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Original article

Fiber tracking of white matter integrity connecting the mediodorsal nucleus of the thalamus and the prefrontal cortex in schizophrenia: A diffusion tensor imaging study

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Abstract

The goal of this study was to detect abnormalities in white matter integrity connecting the mediodorsal nucleus of the thalamus and the prefrontal cortex using fiber-tracking technique. Diffusion tensor imaging was acquired in 20 patients with schizophrenia and 20 normal comparison subjects. Fiber tracking was performed on the anterior thalamic peduncle, and the tractography was used to determine the cross-sectional area, mean fractional anisotropy, and standard deviation of fractional anisotropy for every step separately in the right and left hemispheres. Compared with normal subjects, patients showed a significant reduction in the cross-sectional area of the left anterior thalamic peduncle. There were no significant differences for the mean fractional anisotropy bilaterally between the two groups, but significant differences for the standard deviation of fractional anisotropy in both hemispheres. Reduction in the cross-sectional area of the left anterior thalamic peduncle suggests the presence of the failure of left-hemisphere lateralization. In schizophrenic patients a significant increase of the standard deviation of fractional anisotropy raise the possibility that the inhomogeneity of white matter integrity, which is densely or sparsely distributed by site. These findings might provide further evidence for disruption of white matter integrity between the thalamus and the prefrontal cortex in schizophrenia.

Keywords: Diffusion tensor imaging; Tractography; Fiber tracking; Schizophrenia; Fractional anisotropy; MRI

1. Introduction

Diffusion tensor imaging is a non-invasive method of measuring the diffusion phenomenon of water molecules in vivo. In the cerebral white matter, diffusion in the same direction as nerve fibers is unrestricted, whereas diffusion perpendicular to nerves fiber is restricted. By qualifying and quantifying the magnitude and direction of water diffusion in the white matter, it is possible to detect structural abnormalities in the nerve fibers [17,30].

Research on the cerebral white matter of schizophrenia patients using diffusion tensor imaging was first reported in 1998 by Buchsbaum et al. [5]. These researchers used magnetic resonance imaging and positron emission tomography to describe abnormalities of the white matter region in the frontal lobe and the anterior limb of the internal capsule [5]. It also became clear that, as a result of comparing a schizophrenic patient group with a healthy subject group, the former did not show a decrease in the volume of the cerebral white matter [20], but showed a decline in diffusion anisotropy that indicated structural abnormalities of the white matter integrity over a broad region [1,6,20,21]. Reduced diffusion anisotropy in the white matter region such as this is an indication of structural abnormalities in the integrity of the white matter, which is responsible for neural connectivity among the different brain regions. It supports findings obtained in research that have adopted a molecular biological approach targeting myelin and oligodendrocyte, using postmortem brains [12,13,31]. Regarding a decline in diffusion anisotropy

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in specific neuronal tract, abnormalities at the following sites have been reported: in the corpus callosum that connects the right and left hemispheres [1,6]; the uncinate fasciculus that connects the frontal lobe and the temporal lobe within the ipsilateral hemisphere [8,18,24]; the arcuate fasciculus that connects the frontal lobe and the parietal lobe [8]; the superior longitudinal fasciculus [6]; the cingulate fasciculus [19]; and the middle cerebellar peduncles [23]. It is also reported that fractional anisotropy in the left frontal white matter and middle cerebellar peduncles of schizophrenic patients are correlated with the dosages of antipsychotics [21,23]. These findings were obtained by analytical methods such as the region-of-interest technique (ROI), and voxel-based morphometry (VBM), and chiefly report on abnormalities of the neuronal tract that are primarily responsible for cortico-cortical connections. Recently diffusion tensor imaging studies using tractography revealed structural abnormalities of white matter integrity in the corpus callosum [26], the left uncinate fasciculus [27], and the left inferior longitudinal fasciculus [2]. Jones et al. [14,15] reported that reduction of fractional anisotropy was seen in the uncinate, superior longitudinal, and inferior fronto-occipital fasciculi, and the cingulum as compared with age-matched comparison subjects using tractography, but the difference was observed in very young schizophrenic patients, and it diminished with increasing age. On the other hand, postmortem and magnetic resonance imaging studies have revealed structural abnormalities and volume reductions in the thalamus and prefrontal cortex in schizophrenia [9,10,16,28,31]. Interestingly, several diffusion tensor imaging studies have shown abnormalities in the anterior limb of the internal capsule, suggesting disruption of white matter integrity between the thalamus and the prefrontal cortex involved in the pathophysiology of schizophrenia [5,6,7,29]. Therefore, we sought to investigate structural abnormalities in white matter integrity of the anterior thalamic peduncle connecting the mediodorsal nucleus of the thalamus and the prefrontal cortex.

The goal of this study was to detect structural abnormalities in white matter integrity of the anterior thalamic peduncle using fiber-tracking technique and the tractography (tractography-based ROI).

2. Materials and methods

A total of 20 patients (11 males and 9 females) who met the DSM-IV-TR criteria of schizophrenia and 20 normal comparison subjects (11 males and 9 females) participated in this study. All subjects gave written informed consent for study participation after a full explanation of procedures. Exclusion criteria for all subjects included a history of convulsive disease, head injury, and a history of alcohol and substance dependence. In addition, the following were excluded as study subjects: those with diabetes and hypertension; those who had undergone electroconvulsive therapy; and those whose brain magnetic resonance imaging scans already showed clear abnormalities. All subjects included in this study were right-handed, and no significant differences in age or sex were seen between the schizophrenic patients and comparison subjects. Demographic characteristics of schizophrenic patients and normal comparison subjects who participated in the present study are shown in Table 1. The mean duration of illness in the patients was 7.1 ± 6.4 years, and the mean dosage of antipsychotics was 270 ± 232 mg/day (chlorpromazine equivalents) [32]. Prior to implementing this study, we obtained the approval of Kyorin University School of Medicine's Ethics Committee.

Diffusion tensor imaging was conducted on a 1.5-T Intera Achieva Nova Dual (Philips Electronics). The image-taking conditions were set as follows: TR 2900 ms, TE 60 ms, NEX (the number of excitations) 6, FOV (field of view) 240 mm, voxel size $1.88 \times 1.88 \times 5.0\ mm^3$, image matrix 128×128, slice thickness 5 mm, 25 slices, MPG 6 directions ([0.3333, 0.6666, −0.6666], [0.6666, 0.3333, 0.6666], [−0.6666, 0.6666, 0.3333], [0.7071, 0.7071, 0], [0, 0.7071, 0.7071], [−0.7071, 0, 0.7071]), b value $1000\ s/mm^2$. Fractional anisotropy measures were calculated as described by Basser et al. [3]. The present study targeted the anterior thalamic peduncle, which is a neuronal tract that runs from the mediodorsal of the thalamus towards the prefrontal cortex (mainly the dorsolateral prefrontal cortex) by way of the anterior limb of the internal capsule. As for setting the region of interest in the target nervous bundle, we first established the cross-section of the internal capsule in the coronal section that includes the anterior commissure as the starting region for fiber tracking, and established the coronal section that includes the anterior genu of the corpus callosum as the ending region for fiber tracking. Each of these starting regions and ending regions in the right and left hemispheres were adjusted separately back and forth within a range of 8 mm, after which fiber tracking was performed. The sites where the largest number of streamlines could be tracked were finally selected as the starting and ending regions for the fiber tracking, and, based on these, tractography was applied (Fig. 1). In identifying the fiber bundles in the regions of interest, we dispersed the

Table 1
Demographic characteristics of schizophrenia patients and normal comparison subjects.

Characteristics	Comparison subjects		Schizophrenia patients		Statistical analysis		
	Mean	SD	Mean	SD	t	df	p
Age (years)	32.5	7.4	32.9	8.6	−0.14	38	0.891
	N		N		χ	df	p
Sex					0.00	1	1.000
Male	11		11				
Female	9		9				
Antipsychotics							
Risperidone			7				
Olanzapine			4				
Aripiprazole			3				
Quetiapine			1				
Others			3				
None			3				

Others include perphenazine, haloperidol, and chlorpromazine.
One out of 20 schizophrenia patients was receiving two antipsychotics.