

# **Utility of Fractional Anisotropy Imaging Analyzed by Statistical Parametric Mapping for Detecting Minute Brain Lesions in Chronic-Stage Patients Who Had Mild or Moderate Traumatic Brain Injury**

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## **Abstract**

Diffusion tensor imaging (DTI) has recently evolved as valuable technique to investigate diffuse axonal injury (DAI). This study examined whether fractional anisotropy (FA) images analyzed by statistical parametric mapping (FA-SPM images) are superior to T<sub>2</sub>\*-weighted gradient recalled echo (T<sub>2</sub>\*GRE) images or fluid-attenuated inversion recovery (FLAIR) images for detecting minute lesions in traumatic brain injury (TBI) patients. DTI was performed in 25 patients with cognitive impairments in the chronic stage after mild or moderate TBI. The FA maps obtained from the DTI were individually compared with those from age-matched healthy control subjects using voxel-based analysis and FA-SPM images ( $p < 0.001$ ). Abnormal low-intensity areas on T<sub>2</sub>\*GRE images (T<sub>2</sub>\* lesions) were found in 10 patients (40.0%), abnormal high-intensity areas on FLAIR images in 4 patients (16.0%), and areas with significantly decreased FA on FA-SPM image in 16 patients (64.0%). Nine of 10 patients with T<sub>2</sub>\* lesions had FA-SPM lesions. FA-SPM lesions topographically included most T<sub>2</sub>\* lesions in the white matter and the deep brain structures, but did not include T<sub>2</sub>\* lesions in the cortex/near-cortex or lesions containing substantial hemosiderin regardless of location. All 4 patients with abnormal areas on FLAIR images had FA-SPM lesions. FA-SPM imaging is useful for detecting minute lesions because of DAI in the white matter and the deep brain structures, which may not be visualized on T<sub>2</sub>\*GRE or FLAIR images, and may allow the detection of minute brain lesions in patients with post-traumatic cognitive impairment.

Key words: diffuse brain injury, diffusion tensor magnetic resonance imaging, fractional anisotropy, statistical parametric mapping, cognitive impairment

## **Introduction**

Cognitive, behavioral, and emotional impairments can sometimes be observed in patients in the chronic stage after mild or moderate traumatic brain injury (TBI). Diffuse axonal injury (DAI) is one of the most common pathologies causing these symptoms, but the pathological effect of DAI cannot always be detected by conventional neuroimaging. Therefore,

such impairments have so far been called “invisible damage of the brain.” The representative symptoms of these impairments are memory disturbance, decreased activity, failures of emotion control, easy anger, carelessness, excessive tenacity, planning and execution failures, and excessive dependence. These symptoms often cause social problems in families, schools, work places, and other communities. Recent investigations have speculated that these impairments are the result of functional or anatomical disconnections, or both, between the cerebral cortex and deeper brain structures including the limbic sys-

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tem, and that the disconnection presumably occurs because of DAI due to either shearing or neurapraxia.<sup>27)</sup>

In patients with DAI, multifocal lesions in the white matter are characterized by axonal stretching, disruption, and eventual separation of nerve fibers.<sup>1,28)</sup> Conventional magnetic resonance (MR) imaging techniques can easily visualize posttraumatic focal structural lesions, but cannot adequately detect DAI lesions.<sup>14,18)</sup> Recent studies using MR imaging have shown that fluid-attenuated inversion recovery (FLAIR) imaging, diffusion-weighted imaging, and T<sub>2</sub>\*-weighted gradient recalled echo (T2\*GRE) imaging are useful methods for detecting traumatic axonal injury.<sup>4,15,26,30)</sup> Nevertheless, some lesions, such as non-hemorrhagic DAI, especially in the chronic stage, are not detected with these MR imaging techniques.

Diffusion tensor imaging (DTI) may be more useful to assess DAI.<sup>16)</sup> DTI uses the characteristics of water diffusion in the brain to assess the microstructural integrity of the white matter pathways.<sup>7)</sup> In the white matter, water diffuses more readily along the direction of the axonal fibers than across the fibers because of obstruction from structural elements such as the myelin sheath. DTI can provide quantitative measures of fiber-tract integrity and orientation on fiber-tracking images (tractograms) in patients with DAI.<sup>23,29)</sup> DTI can be used to measure diffusion anisotropy in vivo, and is a promising method for noninvasive detection of the degree of fiber damage in various disease processes affecting the white matter.<sup>11,19)</sup> Fractional anisotropy (FA) as determined with DTI has been used to evaluate traumatic axonal injury, and the clinical utility of this technique has been described.<sup>2)</sup> T2\*GRE imaging is superior to T<sub>1</sub>-weighted, T<sub>2</sub>-weighted, and FLAIR imaging for the detection of hemorrhagic DAI lesions. Abnormal low intensity areas on T2\*GRE images (T2\* lesions) are frequently useful clues to the presence of minute brain lesions secondary to DAI. We recently established an analytic method of FA mapping in individual patients using statistical parametric mapping (SPM) (FA-SPM images), which can demonstrate brain areas with significantly decreased FA in individual patients as compared with a normal group.

The present study examined whether FA-SPM images are superior to T2\*GRE or FLAIR images for detecting minute traumatic lesions in patients with cognitive, behavioral, or emotional impairments in the chronic stage after mild or moderate TBI.

## Methods

Twenty-five consecutive patients, 15 men and 10

women aged 18–64 years (mean 37.1 ± 13.2 years), with cognitive, behavioral, or emotional impairments in the chronic stage after mild or moderate TBI in traffic accidents were treated at Kizawa Memorial Hospital between January 2008 and July 2009. No patient had a history of intracranial surgery or a history of penetrating head injury, open skull fracture, neurological disease unassociated with injury, mental retardation, psychiatric disease, or alcohol or substance abuse. All 25 patients underwent neurological and neuropsychological examinations including the Mini Mental State Examination (MMSE) and Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Full Scale intelligence quotient (IQ), and neuroimaging within 2 weeks after consultation. Mean post-injury time was 30.9 ± 24.2 months (range 6–99 months) at the time of examination. No patient had any morphological abnormalities such as large focal neuroradiological lesions, hydrocephalus, or brain atrophy on MR imaging. Eight of the 25 patients were diagnosed with mild TBI (initial Glasgow Coma Scale [GCS] score after the traffic accident: 13–15 points) and the other 17 had moderate TBI (initial GCS score after the traffic accident: 9–12 points). Age-matched control volunteers were recruited. Individuals with a prior history of contact with neurological or psychiatric services were excluded. The control volunteers were divided into four groups based on age: 20–29-year-olds (7 women and 8 men; average age 25 years), 30–39-year-olds (11 women and 7 men; average age 34.6 years), 40–49-year-olds (10 women and 7 men; average age 44.2 years), and >50-year-olds (16 women and 7 men; average age 54.8 years). Patients and control participants with left hand dominance were excluded. This study was approved by our institutional ethics committee, and informed consent was obtained from all subjects.

Whole-brain conventional MR imaging and DTI were acquired using a 1.5-tesla MR scanner (GE Medical Systems, Milwaukee, Wisconsin, USA) using a quadrature transmit-receive head coil. The conventional MR imaging protocol included T<sub>2</sub>-weighted fast-spin echo (repetition time [TR]/echo time [TE]/number of excitations [NEX] = 2600 msec/107 msec/20), T<sub>1</sub>-weighted FLAIR (TR/TE/inversion time/NEX = 1850 msec/34 msec/805 msec/1), T<sub>2</sub>-weighted FLAIR (TR/TE/inversion time/NEX = 8000 msec/115 msec/2000 msec/1), and T2\*GRE (TR/TE/NEX/flip angle = 1550 msec/18 msec/1/20°) sequences. In all sequences, a total of 16 contiguous sections were acquired in the axial plane with 6 mm slice thickness, 512 × 256 matrix size, and a 240 mm × 240 mm field of view (FOV). DTI was acquired with a single-shot echo planar sequence (TR/TE/

NEX = 10000 msec/80 msec/4, slice thickness = 3 mm, matrix size =  $128 \times 128$ , and FOV = 250 mm  $\times$  250 mm). Diffusion gradients were set in six non-colinear directions using 2 b-values (b = 0 and 1000 sec/mm<sup>2</sup>).

Individual FA maps were calculated using an Advantage Workstation (GE Medical Systems). The structural distortion induced by large diffusion gradients was corrected based on T<sub>2</sub>-weighted echo planar images (b = 0 sec/mm<sup>2</sup>). The FA maps were analyzed using SPM software (SPM5; Wellcome Department of Imaging Neuroscience, London, UK) running on Matlab version 6.5.1 (Mathworks, Natick, Massachusetts, USA). Firstly, all images were spatially normalized to a standard template. The b = 0 images of all participants, which were T<sub>2</sub>-weighted images obtained without a diffusion gradient, were normalized to the standardized T<sub>2</sub> template using linear transformations.<sup>3,12</sup> The FA maps were then normalized using the parameters determined from the normalization of the b = 0 images. The normalized FA maps were smoothed with a 6-mm full-width at half-maximum isotropic Gaussian kernel to improve the signal-to-noise ratio, to increase the validity of the statistical inference, and to improve normalization. Absolute masking, with a threshold of 0.15, was used to exclude voxels outside the brain or in the ventricles from analysis.

The spatially normalized and smoothed images of patients were compared with those of control volunteers in a voxel-wise manner using SPM5 for both between group analysis and for individual to group analysis. For the group analysis, a 2-sample t test was used to detect differences between the patient group and the control volunteer group. For the individual analyses, a 2-sample t test was performed for each patient, so that each patient as a group (n = 1) was compared with the age-matched control group. The statistical parametric map for comparison of both between group analysis and individual to group analysis was thresholded to a value of uncorrected  $p < 0.001$  at the voxel level and at a minimum cluster size of 10 voxels. Two contrasts were used to detect whether each voxel had a higher or lower anisotropy in both between group analysis and individual to group analysis. The statistical parametric map, named the FA-SPM image, was overlaid on the normal brain FA template.

To elucidate the differences between mild and moderate TBI, the number of voxels with significantly decreased FA value in FA-SPM images was counted. The relationship between the scores of neurophysiological examinations and the number of voxels with significantly decreased FA value in FA-SPM images was investigated in TBI patients. These

statistical analyses were performed using SPSS software 19.0, with  $p < 0.05$  considered statistically significant. The statistical parametric maps for covariate effects of MMSE and WAIS-III by using regression modeling were thresholded at a value of uncorrected  $p < 0.001$  at the voxel level and at a minimum cluster size of 10 voxels. These areas were displayed as maximum intensity projections on a glass brain in three orthogonal projections.

## Results

### I. Comparison between the patient and normal control groups

Group comparative analysis between the patient and normal control groups revealed areas with significant decrease of FA in the corpus callosum, cingulum, fornix, thalamus, bilateral frontal lobes, parietal lobes, occipito-frontal fasciculus, superior longitudinal fasciculus, and inferior longitudinal fasciculus in the patient group. The anatomical locations, Talairach coordinates (X, Y, Z), Z score, and cluster sizes are listed in Table 1. The results are shown on the orthogonal projections in Fig. 1A and superimposed on a normal brain template in Fig. 1B. There were no areas with significantly increased FA in the patient group as compared with the control group.

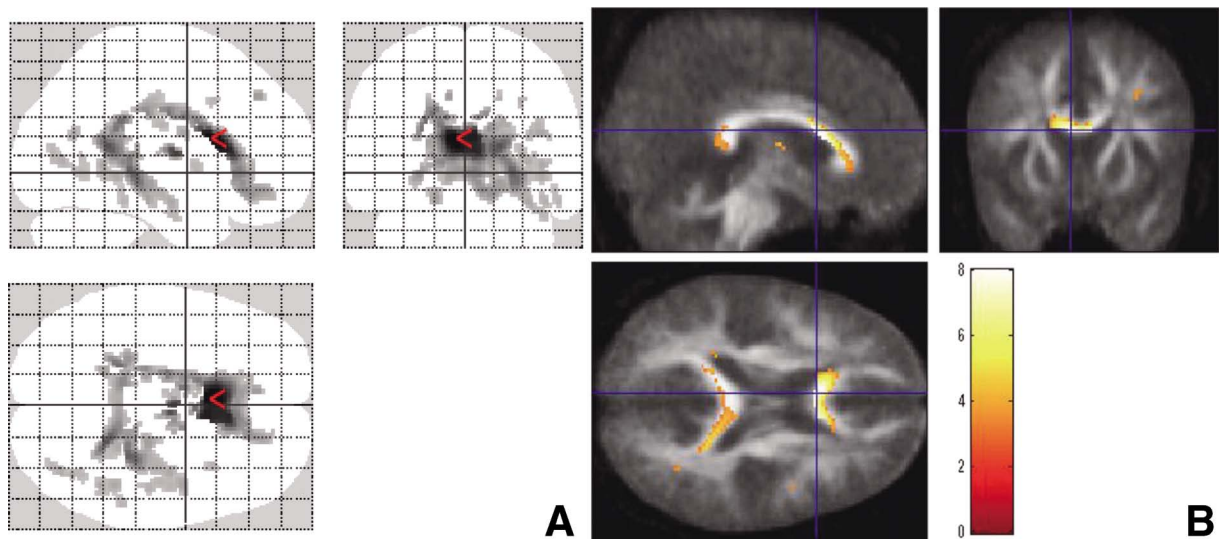
### II. Comparison between individual patients and the age-matched control group

The clinical characteristics of the patients are shown in Table 2. T2\* lesions were found in 10 patients (40.0%) and abnormal high intensity areas on FLAIR images were detected in 4 patients (16.0%). Areas with significantly decreased FA on FA-SPM images (FA-SPM lesions) were found in 16 patients (64.0%). Nine of the 16 patients with FA-SPM lesions did not have T2\* lesions and 9 of the 10 patients with T2\* lesions had FA-SPM lesions. FA-SPM lesions topographically included most T2\* lesions in the white matter and the deep brain structures, but did not include T2\* lesions in the cortex/near-cortex or lesions containing substantial hemosiderin regardless of location. All 4 patients with lesions on FLAIR had FA-SPM lesions. None of the 8 patients with mild TBI had T2\* lesions or FLAIR lesions, but 3 of these patients had FA-SPM lesions (Table 3).

The mean numbers of voxels in FA-SPM images of mild and moderate TBI patients were  $65.9 \pm 141.5$  and  $385.5 \pm 572.8$ , respectively, showing a significant difference between the two groups ( $p < 0.05$  by Welch's t test) (Fig. 2A). There were significant inverse correlations between the number of

**Table 1** Areas of significant decreases in fractional anisotropy in the patient group compared with the control group

Location	Side	Coordinate (mm)			Z score	Cluster size
		X	Y	Z		
Corpus callosum	left	-4	14	17	6.76	977
	right	6	13	19	6.37	
Cingulum	right	8	-4	28	4.36	12
Fornix	right	4	-7	12	5.49	21
	right	22	-32	8	4.71	
Thalamus	left	-8	-9	13	3.36	10
	right	32	17	36	3.50	
Frontal lobe	left	-12	-6	46	3.30	17
	right	50	-30	29	3.54	
Parietal lobe	left	-44	-37	31	3.15	14
	right	20	-16	40	3.58	
Occipito-frontal fasciculus	left	-22	-36	28	4.96	46
	right	42	-12	24	3.50	
Superior longitudinal fasciculus	left	-34	-1	33	3.24	18
	right	-44	-26	-9	3.22	



**Fig. 1** **A:** Orthogonal projection of brain regions showing significantly decreased anisotropy in the patient group compared with the control group, thresholded at an uncorrected  $p < 0.001$ . Red arrow indicates the maximal  $t$ -value (-4, 14, 17) within the glass brain. **B:** Results from anisotropy map analyses. Color indicates areas of decreased anisotropy. Images are thresholded at an uncorrected  $p < 0.001$  and superimposed on mean images of all participants. Crosshairs indicate maximum decreased anisotropy in the corpus callosum, Talairach coordinates (-4, 14, 17).

voxels with significantly decreased FA value in FA-SPM images of TBI patients and the MMSE score ( $r = -0.467$ ,  $p = 0.009$ ) (Fig. 2B) and WAIS-III Full Scale IQ ( $r = -0.567$ ,  $p = 0.002$ ) (Fig. 2C). The statistical parametric maps for covariate effects of MMSE and WAIS-III using regression modeling were thresholded at a value of uncorrected  $p <$

0.001 at the voxel level and at a minimum cluster size of 10 voxels. No significant correlation effect of MMSE and WAIS-III Full Scale IQ was observed under this condition.

**Table 2 Clinical characteristics of 25 patients with chronic traumatic brain injury (TBI)**

Case No.	Age (year)	Sex	TBI (mild/moderate)	MMSE score	WAIS-III Full Scale IQ	Time since TBI (month)	Conventional MR imaging findings		FA-SPM findings
							T2*GRE	FLAIR	
1	37	M	moderate	26	59	99	rt temporal TMH, bil occipital TMH	rt temporal CC, bil occipital CC	bil occipital DFA, DFA in corpus callosum, DFA in fornix
2	36	F	mild	30	78	57	normal	normal	normal
3	36	M	mild	29	85	44	normal	normal	lt parietal DFA
4	33	F	mild	30	91	84	normal	normal	normal
5	54	M	moderate	28	75	25	rt occipital TMH	normal	normal
6	19	M	moderate	26	83	19	rt frontal TMH, lt parietal TMH, rt temporal TMH, TMH in rt thalamus, TMH in corpus callosum	normal	rt temporal DFA
7	41	F	mild	26	54	7	normal	normal	rt parietal DFA, DFA in corpus callosum
8	18	M	moderate	30	108	60	normal	normal	rt parietal DFA
9	20	M	moderate	28	93	37	bil frontal TMH, rt parietal TMH	normal	rt parietal DFA, DFA in fornix, DFA in lt thalamus
10	42	M	mild	28	72	6	normal	normal	normal
11	35	F	mild	26	86	9	normal	normal	normal
12	37	F	moderate	23	52	25	TMH in corpus callosum	normal	rt frontal DFA, DFA in corpus callosum
13	47	M	moderate	24	59	36	normal	normal	DFA in lt mid-brain
14	26	M	moderate	30	93	14	bil frontal TMH, rt temporal TMH	bil frontal CC, rt temporal CC	bil frontal DFA, rt temporal DFA
15	32	M	moderate	30	109	7	normal	normal	normal
16	53	F	mild	24	89	36	normal	normal	normal
17	21	F	moderate	30	91	24	bil parietal TMH, TMH in lt thalamus, TMH in corpus callosum	normal	rt parietal DFA
18	22	M	moderate	23	75	22	normal	normal	normal
19	33	F	moderate	29	67	7	normal	normal	bil parietal DFA, DFA in corpus callosum
20	59	F	mild	28	104	60	normal	normal	DFA in corpus callosum
21	64	M	moderate	25	83	14	TMH in corpus callosum	normal	lt parietal DFA, DFA in corpus callosum
22	43	F	moderate	29	82	20	normal	normal	normal
23	33	M	moderate	25	64	9	bil frontal TMH, TMH in lt thalamus, TMH in corpus callosum	CC in lt thalamus, CC in corpus callosum	DFA in corpus callosum
24	25	M	moderate	29	83	36	normal	normal	rt parietal DFA
25	62	M	moderate	28	83	15	lt frontal TMH	lt frontal CC	bil frontal DFA, DFA in corpus callosum

bil: bilateral, CC: chronic contusion, DFA: decreased area of fractional anisotropy, F: female, FA-SPM: fractional anisotropy imaging analyzed by statistical parametric mapping, FLAIR: fluid-attenuated inversion recovery, IQ: intelligence quotient, lt: left, M: male, MMSE: Mini Mental State Examination, MR: magnetic resonance, rt: right, T2\*GRE: T<sub>2</sub>\*-weighted gradient recalled echo, TMH: traumatic microhemorrhages, WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.

## Illustrative Cases

### I. Case 6: Moderate TBI

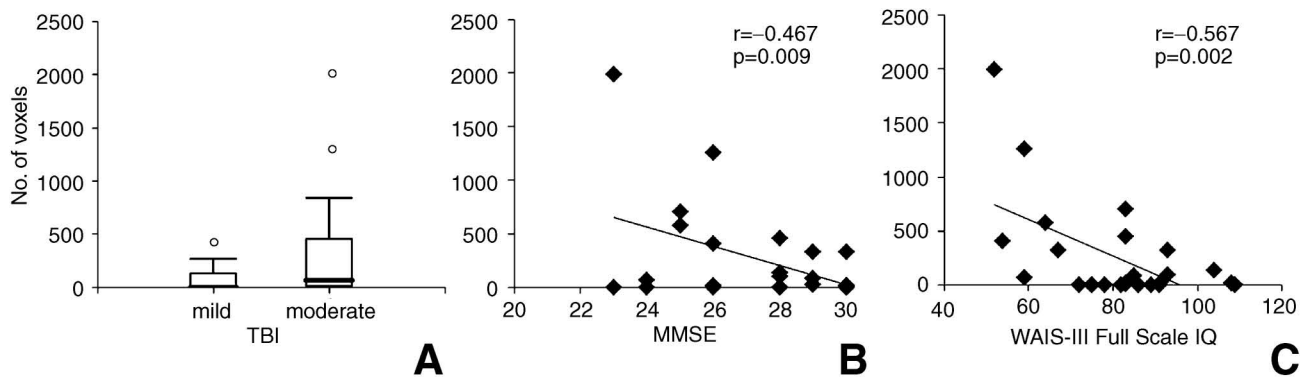
A 19-year-old right-handed man sustained a severe head injury in a road traffic accident. His initial GCS score was 9 points (E2V2M5). He had a 5-day period of consciousness disturbance and was treated conservatively. Nineteen months after the accident, he consulted our hospital and complained of memory disturbance, decreased activity, failure of emotion

control, and easy anger. Neuropsychological examinations showed moderately impaired cognitive function as follows: MMSE 26/30, WAIS-III Full Scale IQ 83, Computer-adaptive test for depression (D-CAT) 30, and Wisconsin Card Sorting Test (Keio Version) (KW CST) 6. T<sub>1</sub>- and T<sub>2</sub>-weighted, and FLAIR MR images did not show trauma-related lesions, but T2\*GRE images showed multiple hemorrhagic contusion in the right frontal region, the left parietal region, right temporal region, right thala-

**Table 3** Detection of lesions by T<sub>2</sub>\*-weighted gradient recalled echo (T<sub>2</sub>\*GRE) imaging and fractional anisotropy imaging analyzed by statistical parametric mapping (FA-SPM imaging)

	No. of patients with detectable lesions in the deep brain structure	
	All patients	Patients with mild TBI
Abnormal low intensity on T <sub>2</sub> *GRE images (T <sub>2</sub> * lesion)	10/25 <sup>†</sup> (40.0%)	0/8 (0%)
Areas with significant decreased FA on FA-SPM images (FA-SPM lesions)	16/25* (64.0%)	3/8 (37.5%)

<sup>†</sup>Nine of the 10 patients with T<sub>2</sub>\* lesions had FA-SPM lesions. \*Nine of the 16 patients did not have any T<sub>2</sub>\* lesions.



**Fig. 2** A: Boxplots showing the 10th, 25th, 50th, 75th, and 90th percentiles of the number of statistically significant voxels in fractional anisotropy images analyzed by statistical parametric mapping (FA-SPM images) of mild and moderate traumatic brain injury (TBI) patients. All values above the 90th and below the 10th percentile are plotted separately. There was a significant difference between the two groups ( $p < 0.05$  by Welch's *t* test). B: Scatter plot showing the relationship between the number of statistically significant voxels in FA-SPM images of TBI patients and their Mini Mental State Examination (MMSE) score. There was a significant inverse correlation between the number of voxels and the MMSE score (Pearson correlation coefficient  $-0.467$ ,  $p = 0.009$ ). C: Scatter plot showing the relationship between the number of statistically significant voxels in FA-SPM images of TBI patients and their Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Full Scale intelligence quotient (IQ) score. There was a significant inverse correlation between the number of voxels and the WAIS-III Full Scale IQ score (Pearson correlation coefficient  $-0.567$ ,  $p = 0.002$ ).

mus, and corpus callosum (Fig. 3A-D). Tractography of the corpus callosum showed slight local tract deficits (Fig. 3E). FA-SPM images showed areas of significantly decreased FA in the bilateral frontal and right temporal regions, and the corpus callosum (Fig. 3F, G).

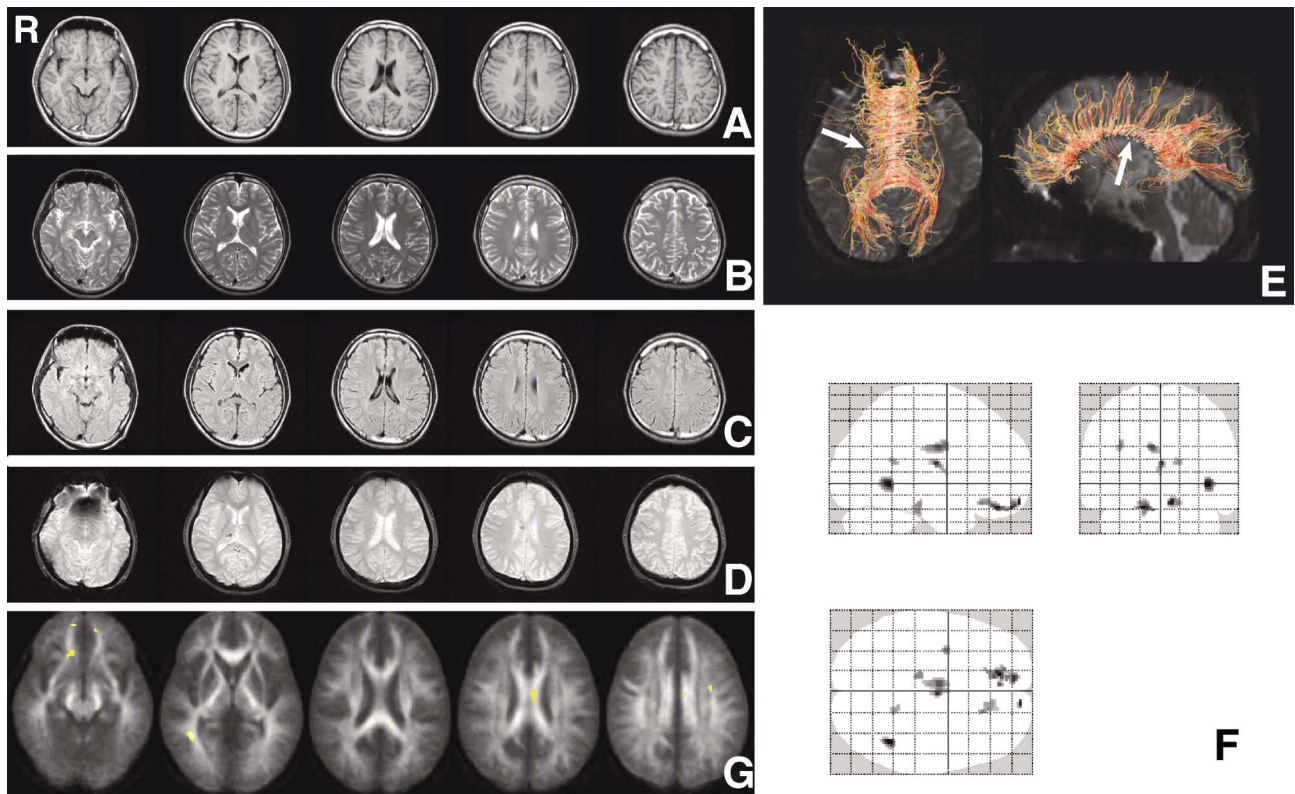
## II. Case 7: Mild TBI

A 41-year-old right-handed woman sustained a mild, closed head injury in a traffic accident. Seven months after the accident, she consulted our hospital and complained of disturbances of attention, memory, and speed of information processing. Neuropsychological examinations showed moderately impaired cognitive function as follows: MMSE 26/30, WAIS-III Full Scale IQ 54, Rivermead Behavioral Memory Test 6/24, D-CAT  $< 20$ , and KWCSST 4.

Conventional MR images could not detect trauma-related lesions (Fig. 4A-D) and tractography of the corpus callosum showed no local or diffuse tract deficits (Fig. 4E). FA-SPM images showed significantly decreased FA in areas of the corpus callosum (Fig. 4F, G).

## Discussion

The microscopic structural changes associated with mild TBI remain unclear. Pathological information has been acquired from a few human postmortem studies of patients with mild TBI who died because of other causes. Five patients who sustained mild concussive head injury and died of other causes all had multifocal axonal injury based on immunostaining.<sup>9</sup> Microscopy analysis of the brain of a patient



**Fig. 3** Representative case of moderate traumatic brain injury case (Case 6). **A–D:** Axial  $T_1$ -weighted (**A**),  $T_2$ -weighted (**B**), fluid-attenuated inversion recovery (**C**), and  $T_2^*$ -weighted gradient recalled echo (**D**) magnetic resonance images showing multiple hemorrhagic contusions in the right frontal, left parietal, and right temporal regions, the right thalamus, and the corpus callosum. **E:** Axial and lateral views of fiber tracking in the corpus callosum revealing slight local tract deficits (arrows). **F:** Orthogonal projection of brain regions showing significantly decreased anisotropy compared with the age-matched control group, thresholded at an uncorrected  $p < 0.001$ . **G:** Fractional anisotropy images analyzed by statistical parametric mapping showing areas of significantly decreased anisotropy in the bilateral frontal and right temporal regions, and the corpus callosum.

with mild TBI revealed collections of hemosiderin-laden macrophages in the perivascular space and increased number of macrophages in the white matter, particularly the section taken from the frontal lobe.<sup>8)</sup>

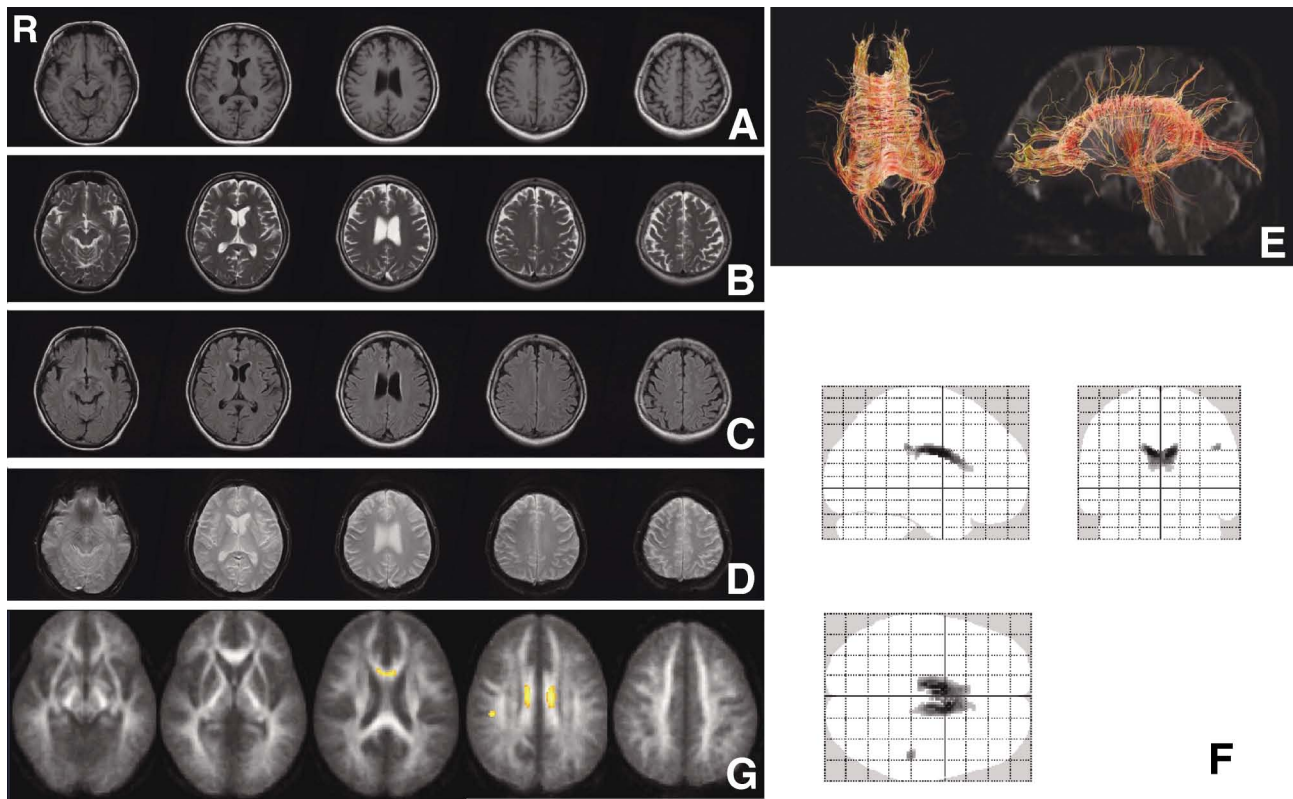
The appearance of DAI on MR imaging depends on several factors.  $T_2^*$ GRE imaging has been reliably shown to be more sensitive than echo planar imaging in the detection of hemorrhagic DAI lesions. On the other hand, FLAIR and diffusion-weighted images are considered to provide more diagnostic information related to non-hemorrhagic DAI compared with  $T_1$ -weighted imaging,  $T_2$ -weighted imaging, or  $T_2^*$ GRE imaging. However, conventional MR imaging including FLAIR imaging may actually underestimate the existence of minute non-hemorrhagic DAI lesions in a number of cases.

Susceptibility-weighted imaging (SWI) was not performed on this study. At the time of this study, SWI was not available on our 1.5 tesla MR scanner used to image the patients of this study. Recent stu-

dies have found that SWI was more sensitive than conventional  $T_2^*$ GRE sequences in detection of hemorrhagic lesions in pediatric DAI patients.<sup>5,6)</sup> However, SWI has yet to be found superior to other more common imaging modalities such as  $T_2$ -weighted and FLAIR sequences, and DTI. SWI for adult DAI patients would benefit from comparison to other imaging modalities in future studies.

DTI is a noninvasive MR technique that quantifies water diffusion in the brain tissue. The degree of anisotropic water diffusion in the white matter is related to the degree of directionality and the integrity of the fibers running in the white matter. FA calculated from DTI is one of the major diffusion variables that have been used for characterizing the integrity and the directionality of the diffusion in the white matter by expressing a ratio of 0 to 1 that represents the degree of alignment of the underlying fibers in a voxel.<sup>7,24)</sup>

The voxel-based analysis of FA maps obtained



**Fig. 4** Representative case of mild traumatic brain injury case (Case 7). A–D: Axial T<sub>1</sub>-weighted (A), T<sub>2</sub>-weighted (B), fluid-attenuated inversion recovery (C), and T<sub>2</sub>\*-weighted gradient recalled echo (D) magnetic resonance images showing no abnormal findings. E: Axial and lateral views of the fiber tracking in the corpus callosum revealing no local or diffuse tract deficits. F: Orthogonal projection of brain regions showing significantly decreased anisotropy compared with the age-matched control group, thresholded at an uncorrected  $p < 0.001$ . G: Fractional anisotropy images analyzed by statistical parametric mapping showing areas of significantly decreased anisotropy in the corpus callosum.

from DTI is more sensitive for detecting minute fiber disruptions in the white matter and the deep brain structures compared with conventional MR imaging. A number of group comparison studies using voxel-based analysis for TBI have already been published and revealed that preferential sites for DAI included the subcortical white matter, internal capsules, corpus callosum, cingulum, fornix, and infratentorial white matter.<sup>1,13,22</sup> Generally, FA reduction in the internal capsules, brain stem, and cerebellum are suggested to be markers of more severe TBI, and these regions were not frequently involved in the patients of this study who were generally classified with mild head injury.<sup>25</sup>

Our study showed the vulnerability of the corpus callosum, cingulum, fornix, thalamus, bilateral frontal lobes, parietal lobes, and long association fibers. Damage to these areas might cause functional or anatomical fiber disconnections, or both, between the cerebral cortex and deeper brain structures including the limbic system, and the disconnection

presumably occurs because of DAI due to either shearing or neurapraxia.<sup>26</sup> In our previous studies of cognitive impairment following TBI by analysis of cerebral glucose metabolism, cognitive impairment is strongly suggested to be caused by regional glucose hypometabolism in the bilateral medial prefrontal regions, medial frontobasal regions, cingulate gyrus, and thalamus.<sup>17,21</sup> This hypometabolism might be the result of secondary functional dysfunctions because of disconnections of the neural networks in areas remote to hypometabolic regions rather than of direct cerebral focal contusion. Therefore, possible explanations for cognitive impairment following TBI are both direct functional or anatomical fiber disconnections because of either shearing or neurapraxia, and secondary functional dysfunction due to disconnections of the neural networks in remote areas of the brain.

Another method for analyzing DTI is a region-of-interest (ROI) approach. Tractography is a type of the ROI study of FA in individual patients with DAI.



This extraordinary technique has the advantages of neuro-imaging because of its three-dimensional anatomical display of axonal structures,<sup>20)</sup> but also has some shortcomings. Tractography can only evaluate the ROI and the evaluation lacks objectivity and reproducibility. Additionally, fiber tracking is feasible in every voxel as long as the directionality of water diffusion remains, even if the FA is decreased, so fiber damage may be underestimated.

This study used voxel-based analysis of FA maps, FA-SPM imaging, in individual patients, which is observer-independent and objective, and can search for abnormal lesions throughout the whole brain, as distinct from the ROI approach. This study revealed that FA-SPM imaging was highly sensitive for detecting lesions with minute decrease of FA, most of which could not be detected by conventional MR imaging. However, there are several limitations of this study of FA-SPM imaging. Firstly, no histopathological confirmation of FA-SPM lesions was obtained. If pathological information could be acquired from postmortem studies of the patients with FA-SPM lesions, the reliability of FA-SPM images for detecting minute traumatic lesions could be undoubtedly established. Secondary, this study is a cross-sectional study and the time between injury and imaging is variable. Serial changes in anisotropy may occur during the chronic phase.<sup>10)</sup> Longitudinal studies are needed to represent the time course of diffusion changes in TBI. Thirdly, the voxels involving hemosiderin were excluded from the SPM analysis by threshold masking. If the value at any voxel in any of the images fell below the threshold of 0.15, then the voxel in the background or included hemosiderin was excluded from the analysis. No single imaging method, including FLAIR, T2\*GRE, SWI, and so on, can capture all the complex phenomena of TBI, which involves hemorrhagic and non-hemorrhagic lesions. It is necessary to use not only FA-SPM images, but also T2\*GRE images or SWI for the diagnosis of DAI.

Antemortem diagnosis of DAI is difficult without neuroimaging evidence in the chronic stage in patients with mild or moderate TBI. So far, conventional MR imaging may have underestimated the extent of DAI lesions and the complaints of TBI patients may be dismissed because of normal findings on conventional MR imaging. In such patients, the absence of MR imaging evidence may account for the transient clinical pathologic conditions following TBI or post-traumatic stress disorder. FA-SPM imaging may be a useful clinical tool to document the presence of minute brain lesions in patients with post-traumatic cognitive, behavioral, or emotional impairments, and may lead to the dis-

covery of more patients with a correct diagnosis of DAI.

FA-SPM imaging is useful for detecting minute DAI lesions in the white matter and the deep brain structures, which may not be visualized on either T2\*GRE or FLAIR images, and may allow detection of minute brain lesions in patients with post-traumatic cognitive, behavioral, or emotional impairments.

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