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Increased Diffusion in the Brain of Professional Boxers: A Preclinical Sign of Traumatic Brain Injury?

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BACKGROUND AND PURPOSE: **Professional boxing is associated with chronic, repetitive head blows that may cause brain injuries. Diffusion-weighted imaging is sensitive to microscopic changes and may be a useful tool to quantify the microstructural integrity of the brain. In this study, we sought to quantify microscopic alterations associated with chronic traumatic brain injury in professional boxers.**

METHODS: **MR and diffusion-weighted imaging were performed in 24 boxers and in 14 age- and sex-matched control subjects with no history of head trauma. Using distribution analysis, the average diffusion constant of the entire brain (BD_{av}) and diffusion distribution width (σ) were calculated for each subject; findings in professional boxers were compared with those of control subjects. In the boxer group, correlations between diffusion changes and boxing history and diffusion changes and MR imaging findings were assessed.**

RESULTS: **The measured diffusion values in the boxer group were significantly higher than those measured in the control group (BD_{av}, $P < .0001$; σ, $P < .01$). In the boxer group, a robust correlation was found between increased BD_{av} and frequency of hospitalization for boxing injuries ($r = 0.654$, $P < .05$). The most common MR finding in the boxer group was volume loss inappropriate to age followed by cavum septum pellucidum, subcortical white matter disease, and periventricular white matter disease.**

CONCLUSION: **Boxers had higher diffusion constants than those in control subjects. Our data suggest that microstructural damage of the brain associated with chronic traumatic brain injury may elevate whole-brain diffusion. This global elevation can exist even when routine MR findings are normal.**

Brain injury from repetitive head blows has been reported in the boxer population (1–8). Diffuse axonal injury has been described as a major form of primary damage to the brain in blunt head injury. Chronic traumatic encephalopathy (CTE) and traumatic brain injury (TBI) often result in dementia pugilistica, a neurologic abnormality caused by repetitive exposure to head blows in contact sports such as soccer and boxing (2–4, 6, 7). A prevalence study of retired professional boxers revealed that 20% of those assessed developed CTE (8).

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Commonly, CT and MR imaging findings of CTE are negative or nonspecific. Imaging findings of brain atrophy and hyperintensity are associated with periventricular white matter disease (PWMD) with or without cavum septum pellucidum (CSP) (3, 9, 10). None of these findings are definitive signs of early CTE (11).

MR diffusion-weighted imaging is sensitive to changes of microscopic Brownian motion of water molecules in brain tissue. The underlying microstructure of the brain tissue imposes restriction on the diffusion of water. Changes in the microstructure of the brain can be inferred from increased diffusion. This information cannot be obtained from routine MR imaging (12–14).

Experimental models of TBI show that diffusion initially decreases in the acute phase after trauma and subsequently increases (15). Some data suggest that diffusion was changed at the site of trauma and surrounding tissue even when T2-weighted findings were unremarkable (16). We hypothesize that the global

diffusion of the brains exposed to chronic trauma is different from that of normal age-matched controls.

Methods

Study Participants

We studied 24 professional boxers (aged 21–53 years, average 32.3 years ± 7.2) and 14 age-matched healthy volunteers as controls (aged 23–45 years, average 32.2 years ± 7.3). Control subjects were free of neurologic disease and had no boxing history. All participants were male. Informed consent was obtained from all participants. Imaging protocols were approved by our institutional review board.

MR Imaging Protocol

The following sequences were performed in all the subjects by using a 1.5-T clinical MR system (Signa; GE Medical Systems, Milwaukee, WI) equipped with a quadrature head coil. Imaging parameters were: axial T1-weighted imaging (TR/TE, 500/14), axial T2-weighted imaging (TR/TE, 4000/102), fluid-attenuated inversion recovery imaging (TR/TE/TI,10,000/162/2200; matrix, 256 × 192), and diffusion-weighted imaging (TR/TE, 10500/106; matrix, 128 × 128). For all imaging protocols, section thickness was 0.5 cm, (no intersection gap); field of view, 22 cm; and number of excitations, 1. We used 30 sections covering the entire brain from the top convexity to the brain stem.

Diffusion was measured in three orthogonal directions (x, y, z) at b = 1000s/mm^2. Another set of images (S_o) were obtained at b = 0. By using the diffusion-weighted images in three orthogonal directions, an orientation-independent diffusion image related to trace of diffusion tensor was obtained as

$$1) \qquad DWI_{trace} = \sqrt[3]{DWI_{RL}\, DWI_{AP}\, DWI_{SI}}$$

where DWI_{RL} is the diffusion-weighted image with a diffusion gradient in the right-left direction (anteroposterior and superoinferior). The diffusion trace images and b = 0 images were transferred to a computer workstation for further data processing. The D_{av} maps were calculated from the DWI_{trace} and S_o images by using the following equation:

$$2) \qquad D_{av} = (1/b) \log (S_o/DWI_{trace})$$

Distribution Analysis and BD_{av} Calculation

In each subject, a computer program was used to calculate the whole-brain diffusion distribution histogram (Fig 1). This program distributed the pixels into 250 bins with a bin width of 0.02 10^{-5} cm^2/s. This histogram was then fitted to a triple Gaussian curve by using commercial software (KaleidaGraph, Adelbeck Software, Reading PA). This curve ($C_1e\text{-}[(D_{av}\text{-}BD_{av})/\sigma]^2 + C_2e\text{-}[(D_{av}\text{-}D_2)/\sigma_2]^2 + C_3e\text{-}[(D_{av}\text{-}D_3)/\sigma_3]^2$) represents a two-compartment model with mixing (three compartments): 1) brain tissue compartment, 2) brain tissue mixed with CSF, 3) high diffusion compartment of CSF and nonbrain tissue. The mean of the brain tissue distribution is recognized as a mean diffusion constant for the whole brain (BD_{av}). Peak locations and peak widths were determined from the fitted data. The peak location of the brain tissue compartment was interpreted to be BD_{av}, and the D_{av} distribution width to be σ.

Details of this brain model and distribution analysis have been described elsewhere (17).

Scoring of MR Findings

For each boxer, volume loss, CSP, SWM, PWMD, and negative findings were independently scored. Any of the findings above were scored as one if listed in any of the MR findings in the boxer group; otherwise, the score was 0. Volunteers did not have any positive MR signs.

Statistical Analysis

The means and standard deviations of the measured diffusion parameters were calculated for the boxer and control groups. A Student t test was then used to determine the significance of the results. $P < .05$ was considered to be statistically significant. Pearson product-moment correlations were conducted on calculated diffusion parameters, BD_{av} and σ; measures of boxing performance and history; and routine MR imaging findings.

Results

BD_{av} and σ and MR findings in boxers are summarized in Table 1. BD_{av} values in boxers and control subjects were 0.760 ± 0.018 (10^{-5}cm^2/s) and 0.732 ± 0.013 (10^{-5}cm^2/s), respectively. Average BD_{av} in control subjects was consistent with that cited in a previous report (17). Thirteen boxers had BD_{av} values more than two SD above the controls' mean, and five boxers had BD_{av} values more than four SD above the controls' mean. The statistical analysis is summarized in Table 2. No statistically significant difference existed between the age of boxers and that of control subjects ($P > .05$). BD_{av} and σ values were significantly higher in the boxers compared with those in control subjects ($P < .0001$and $P < .01$, respectively). The difference between boxers and control subjects remained significant even when the measured diffusion results (BD_{av} and σ) of boxers with normal MR findings were compared with those of control subjects, the diffusion values of boxers with normal MR images were still significantly different from those of control subjects ($P < .01$).

Figure 1 shows diffusion distribution histograms from a control subject and a boxer (case 15). The diffusion distribution of the boxer has a tissue peak that is wider and lower than that of the control subject. The peak is also shifted to the higher diffusion value. Figure 2 displays the diffusion data from all boxers and control subjects. Overall, BD_{av} is higher and σ wider in the boxers as compared with control subjects.

We compared increased BD_{av} with times of hospitalization for boxing injury and found a robust correlation ($r = 0.65$, $P < .05$). Similar analyses between BD_{av} and age when boxing was started, total rounds, years of performance, or number of wins and losses did not reveal any significant correlation ($P > .05$). MR findings in boxers are summarized in Table 3. General or focal volume loss inappropriate for age was found in eight boxers, CSP in five, nonspecific PWMD in two, and SWM in four (Fig 3). Scores of the positive MR findings for the boxers were not correlated to BD_{av} ($P > .05$).

Discussion

Diffusion-weighted imaging is sensitive to microscopic Brownian movement (18–20). Microscopic change occurs in the structure and diffusion of the brain after TBI (21, 22). Decreased diffusion has been reported in association with diffuse brain injury (23). Animal studies have shown reductions in diffusion

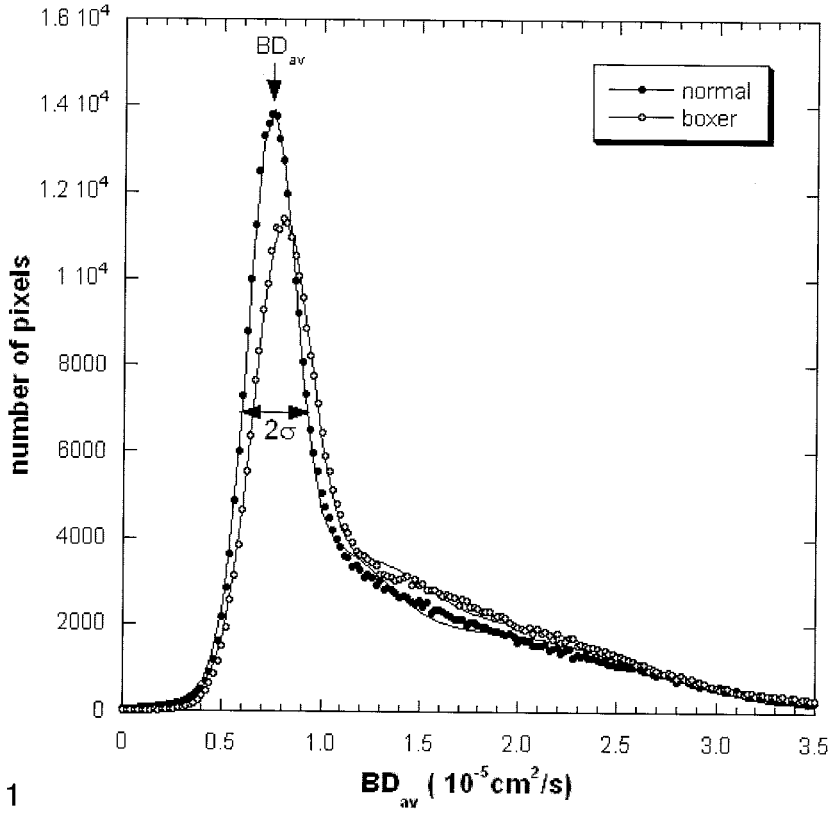

FIG 1. Normalized brain diffusion distribution histograms in a control subject and a boxer (case 15). The areas under the two curves are the same. The D_{av} data (*dots* and *circles*) are fitted with a triple Gaussian function to represent the two-compartment nature and the mixing between the two compartments (*lines*). The narrow peak represents the distribution of the brain tissue about its mean. The second and the third compartments have a broader distribution. The mean of the brain tissue pixel distribution is recognized as a mean diffusion constant for the entire brain (BD_{av}). The distribution width (σ) of the brain tissue compartment is also recorded. The fitted curve of the boxer (*circles*) shifts to the right as compared with the curve of the control subject (*dots*). The second compartment level of the boxer's curve is higher than that of the control subject.

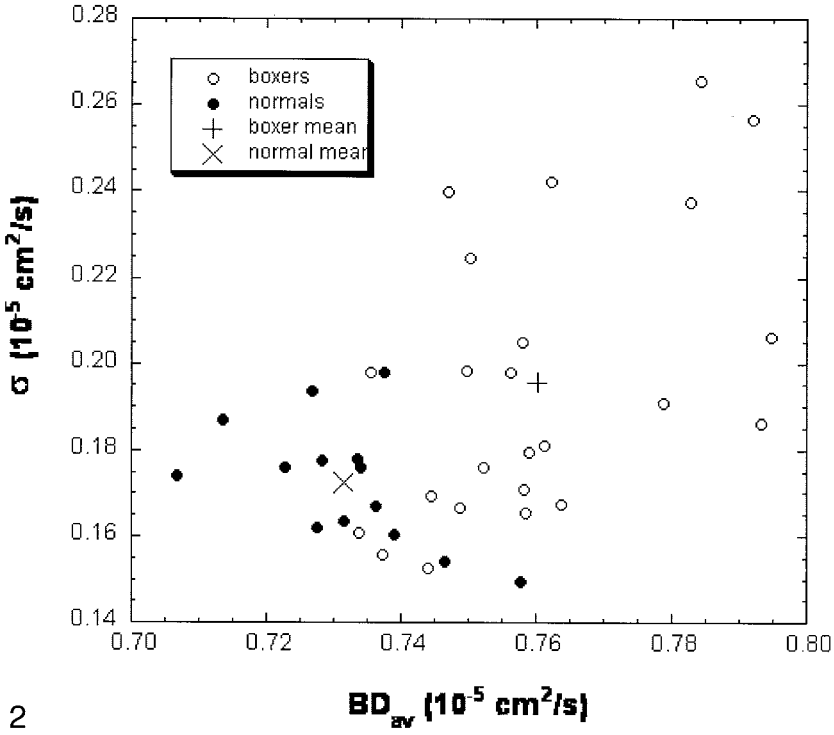

FIG 2. BD_{av} versus σ for boxers and control subjects: Overall, the boxer group shows elevated BD_{av} and σ.

after acute spinal cord injury involving both gray and white matter as well as abnormalities in tissues beyond the site of injury (13, 15). In this study, the average diffusion in brain tissue, as measured by BD_{av}, was higher in the brains of professional boxers as compared with the brains of nonboxing control subjects ($P < .0001$). In addition, the distribution of D_{av} in brain (σ) was wider in boxers than that in control subjects ($P < .01$) (Figs 1 and 2). These phenomena may be explained by less restricted diffusion of water molecules in the brains of boxers as compared with control subjects. The widened distri-

TABLE 1: Comparison of diffusion values and MR findings in boxers

Case (No.)	Age (y)	BD_{av}	σ	MR Findings
1	20.84	0.7562	0.1980	Normal
2	22.52	0.7502	0.2245	Left minimal hippocampal atrophy, otherwise normal
3	24.68	0.7933	0.1861	Volume loss, CSP
4	26.00	0.7637	0.1672	CSP, mild atrophy, nonspecific SWM
5	26.51	0.7622	0.2419	Normal
6	27.04	0.7372	0.1558	Normal
7	27.09	0.7590	0.1795	Normal
8	27.71	0.7613	0.1812	Normal
9	27.72	0.7486	0.1667	Normal
10	30.00	0.7580	0.2048	Normal
11	30.07	0.7497	0.1984	CSP, nonspecific SWM
12	30.17	0.7586	0.1655	Nonspecific SWM in left frontal lobe
13	32.29	0.7920	0.2564	Mild volume loss inappropriate to age
14	33.64	0.7828	0.2376	CSP, SWM, mild volume loss
15	33.72	0.7947	0.2061	Normal
16	34.13	0.7842	0.2655	CSP
17	35.14	0.7444	0.1695	Normal
18	36.10	0.7439	0.1526	Normal
19	36.12	0.7337	0.1606	Cerebellar atrophy, mild non-specific PWMD
20	38.05	0.7584	0.1711	Atrophy in left inferior cerebella, mild dilatation of sulci
21	38.52	0.7522	0.1759	Nonspecific SWM, atrophy inappropriate to age
22	40.00	0.7469	0.2397	PWMD
23	42.92	0.7355	0.1979	Normal
24	53.09	0.7786	0.1909	Normal

Note.—CSP indicates cavum septum pellucidum; PWMD, nonspecific periventricular white matter disease; and SWM, subcortical white matter disease.

TABLE 2: Distributions of BD_{av} and σ in boxer group versus those in control group

	Age (y)	BD_{av} (10^{-5} cm^2/s)	σ (10^{-5} cm^2/s)
Boxers	32.3 ± 7.2*	0.760 ± 0.018*	0.197 ± 0.033*
Control subjects	32.2 ± 7.3*	0.732 ± 0.013*	0.173 ± 0.014*
Increase (%)	0.3	3.68	12.18
Significance	$P > .05$	$P < .0001$	$P < .01$

* Mean ± SD.

TABLE 3: MR findings in boxers

	Premature Volume Loss	CSP	PWMD	SWM	Normal
Number (n)	8	5	2	4	13
Percentage	33.3%	20.8%	8.3%	16.7%	54.2%

Note.—Some boxers had more than one positive finding. CSP indicates cavum septum pellucidum; PWMD, nonspecific periventricular white matter disease; and SWM, subcortical white matter disease.

bution (σ) within the brain tissue compartment may indicate greater heterogeneity of diffusion within the brain. Factors such as damage to the integrity of cells and microvasculature of brain, which increase intercellular space and decrease restriction of diffusion, may contribute to the increased diffusion in the brains of boxers. It is, however, difficult to correlate, noninvasively and in vivo, these diffusion changes to damage to the cells and microvasculature of the brain. Future investigation is needed to explore the histologic detail and pathologic evolution occurring in the brain after traumatic injury.

In this study, five boxers had high BD_{av} and σ values, similar values reported in previous studies of dementia (24, 25). Of these five cases, case 15 had no positive MR findings, whereas three of the remaining four cases had CSP revealed by MR imaging. This may suggest that increased BD_{av} is highly associated with CSP because of CSF fluid dynamics. It is believed that CSP in boxers is acquired rather than congenital and results from rotational injuries with tearing of the septum pellucidum. A larger study sample may further elucidate the correlation between history of trauma and pathologic findings. It would be of interest to track the changes in diffusion in the brain associated with repetitive trauma and the corresponding clinical correlation. A robust correlation exists between increased BD_{av} values in boxers and number of times hospitalized for boxing-related injuries ($r = 0.65$, $P < .05$). This supports our assumption that accumulative exposure to severe head trauma in boxing causes brain injury and increases entire brain diffusion. Similar analyses revealed no significant correlation between BD_{av} or σ and the total rounds of performance, years of performance, age when boxing began, years of boxing, or number of losses.

Eleven boxers were found to have abnormalities on brain MR images. Volume loss inappropriate for age was the most frequent finding (n = 8), followed by CSP (n = 5) and SWM (n = 4); some boxers had more than one positive MR finding. This is in agreement with previous studies (3, 4, 8, 9). None of these factors were independently correlated with an increase in BD_{av} and summed scores. BD_{av} values in boxers with negative MR findings were significantly different from those in control subjects ($P < .01$). This supports the theory that BD_{av} increase occurs before abnormalities appear on MR images.

Four of our cases had nonspecific SWM either with or without CSP and mild volume loss. Etiology could include infarct, demyelination, or gliosis. Myelination is among the major sources for restricted diffusion of water in brain, and demyelination may explain increases in BD_{av}. MR spectroscopy may help detect the focal or general integrity of myelin in injured brains. Previous studies reported increase in choline- and *myo*-inositol-containing compounds increase after trauma (26–28). A recent MR spectroscopy study revealed that myelin degradation occurred 2 days after blunt head trauma, which likely evolves during the postinjury period (27). This increase may reflect membrane disruption and the consequent release of choline-containing compounds. Membrane disruption leads to damage of cell integrity; thus, increased diffusion of inter- and intra-

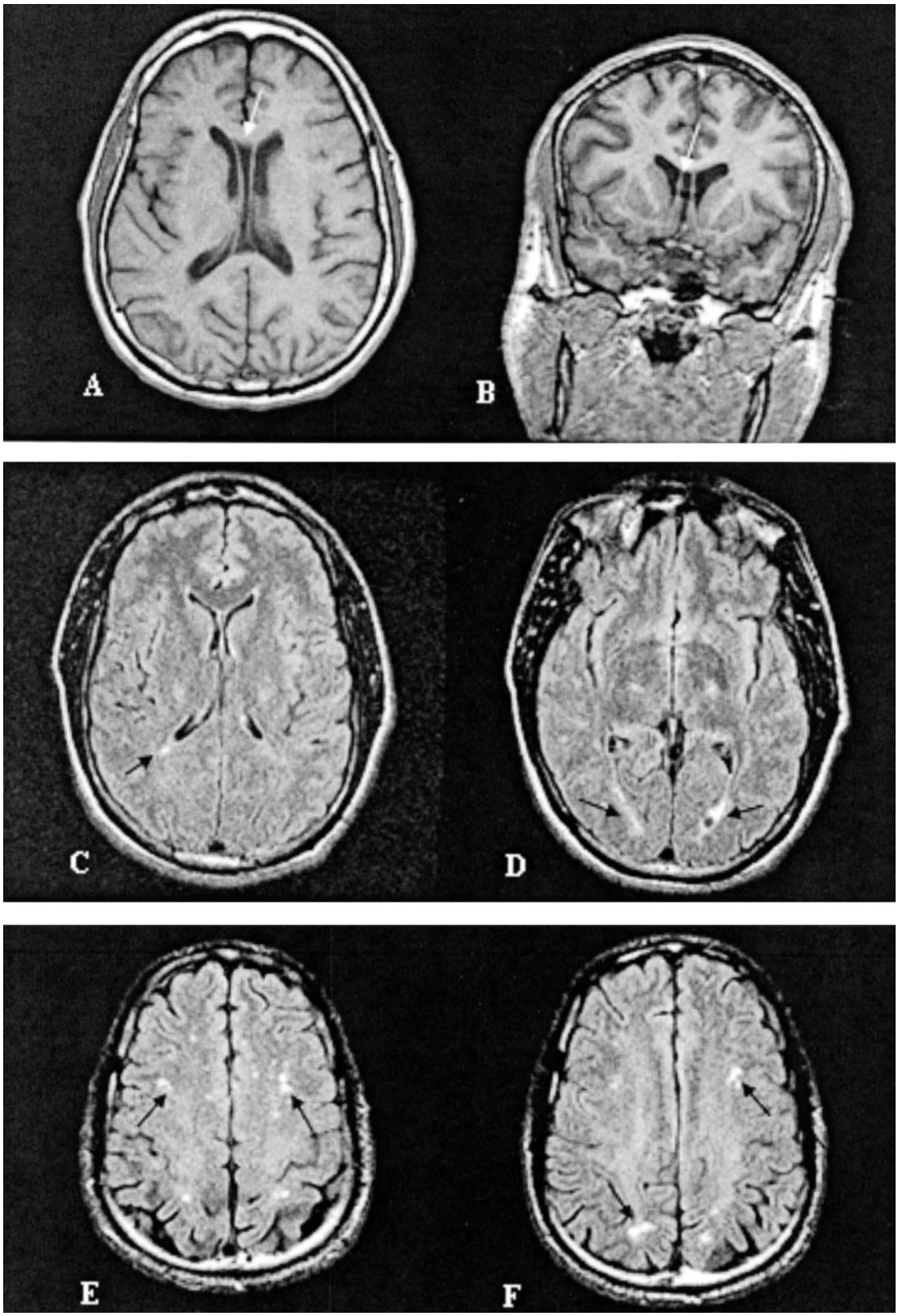

FIG 3. Representative images of MR findings in boxers: *A*, Cavum septum pellucidum (case 14); *B*, nonspecific periventricular white matter disease (case 22); and *C*, mild subcortical white matter demyelination (case 21).

cellular water molecules could lead to a higher measured BD_{av}.

Changes in BD_{av} in boxers' brains may be explained by cumulative exposure to TBI, and cerebral self-restoration may lead to complex diffusion changes in the brain. BD_{av} increase may appear before positive MR findings; thus, BD_{av} could be a useful tool to help predict neurologic impairment from boxing and dynamically monitor results of treatment for brain injury. We have previously reported increases in BD_{av} values and σ in patients with dementia (24, 25) and therefore speculate that these observations in boxers may represent a preclinical sign of cognitive decline.

There are limitations to our study. None of the boxers had clinical evidence of CTE. This is not surprising given that CTE typically develops after the cessation of boxing. Further studies will be needed to determine the predictive value of increased diffusion in boxers. If this finding is indeed associated with subsequent development of CTE, it may be possible to prevent or decrease the incidence and severity of the disorder. In this study, diffusion-weighted imaging was performed at a single time point. A larger study sample with multiple examinations at several time points may further elucidate the correlation between history of trauma and pathologic findings. It would be of interest to track the changes in diffusion associated with repetitive trauma and to identify correlations between diffusion changes and cognitive function. It may be possible in the future to use diffusion-weighted imaging to track brain damage, spontaneous healing, and treatment response in boxers.

Conclusion

Quantitative diffusion-weighted imaging revealed statistically significant increases in BD_{av} and σ in the brains of professional boxers compared with diffusion measures in age-matched, nonboxing control subjects. These increased diffusion values were observed even when routine MR imaging results were negative or nonspecific. Our data suggest that diffusion tensor imaging can show early pathologic changes in the cellular and microvascular structures of the brain in the boxer population, and because these changes have also been reported in demented subjects, increased BD_{av} and σ may represent preclinical signs of cognitive decline. Correlation between increased BD_{av} and frequency of hospitalization for boxing-related injury was significant; thus, BD_{av} may be a useful index for monitoring the neurologic health of boxers.

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