Original Research

Distribution of Microstructural Damage in the Brains of Professional Boxers: A Diffusion MRI Study

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Purpose: To investigate and localize cerebral abnormalities in professional boxers with no history of moderate or severe head trauma.

Materials and Methods: Diffusion tensor imaging (DTI) was used to determine the apparent diffusion coefficient (ADC) and fractional anisotropy (FA) in the brains of 81 professional male boxers and 12 male control subjects. Voxel-based analysis (VBA) of both the diffusion and anisotropy values was performed using statistical parametric mapping (SPM). From this objective analysis, regions of microstructural abnormalities in the brains of the boxers were located.

Results: Increases in the ADC, and decreases in FA were identified in deep white matter (WM), while decreases in ADC were identified in cortical gray matter (GM). Regions of positive correlation between ADC and age were also found in both the boxer and control groups, although the regions and strength of the correlation were not the same in each group.

Conclusion: Using VBA, we localized previously unreported abnormalities in the brains of professional boxers. These abnormalities are assumed to reflect cumulative (chronic) brain injury resulting from nonsevere head trauma.

Key Words: boxers; diffusion tensor imaging (DTI); apparent diffusion coefficient (ADC); fractional anisotropy (FA); traumatic brain injury (TBI); voxel-based analysis (VBA)
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BRAIN INJURIES from repetitive blows to the head are well reported (1–6). The behavioral symptoms of such injuries may appear immediately or after a period of many years. Here we report the use of voxel-based analysis (VBA) of diffusion tensor MRI (DTI) data to better understand the distribution of microscopic injuries throughout the brain. This may lead to improved clinical diagnosis of brain damage, and management of cumulative brain damage resulting from repeated but nonsevere blows to the head.

Traumatic brain injury (TBI) has been conventionally thought of as either focal (with macroscopic lesions large enough to be visible to the naked eye in postmortem dissections) or diffuse axonal injury (DAI) (7), where the effects are distributed throughout the white matter (WM). Postmortem studies have supported the belief that DAI is spread more or less uniformly throughout the WM. Recently, however, reservations have been expressed about contrasting DAI with focal traumatic injury. The reality of the damage may be somewhere between these two models (2,8).

It is difficult to reliably detect mild TBI using CT and conventional MRI (9,10). This is because the effects of TBI on cell tissue are microscopic and diffuse (11). There are many reported cases of patients who had normal-appearing CT and/or MRI scans but later presented with unmistakable symptoms of TBI (6,8,12). Similarly, EEG can be used to detect pathologic unspecific alterations with high accuracy, but is not useful for specifying the findings for an exact diagnosis (13). In this study we used DTI (14) to investigate the microscopic abnormalities of the brains of professional boxers. Because DTI is sensitive to diffusion, and diffusion is sensitive to microstructural changes, DTI is able to detect these changes where other imaging techniques may fail (1–6).

Zhang et al (6) found statistically significant increases in the whole-brain apparent diffusion coefficient (ADC) of boxers compared to controls. They also revealed an increase in the spread of the boxers' distribution of coefficients compared to the controls' distribution, suggesting greater heterogeneity of diffusion within the boxers. Furthermore, these increases in diffusion were found to occur before brain abnormalities appeared on standard MR images, establishing diffu-

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sion imaging as an important tool for monitoring the neurological health of boxers.

MATERIALS AND METHODS

In vivo data were acquired from 81 professional male boxers (20–42 years old, median age = 28 years) and 12 male control subjects (22–31 years old, median age = 25.5 years). The control subjects were free from neurological disease and had no boxing history. Informed consent was obtained from all participants. Imaging protocols were approved by the institutional review board. This was part of a screening program that assessed boxers with no symptoms of neurological damage. Conventional MRI of these subjects produced negative or nonspecific findings, including cavum septum pellucidum, subcortical WM disease, and periventricular WM disease.

Whole-brain scans were performed on two GE 1.5T MRI scanners (General Electric Medical Systems, Milwaukee, WI, USA) with 22 mT/m gradient strength. A quadrature head coil was used, and in all cases the section thickness was 5 mm, with no intersection gaps. A 2D spin-echo EPI acquisition was used with TE/TR = 100 msec/12 seconds. An acquisition matrix of $128 \times 128 \times 30$ and $1.7 \times 1.7 \times 5$ mm^3 voxels in 26 gradient directions with b-values of 815–1152 sec.mm^{-2}, and six acquisitions with no diffusion weighting was used. The total acquisition time was 6 minutes 24 seconds. No subjects, whether boxers or controls, were excluded from the analysis.

A 3×3 diffusion tensor $\bar{D}$ was fitted at each voxel. From this, the frame-independent ADC and fractional anisotropy (FA) were calculated for each voxel. With D_{11}, D_{22}, and D_{33} being the three eigenvalues of the tensor, we have:

$$ADC = \frac{Trace(\bar{D})}{3} = \frac{D_{11} + D_{22} + D_{33}}{3} \quad (1)$$

$$FA = \sqrt{\frac{3}{2}} \frac{\sqrt{(D_{11} - ADC)^2 + (D_{22} - ADC)^2 + (D_{33} - ADC)^2}}{\sqrt{D_{11}^2 + D_{22}^2 + D_{33}^2}} \quad (2)$$

Statistical parametric mapping (SPM) (15), using the SPM2 package, was used in the analysis. In SPM, each brain is first warped, or normalized, to a standard template such that any given voxel (with fixed coordinates) will represent the same part of the brain in every subject. After smoothing with an 8-mm FWHM Gaussian kernel, the general linear model is used to analyze the variance of measurement at each voxel. To be able to separate voxels with increased ADC (or FA) from those with decreased ADC (or FA), we performed two one-tailed t-tests on both ADC and FA. Since the MR images were collected on two different MRI scanners, we removed any scanner effect from the results by using analysis of covariance (ANCOVA), with the scanner treated as a confounding variable.

Once the statistically significant clusters had been identified, the coordinates of the most significant voxel in each cluster were used to identify that voxel as being within the WM or gray matter (GM). This was done using the predefined WM/GM templates of a normal brain in the FreeSurfer software based on the theory of Fischl et al (16) and Witzel et al (17), and then checked against the segmented images of the subjects of this study as produced by SPM5. The appropriate average ADC or FA values for the boxers and the controls at each cluster maximum were then tabulated.

RESULTS

There were regions of increased ADC, decreased FA, and decreased ADC in the boxer group compared to the controls. No regions of increased FA were detected. These regions included the lower brain, the splenium, and cortical regions located laterally and dorsolaterally in both the frontal and posterior lobes. Any apparent differences detected near the edge of the brain should be interpreted with caution because of the possibility of susceptibility artifacts in this region.

Figure 1 shows similar regions of decreased FA to those with increased ADC. The decreases in FA were consistent over neighboring slices and were located primarily in the WM (Table 1). Regions of decreased FA and/or increased ADC, including those that exhibited both effects simultaneously, included the midbrain, internal capsule (including the posterior limb), putamen/globus pallidus, medial temporal lobe, inferior frontooccipital fasciculus and inferior longitudinal fasciculus, and the cerebral peduncle/corticobulbar/corticospinal tracts.

Both the boxers and controls showed regions of positive correlation between the ADC and age (Fig. 2). This effect appears to be stronger in the boxer group throughout multiple cortical and subcortical regions, particularly in cerebellar regions, with a very strong, symmetric correlation of ADC with age on the lateral periphery of both cerebellar hemispheres. Tests for negative correlation of ADC with age for boxers and controls were both negative.

DISCUSSION

Our study provides important evidence that sustained boxing activity, even in the absence of major trauma, causes specific structural abnormalities in the brain, with increased ADC and/or decreased FA in the internal capsule, putamen, medial temporal lobe, inferior frontooccipital and inferior longitudinal fasciculus, cerebral peduncle, and corticobulbar and corticospinal tracts.

Our voxel-based analysis of DTI data provides an important complement to previous attempts to localize cerebral injury caused by nonsevere head trauma. These efforts have included conventional MRI and functional imaging (18,19), as well as psychometric assessment to link structural damage to functional damage (20).

Our study found abnormalities in multiple brain regions that were manifested as both increases and decreases in ADC, and decreases in FA. Although there are fewer reported studies of FA than of ADC, there is general agreement that TBI will cause a decrease in FA (10,21,22). Our findings of significant decreases in FA

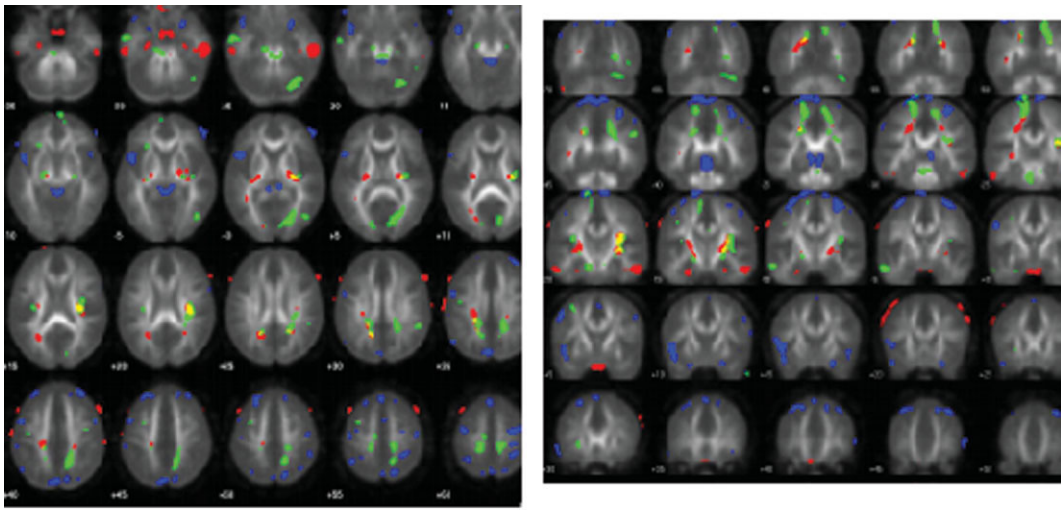

Figure 1. Colored regions showing where the ADC and FA values of the boxers' brains are statistically significantly different from the controls' ($P < 0.001$), axially and coronally. These regions are superimposed on an average FA map of normalized, undamaged brain. Slices are 5 mm apart. Red represents increased ADC, green is decreased FA, yellow is the overlap of increased ADC and reduced FA, and blue is decreased ADC.

in the boxers support these non-boxing-related studies. Importantly, the areas of decreased FA and increased ADC were located in similar regions, with several overlaps, and were primarily located in the WM (Fig. 1). We report the average values of FA for boxers and controls at the clusters that show a statistically significant decrease (Table 1). This decrease ranged from 7% to 17%.

This study extends the approach of Zhang et al (6), who observed an increase in the whole-brain diffusion of boxers by using voxel-based analysis to localize the areas of increased diffusion. They reported an increase in the whole-brain ADC of boxers compared to controls of nearly 4%. This compares with our results in Table 2, which shows that significant clusters had ADC increases ranging from 9% to 17%. These findings are consistent with a heterogeneous distribution of damage, with some parts of the brain (mainly WM) being substantially more susceptible than others.

Our finding of regions where boxers had smaller ADCs than the controls (Table 3) has two important features. First, almost all of the clusters were identified as comprising both CSF and GM. Second, the ADC values in all of these clusters were higher than those in the Table 2 clusters (which are predominantly WM), and were lower for the boxers than for controls. The values presented are higher than would be expected for brain tissue alone, which suggests that these clusters represent a mixture of CSF and tissue. Decreases in ADC in the boxers compared to the controls may be related to differences in the partial volume averaging of GM and CSF.

The observed changes in ADC and FA indicate that the diffusion abnormalities in boxers are not spread uniformly throughout the brain, and that specific brain regions may be more sensitive to injury from boxing-related TBI. The results are important in furthering our

Table 1
Statistically Significant Clusters Where FA Values for Boxers Are Less Than the FA Values for Controls*

Cluster max				Region	Corr.p	t vox	FA		
x	y	z	Tissue				Boxers	Controls	Decrease (%)
14	−60	42	WM	Precuneus	0.000	5.50	0.32 ± 0.04	0.35 ± 0.07	9
28	−72	−22	GM	Declive	0.000	4.97	0.22 ± 0.02	0.25 ± 0.02	10
16	−84	2	WM	Cuneus	0.000	4.93	0.28 ± 0.03	0.32 ± 0.05	14
−12	−20	−24	WM		0.000	4.11	0.46 ± 0.04	0.49 ± 0.06	6
46	−76	−4	GM	Midoccipital gyrus	0.000	4.47	0.24 ± 0.03	0.28 ± 0.03	12
−12	−28	64	WM	Subgyral	0.000	4.72	0.31 ± 0.05	0.36 ± 0.04	15
52	−46	30	GM	Supramarginal gyrus	0.000	4.03	0.23 ± 0.03	0.28 ± 0.04	17
−34	4	52	UNC	Midfrontal gyrus	0.002	3.96	0.26 ± 0.04	0.29 ± 0.03	11
−34	−20	16	UNC	Insula	0.008	3.64	0.30 ± 0.04	0.34 ± 0.05	10
−26	28	−8	WM	Inferior-frontal gyrus	0.009	3.61	0.34 ± 0.04	0.37 ± 0.07	7
22	−78	−42	WM	Pyramis	0.021	3.69	0.29 ± 0.04	0.32 ± 0.04	10
−42	−14	38	UNC	Precentral gyrus	0.147	3.92	0.27 ± 0.03	0.30 ± 0.05	12

*Clusters are recorded in decreasing order of their statistical significance (corr. p). x, y, z are the Montreal Neurological Institute (MNI) coordinates of the most significant voxel in each cluster. That voxel is then identified as being white matter (WM) or gray matter (GM). UNC = voxel unable to be classified, corr p = corrected *P*-value for that cluster, t vox = t-value for the given maximum voxel, FA values = the mean and SD at the cluster maximum, Decrease (%) = percentage decrease in the mean boxers' FA compared with the controls.

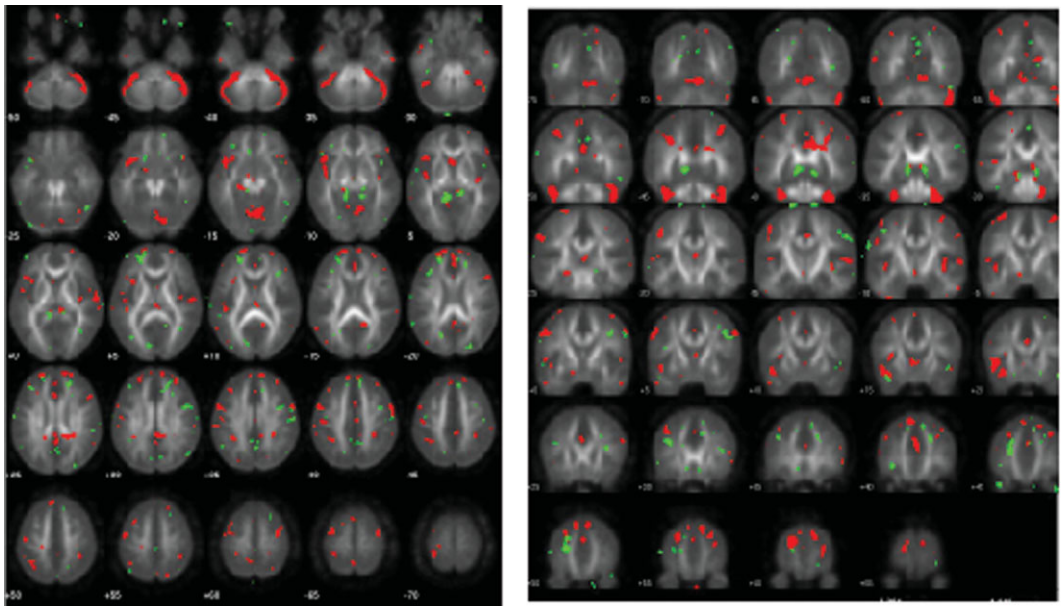

Figure 2. Positive correlations between ADC and age for boxers (red) and controls (green) in axial and coronal sections. Regions of statistically significant correlation ($P < 0.001$) are superimposed on an average FA image of normalized, undamaged brain to contrast WM and GM.

understanding of ADC and FA as markers of TBI, and demonstrate the utility of DTI in providing evidence of specific structural abnormalities after nonsevere TBI.

Both the boxers and controls showed regions of positive correlation between their ADCs and age. With different numbers of boxers and controls, it is hard to make a comparison between the relative strengths of the boxers' and controls' correlations. However, there seems to be a strong correlation in the cerebellum of the boxers with age, which is not apparent with the controls. This may suggest that boxers sustain chronic damage to their cerebellum that increases with age. Based on this interpretation, age may be seen as a proxy variable for length of time fighting, linking cerebellar damage with the number of shocks sustained. However, Zhang et al (6) found no correlation between diffusion and total rounds of performance, or years of boxing. Also, given that our controls also showed a positive correlation, albeit a weaker and spatially different one, between diffusion and age, further study is needed to determine whether the boxers are different in this regard.

Jantzen et al (9) performed a prospective MR study of sports-related concussion in eight college football players. They observed the effects of mild TBI (MTBI) in several regions, including cerebellar. Soto-Ares et al (23) studied 13 infants with severe TBI and found "unexpected cerebellar atrophy." Chun et al (24) studied 11 healthy volunteers and 27 patients (26–86 years old), and found that diffusion increased with age in periventricular WM. It is possible that other regions have age-dependent diffusion characteristics. Further investigation is needed to determine why the stronger correlation reported in this paper between age and ADC in the boxers did not manifest itself in statistically significant group differences in ADC between the boxers and the controls in the cerebellar region.

Table 2
Statistically Significant Clusters Where ADC Values for Boxers Are Greater than the ADC Values for Controls*

Cluster max			Tissue	Region	Corr.p	t vox	ADC ($\times 10^{-3}$ mm^2 second^{-1})		
x	y	z					Boxers	Controls	Increase (%)
−26	−16	−32	UNC	Subgyral	0.000	4.10	0.79 ± 0.08	0.67 ± 0.11	17
34	−22	18	GM	Insula	0.000	4.07	0.73 ± 0.06	0.65 ± 0.06	13
−24	−18	6	WM	Extranuclear	0.000	3.93	0.62 ± 0.03	0.56 ± 0.11	11
−28	−62	14	WM	Subgyral	0.000	3.92	0.75 ± 0.05	0.67 ± 0.05	12
26	−54	24	WM	Subgyral	0.000	3.60	0.72 ± 0.05	0.66 ± 0.03	10
24	−32	38	WM	Subgyral	0.016	3.45	0.64 ± 0.04	0.59 ± 0.05	9
−40	−48	0	WM	Subgyral	0.038	3.49	0.70 ± 0.04	0.63 ± 0.05	10
28	−16	−28	GM	Parahippocampal gyrus	0.094	3.86	0.80 ± 0.05	0.74 ± 0.05	9

*Clusters are recorded in decreasing order of their statistical significance (Corr. p). x, y, z are the Montreal Neurological Institute (MNI) coordinates (in mm) of the most significant voxel in each cluster. That voxel is then identified as being white matter (WM) or gray matter (GM). UNC = a voxel that was unable to be classified, Corr.p = corrected *P* value for that cluster, t vox = t-value for the given maximum voxel, ADC = mean and SD at the cluster maximum, Increase (%) = percentage increase in the mean boxers' ADC compared with the controls.

Table 3
Statistically Significant Clusters Where ADC Values for Boxers Are Less Than the ADC Values for Controls*

Cluster max			Tissue	Region	Corr.p	t vox	ADC ($\times 10^{-3}$ mm^2 second^{-1})		
x	y	z					Boxers	Controls	Decrease (%)
−48	12	−6	GM/CSF	Superior temporal gyrus	0.000	7.66	1.06 ± 0.13	1.26 ± 0.17	18
26	16	−28	GM/CSF		0.000	5.69	1.06 ± 0.11	1.23 ± 0.12	14
2	−38	−16	GM/CSF		0.000	4.90	1.17 ± 0.11	1.37 ± 0.23	14
36	−8	64	GM/CSF	Midfrontal gyrus	0.000	4.83	0.94 ± 0.17	1.22 ± 0.33	23
32	−44	58	GM/CSF	Inferior parietal lobule	0.000	4.73	0.95 ± 0.12	1.14 ± 0.28	17
−24	30	52	GM/CSF	Midfrontal gyrus	0.000	4.47	0.94 ± 0.12	1.10 ± 0.17	15
−52	6	44	GM/CSF	Midfrontal gyrus	0.000	4.38	0.99 ± 0.14	1.16 ± 0.17	15
32	−30	62	UNC	Precentral gyrus	0.000	4.18	0.92 ± 0.13	1.12 ± 0.26	18
18	44	44	GM/CSF	Superior front gyrus	0.000	4.17	1.01 ± 0.14	1.19 ± 0.24	16
54	6	38	GM/CSF	Inferior frontal gyrus	0.000	3.90	0.94 ± 0.14	1.11 ± 0.20	15
−42	−52	56	GM/CSF	Inferior parietal lobule	0.000		1.20 ± 0.21	1.41 ± 0.32	14
48	16	−10	GM/CSF	Superior temporal gyrus	0.001	3.58	1.12 ± 0.13	1.25 ± 0.15	11
−46	−16	54	GM/CSF	Precentral gyrus	0.002	3.94	0.93 ± 0.11	1.06 ± 0.14	12
52	−42	50	UNC	Inferior parietal lobule	0.002	3.89	1.02 ± 0.14	1.22 ± 0.25	16
50	−14	54	GM/CSF	Precentral gyrus	0.002	3.86	0.89 ± 0.13	1.05 ± 0.17	15
−58	−32	44	GM/CSF	Postcentral gyrus	0.008	3.90	0.94 ± 0.13	1.09 ± 0.17	13
40	−62	50	GM/CSF	Superior parietal lobule	0.019	3.79	1.09 ± 0.17	1.27 ± 0.27	15
−22	8	−30	GM/CSF	Uncus	0.074	4.08	1.03 ± 0.11	1.16 ± 0.12	11

*Clusters are recorded in decreasing order of their statistical significance (Corr. p). x, y, z are the Montreal Neurological Institute (MNI) coordinates of the most significant voxel in each cluster. That voxel is then identified as being gray matter (GM) or cerebrospinal fluid (CSF) or comprising both (GM/CSF).
UNC = voxel unable to be classified, Corr p = corrected *P*-value for that cluster, t vox = t-value for the given maximum voxel, ADC = mean and SD at the cluster maximum, Decrease (%) = percentage decrease in the mean boxers' ADC compared with the controls.

Our study differs from many diffusion studies in that our subjects were not scanned because of recent known trauma. Our results therefore relate to the chronic, cumulative effects of repeated blows to the head. Chronic TBI, which represents the cumulative, long-term neurological consequences of repetitive concussive and subconcussive blows to the brain has been studied primarily in relation to boxing, though it may also apply to other contact sports such as soccer, football, ice hockey, and martial arts (5). Slemmer et al (25) hypothesized that repeated TBI may result in cumulative damage to cells of the brain, but they lacked the means to test this in vivo. In vitro tests revealed that cells of the hippocampus may be susceptible to cumulative damage following repeated mild traumatic insults, which is consistent with the abnormalities we observed in the medial temporal lobe in our boxer group. However, they also postulated that cell damage from repeated mild shocks may be quite different from that activated by a single more severe shock.

In conclusion, we have shown that DTI's ability to identify microstructural abnormalities makes it an important diagnostic tool. As far as we are aware, this is the first study to use VBA to objectively analyze microstructural changes throughout the entire brain caused by cumulative, chronic blows to the head. This is an important step in providing in vivo evidence of the effects of chronic head injury, and evaluating the competing theories about concussion. Our results show that these effects on the diffusion in the brain may differ among the WM, GM, and CSF. These results add another dimension to understanding the adverse impact on the brain that multiple concussions can have. While they are not incompatible with current theories on the biomechanics and adverse physical impact of head trauma (26), our observations of the location and extent of cerebral abnormalities within the brain provide important new information about the adverse physical impact of nonsevere head trauma in contact sports, such as boxing.

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