Schizophrenia Research 111 (2009) 78–85

Contents lists available at ScienceDirect

Schizophrenia Research

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

Reduced white matter integrity correlated with cortico–subcortical gray matter deficits in schizophrenia

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ARTICLE INFO

Article history:
Received 2 December 2008
Received in revised form 3 March 2009
Accepted 5 March 2009
Available online 10 April 2009

Keywords:
Basal ganglia–thalamocortical circuits
Diffusion tensor imaging
Disconnection hypothesis
Language processing networks
Tract-based spatial statistics
Voxel-based morphometry

ABSTRACT

Background: The pathology of schizophrenia is thought to involve multiple brain regions and the connections among them. Although a number of MRI studies have demonstrated gray matter reductions and abnormal white matter integrity in schizophrenia, to date no study has investigated their association in the whole brain.
Methods: Twenty-seven schizophrenia patients and 33 healthy controls were recruited. Voxelwise group comparison of white matter fractional anisotropy (FA) was performed using tract-based spatial statistics (TBSS). Comparison of gray matter concentration (GMC) was performed using voxel-based morphometry (VBM). Voxelwise correlational analyses were performed for patients inside a significant GMC reduction mask created by VBM, using simple regression models with mean FA values of each significant TBSS cluster as explanatory variables.
Results: TBSS revealed FA reduction in left prefrontal and occipital regions in the patients. Mean FA values of both areas revealed significant correlation with gray matter reduction in multiple cortical and subcortical areas, with overlapping but different patterns.
Conclusions: Voxelwise correlational analysis of white and gray matter pathology, as performed here, further elucidated the pathophysiology of schizophrenia, and provided a novel view of the "disconnection hypothesis" of schizophrenia.

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1. Introduction

Volumetric magnetic resonance imaging (MRI) studies on patients with schizophrenia have demonstrated gray matter reductions in several cortical and subcortical areas, including the prefrontal cortex, the superior temporal gyrus (STG), medial temporal lobe structures, the thalamus, and basal ganglia (Shenton et al., 2001; Suzuki et al., 2005). Considering this widespread pathology, it is reasonable to hypothesize that the nature of this disorder resides in the disrupted connectivity of the networks among these cortical and subcortical gray matters. Such a "disconnection hypothesis" (Friston, 1998) of schizophrenia was originally shown to be "functional" disconnectivity (Frith et al., 1995), and anatomical substrates of such disconnectivity were postulated to exist at the synaptic level in gray matter (McGlashan and Hoffman, 2000; Selemon and Goldman-Rakic, 1999), rather than in the white matter tracts that wire distant gray matter regions.

Diffusion tensor imaging (DTI) provides information about white matter tracts and their organization based on water diffusion (Basser et al., 1994). DTI is thought to be more sensitive to subtle abnormalities in white matter than anatomical MRI. Fractional anisotropy (FA) is the most commonly used index and its reduction implies decreased white matter tract integrity. DTI studies on schizophrenia that examined FA in defined regions of interest, though not

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doi:10.1016/j.schres.2009.03.010

completely consistent, reveal subtle FA reductions in several areas including frontal white matter, the corpus callosum (CC), and the cingulum bundle (Kanaan et al., 2005; Kubicki et al., 2007; Walterfang et al., 2006). These findings suggest that regional white matter pathologies are also anatomical substrates in the pathology of connectivity in schizophrenia.

As these gray and white matter abnormalities are subtle and multiregional, it is necessary to explore such abnormalities in the whole brain. Voxel-based morphometry (VBM; Ashburner and Friston, 2000) is a fully automated structural MRI analysis method that can reveal the patterns of regional gray matter volume alterations at the whole brain level, without any specific hypotheses about search areas. Consistent findings have been reported in VBM studies on schizophrenia (Honea et al., 2005). With respect to white matter pathologies, VBM style analysis has also been applied to DTI data (Buchsbaum et al., 2006; Kyriakopoulos et al., 2008), and the results show FA reductions in diverse areas. However, the methodological pitfalls of VBM style analysis seem to be more problematic when it is applied to DTI data; misregistration of white matter tracts between subjects can mistakenly be interpreted as a FA difference in the same tract. A smoothing procedure is necessary to compensate for such misregistration; however, the smoothing kernel sizes substantially affect the results of FA analyses (Jones et al., 2005). A recently developed technique, tract-based spatial statistics (TBSS; Smith et al., 2006), maps each subject's DTI data on a common white matter tract center ('skeleton') and does not need smoothing. This technique is considered more robust and suitable for whole brain DTI data analysis.

As gray and white matter both constitute networks, with gray matter as nodes and white matter as wiring, their abnormalities in schizophrenia may be associated with each other. To date, only a limited number of studies have attempted to elucidate the covariation of gray and white matter abnormalities: Hulshoff Pol et al. (2001) used VBM to demonstrate gray matter volume reductions in several cortical and subcortical areas and volume increases in the caudate and globus pallidus in schizophrenia. They also applied VBM to white matter in the same sample, and revealed white matter volume reductions in the CC, the internal capsule, and the anterior commissure in schizophrenia (Hulshoff Pol et al., 2004). Moreover, they revealed correlations between gray matter volume changes and white matter volume reductions. Among the DTI studies, Douaud et al. (2007), using VBM for gray matter and TBSS for DTI data, superimposed both results, visualizing the anatomical association between regional gray matter reduction and FA reduction at the whole brain level. However, to date no study has examined the covariation between gray matter reduction and DTI abnormality in the whole brain using voxelwise correlational analysis.

The present study aimed to elucidate the association between gray matter volume reductions and white matter FA abnormalities by using voxelwise correlational analysis in the whole brain. We hypothesized that regional FA reductions in the patients would have positive correlations with regional gray matter reductions. Considering the network pathology of schizophrenia, as predicted by the "disconnection hypothesis", we expected such associations not only between gray and white matters that are located adjacent to each other, but also between those areas that are distant from each other.

2. Materials and methods

2.1. Subjects

Twenty-seven schizophrenia patients, diagnosed by the patient edition of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al., 1996), were studied. None of the patients had comorbid psychiatric disorders. Antipsychotic medication was prescribed to all patients. The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was used to assess the severity of clinical symptoms. Thirty-three healthy controls matched by age, sex, handedness and education levels with the patient group were recruited. The controls had no history of psychiatric illness as determined by using the non-patient edition of the SCID (First et al., 1998). There was no history of psychotic disorders among their first-degree relatives. Exclusion criteria for all individuals included a history of head trauma, neurological illness, serious medical or surgical illness and substance abuse. After receiving a complete description of the study, all participants gave written informed consent. The study design was approved by the Committee on Medical Ethics of Kyoto University.

2.2. MRI acquisition

The DTI data were acquired using single-shot spin-echo echo-planar sequences and structural MRI data using three dimensional magnetization prepared rapid gradient echo (3D-MPRAGE) sequences, on a 3.0-T MRI unit (Trio; Siemens, Erlangen, Germany) with a 40 mT/m gradient. A generalized autocalibrating partially parallel acquisition algorithm was applied for parallel imaging using a reduction factor of two, 24 additional autocalibrating phase-encoding steps in the center of k-space, and a 75% partial Fourier technique in the phase-encoding direction. Parameters for the DTI were as follows; TE 79 ms, TR 5200 ms, 128×128 matrix, FOV 220×220 mm, 40 contiguous axial slices of 3.0 mm thickness, 12 noncolinear axis motion probing gradient, $b=700$ s/mm^2. To enhance the signal-to-noise ratio, imaging was repeated four times. Parameters for the 3D-MPRAGE imaging were as follows; TE 4.38 ms, TR 2000 ms, inversion time 990 ms, 256×256 matrix, FOV 240×240 mm, 208 axial slices of 1.0 mm thickness. Axial slices were adjusted to be parallel to the anterior commissure–posterior commissure line in each subject.

2.3. Imaging data processing and statistical analysis

2.3.1. TBSS analysis of white matter

DTI data processing was performed using FSL 3.3 (http://www.fmrib.ox.ac.uk/fsl). All DTI source data were corrected for eddy currents and head motion, by registering each data to the first $b=0$ image of the first repetition, with affine transformation. Averaged data of these 4 repetitions were created for each subject. FA maps were calculated by FSL DTIFit. The TBSS program, part of the FSL program, was used for voxelwise statistical analysis of FA data. Briefly, all subjects' FA maps were first co-registered using non-linear registration (Rueckert et al., 1999) to the most 'typical' subject's FA map, which minimized the total amount of warping required for all the subjects. This target FA map was affine-transformed into

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