Table 2 Differences in values of FA and axial/radial diffusivity in VOI between patients and healthy control subjects

			ANCOVA†	
FA and axial/radial diffusivity	Stroke patients (*n* = 18)	Healthy control subjects (*n* = 22)	$F_{1,36}$	*P*-value
Left anterior limb of internal capsule				
FA	0.41 ± 0.08	0.48 ± 0.03	16.4	<0.001**
Axial diffusivity (×10^{-3})	4.16 ± 0.32	4.37 ± 0.30	4.24	0.05*
Radial diffusivity (×10^{-3})	3.96 ± 0.30	4.04 ± 0.29	0.48	0.49
Right anterior limb of internal capsule				
FA	0.43 ± 0.06	0.50 ± 0.03	23	<0.001**
Axial diffusivity (×10^{-3})	4.14 ± 0.33	4.35 ± 0.30	4.03	0.05
Radial diffusivity (×10^{-3})	3.93 ± 0.31	4.01 ± 0.30	0.46	0.50
Bilateral anterior limb of internal capsule				
FA	0.42 ± 0.07	0.49 ± 0.03	20.6	<0.001**
Axial diffusivity (×10^{-3})	4.15 ± 0.32	4.36 ± 0.30	4.15	0.05*
Radial diffusivity (×10^{-3})	3.95 ± 0.30	4.02 ± 0.29	0.47	0.50

†Age and gender are entered as covariates. Data are mean ± SD. *$P < 0.05$, **$P < 0.01$.
FA, fractional anisotropy; VOI, volume of interest.

Table 3 Change in psychometry scores, FA values, and axial/radial diffusivity over 6 months in patients (*n* = 12)

	10–28 days after stroke	6 months after first exam	Paired *t*-test	*P*-value
Patients				
mRS score	1.9 ± 0.5	1.6 ± 0.5	$t_{11} = 2.35$	0.04*
NIHSS score	2.8 ± 1.0	1.8 ± 0.7	$t_{11} = 4.00$	0.002**
MMSE score	29.0 ± 1.5	29.7 ± 0.5	$t_{11} = 1.54$	0.15
HAM-D score	3.7 ± 2.9	2.3 ± 3.0	$t_{11} = 1.13$	0.28
Anterior limb of internal capsule				
FA	0.40 ± 0.06	0.43 ± 0.06	$t_{11} = 2.26$	0.04*
Axial diffusivity (×10^{-3})	4.22 ± 0.30	4.13 ± 0.2	$t_{11} = 0.74$	0.48
Radial diffusivity (×10^{-3})	4.01 ± 0.26	3.87 ± 0.25	$t_{11} = 1.50$	0.16

Data are mean ± sd. * $P < 0.05$, ** $P < 0.01$.
FA, fractional anisotropy; HAM-D, Hamilton Rating Scale for Depression; MMSE, Mini-Mental State Examination; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale.

related to the change in depression scale scores (HAM-D) after 6 months, the ratio of FA values was found to be negatively related to the change in the HAM-D scores ($\beta = -0.46$, $P = 0.04$).

Lymphocyte subsets and their relation to FA values in patients

Patients showed significantly decreased numbers of T_{reg} compared with healthy controls (Table 4, Fig. 3a). We also found a significant positive relationship between the level of circulating T_{reg} and the FA value in the anterior limb of the internal capsule in the patients ($r = 0.50$, $P = 0.04$) (Fig. 3b). There was no significant relationship between the level of circulating T_{reg} and the HAM-D scores.

When multiple regression analysis was used to evaluate whether the level of circulating T_{reg} was related to the FA value in the anterior limb of the

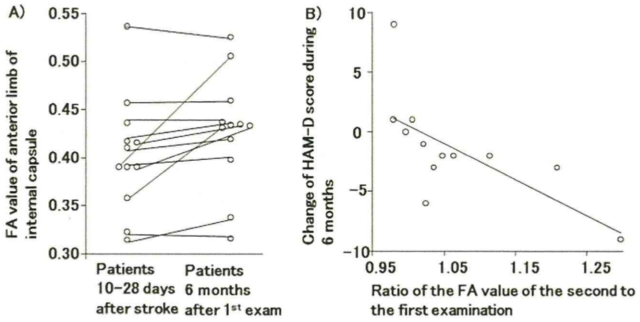

Figure 2 (a) Scatter plots of fractional anisotropy (FA) values in the region of FA reduction among stroke patients (*n* = 12) at 10–28 days after the stroke and at the 6-month follow-up. A significant FA increase was observed in the patients at the 6-month follow-up ($P < 0.05$). (b) Scatter plots showing the relationship between the ratio of the FA values of the second to the first examination and the change in depression scale scores among patients (*n* = 12). Significant correlations were observed between the ratio of the FA values of the second to the first examination and the changes in depression scale scores ($r = -0.67$, $P = 0.02$). HAM-D, Hamilton Rating Scale for Depression.

Table 4 Differences in percentage of lymphocytes in the circulation between patients and healthy control subjects

			ANCOVA†	
	Stroke patients (*n* = 18)	Healthy control subjects (*n* = 22)	$F_{1,36}$	*P*-value
Helper T lymphocyte	67.2 ± 15.1	61.5 ± 12.0	1.00	0.32
Cytotoxic T lymphocyte	27.9 ± 13.5	33.2 ± 10.6	0.92	0.35
B lymphocyte	17.7 ± 8.3	12.2 ± 7.8	5.42	0.03
NK cell	21.6 ± 11.3	27.5 ± 10.4	1.78	0.19
Regulatory T lymphocyte	2.1 ± 1.6	3.8 ± 2.3	7.89	0.008*

†Age and sex are entered as covariates. Data are mean ± SD. *Significant after correction for multiple statistical tests to avoid type I errors ($P < 0.01$ (0.05/5)). NK, natural killer.

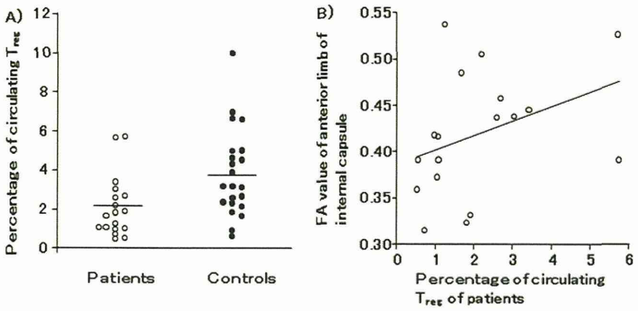

Figure 3 (a) Scatter diagrams showing the differences in circulating T_{reg} between patients and controls. A significant difference in the percentage of T_{reg} was observed between groups ($F_{1,36} = 7.89$, $P = 0.008$). (b) The relationship between the percentage of circulating T_{reg} and FA values of the anterior limb of the internal capsule in patients. A significant correlation was observed between the percentage of T_{reg} and FA values ($r = 0.50$, $P = 0.04$). FA, fractional anisotropy; T_{reg}, regulatory T lymphocytes.

internal capsule, the T_{reg} level was found to be positively related to the FA values ($\beta = 0.59$, $P = 0.02$).

DISCUSSION

Our findings showed that stroke patients had lower FA in the bilateral anterior limb of the internal capsule relative to healthy control subjects. Six months after initial assessment, a significant increase in FA was noted, and it revealed an association with a reduction in depression scale scores. Our findings are not the result of direct neuronal damage caused by the infarction located on the internal capsule, as no patients had a lesion in this location. Also, there was no direct relationship between the FA value in this region and the volume of infarcts or the severity of stroke.

Reduced FA level was associated with decreased axial diffusivity. Axonal damage leads to a marked decrease in axial diffusivity, while demyelination leads to an increase in radial diffusivity.[13] Therefore, our finding was not a result of demyelination but of gross reduction in axonal number and/or size, possibly reflecting Wallerian degeneration secondary to neuronal loss due to stroke.[14] From an anatomical perspective, the anterior limb of the internal capsule represents the intercept point in the course of the frontal-subcortical circuits,[15] and it has extensive connectivity with the cortical and subcortical areas. Its reduced FA may reflect the conjunctive focus of degeneration due to stroke in the spatially different sites of cortical and subcortical areas.

The frontal-striatal-thalamic-cortical circuits, connected by the anterior limb of the internal capsule, play an important role in behavioural regulation,[16] and based on MRI, microstructural change of the anterior limb of the internal capsule is related to the severity of depressive symptoms in adults with major depressive disorder.[17] Degeneration in this region may relate to a loss of white matter integrity of these neural circuits,[18] and this abnormality might trigger the onset of negative mood change. Our findings on the association between the change in FA values of the internal capsule and depression scale scores might reflect an association between axonal damage of the internal capsule and depressive mood in stroke patients.

Our findings demonstrate that patients had reduced amounts of circulating T_{reg}, with the degree of reduction being related to the decrease in FA value in the internal capsule. This may indicate that a decrease in T_{reg} is related to the axonal damage of the internal capsule in stroke patients. Our findings showed no direct relationship between T_{reg} level and depression scale scores, but T_{reg} may indirectly affect post-stroke depressive symptoms via its effect on the cerebral damage.

An ischemic stroke caused T lymphocytes to become activated, infiltrate the brain, and then function as sources of pro-inflammatory cytokines and cytotoxic substances.[19–21] However, not all T-cell subtypes are detrimental to acute stroke outcome, and recent evidence indicates a novel role of T cells in promoting brain tissue repair and regeneration. T_{reg} cell is an important T-cell subtype, and it supports brain tissue repair and regeneration.[22] T_{reg} cells act to limit the immune response by releasing transforming growth factor-β and interleukin-10,[23] and they have also been reported to be required for neurogenesis.[24] Infarct volume and neuronal dysfunction were significantly increased in mice treated with an anti-CD25 monoclonal antibody to neutralize T_{reg} compared with controls.[23] Furthermore, this protection was observed only 7 days after a modest ischemic insult.[23] These findings of the brain-protecting and outcome-improving effects of T_{reg} were also confirmed by Li *et al.* using post-stroke T_{reg} cell therapy.[25]

One possible explanation for our results of T_{reg} is that people with lower circulated T_{reg} are more likely to develop stroke and tend to have severe axonal damage after stroke. Another possibility is that the reduction in circulated T_{reg} after stroke might be induced by the consumption of T_{reg} to repair cerebral neuronal injuries, including axonal damage. Our findings of lower circulated T_{reg} are based on cross-sectional data, which provide limited ability to infer which explanation is right. In any case, our results are consistent with previous reports of the brain-protecting and outcome-improving effects of T_{reg}. In principle, our findings showed the possibility of improving stroke outcome by targeting the role of T_{reg} in protecting brain tissue damage after a stroke.

Ren *et al.* and Kleinschnitz *et al.* respectively demonstrated no role or an opposite role for T_{reg} in exacerbating brain injury early after transient ischemia.[26,27] The animal model they used was different from that of the Liesz study in several aspects, including the duration of ischemia and methods for T_{reg} depletion. Furthermore, the late stage effect of T_{reg} depletion was not addressed in their studies. In our study, stroke patients were predominantly of modest ischemic insult, and their circulating lymphocytes were studied after 10–28 days. There is a possibility that the differences in the severity and stage of the ischemic insult caused different results regarding the role of T_{reg} in their studies and ours.

Our study has some limitations. First, patients with significant comprehension deficits were excluded because clinical verbal interviews could not be conducted. Second, all of the patients took anticoagulant or anti-platelet medicine. Specifically, 13 patients took acetylsalicylic acid, which has an anti-inflammatory effect, and this may have affected our results. However, the extent to which our findings relate to medication remain uncertain. Further analysis, inclusive of considerations of these points, is needed to confirm our present findings.

In conclusion, the present study suggests that FA reduction in the bilateral anterior limb of the internal capsule is evident in stroke patients. This regional damage relates to abnormality of neuroanatomical pathways in frontal-subcortical circuits and renders a biological vulnerability, which then gives rise to the onset of depressive symptoms. Our findings also demonstrate that patients have reduced amounts of circulating T_{reg}, with the degree of reduction being related to the decrease in FA value in the internal capsule. T_{reg} cells might have a role in improving post-stroke white matter tissue damage by limiting the immune response and promoting neurogenesis.

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Decision-making deficit of a patient with axonal damage after traumatic brain injury

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ABSTRACT

Patients with traumatic brain injury (TBI) were reported to have difficulty making advantageous decisions, but the underlying deficits of the network of brain areas involved in this process were not directly examined. We report a patient with TBI who demonstrated problematic behavior in situations of risk and complexity after cerebral injury from a traffic accident. The Iowa gambling task (IGT) was used to reveal his deficits in the decision-making process. To examine underlying deficits of the network of brain areas, we examined T1-weighted structural MRI, diffusion tensor imaging (DTI) and Tc-ECD SPECT in this patient. The patient showed abnormality in IGT. DTI-MRI results showed a significant decrease in fractional anisotropy (FA) in the fasciculus between the brain stem and cortical regions via the thalamus. He showed significant decrease in gray matter volumes in the bilateral insular cortex, hypothalamus, and posterior cingulate cortex, possibly reflecting Wallerian degeneration secondary to the fasciculus abnormalities. SPECT showed significant blood flow decrease in the broad cortical areas including the ventromedial prefrontal cortex (VM). Our study showed that the patient had dysfunctional decision-making process. Microstructural abnormality in the fasciculus, likely from the traffic accident, caused reduced afferent feedback to the brain, resulting in less efficient decision-making. Our findings support the somatic-marker hypothesis (SMH), where somatic feedback to the brain influences the decision-making process.

1. Introduction

Traumatic brain injury (TBI) is a major public health problem. Although medical disabilities usually stabilize after onset, neuropsychological consequences can cause chronic handicaps that often do not receive appropriate attention and treatment (Dombovy & Olek, 1997). In particular, they show significant deficits in tasks relying on focused and divided attention (Stuss et al., 1989), on verbal memory (Crosson, Novack, Trenerry, & Craig, 1988) and on executive functions (Stuss & Gow, 1992). Executive impairments are related to planning, inhibitory control, monitoring, and mental flexibility.

Patients with TBI also have difficulties in making deliberate and advantageous decisions (Levine et al., 2005; Santoro & Spiers, 1994; Yody et al., 2000). As, after TBI, patients are often confronted with a completely new and difficult living situation, important decisions have to be made by them and their relatives. Spontaneous wrong decisions may have disastrous long-lasting consequences, such as unemployment, alienation from family and friends and legal problems, which are often linked to the disability to make adequate and advantageous choices (Warriner & Velikonja, 2006).

Damasio has proposed an influential model of human decision-making – the somatic-marker hypothesis (SMH), where he argues that somatic feedback to the brain influences decision-making in man (Damasio, 1994). It is proposed that when choosing between options that differ in relative risk, a somatic marker (e.g. a 'gut feeling') feeds back to the brain and influences decision-making. In line with this hypothesis, the reduced afferent feedback of a somatic marker to the brain would result in abnormal decision-making.

In the present study we report a patient with TBI who demonstrated problematic behaviors in situations of risk and complexity after cerebral injury due to a traffic accident. The Iowa gambling task (IGT) was used to test and confirm his deficits of the decision-making process (Bechara, Damasio, Damasio, & Anderson, 1994). To examine underlying deficits of the network of brain areas involved in his decision-making process, we compared the diffusion tensor and gray matter images of MRI between the patient and healthy control subjects. We expected that the patient would show microstructural abnormality in the fasciculus as a result of

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the traffic accident, causing reduced afferent feedback to the brain that would lead to less efficient decision-making.

2. Methods

2.1. Case report

The patient was a 30-year-old right-handed man. He had no history of alcohol or illicit drug abuse. His parents reported no family history of any major mental illness. His early childhood development was reportedly unremarkable. Before the accident, he had no significant medical problems or past psychiatric history. His personality before the accident was described by his homeroom teacher at high-school as humorous, popular, and cooperative.

At the age of 17, the patient sustained a TBI in a motorcycle accident. He was transported to a local hospital. There is no record of the Glasgow Coma Scale score, but his family reported that he fell into a coma for 6 h. The initial CT scans of the head revealed no particular change. After awakening, he was discharged to his home. According to the family, after the accident, he began to show outbursts of anger and physically aggressive behavior. He came to act recklessly and unexpectedly. He repeatedly changed his job at short intervals. He was deeply in debt and often had girl troubles.

To investigate whether traumatic brain dysfunction existed and was related to the problematic behaviors, he was referred to the outpatient psychiatry unit at our hospital for judicial psychiatric evidence. A physical examination revealed no abnormalities. He was alert, attentive and oriented. Spontaneous speech, comprehension, repetition, and naming were normal, as were calculation, mapping, praxis, right-left orientation, and finger naming. He did not have a history or present diagnosis of any axis I disorders of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) or any neurological illness. Electroencephalography showed no relevant abnormalities.

2.2. Neuropsychological evaluation

2.2.1. General cognitive testing (see Table 1)

A more extensive neuropsychological evaluation was performed. The patient was alert, attentive, socially appropriate, and had normal digit span performances, seven digits forward and four backward.

Intellectual functioning as assessed by Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler, 1981) and Raven's Coloured Progressive Matrices (RCPM) (Raven, 1958) was adequate. Word fluency (Borkowski, Benton, & Spreen, 1967) was normal, and all language and language-related functions were intact. The patient had no memory deficits. Results with the Rey Auditory Verbal Learning Test-Revised (RAVLT-R) (Spreen & Strauss, 1991) and performance on the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1987) were also excellent.

In the assessment of frontal function, the results of Frontal Assessment Battery (FAB) (Dubois, Slachevsky, Litvan, & Pillon, 2000), Wisconsin Card Sorting Test (WCST) (Berg, 1948), and Stroop test (Stroop, 1935) were normal. The Behavioral Assessment of Dysexecutive Syndrome (BADS) (Wilson, Alderman, Burgess, Emslie, & Evans, 1996) showed excellent scores. The total scores of the Dysexecutive Questionnaire (DEX) rated by the patient and his family were within normal range. However, his family rated high scores in the questionnaire of impulsiveness and aggressiveness.

2.2.2. Iowa gambling task (Bechara et al., 1994)

From the patient's reports of problematic behavior after the motorcycle accident, we suspected that he had difficulty with the decision-making process due to his TBI. IGT was used to test his ability of decision-making. It consists of a computerized card game where the player is instructed to try to win as much money as possible with 100 selections from any one of four decks. The rules are not disclosed, and the player gradually learns that two of the decks are 'high risk' (A and B), i.e., intermittently produce large rewards but in the long term lead to significant financial losses, whereas two decks (C and D) lead to modest but consistent gains. Healthy individuals have previously been shown to learn to avoid the risky decks, whereas patients with decision-making difficulty process select an excessive number from the risky decks, and consequently lose money. Data analysis examined the quality of the decision-making as measured by the net score [choice of advantageous decks (C and D) – disadvantageous decks (A and B)] across five 20-trial blocks. The patient's result was compared to those of healthy male controls ($n = 12$, age: 31.9 ± 10.5).

Table 1
Neuropsychological test results.

	Patient's scores
General intelligence	
MMSE	30/30
RCPM	35/36
WAIS-R (vIQ, pIQ, fIQ)	91, 90, 89
Memory	
RAVLT-R	
Trials 1–5	7, 11, 14, 14, 14
Post-interference	13
Delayed recognition	13
WMS-R (Index)	
General memory index	101
Verbal memory index	95
Visual memory index	116
Attention/concentration	97
Delayed index	104
Frontal function	
Trail making A	25 s
Trail making B	70 s
Frontal assessment battery (FAB)	17/18
WCST (category achieved)	6
Stroop test: word, color, word-color	98, 82, 59
BADS (index)	118
DEX (self-version, family-version)	19, 18

MMSE = mini-mental state examination; RCPM = Raven's colored progressive matrices; WAIS-R = Wechsler adult intelligence scale revised; RAVLT-R = Rey auditory verbal learning test revise; WMS-R = Wechsler memory scale revised; WCST = Wisconsin card sorting test; BADS = Behavioral Assessment of Dysexecutive Syndrome; DEX = Dysexecutive Questionnaire.

2.3. Data acquisition of MRI

All MRI examinations were performed by 3.0-T scanner (Magnetom Verio, Siemens AG, Erlangen, Germany). DT images were acquired with echo-planar imaging (EPI) sequence ($TR = 14{,}000$ ms, $TE = 84$ ms, $b = 1000\ \mathrm{s/mm^2}$, $FOV = 256$ mm, matrix = 128×128, slice spacing = 2 mm, slice thickness = 2 mm, averaging = 3). The reconstruction matrix was 256×256 matrix by interpolation, and $2\ \mathrm{mm} \times 2\ \mathrm{mm} \times 2\ \mathrm{mm}$ voxel data were obtained. Motion probing gradient (MPG) was applied in 12 directions. High-resolution three-dimensional T1-weighted images were acquired using a magnetization prepared rapid gradient echo (MPRAGE) sequence ($TR = 1800$ ms, $TE = 2.4$ ms, $TI = 800$ ms, flip angle = 10°, FOV × 256 mm, slice thickness = 1 mm; 208 sections in the sagittal plane; acquisition matrix, 256×256; acquired resolution, $1 \times 1 \times 1$ mm). The patient's result was compared to those of healthy controls ($n = 13$, 7 males and 6 females, age: 30.0 ± 9.5).

2.4. Imaging processing of MRI

Fractional anisotropy (FA) maps were generated from each individual using "dTV II" software (Masutani, Aoki, Abe, Hayashi,

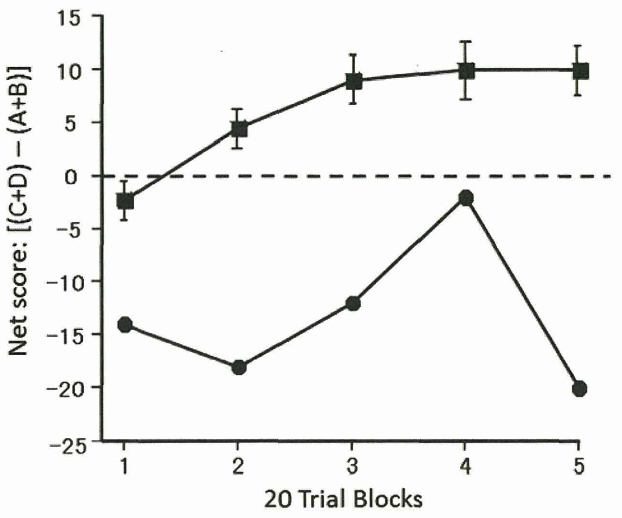

Fig. 1. Decision-making performance on the Iowa gambling task (IGT) of the patient (circles) and control subjects (squares). The figures shows the net score (choice of advantageous decks–disadvantageous decks) across 100 test trials, divided into five 20-trial blocks.

& Otomo, 2003). Image preprocessing and statistical analysis were carried out using SPM8 (Wellcome Department of Imaging Neuroscience, London, England). Each subject's image was spatially normalized to the Montreal Neurological Institute image template using parameters determined from the normalization of the image with a b value of 0 s/mm^2 and the echo planar image template in SPM8. Images were resampled with a final voxel size of 2 × 2 × 2 mm^3. Normalized gray matter image maps were generated from each individual using the VBM8 toolbox with SPM8 software. Normalized maps were spatially smoothed using an isotropic Gaussian filter (8-mm full-width at half-maximum). Normalized and smoothed FA and gray matter image maps were compared with voxel-based analysis between the patient and healthy controls with Jack-knife analysis. Statistical inferences were made with a voxel-level threshold of $p < 0.001$, uncorrected, with a minimum cluster size of 50 voxels.

2.5. Data acquisition and analysis of SPECT

Tc-ECD SPECT studies were performed using a dual-headed γ-camera (TOSHIBA SYMBIA E, Toshiba, Japan). Tc-ECD SPECT imaging with a fan-beam collimator was started 10 min after an intravenous bolus injection of 600 MBq Tc-99 m ECD. Tomographic data with a slice thickness of 5.39 mm were obtained continuously for 24 min. Static data were acquired in 128 × 128 matrices. The data were prefiltered using a Ramp filter with a high cut-off value. Stereotactic statistical imaging analysis of the brain using the easy *Z*-score imaging system was performed, and decrease in regional cerebral blood flow of the patient was investigated (Mizumura & Kumita, 2006).

3. Results

The patient produced normal performance on a variety of neuropsychological tests (Table 1), but showed abnormality in IGT. As shown in Fig. 1, beginning at approximately the 20th trial, control subjects shifted their preference toward advantageous decks, whereas the patient preferred disadvantageous decks and his net scores were less than zero over the 100 trials.

DTI-MRI results showed that the patient had a significant decrease of FA. As shown in Fig. 2 and Table 2, the patient had

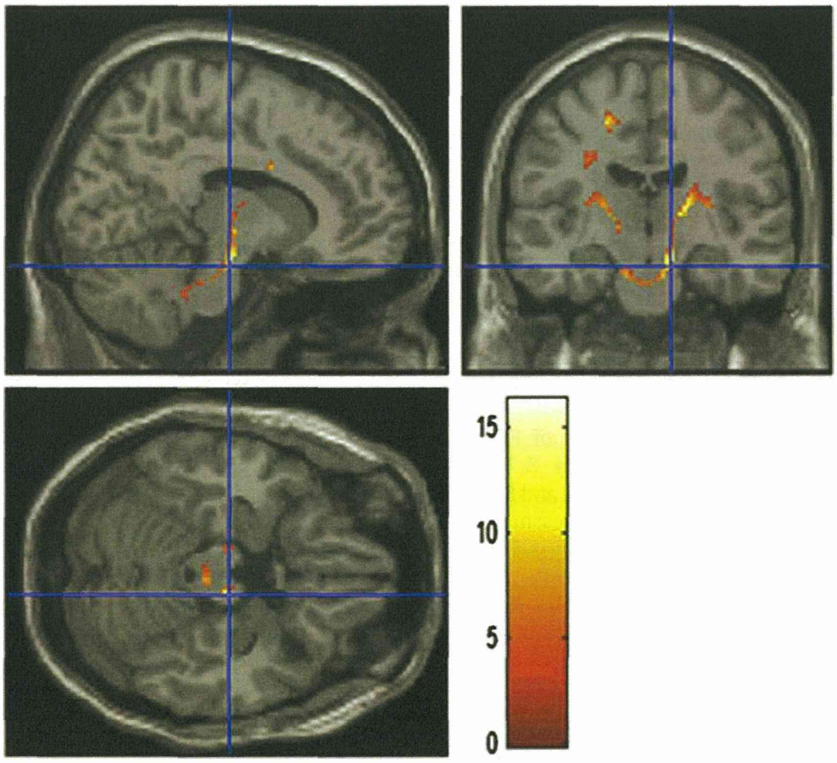

Fig. 2. Significant decrease of regional FA values in the patient when compared to healthy controls. Detected areas exceed uncorrected p value of 0.001 with 50 or more contiguous voxels. These statistical parametric mapping projections were then superimposed on representative transaxial ($z = -23$), sagittal ($x = 12$), and coronal ($y = -14$) magnetic resonance images.

Table 2
Brain areas manifesting significant decrease of FA and gray matter volumes in the patient.

Region	MNI (*x*,*y*,*z*)	Voxels	*Z* score
FA			
Left superior longitudinal fasciculus	−20, −36, 48	335	6.23
Left thalamic radiation	−18, −10, 14	189	5.42
Right thalamic radiation	16, −18, 4	816	5.88
Gray matter volume			
Middle cingulate cortex	10, −20, 46	158	5.50
Right inferior parietal cortex	56, −38, 50	96	4.77
Medial occipital cortex	2, −90, −8	133	4.74
Hypothalamus	0, 10, −6	97	4.66
Left insular cortex	−50, −4, 4	67	4.58
	−36, −22, 12	182	4.45
Right insular cortex	42, −10, 12	64	4.49

significantly smaller FA values in the left superior longitudinal fasciculus and bilateral thalamic radiation including the fasciculus between the brain stem and the cortical regions via the thalamus.

From the voxel-based morphometry results, we found regional decrease of gray matter volumes in the patient. The patient showed significantly smaller gray matter volumes in the bilateral insular cortex, posterior cingulate cortex, hypothalamus, right parietal cortex and medial occipital cortex (Fig. 3, Table 2).

As shown in Fig. 4, in the patient, a significant decrease in regional cerebral blood flow, in broad cortical areas including the ventromedial prefrontal cortex (VM), was revealed by Tc-ECD SPECT.

4. Discussion

The patient showed behavioral problems following cerebral injury from a traffic accident. The patient performed normally on a variety of neuropsychological tests, but had an abnormal outcome on IGT, which assesses the decision-making process. The patient's problem may stem from insensitivity to future consequences, positive or negative, as a result being primarily guided by immediate prospects. This 'myopia for the future' of the patient may persist in the face of a problematic behavior pattern that should result in severe adverse consequences.

DTI-MRI results showed that the patient had a significant decrease of FA in the fasciculus between the brain stem and insula via the thalamus. To the extent that FA is related to axonal integrity, density, caliber and myelination, our findings of a subnormal level of FA suggest the presence of microstructural abnormalities in the fasciculus of the patient. Damasio et al. proposed that somatic feedback helps guide the decision-making process in humans—the somatic-marker hypothesis (SMH) (Damasio, 1994). Evidence in favor of this hypothesis was provided by a study demonstrating that cerebrally intact individuals with peripheral neuropathy showed abnormal decision-making in IGT, suggesting that the peripheral neuropathy resulted in reduced afferent feedback to the brain (Bechara et al., 1998). In terms of SMH, microstructural abnormalities in the fasciculus of the patient resulted in reduced afferent feedback to the brain, resulting in less efficient decision-making.

When we focused on the cortical gray matter changes, we found significant decrease in gray matter volumes in the bilateral insular cortex, hypothalamus, posterior cingulate cortex, medial occipital and right parietal cortex, possibly reflecting Wallerian degeneration secondary to the microstructural abnormalities in the fasciculus. These atrophic regions may be a part of neural networks connected with the brain stem by the damaged fasciculus, which is related to the decision-making process.

Recently, Damasio et al. proposed the hypothesis that feelings first emerge from the integrated operation of structures in the brain stem and hypothalamus. The activity patterns present in

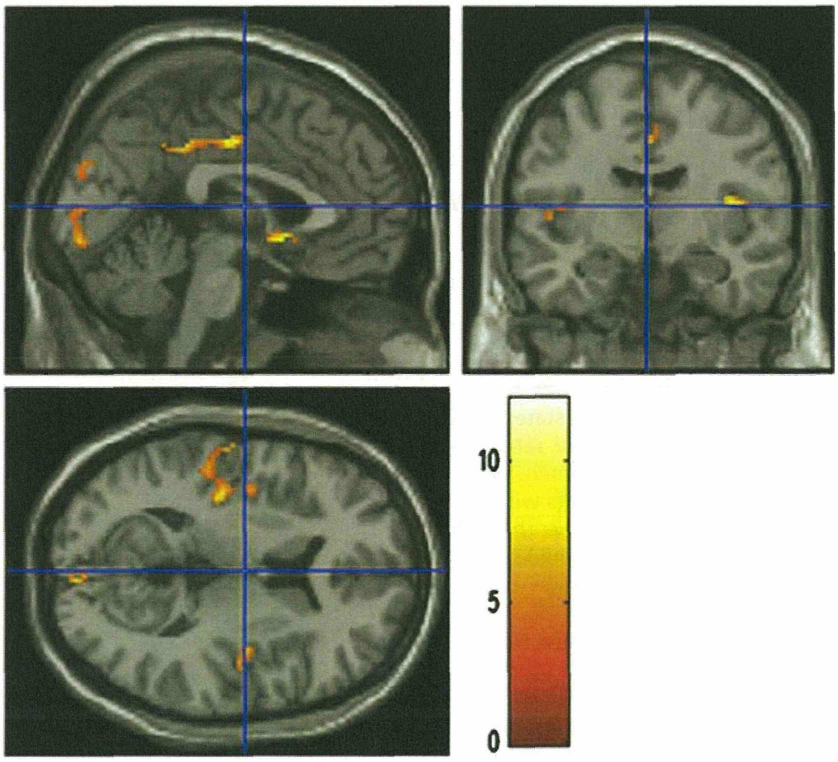

Fig. 3. Significant decrease of gray matter volumes in the patient compared to healthy controls. Detected areas exceed uncorrected p value of 0.001 with 50 or more contiguous voxels. These statistical parametric mapping projections were then superimposed on representative transaxial ($z = 10$), sagittal ($x = 0$), and coronal ($y = -11$) magnetic resonance images.

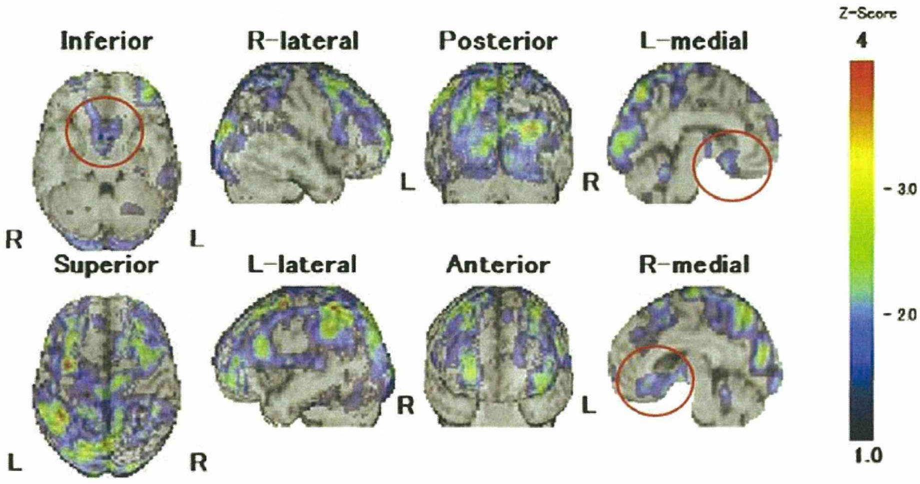

Fig. 4. Tc-99m ECD-SPECT results statistically analyzed by comparing with standard SPECT images obtained from easy *Z*-score imaging system; eZIS. Hypoperfusioned areas showing more than 2SD deviation from the standard SPECT images were 3D-rendered on brain template. The area shown in the red circle is the ventromedial prefrontal cortex (VM).

the insular cortex during feeling states would constitute a second-order mapping of activity patterns first assembled subcortically. The information contained in insular maps would be suitable for interaction with information in cortical systems involved in sensory processing (including visuo-perceptual processing in parieto-occipital cortex) and in higher-order functions such as decision-making (Damasio, Damasio, & Tranel, 2012). The posterior cingulate cortex is related to emotional processing via its connection with the insular cortex (Immordino-Yang, McColl, Damasio, & Damasio, 2009; Parvizi, Van Hoesen, Buckwalter, & Damasio, 2006). The atrophic change of cortical and subcortical regions and their disconnection with the brain stem may disturb the efficient generation of feelings accompanying anticipation, which is necessary for the final decision.

By SPECT, there was a significant blood flow decrease in the broad cortical areas. There is a possibility that the presence of microstructural abnormalities in the fasciculus, which projects to these areas, caused the inactivity of cortical function. In these areas, a significant decrease of blood flow in VM should be regarded as important, although there was no significant cortical change according to MRI. VM has been widely recognized as playing a critical role in successful decision-making, fueled in part by well-studied single cases (Cato, Delis, Abildskov, & Bigler, 2004; Dimitrov, Phipps, Zahn, & Grafman, 1999; Eslinger & Damasio, 1985).

The insular cortex has extensive reciprocal connectivity with VM (Augustine, 1996; Ongür & Price, 2000), and inactivity of the insular cortex may also decrease the activity of the VM region. SMH proposed that during decision-making, bodily states that were previously associated with choice options, were retrieved by VM, and it guides the decision-making process in humans in situations of risk and complexity (Damasio, 1994). Patients with VM lesions are known to have "myopia" for the future in that they are oblivious to the consequences of their actions and are guided only by immediate prospects (Bechara et al., 1994). These behaviors are similar to those of our patient after cerebral damage.

While our findings seemed to support SMH, where somatic feedback to the brain influences the decision-making process, a note of caution must be expressed as to the role of VM for decision-making process in IGT. There is another explanation of the failure of patients with VM lesions to perform well in the IGT. It was suggested that the difficulties of the patient with VM lesions might be due to a deficit in reversal learning – the ability to adjust their responses when the reinforcement values of stimuli are reversed (Maia & McClelland, 2005). It was argued that the difficulties of patients with VM lesions in IGT performance can be explained by an inability to reverse a learned contingency (Clark, Cools, & Robbins, 2004; Fellows & Farah, 2005; Maia & McClelland, 2004, 2005). We require additional empirical support to clarify the role of VM in the SMH.

In conclusion, we can postulate that the patient had a dysfunction of the decision-making process. Inefficiency of the decision-making process is likely to be related to the patient's problematic behavior after the traffic accident. The microstructural abnormality in the fasciculus, which may have resulted from the traffic accident, caused reduced afferent feedback to the brain, resulting in less efficient decision-making. Our findings seem to support SMH, where somatic feedback to the brain influences the decision-making process. Dysfunction of cortical and subcortical regions disconnected from the brain stem may also disturb the efficient generation of the feelings from somatic feedback, which is necessary for the final decision.

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