Psychiatry Research: Neuroimaging 222 (2014) 52–59

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Cerebral white matter abnormalities and their associations with negative but not positive symptoms of schizophrenia

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ARTICLE INFO

Article history:
Received 1 August 2013
Received in revised form
11 December 2013
Accepted 12 February 2014
Available online 19 February 2014

Keywords:
Schizophrenia
Diffusion tensor imaging (DTI)
Tract-Based Spatial Statistics (TBSS)
Fractional anisotropy (FA)
Negative symptoms
Frontal lobe

ABSTRACT

Although diffusion tensor imaging (DTI) studies have reported fractional anisotropy (FA) abnormalities in multiple white matter (WM) regions in schizophrenia, relationship between abnormal FA and negative symptoms has not been fully explored. DTI data were acquired from twenty-four patients with chronic schizophrenia and twenty-five healthy controls. Regional brain abnormalities were evaluated by conducting FA comparisons in the cerebral and each lobar WMs between groups. Focal abnormalities were also evaluated with a voxel-wise tract specific method. Associations between structural WM changes and negative symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS). The patient group showed decreased FA in the cerebrum, especially in the frontal lobe, compared with controls. A voxel-wise analysis showed FA decreases in almost all WM tracts in schizophrenia. Correlation analyses demonstrated negative relationships between FA in the cerebrum, particularly in the left hemisphere, and SANS global and global rating scores (Anhedonia–Asociality, Attention, and Affective-Flattening), and also associations between FA of left frontal lobe and SANS global score, Anhedonia–Asociality, and Attention. This study demonstrates that patients with chronic schizophrenia evince widespread cerebral FA abnormalities and that these abnormalities, especially in the left hemisphere, are associated with negative symptoms.

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1. Introduction

Symptoms of schizophrenia are thought to arise from inadequate communication between brain regions, particularly the frontal and temporal lobes. Recent postmortem and genetic studies in schizophrenia provide evidence demonstrating myelin abnormalities that might affect this communication (Hakak et al., 2001; Katsel et al., 2005). These findings support the hypothesis that deficits in structural brain connectivity are evident in schizophrenia and, importantly, that they may constitute a trait maker of pathology.

Previous diffusion tensor imaging (DTI) studies have observed both local and widespread fractional anisotropy (FA) reductions in white matter (WM) regions in schizophrenia compared with healthy control subjects (HC) (for review, see Kubicki et al. (2007)), and these abnormalities have been attributed to disruptions in connectivity. Although WM abnormalities have been frequently reported in the schizophrenia literature, their clinical significance remains less studied.

It is thought that negative symptoms become more pronounced in the chronic stage of illness (Tandon et al., 2009). Negative symptoms include flattened affect, social withdrawal, and attentional deficits, and the severity of negative symptoms is associated with impairment in various cognitive functions such as memory, learning, and executive function (Bilder et al., 2000; Sanfilipo et al., 2002). Negative symptoms are also strongly associated with social dysfunction (Tsai et al., 2010) and poor long-term outcome (Javitt, 2001). It is therefore important to elucidate the pathology of negative symptoms in chronic schizophrenia.

Negative symptoms are hypothesized to be the result of structural brain deficits (Crow, 1980). Considering the presumed

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http://dx.doi.org/10.1016/j.pscychresns.2014.02.007
0925-4927 Published by Elsevier Ireland Ltd.

Table 1
Demographic and clinical characteristics of the study groups.

Variable	SZ group (n=24) Mean (SD)	HC group (n=25) Mean (SD)	df [a]	t test	p
Age, mean (SD) [range], years	44.4 (9.7) [22–55]	40.4 (11.4) [21–55]	47	1.31	0.20
Sex, No. M/F	24/0	25/0			
Handedness[b]	0.71 (0.25)	0.78 (0.18)	45	1.10	0.28
Socioeconomic Status[c]					
Subject's	3.5 (1.1)	2.5 (1.2)	46	2.91	0.01*
Parental	2.6 (1.2)	2.7 (1.3)	45	0.28	0.78
WRAT-3: reading score	97.6 (12.1)	103.5 (11.6)	43	1.68	0.10
Symptom onset, years	23.9 (5.9)	NA			
Duration of illness, years	20.5 (10.3)	NA			
Antipsychotic medication dosage (mg/day)[d]	346.9 (265.5)	NA			
Neuroleptics, no. of patients TYP/ATYP/Overlap/non-medication	**2/17/2/3**	NA			
Number with/without family history of first-degree relatives with psychosis[e]	3/17	NA			
SANS global score	11.9 (7.0)	NA	(n=23)		
SAPS global score	9.3 (4.1)	NA	(n=23)		

Abbreviations: SZ, schizophrenia; HC, healthy control subject; WRAT-3, wide range, Achievement Test-3; SANS, the Scale for the Assessment of Negative Symptoms; SAPS, the Scale for the Assessment of Positive Symptoms; NA, data not applicable; **TYP/ATYP, typical/atypical antipsychotics**

* $p < 0.05$.

associations between negative symptoms and various cognitive dysfunctions, we speculate that negative symptoms may be associated with abnormalities in multiple brain regions in chronic schizophrenia. Indeed, previous neuroimaging studies have reported associations between negative symptoms and abnormal gray and white matter volumes in several brain regions, such as the prefrontal cortex (Ho et al., 2003; Wible et al., 2001), thalamus (Yoshihara et al., 2008), precentral cortex, and inferior parietal gyrus (Premkumar et al., 2009), in schizophrenia. These findings led us to investigate WM connectivity abnormalities in various brain regions and their associations with negative symptoms in chronic schizophrenia.

With respect to DTI studies, only a small number of studies have identified associations between negative symptom severity and FA abnormalities in patients with schizophrenia. Such studies, however, focused on either localized WM regions (Wolkin et al., 2003) or specific tracts (Mitelman et al., 2007; Kubicki et al., 2008; Whitford et al., 2010). We believe that it is important to identify which WM regions are most associated with negative symptoms at each anatomical level (i.e., whole brain WM, regional WM, a specific tract), in order to understand further the pathology of negative symptoms in schizophrenia. To the best of our knowledge, there are no studies that have investigated structure–symptom relationships at each of these anatomical levels simultaneously, as is proposed here.

Previous DTI studies of schizophrenia have also reported associations between positive symptoms and localized WM or tracts (Fujiwara et al., 2007; Skelly et al., 2008; Whitford et al., 2010, 2012; Lee et al., 2013). These findings are, however, inconsistent. For example, some previous studies have shown positive associations between positive symptoms and structural deficits in the regional WM, while others have detected negative relationships between them. Therefore, it is also important to explore associations between positive symptoms and WM at each anatomical level to better understand the neurobiology of positive symptoms in schizophrenia.

Based on the aforementioned postmortem, structural, DTI, and cognitive findings, the goal of the current study was to detect abnormalities in WM integrity and their association with negative symptoms in chronic schizophrenia. The Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006) approach was used in this study. In addition to a standard voxel-based approach, TBSS, when combined with WM atlases, also allows for region of interest (ROI) analysis, where WM of either the entire hemisphere, entire lobe, or an individual fiber bundle can be analyzed (Karlsgodt et al., 2009).

In the current study, we first evaluated FA abnormalities in cerebral and lobar WM in patients with chronic schizophrenia compared with healthy controls (HC). Second, a voxel-wise comparison was conducted to evaluate FA abnormalities along all WM tracts. Finally, relationships were evaluated between WM abnormalities in cerebrum, each lobe, and each tract and clinical symptoms, particularly negative symptoms, in schizophrenia.

2. Methods

2.1. Subjects

Participants comprised 24 patients with chronic schizophrenia and 25 HC. Participants' recruitment and detailed study criteria were described in our previous report (Choi et al., 2011). Groups were matched in age, handedness, and parental socioeconomic status or premorbid IQ derived from the Wide Range Achievement Test-3 reading scores (Wilkinson, 1993). The mean global scores of the Scales for the Assessment of Negative Symptoms (SANS) and Positive Symptoms (SAPS) (Andreasen, 1983, 1984) were $11.9 \pm 7.0/9.3 \pm 4.1$. Demographic and clinical data are presented in Table 1. Of all patients included in this study, two received only typical antipsychotics, 17 patients received only atypical antipsychotics, two received both typical and atypical antipsychotics, and three patients received no antipsychotics at the time of the scan. This study was approved by the local IRB at both the VA and Brigham and Women's Hospital. Written informed consent was obtained from all subjects before study participation.

2.2. MRI protocol

All subjects were scanned on a 3T GE Echospeed system, using an echo planar imaging (EPI) DTI sequence. A double echo sequence with an eight-channel coil was used to reduce eddy-current and EPI (echoplanar imaging) spatial related distortions. Fifty-one noncolinear diffusion directions (B=900) and nine baseline scans (B=0) were acquired with the following scan parameters: repetition time 17,000 ms, echo time 78 ms, field of view 24 cm, 144×144 encoding steps, and 1.7 mm slice thickness. Eighty-five axial slices spanning the entire brain were collected for each subject.

2.3. Image processing

After reconstruction, diffusion-weighted images were transferred to a LINUX workstation, on which FA and trace maps of the diffusion tensor were calculated.

In this study, TBSS 1.2 (Smith et al., 2006, 2007) was used. FA images were first reoriented using rigid body transformation. Next, the reoriented images were transformed into FMRIB58_FA standard space using a non-linear registration of FMRIB's Nonlinear Image Registration Tool. A mean FA image was then created by averaging all the registered FA images, and a group skeleton, which represents the