 after injury). Our study did not consider time after the onset of head injury (eg, the latest knockout). However, boxers who are exposed to repeated blows to the head, should be considered separately from patients with mild TBI, who generally have a single incidence of head injury. The decreased LD and TD among boxers in our study might be related to this repeated pattern of brain tissue injury and recovery. Further studies are needed to assess this possibility.

Although boxers in our study had increased LD and TD in various white matter regions predicted by number of knockouts, mixed martial arts fighters had decreased FA in the posterior corpus callosum and increased TD in the posterior cingulate region only predicted by the number of knockouts. Furthermore, when considering the posterior corpus callosum where the number of knockouts predicted FA in both boxers and the mixed martial arts fighters, the higher magnitude of coefficient for the number of knockouts over FA in boxers versus mixed martial arts fighters was

observed ($-18.90 \times 10^{-6} \text{ mm}^2/\text{s}$ versus $-7.27 \times 10^{-6} \text{ mm}^2/\text{s}$). This may reflect the different natures of boxing and mixed martial arts. Boxers mainly target the head of their opponent, which exposes the boxers to a higher risk of repetitive head injuries; mixed martial arts fighters use striking and grappling techniques.

DTI is known to be affected by a patient sex,³⁹ age,³⁹⁻⁴² intelligence level,^{43,44} and body weight.⁴⁵ We therefore included only male fighters in our study and used multiple hierarchical linear regression analyses to control for age, years of education, and weight. Although we assumed that body weight was an individual factor for the purpose of this analysis, it is possible that weight plays a role in the severity of brain injury, as a blow from a heavy-weight fighter would be expected to cause more damage than a blow from a light-weight fighter. In future research, weight class should be considered as an individual factor. We also plan to recruit an age- and education-matched control group for future studies of longitudinal MR changes, but we believe that our findings in the current study are not limited by the absence of a control group.

A previous study suggested that sports-related concussions are often unreported by athletes.⁴⁶ For this study, we used the number of knockouts in both the amateur and professional career periods, and the number of knockouts includes not only the loss of consciousness, leading to down more than 10 counts, but also the technical knockout including referee stop, corner stop, and multiple knockdowns caused by lack of the self-defense ability. The information of the number of knockouts from professional fights was collected and verified from the fighters' official log, whereas the information from amateur fights was collected through a self-reporting questionnaire. Inaccuracy in self-reporting may therefore be a confounding variable. Additionally, there probably are differences in the threshold of trauma required to cause a knockout in individuals, a factor we plan to address in future research.

This study involved data from one time point, but we intend to follow these fighters for at least 4 years. Although we do not know which, if any, of these fighters will have development of chronic traumatic encephalopathy, the results of the current study suggest that measurable microstructural changes or diffusion metrics can be predicted by history of repeated head injuries or severity in fighters' careers after controlling for individual variations.

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