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Abnormal asymmetry of white matter tracts between ventral posterior cingulate cortex and middle temporal gyrus in recent-onset schizophrenia

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ABSTRACT

Introduction: Previous studies have reported abnormalities in the ventral posterior cingulate cortex (vPCC) and middle temporal gyrus (MTG) in schizophrenia patients. However, it remains unclear whether the white matter tracts connecting these structures are impaired in schizophrenia. Our study investigated the integrity of these white matter tracts (vPCC-MTG tract) and their asymmetry (left versus right side) in patients with recent onset schizophrenia.
Method: Forty-seven patients and 24 age-and sex-matched healthy controls were enrolled in this study. We extracted left and right vPCC-MTG tract on each side from T1W and diffusion MRI (dMRI) at 3 T. We then calculated the asymmetry index of diffusion measures of vPCC-MTG tracts as well as volume and thickness of vPCC and MTG using the formula: $2 \times (\text{right} - \text{left}) / (\text{right} + \text{left})$. We compared asymmetry indices between patients and controls and evaluated their correlations with the severity of psychiatric symptoms and cognition in patients using the Positive and Negative Syndrome Scale (PANSS), video-based social cognition scale (VISC) and the Wechsler Adult Intelligence Scale (WAIS-III).
Results: Asymmetry of fractional anisotropy (FA) and radial diffusivity (RD) in the vPCC-MTG tract, while present in healthy controls, was not evident in schizophrenia patients. Also, we observed that patients, not healthy controls, had a significant FA decrease and RD increase in the left vPCC-MTG tract. There was no significant association between the asymmetry indices of dMRI measures and IQ, VISC, or PANSS scores in schizophrenia.
Conclusion: Disruption of asymmetry of the vPCC-MTG tract in schizophrenia may contribute to the pathophysiology of schizophrenia.

1. Introduction

Many studies have used CT or MRI to elucidate the pathogenesis of schizophrenia over the past 40 years (Johnstone et al., 1976; Smith et al., 1985; Kambeitz et al., 2015; Haijma et al., 2013; Bakhshi and Chance, 2015). Although previous studies have reported structural changes in various brain areas in patients with schizophrenia (Chiapponi et al., 2013; Shenton et al., 2001; Haijma et al., 2013; Bakhshi and Chance, 2015), there are few reports of brain areas with consistent abnormalities. These include, but are not limited to, reduced gray matter (GM) volume in the frontal and temporal lobes (Bachmann et al., 2004; Nakamura et al., 2008), decreased total brain volume (Haijma et al., 2013; Veijola et al., 2014; Shenton et al., 2001), decreased volume of hippocampus, and increased ventricles (Steen et al., 2006; van Erp et al., 2016) in schizophrenia patients. Such findings notwithstanding, the association between structural or functional abnormalities in various brain regions and clinical symptoms have been more elusive (Bersani et al., 2014; Samartzis et al., 2014; Nenadic et al., 2012).

Further, some studies have reported disconnections as causative. Evidence includes abnormalities in myelin and oligodendrocytes (by postmortem study) and abnormal functional association (by functional imaging studies) (Sadock et al., 2015; Uranova et al., 2001; Tu et al., 2012; van den Heuvel and Hulshoff Pol, 2010).

Diffusion MRI (dMRI) makes it possible to non-invasively investigate the integrity and microstructure of white matter (WM) fiber bundles and their connection among brain regions (Beaulieu, 2002). Findings demonstrate that schizophrenia patients evince irregularities in several

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WM tracts, including the genu and splenium of the corpus callosum, arcuate fasciculus, superior/inferior longitudinal fasciculus, uncinate fasciculus, and cingulum bundle (Kubicki et al., 2007; Kyriakopoulos et al., 2008; Wheeler and Voineskos, 2014).

A strength of dMRI is the extraction of fiber bundles that link specific regions of interest (ROIs) to investigate fiber integrity by quantifying the diffusion properties of WM. Several algorithms to automatically delineate WM tracts have been introduced. The traditional diffusion tensor model cannot provide correct fiber orientations in regions of crossing WM tracts because the model is based on only one major eigenvector (Alexander et al., 2001). In fact, it is accepted that over 90% of voxels in WM include two or more crossing fibers (Jeurissen et al., 2013). The challenge of fiber-crossing can be overcome using several methods, one being an unscented Kalman filter tractography with a two-tensor model (Rathi et al., 2011). Using this algorithm, it was noted that patients with a first episode of schizophrenia had at least one significantly different diffusion measure in 740 among 1254 fiber bundles compared to healthy controls (Rathi et al., 2011). Additionally, a previous study reported that patients with a first episode of schizophrenia had abnormalities of the WM tracts connecting the striatum and frontal areas such as the rostral middle frontal gyrus and the inferior frontal gyrus (Quan et al., 2013).

Regarding dMRI studies investigating the association between clinical symptoms with tract integrity, it has been considered important to select and define ROIs. While abnormalities of the ventral posterior cingulate cortex (vPCC) and the middle temporal gyrus (MTG) in schizophrenia have been reported individually, however, there is little evidence with respect to fibers linking vPCC and MTG. Multiple studies have demonstrated that the GM of MTG has a role in semantic memory processing and language (Cabeza and Nyberg, 2000), observation of motion (Rizzolatti et al., 1996), deductive reasoning (Goel et al., 1998), dynamic facial expressions (Sato et al., 2012), and in multimodal and higher sensory processing (Mesulam, 1998). Compared with healthy controls, both first-episode and chronic schizophrenia patients exhibit reduced bilateral MTG GM volumes (Kuroki et al., 2006; Onitsuka et al., 2004). Decreased MTG GM volumes were associated with decreased facial memory exhibited by patients with schizophrenia (Johnston et al., 2005) and youth at a high familial risk (Brent et al., 2016). Recently, we reported increased trace in the right MTG and a correlation between trace and decreased social function (Lee et al., 2016b).

Of further note, the vPCC has a strong functional connection to the other areas of the default mode network, while the dorsal portion is highly connected to fronto-parietal networks which are involved in cognitive control (Leech et al., 2012). There are some studies reporting that patients with schizophrenia showed structural and functional abnormalities in the PCC. Compared with healthy subjects, drug-naïve patients with schizophrenia exhibit reduced volumes in the left PCC, which are significantly correlated with working memory (Liu et al., 2016). Patients with schizophrenia also demonstrate increased connectivity between PCC and the left inferior gyrus, left MTG, and left middle frontal gyrus (Woodward et al., 2011).

Left-right asymmetries are exhibited in both structural and functional imaging of healthy controls (Okada et al., 2016; Renteria, 2012), and are believed to be associated with complementary functions and possibly specialized functions such as language (Cai et al., 2013; Corballis, 2014). However, some studies which reported schizophrenia showed changes in this asymmetry because of disruptions in left hemisphere dominance (Mitchell and Crow, 2005). Several studies have shown this disruption to be structural as well as functional (Ribolsi et al., 2014). Concerning asymmetry in WM tracts, a significant reduction of leftward asymmetry in schizophrenia has been reported in the anterior cingulum bundle, uncinate fasciculus, and superior and inferior occipitofrontal fasciculi (Ribolsi et al., 2014).

As described above, the important roles of these ROIs in schizophrenia have been widely reported. In regard to the connection between these ROIs, few post-mortem studies have reported connections between two ROIs in humans (Leech and Sharp, 2014). However, the results of several studies indicate possible connections between two ROIs: high correlations in some fMRI studies on schizophrenia or autism (Woodward et al., 2011; Teipel et al., 2010; Monk et al., 2009), and anatomical connections between the PCC and MTG or superior temporal sulcus, which is the upper boundary of the MTG in monkeys (Morris et al., 1999; Leech and Sharp, 2014). Until now, it is still unknown if the integrity of the WM fiber tracts connecting the vPCC and MTG in patients with schizophrenia are also impaired. Our study investigated the integrity of these fiber tracts extracted by two-tensor tractography in patients with recent onset schizophrenia. Our hypothesis was that the asymmetry of the diffusion measures in the fiber tracts between the MTG and vPCC (vPCC-MTG tract) in healthy controls would not be seen in patients with schizophrenia.

2. Materials and methods

2.1. Subjects

Subjects were recruited from the Asan Medical Center which is a university–affiliated hospital. An experienced psychiatrist diagnosed patients according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV). For all patients, the onset of first psychotic symptoms, including delusion or hallucination, occurred five or fewer years, prior to enrollment. In the control group, subjects and their first-degree relatives had no Axis I psychiatric diagnoses based on the DSM-IV-TR. Each subject was right-handed and aged 20–40 years. Exclusion criteria included: diseases that affect the functioning of the brain, or inability to complete neuropsychological testing or the MRI scanning session.

We excluded 20 subjects due to poor image quality, incidental brain lesions, or a change in the original diagnosis to other psychotic disorders (e.g., bipolar disorder) when we re-evaluated them 1–6 months after enrollment. Finally, we used the clinical information and MRI images of 47 schizophrenia patients and 24 healthy controls.

All subjects provided written informed consent before enrollment and ethical approval for the study was obtained from the Institutional Review Board of Asan Medical Center (IRB File No. 2012-0485).

2.2. Neuropsychological and clinical measures

Assessment of symptoms, neurocognition, and social cognition was completed within a week from the date of the MRI scan. All subjects were also evaluated by the age and sex adjusted short form of the Wechsler Adult Intelligence Scale-Third edition (WAIS-III), and the video-based social cognition scale (VISC) (Jang, 2007; Lee et al., 2016a). The age and sex adjusted short form of the WAIS consists of six subtests, including the digit span, vocabulary, arithmetic, picture arrangement, block design, and digit symbol. VISC is a scale, which was made by our research team, for evaluating social cognition based on video clips. This scale consists of 20 video clips portraying frequently experienced social interactions in real life. Patients were asked to point out socially unnatural behavior or speech or to state the reasons for lies made by actors or actresses. Each question has a 0–2 scoring scale, with a maximum total score of 40. Patients' psychiatric symptoms were rated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

2.3. MRI protocol

MR scans were performed with an 8-channel SENSE head coil at 3 T (Philips Achieva). dMRI images were acquired via echo-planar imaging (EPI) dMRI sequence. One baseline ($b = 0$) image and 32 diffusion gradient directions with a b-value of 1000 s/mm^2 were also acquired. Scan parameters for dMRI were: field of view (FOV): $224 * 224 * 135$ mm, voxel size: $2 * 2 * 3$ mm^3, echo time (TE): 70 ms, flip angle: 90°, and

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