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博 士 論 文

Cognitive Impairments in Patients with Diffuse Axonal Injury

(びまん性軸索損傷患者の認知機能障害)

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Cognitive Impairments in Patients with Diffuse Axonal Injury

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Abstract

Focal brain injury and diffuse axonal injury (DAI) are two major types of traumatic brain injury. It is well established that patients with frontal lobe injury show cognitive impairments. However, the neurocognitive sequelae of DAI and the neural basis of the associated symptoms are poorly understood. To examine these parameters, in this study, 10 patients with DAI (10 males, 30.8 ± 10.5 years) and 12 age and gender matched normal control subjects underwent neuropsychological assessments and high-resolution structural magnetic resonance imaging (MRI). Voxel-based morphometry (VBM) was applied to investigate regional brain alterations. In patients with DAI, the mean WAIS-III IQ was 79.9 ± 10.9 , while the Eyes test score was worse than that in normal subjects. In VBM analyses, DAI patients exhibited widespread subcortical grey matter (GM) reductions, including the thalamus, cingulate cortex, insula, and putamen. Further, the IQ index of processing speed in DAI patients was associated with GM reduction in the right thalamus, while of the Eyes test scores were associated with GM reduction in the left amygdala. This preliminary study suggests that a specific brain network may play a key role in the development of cognitive impairments in DAI.

Keywords: Eyes test, processing speed, voxel based morphometry, theory of mind

Introduction

Closed head injury causes two major types of traumatic brain injury (TBI); focal brain injury and diffuse axonal injury (DAI). In focal brain injury, the orbitofrontal cortex (OFC), the ventromedial prefrontal cortex (VMPFC), and the temporal pole are most frequently damaged because of the shape of the skull base ¹⁾. As to DAI, subcortical damage results from stretching, straining and shearing of axons as the brain moves inside the skull. The pathology of DAI is characterized histologically by Wallerian-type axonal degeneration in the parasagittal white matter, corpus callosum, and dorsal upper brainstem due to shearing forces by acceleration, deceleration, or rotation of the brain ²⁾. In DAI, different from focal brain injury, brain damage was originally thought to occur diffusely in the white matter ³⁾, while the effect of such damage to the grey matter or whole brain is poorly understood. For focal brain injury, many of the symptoms after TBI are caused by the dysfunction of the damaged brain region. Therefore, numerous studies have focused on the dysfunction of the OFC or VMPFC, and reported that damage to these areas led to disinhibition, apathy, or dysfunction of the ‘theory of mind’ (ToM) ⁴⁾, which is regarded as the ability to infer the mental states of other individuals ^{5) 6) 7)}. Thus, these studies suggest that TBI can result in not only impairment of basic cognition such as memory function and information processing speed, but also impairment in social cognition including basic cognition of facial expressions and ToM ⁸⁾. However, there are few studies examining the sequelae of DAI and the neural mechanisms underpinning those symptoms.

Recent advances in neuroimaging techniques have provided several methods that can directly detect brain volume reductions in DAI cases. Voxel based morphometry (VBM) is an automated imaging analysis developed by Ashburner and Friston⁹⁾. Using VBM, brain atrophy changes after DAI were reported in grey matter (GM) areas including the frontal and temporal cortices, cingulate gyrus, and subcortical regions such as the thalamus and caudate ^{10) 11) 12)}, suggesting that brain alterations are regional rather than diffuse, even in the case of DAI patients. However, only a few studies have reported an association between neuropsychological performance and volumetric loss in specific brain areas; for example, volume reduction in GM structures correlated with poor cognitive function such as working memory, attention, executive function, and memory ¹³⁾. Furthermore, to our knowledge there are no studies examining the neural basis of impairment in social cognition in patients with DAI.

The aim of the present study was to assess structural brain damage in subjects with chronic DAI,

and to examine the relationship with basic and social cognitive impairment. To investigate this, we applied the VBM method and assessed basic cognition and social cognition using the ToM task. Further, we explored the relationship between neuropsychiatric sequelae and brain alteration to determine the neural basis of cognitive impairment in chronic patients with DAI. We hypothesized that impairments in social cognition are caused by similar specific lesions as for basic cognition impairments in patients with DAI.

Methods

Participants

Participants were recruited from outpatients of the Department of Psychiatry, Kyoto University Hospital. The inclusion criteria for patients were as follows: age between 18-65 years, sustained closed-head TBI and hospitalization for conservative treatment, and normal brain CT or focal injury without parenchymal hemorrhage (< 2 mm of the maximum diameter). The exclusion criteria included the following: a history of previous TBI or neurological or psychiatric illness (including drug or alcohol abuse), a history of neurocognitive disorder, and any other condition that could result in cognitive changes and language dysfunction.

Ten male patients with chronic phase TBI between the age of 19 and 44 (30.8 ± 10.5) completed the study. Table 1 shows patient demographic and clinical information. Education ranged from 9–14 years of schooling (11.3 ± 1.7), and the months since TBI onset ranged from 12–262 months (106.9 ± 79.4). Most patients sustained their head injuries in traffic accidents. Severity of injury was assessed by duration of post traumatic amnesia, range was 3 to 150 days. The comparison group consisted of 12 normal individuals (all male, 29.8 ± 6.3 years) who were matched to the TBI group with respect to age and gender. This study was approved by the Committee on Medical Ethics of Kyoto University and was performed in accordance with The Code of Ethics of the World Medical Association. Written informed consent was obtained after a complete description of the study to the participants.

Measures

Neuropsychological assessment: Patients with DAI completed a standardized comprehensive neuropsychological test battery. Basic cognitive assessment was performed by the Wechsler Adult

Intelligence Scale-III (WAIS-III). Full IQ, verbal IQ, and performance IQ was scored based on the results from the subtests. For the WAIS-III, four IQ indices (Verbal Comprehension, Perceptual Organization, Working Memory, and Processing Speed) were calculated to assess more specified domains of cognitive functions.

*Reading the Mind in the Eyes test (Eyes test)*¹⁴⁾: The Japanese version of the Eyes test was used for assessing participants' ability of theory of mind. Participants were presented with a series of 36 photographs of eyes and asked to indicate which of four simultaneously presented words best described the mental state of the photographed person (see Figure 1 for example). Participants were asked to choose the word they considered the most suitable. They were instructed to perform the task as quickly as possible, but were not timed. Participants could also make sure of the meanings of the mental state words presented in the test by referring to a prepared glossary. Participants received one point for each correct answer.

MRI acquisition and pre-processing

All participants underwent MRI scans on a 3T whole-body scanner with a 40 mT/m gradient and a receiver-only 8-channel phased-array head coil (Trio, Siemens, Erlangen, Germany). The scanning parameters of the three-dimensional magnetization-prepared rapid gradient-echo (3D-MPRAGE) sequence were as follows: TR = 2000 ms, TE = 4.38 ms, TI = 990 ms, FOV = 225 × 240 mm, matrix = 240 × 256, resolution = 0.9375 × 0.9375 × 1.0 mm³, and 208 total axial sections without intersection gaps. MRI data were processed and analyzed using an extension of statistical parametric mapping 8 (SPM8; Wellcome Department of Imaging Neuroscience, London, UK); VBM8.1 toolbox written by Gaser (<http://dbm.neuro.uni-jena.de/vbm>) running in Matlab 2012b (Math Works, Natick, MA, USA). A unified segmentation model¹⁵⁾ (Ashburner and Friston, 2005) was used, which combined both normalization and segmentation parameters in a single generative model. The outputs from the segmentation procedure were rigid-body aligned segmentations for each subject. The GM, white matter (WM) and cerebrospinal fluid (CSF) segmentations were input into DARTEL (diffeomorphic anatomical registration through exponentiated lie algebra¹⁶⁾ in SPM8. DARTEL is a high-dimensional, diffeomorphic registration algorithm that has performed well in a comparison of registration algorithms¹⁷⁾. DARTEL creates an

average template from the data, and the images are registered to this space. Therefore, in an additional step, the DARTEL-transformed to Montreal Neurological Institute (MNI) space. The output images of GM, WM, and CSF partitions were resliced into $1 \times 1 \times 1$ mm voxels. The voxel values of segmented and normalized GM images were multiplied (modulated) by the Jacobian determinants obtained from non-linear normalization steps. The resultant GM images were smoothed with Gaussian kernels of 12 mm full width at half maximum, on which all analyses were performed.

Data analyses

Cognitive task performance: Independent sample t-tests were applied to identify group differences on Eyes test. Data were analyzed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $p < 0.05$.

Regional GM reductions in patients relative to controls: To identify the brain regions where patients with DAI showed GM reductions relative to controls, a two-sample t-test was undertaken in SPM8. The effect of age was excluded from the data as a nuisance covariate. A liberal statistical threshold of $p < 0.001$ (uncorrected) was applied. MNI coordinates were transformed into Talairach coordinates¹⁸⁾ using the mni2tal.m Matlab script written by Matthew Brett

(<http://imaging.mrcmbu.cam.ac.uk/imaging/MniTalairach>).

Correlation of neuropsychological tests scores with GM volume: To explore the relationship between GM volume and neuropsychological tests scores, representative clusters which were still significant with a more conservative threshold of $p < 0.05$ (FWE) with the extent threshold of 100 voxels were selected. Each participants' GM density data of these clusters (eigenvariates) were extracted using the Volume Of Interest (VOI) function in SPM8. Correlation analyses between extracted GM density data and each neuropsychological test score were performed using SPSS. The statistical significance level was defined as $p < 0.05$ for these correlation analyses. Because of the exploratory nature of this study, multiple comparison correction was not applied.

Results

Cognitive task performance

Basic neuropsychological assessment: Table 2 shows mean, standard deviation, and the standard scores

for IQ and IQ index by WAIS-III. Patients with DAI had IQ scores approximately over one standard deviation (SD) below the mean in the standard scores. Mean full IQ in the patients with DAI was 79.0 ± 19.0 , with a reduction of all IQ index scores. Among IQ index scores, only the processing speed index was less than over 2SD from standard scores.

ToM task: An independent sample t-test revealed that the patient group performed significantly worse (mean accuracy $53.6 \pm 9.2\%$) than the control group (mean accuracy $63.3 \pm 9.4\%$) on the Eyes test ($t = -2.397$, $p < 0.05$). There were no significant correlations between the Eyes test scores and demographic variables such as age, sex, and education level in DAI patients. There were no significant correlations between the Eyes test scores and either injury severity or time from onset.

Regional GM reductions in patients relative to controls

The patients with DAI exhibited GM reductions in wide areas that contained mainly the temporal lobe, cingulate gyrus, thalamus, basal ganglia, insula, and cerebellum (uncorrected, $p < 0.001$) (Fig. 2). The left parahippocampal gyrus, bilateral amygdala, left insula, right putamen, and right thalamus were still significantly detected with FWE ($p < 0.05$) with the 100 voxel extent threshold (Fig. 3).

Correlation analyses for GM volume and cognitive scores

The GM density data were extracted from the six clusters in the DAI group: the left parahippocampal gyrus, bilateral amygdala, left insula, right putamen, and thalamus. We confirmed simple correlation coefficients between the two scores of cognitive tasks: processing speed index score of WAIS-III, the Eyes test, and GM. For the IQ index scores, only the processing speed index was less than over 2SD compared to standard mean score, indicating impairment of this ability. Significant correlations were found between the processing speed index score of WAIS-III and GM density of the right thalamus ($r = 0.682$, $p = 0.03$) (Fig.4), and the score of the Eyes test and the left amygdala ($r = 0.69$, $p = 0.027$) (Fig.5).

Discussion

In the present study, we investigated the relationship between GM abnormalities and cognitive impairments in patients with DAI using the VBM technique. Our study revealed that volume reductions

in some subcortical areas were correlated with cognitive impairments. In the neuropsychological test, participants were impaired in both the basic and social cognition tasks. The main finding was that impairment in processing speed was correlated with GM volume reduction in the right thalamus, while impairment in social cognition was correlated with GM volume reduction in the left amygdala.

Neuropsychological assessment revealed that patients with DAI showed reduction of IQs and IQ index scores. Among the IQ index scores, the processing speed index score was low over 2SD compared to the standard score. Processing speed has been most frequently investigated in TBI subjects, where impairments in this ability have been repeatedly reported ^{19) 20)}. With respect to social cognition, the result of the Eyes test revealed that the ability of ToM was significantly impaired in patients with DAI compared to normal controls. This finding is consistent with previous reports using the Eyes test and other ToM tasks in TBI subjects ^{21) 22) 23) 24)}. However, the injury types of these subjects were focal lesions or mixed type of focal lesions and DAI. Our results suggest that patients with only DAI can also show impairment in ToM, similar to patients with focal lesions.

Our results of brain volume reductions in patients with DAI were largely in accordance with earlier VBM studies, with changes in a variety of central subcortical areas ^{10) 11)}. Although DAI was originally defined as axonal injury, GM volume reductions have also been found in a variety of regions. In our data, GM volume reductions were found in one side such as right thalamus or left amygdala with a conservative threshold of $p < 0.05$ (FWE). In DAI, axonal injury occurs diffusely and bilaterally due to shearing forces by acceleration, deceleration, or rotation of the brain. In fact, we found regional GM volume reduction bilaterally with liberal threshold of $p < 0.001$ (uncorrected). As our sample size was small, it might be that GM volume reductions occur in one side as a result of differentiation of cause of injury for each subjects. Nevertheless, our findings suggest that such reductions could have effects on neuropsychiatric sequelae, in line with previous studies.

In the correlation analysis, the right thalamus GM volume was positively correlated with the score of processing speed index in WAIS-III in the patient group. Bilateral thalamus volumes were previously reported to be associated with task performance of processing speed in patients with DAI ²⁵⁾. The thalamus consists of cortico-striato-thalamic ‘loops’, which control cognitive processes ²⁶⁾. Dysfunction of these neural circuits may affect task performance of processing speed in patients with DAI. In our study, only the right thalamus volume correlated with the score of processing speed, it would be bilateral

thalamus volume associate with processing speed in large sample. Future studies should include large number of subjects.

The left amygdala volume was positively correlated with the score of Eyes test in the patient group. The neural basis of social cognition is thought to be the network that links the areas of the social brain, including the medial prefrontal cortex, superior temporal gyrus, amygdala, and cingulate cortex²⁷⁾²⁸⁾. More specifically, the neural network that links the orbitofrontal cortex with regions adjacent to the amygdala is considered to be involved in emotion perception²⁹⁾³⁰⁾. The Eyes test is frequently used as a ToM task that measures the ability of social emotion perception. Our results showed that volume reduction of the amygdala caused dysfunction of social emotion perception in patients with DAI, as this area plays an important role in emotion perception in social contexts. Furthermore, the left amygdala volume reduction might correlated with this ability because of subjects have to use verbal function to perform the Eyes test that were asked to choose the word they considered the most suitable.

Previous studies have indicated that some basic cognitive impairments correlate with specific GM alterations in patients with DAI. However, no studies have investigated the correlation between social cognition and specific brain alterations. Here, we revealed such a relationship as a neural basis of impairment in social cognition in patients with DAI. These findings suggest that brain morphometry techniques would be useful for finding potential biomarkers for post-traumatic neuropsychological functions. Further, our data suggest that in addition to routine clinical assessments of basic cognitive abilities, assessing social cognition, especially non-verbal ToM (measured by the Eyes test), will be informative. The relatively small sample size and the range of damage severity are potential limitations of this study. Further, for correlation analyses the *p* values were not corrected for multiple comparisons. Finally, we focused on structural alterations in this study. Nevertheless, functional abnormalities are also found in the brains of patients with DAI. Future studies combining structural and functional neuroimaging techniques are warranted to further elucidate the neuropathological basis of ToM impairment in patients with DAI.

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Table 1

Demographic and clinical characteristics of subjects.

	DAI (N=10)		NC (N=12)		Statistics p
	Mean	SD	Mean	SD	
Age (years)	30.8 (19-47)	10.5	29.8 (21-57)	6.3	ns
Gender (male/female)	m:10		m:12		
Handedness (left/right)	r:10		r:12		
Education (years)	11.3	1.7	15.5	1.5	<0.01
Age of onset (years)	21.8	8.7			
Month from onset	106.9	79.4			
Severity (PTA days)	within 7days: 1 within 90 days: 8 within180 days: 1				
Cause of injury	traffic accident: 9 fall: 1				

Abbreviations: DAI: diffuse axonal injury, NC: normal control, PTA: post traumatic amnesia, SD: standard deviation.

Table 2

Basic neuropsychological assessment

	DAI (N=10)		Standard score	
	Mean	SD	Mean	SD
FIQ	79.0	10.9	100	15
VIQ	82.4	12.9	100	15
PIQ	76.6	10.4	100	15
VC	82.4	13.5	100	15
PO	82.7	11.8	100	15
WM	80.7	13.6	100	15
PS	62.6	13.6	100	15

Abbreviations: FIQ: full intelligence quotient, VIQ: verbal intelligence quotient, PIQ: performance intelligence quotient, VC: verbal comprehension, PO: perceptual organization, WM: working memory, PS: processing speed, DAI: diffuse axonal injury, SD: standard deviation.

Figure 1

Joking

insisting

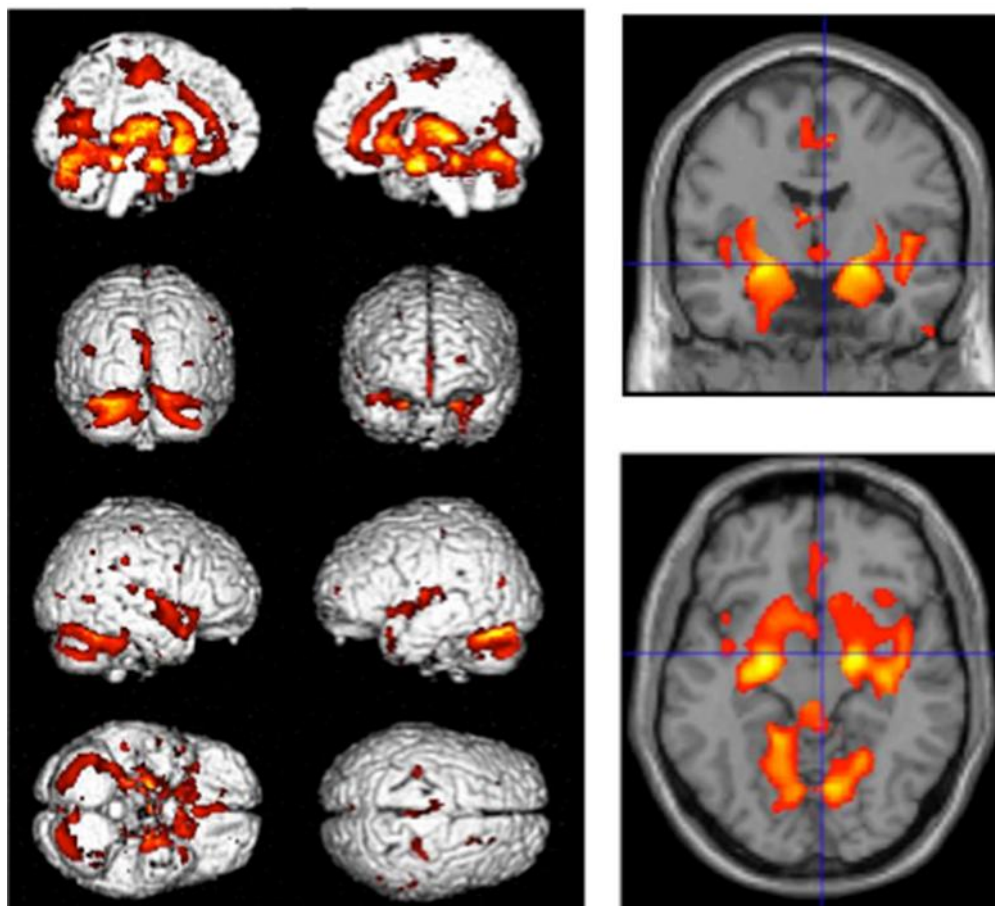


amused

relaxed

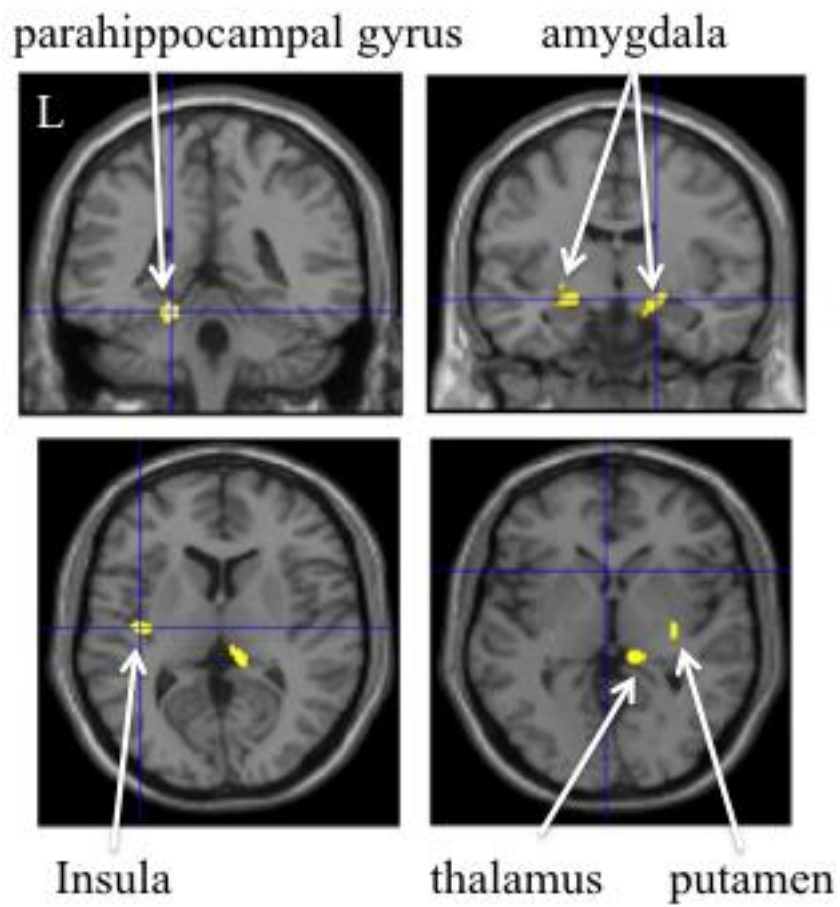
Example of an item in the Eyes test.

Figure 2



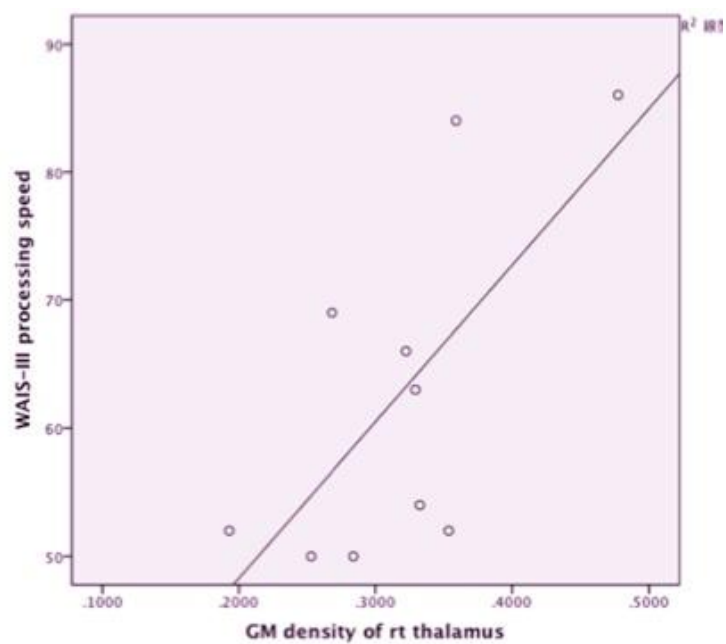
Areas of significant gray matter concentration reduction in patients with DAI compared with normal controls; uncorrected $p < 0.01$. Patient with DAI showed reduced gray matter volume mainly in the central subcortical areas.

Figure 3



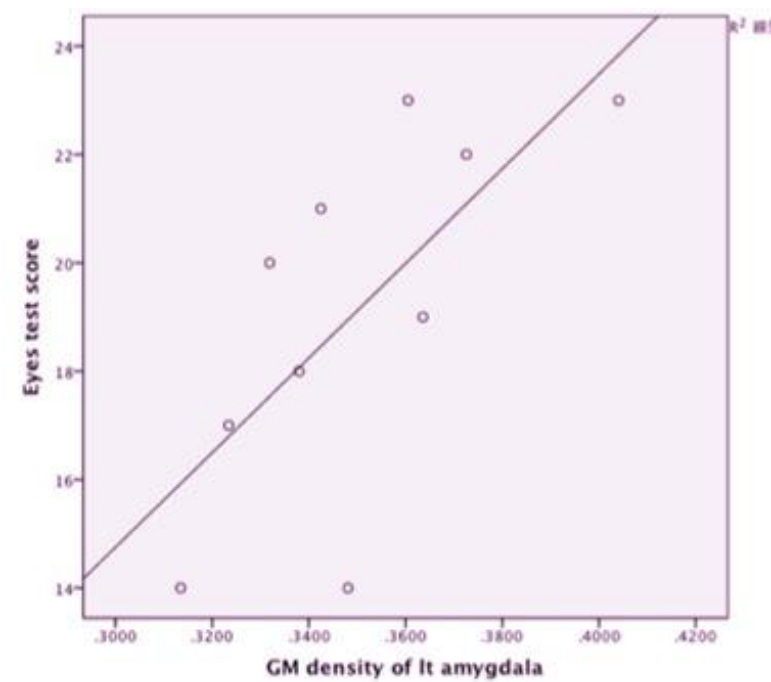
Areas of significant gray matter concentration reduction in patients with DAI compared with normal controls; FWE $p < 0.05$, extent threshold = 100 voxels.

Figure 4



Correlation between the processing speed IQ index score and gray matter density of right thalamus.

Figure 5



Correlation between the score of the Eyes test and grey matter density of left amygdala.