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Increased diffusivity in gray matter in recent onset schizophrenia is associated with clinical symptoms and social cognition

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ABSTRACT

Introduction: Diffusion weighted MRI (dMRI) is a method sensitive to pathological changes affecting tissue microstructure. Most dMRI studies in schizophrenia, however, have focused solely on white matter. There is a possibility, however, that subtle changes in diffusivity exist in gray matter (GM). Accordingly, we investigated diffusivity in GM in patients with recent onset schizophrenia.
Methods: We enrolled 45 patients and 21 age and sex-matched healthy controls. All subjects were evaluated using the short form of the Wechsler Adult Intelligence Scale, the Positive and Negative Syndrome Scale (PANSS), and the video based social cognition scale. DMRI and T1W images were acquired on a 3 Tesla magnet, and mean Fractional Anisotropy (FA), Trace (TR) and volume were calculated for each of the 68 cortical GM Regions of Interest parcellated using FreeSurfer.
Results: There was no significant difference of FA and GM volume between groups after Bonferroni correction. For the dMRI measures, however, patients evinced increased TR in the left bank of the superior temporal sulcus, the right inferior parietal, the right inferior temporal, and the right middle temporal gyri. In addition, higher TR in the right middle temporal gyrus and the right inferior temporal gyrus, respectively, was associated with decreased social function and higher PANSS score in patients with schizophrenia.
Conclusion: This study demonstrates high sensitivity of dMRI to subtle pathology in GM in recent onset schizophrenia, as well as an association between increased diffusivity in temporal GM regions and abnormalities in social cognition and exacerbation of psychiatric symptoms.

1. Introduction

In the last 30 years, various analytical methods that utilize brain magnetic resonance imaging (MRI) have been developed and used in studies of schizophrenia, as well as in other disorders. Nonetheless, the core pathologic changes within the brain have not been clearly delineated and the majority of findings from MRI studies have shown a great deal of variability with the exception of decreased brain volume and increased ventricular volume (Shenton et al., 2001). Finding core pathologic changes has proven to be extremely difficult in part because of the heterogeneity of demographic and clinical characteristics of subjects and in part because of the limitations of the analytic methods used in neuroimaging.

Various MRI modalities and advanced analytic methods have been developed over the past several years in order to improve precision for detecting and characterizing structural pathology in schizophrenia. There is, for example, an increase in interest in exploring white matter connectivity in schizophrenia using diffusion weighted imaging (dMRI). DMRI is a very sensitive method sensitive to microstructural abnormalities (Beaulieu, 2002; Kanaan et al., 2005) including demyelination, axonal loss, edema, and inflammation (Assaf and Pasternak, 2007). Positive dMRI findings that are frequently reported in schizophrenia include: 1) decreased fractional anisotropy (FA) within fibers connecting prefrontal and temporal lobes, such as cingulum bundle, uncinate fasciculus, corpus callosum, and arcuate fasciculus (Abdul-Rahman et al., 2012; Foong, 2000; Kubicki et al., 2002; Kubicki et al., 2003; Price et al., 2005); 2) correlations between dMRI and clinical characteristics, as for example, the correlations between prefrontal WM anisotropy and negative symptoms, cingulum bundle and executive functions, and uncinate fasciculus FA and declarative episode memory (Kubicki et al., 2007). Moreover, abnormalities in WM are detectable

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in schizophrenia (Guo et al., 2012; Kasai et al., 2003; Quan et al., 2013), in high risk patients (von Hohenberg et al., 2014; Hoptman et al., 2008; Muñoz Maniega et al., 2008), and in patients' non psychotic relatives (Camchong et al., 2009; Knöchel et al., 2012).

To date, most dMRI studies in schizophrenia are focusing on white matter. However, subtle structural GM changes at or before schizophrenia onset have been associated with schizophrenia, and multiple biological processes have been suggested to explain those changes. For example, it is well known that many intrinsic connections exist in GM (Barbas and Pandya, 1989; Tardif and Clarke, 2001). In addition, some studies report that decreases in membrane, axon terminals, dendrites, and dendritic spines are among the causes of decreased GM volume in schizophrenia (Bennett, 2011; Costa et al., 2001; Glantz and Lewis, 2000). T1W imaging has been traditionally used for structural, volumetric analysis. Such measures, however, focus only on the gross, anatomical differences, and thus do not capture micro-structural abnormalities. Microstructural changes (which frequently occur before gross volume changes observed) are related to myelin, cell membranes and intracellular organelles, restricted movement of water molecules, all of which result in a measureable difference in the diffusion of water molecules (Uluğ et al., 1999). Moreover, several studies have also taken advantage of the use of dMRI to investigate microscopic changes in GM, which likely predate any gross, structural changes, in other neurodegenerative diseases such as Alzheimer's disease, Creutzfeldt-Jakob disease and multiple sclerosis (Kincses et al., 2014; Pirko et al., 2007; Weston et al., 2015; Zerr et al., 2009).

The most common measures used in dMRI studies are the magnitude and the anisotropy of the diffusion tensor (Alexander et al., 2007). There are several measures derived from combinations of the eigenvalues (λs) of the diffusion tensor that describe the magnitude of the diffusion including radial diffusivity $\{(\lambda 2 + \lambda 3)/2\}$, axial diffusivity (λ1), and trace (λ1 + λ2 + λ3). According to these definitions, axial and radial diffusivity are apparent diffusivities in the directions parallel and perpendicular to the diffusion tensor, respectively, and trace is the sum of diffusivities in all three directions (Beaulieu, 2002). In white matter, where myelinated axons are organized parallel in bundles, axial diffusivity (aligned with predominant diffusion direction in a given voxel) is more specific to axonal degeneration, radial diffusivity is modulated by myelin, and trace is nonspecific, but a sensitive measure of any ongoing pathology (Alexander et al., 2007; Assaf and Pasternak, 2007; Mori et al., 1999; Song et al., 2005). In gray matter, however, where cell bodies and their processes are predominant components of the tissue, axial and radial diffusivity measures lose their biological meaning. Trace, being sensitive to cellularity, cell necrosis, and edema (Alexander et al., 2011), is thus considered a more appropriate, more robust, and more sensitive measure of diffusivity in gray matter. Accordingly, we chose trace as the main measure of diffusivity in gray matter.

We hypothesized that the amplitude of diffusion would be increased and anisotropy of diffusion would be decreased in gray matter in patients with recent onset schizophrenia compared with healthy controls.

2. Methods

2.1. Subjects

Subjects were enrolled from Asan Medical Center which is a university–affiliated hospital. Patients who were right-handed and those patients who were between the ages of 20–40 years old were eligible for the study. Any patients with diseases that affect the functioning of the brain were excluded. Also, patients were excluded if they were unable to complete neuropsychological testing or the MRI scanning session. Subjects within the patient group had a diagnosis of schizophrenia made by a psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR) criteria, and they also evinced psychotic symptoms such as delusions or hallucinations for <5 years. In addition, subjects in the control group did not have any Axis I psychiatric diagnosis in themselves or in their first-degree relatives based on DSM-IV-TR.

We enrolled 91 subjects, but excluded 15 cases due to poor image quality or incidental brain lesions. We then excluded 10 additional patients because their diagnoses changed to other psychotic disorders such as bipolar disorder when we re-evaluated them 1–6 months after the enrollment. The final dataset consisting of sixty-six subjects (patients: $N = 45$; controls: $N = 21$) was used for the analysis.

Written informed consent was obtained from all subjects. Ethical approval for the study was obtained from the local Institutional Review Board.

2.2. Assessment of symptoms, neurocognition and social cognition

Assessment of symptoms, neurocognition, and social cognition was completed within one week from the date of the MRI examination. All subjects were evaluated using an age and sex adjusted short form of the Wechsler Adult Intelligence Scale (WAIS), which consisted of 6 subtests including digit span, vocabulary, arithmetic, picture arrangement, block design, and digit symbol. Patients' psychiatric symptoms were evaluated by a psychiatrist using the Positive and Negative Syndrome Scale (PANSS).

Social cognition for all subjects was measured by the video based social cognition scale (VISC) (Goh et al., 2008; Jang, 2007). VISC consists of 20 video scripts that present a socially inappropriate situation. Subjects watch the video and record answers to questions about these situations. Each question has a 0–2 scoring scale, with a maximum total score of 40.

2.3. MRI protocol

MR scans were performed with an 8 channel SENSE head coil on a 3 Tesla scanner (Philips Achieva). dMRI images were acquired with an echo planar imaging (EPI) dMRI sequence. One baseline ($b = 0$) image and 32 diffusion gradient directions with $b = 1000$ s/mm^2 were also acquired. Scan parameters were as follow: field of view (FOV): $224 * 224 * 135$ mm, voxel size: $2 * 2 * 3$ mm^3, echo time (TE): 70 ms, flip angle: 90°, repetition time (TR): 5422 ms. Structural T1 MRI images with turbo field echo were acquired and scan parameters were as follow: FOV: $240 * 240 * 170$, voxel size $1 * 1 * 1$ mm^3, TE: 4.6 ms, TR: 9 ms, flip angle: 8°.

2.4. Image processing

dMRI images were upsampled to $1 * 1 * 1$ mm^3 voxel size using Slicer V. 4.4 (Fedorov et al., 2012; http://www.slicer.org). Subsequently, motion and eddy current-induced distortions were corrected using affine registration of all gradient volumes with the first $b = 0$ volume (FLIRT: FMRIB software, oxford, UK) (Jenkinson et al., 2002; Jenkinson and Smith, 2001). To exclude the meninges or CSF, we eroded the boundary voxels of each dMRI image. Diffusion tensors were estimated using in-house software based on weighted-least-squares with an added procedure to correct tensors with negative eigenvalues. We then calculated scalar diffusion measures (FA and Trace [TR]) per each subject.

T1 images were parcellated into discrete anatomical regions using the Desikan-Killiany atlas of FreeSurfer V. 5.3 (Fischl et al., 2002) and all parcellated ROIs ($N = 68$, see supplementary table 1) were used in subsequent analysis. We registered a T1 image into a $b = 0$ baseline image of dMRI using a non-linear registration method, part of the Advanced Normalization Tools (Avants et al., 2011; 2010). We then transformed FreeSurfer parcellated labels into dMRI using the same registration transformation. We calculated the mean for the diffusion measures (FA and TR) for each transformed ROI of each subject.

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