Psychiatry Research: Neuroimaging 224 (2014) 49–57

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Positive symptoms and water diffusivity of the prefrontal and temporal cortices in schizophrenia patients: A pilot study

Jin Young Park [a,b], Hae-Jeong Park [c,d], Dae-Jin Kim [c,d], Jae-Jin Kim [a,b,d,*]

[a] Department of Psychiatry, Yonsei University, College of Medicine, Gangnam Severance Hospital, 211 Eonju-ro, Gangnam-gu, Seoul 135-720, Korea
[b] Institute of Behavioral Science in Medicine, Yonsei University, College of Medicine, Seoul, Korea
[c] Department of Radiology, Nuclear Medicine and Research Institute of Radiological Science, Yonsei University, College of Medicine, Seoul, Korea
[d] BK21 Project for Medical Science, Yonsei University, College of Medicine, Seoul, Korea

ARTICLE INFO

Article history:
Received 6 December 2011
Received in revised form
17 July 2013
Accepted 9 July 2014
Available online 19 July 2014

Keywords:
Water diffusivity
Schizophrenia
Positive symptoms
Diffusion tensor imaging
Gray matter

ABSTRACT

The development of diffusion tensor imaging (DTI) has provided information about microstructural changes in the brain. Most DTI studies have focused on white matter (WM). Few DTI studies have examined the gray matter (GM) in schizophrenia and, to date, there has been no attempt to identify the relationship between water diffusivity and symptom severity in schizophrenia. The present study aimed to examine microstructural deficits in the dorsal prefrontal cortex (DPFC) and temporal cortex in schizophrenia patients using fractional anisotropy (FA) and water diffusivity. This study also explored the relationship between DTI measurements and psychotic symptoms. Magnetic resonance imaging (MRI) and DTI were used to study 19 schizophrenia patients and 19 healthy controls. Fractional anisotropy, axial diffusivity, radial diffusivity, and regional volumes were measured in the prefrontal cortex and temporal cortex. On DTI measurements, patients showed increased axial and radial diffusivities in the prefrontal cortex and temporal cortex, but they did not demonstrate any difference in fractional anisotropy and regional volumes. Additionally, axial and radial diffusivities were significantly correlated with positive symptom scores in all regions of interest. These results indicate that water diffusivity measurements, including axial and radial diffusivities, can be used to identify microstructural changes in the gray matter in schizophrenia that may be related to symptom severity.

1. Introduction

Extant morphometric studies have demonstrated cerebral deficits in schizophrenia patients. Adults with schizophrenia show volumetric reductions in the prefrontal cortex, superior temporal gyrus, and medial temporal lobe (McCarley et al., 1999; Pearlson and Marsh, 1999; Kasai et al., 2002). Additionally, a considerable proportion of structural magnetic resonance imaging (MRI) research in schizophrenia has focused on investigating the relationship between regional gray matter (GM) volumes and clinical manifestations of the disorder. Positive symptoms have been found to correlate with smaller frontal and temporal lobe volumes (Nesvag et al., 2009), as well as a reduced volume of the parietal association region (Maruff et al., 2005). Reality distortion syndrome scores have also been associated with left prefrontal cortex and right frontal and parietal cortex volume (Whitford et al., 2005), and superior temporal cortex volume (Wright et al., 1995; Shapleske et al., 2002). The severity of auditory hallucinations also correlates with volume loss in the temporal area (Gaser et al., 2004; O'Daly et al., 2007). Data from volumetric studies of negative symptoms are less clear. Negative symptoms have been found to correlate with both larger frontal volumes (Nesvag et al., 2009) and smaller frontal volumes (Wible et al., 2001; Roth et al., 2004). Reduced prefrontal cortex volume and increased symptoms of psychomotor poverty (Chua et al., 1997) have also been reported. Generally, these studies have focused on changes in GM volume.

The proximate explanation for decreased cortical volume is reduced neuropil, neuronal size, and the number of neurons. These morphometric changes are in turn suggestive of alterations in synaptic, dendritic, and axonal organization (reviewed in Harrison (1999) and Iritani (2007)). Bearing in mind that reduced brain volume is believed to be related to symptom severity, morphological deficits at the cellular level could affect psychotic symptoms. However, the ability to evaluate the relationship between cellular

* Corresponding author at: Department of Psychiatry, Yonsei University, College of Medicine, Gangnam Severance Hospital, 211 Eonju-ro, Gangnam-gu, Seoul 135-720, Korea. Tel.: +82 2 2019 3341; fax: +82 2 3462 4304.
E-mail address: jaejkim@yonsei.ac.kr (J.-J. Kim).

http://dx.doi.org/10.1016/j.pscychresns.2014.07.003
0925-4927/

deficits and symptoms has been limited, since previously cellular morphology was only able to be investigated by examining post-mortem brain tissue or invasive techniques such as biopsies.

Diffusion tensor imaging (DTI) enables the study of microscopic structures in the nervous system non-invasively and in vivo by quantifying the diffusion characteristics of water molecules (Basser et al., 1994b; Le Bihan et al., 2001; Taylor et al., 2004; Assaf and Pasternak, 2008). Diffusion is isotropic when water molecule movement is the same in all directions. However, in the brain, the motion of water molecules is restricted by various tissue components such as myelin sheaths, cell membranes, and microfilaments. Consequently, water diffuses more freely in directions aligned with the internal neuronal structure than across them (Kubicki et al., 2002; Kyriakopoulos et al., 2008). Fractional anisotropy (FA) is a measure of the magnitude of diffusion anisotropy (Basser and Pierpaoli, 1996) and is expressed as a numerical value between 0 and 1. FA values closer to 1 mean a larger degree of anisotropic motion. The apparent diffusion coefficient (ADC; mean diffusivity: $\lambda_1+\lambda_2+\lambda_3$) is a measure of the average magnitude of water molecule diffusion in all directions. The ADC has been applied to detect microstructural changes in neuropsychiatric disorder (Le Bihan et al., 1986; Ardekani et al., 2005). Some studies have reported that axial diffusivity (i.e., $\lambda_{\parallel}=\lambda_1$), the magnitude of the principal diffusivity along gross axonal structure, and radial diffusivity, the mean cross-sectional diffusivity perpendicular to the axial diffusivity (i.e. $\lambda_{\perp}=(\lambda_2+\lambda_3)/2$), may separately provide more information about the microstructure of the neuronal system (Song et al., 2002; Barrick et al., 2010). For example, axonal damage from ischemia results in a marked decrease in axial diffusivity (Song et al., 2003), while demyelination damage to axons, which is observed in multiple sclerosis, leads to an increase in radial diffusivity in the mouse brain (Song et al., 2005). In schizophrenia, higher radial diffusivity was observed compared with healthy controls in several major white matter (WM) tracts, but there was no difference in axial diffusivity (Seal et al., 2008). Radial diffusivity is regarded as showing axon count, extracellular volume, myelin fraction volume, axon spacing and the number of diffusion barriers, such as the cell membrane and myelin sheath (Beaulieu, 2002; Schwartz and Hackney, 2003; Schwartz et al., 2005). In contrast, axial diffusivity is felt to reflect axon count, myelin volume fraction, and axon diameter (Schwartz et al., 2005) in the spinal white matter (WM). Taken together, analyses of and radial diffusivity separately can provide more information.

DTI has typically been used to investigate the WM of the brain (Kyriakopoulos et al., 2008). Additionally, the relationship between DTI parameters and symptoms of schizophrenia has been intensively studied. Recent studies have examined correlations between different aspects of the disease and DTI data by examining specific symptoms and patterns of symptomatology (Hubl et al., 2004; Shin et al., 2006; Skelly et al., 2008).

Although the relationship between GM volume deficits and psychotic symptoms in schizophrenia has been consistently demonstrated with conventional MRI, the GM has received far less attention in DTI research. One reason for this is that diffusion in the GM is much less anisotropic than in the WM; thus, standard techniques used to analyze the principal direction of diffusion, or the degree of anisotropy, become less meaningful (Rametti et al., 2009). However, several studies have demonstrated the value of DTI for the analysis of GM regions in ischemic stroke (Munoz Maniega et al., 2004; Arakawa et al., 2006), multiple sclerosis (Oreja-Guevara et al., 2005), mild cognitive impairment (Ray et al., 2006), and other brain diseases (Vite et al., 2008). The results of these studies indicate that there is a high probability of detecting microstructural changes in the GM related to brain disease using DTI.

In contrast, studies aiming to correlate psychotic symptoms with microstructural changes in the WM of schizophrenia patients using DTI have been widely performed. Until now, however, few DTI studies have investigated the GM in schizophrenia. Previous studies have found decreased FA in the entorhinal cortex (Kalus et al., 2005), increased ADC in the frontal and temporal cortices (Shin et al., 2006), increased ADC in the superior temporal gyrus (Lee et al., 2009), and increased mean diffusivity in the parahippocampal, insula and cingulate gyri (Moriya et al., 2010) in schizophrenia patients versus healthy controls. These findings suggest that DTI would be a useful tool for exploring microstructural changes in the GM in schizophrenia.

To our knowledge, no studies have examined the relationship between DTI measurements in the GM and psychotic symptoms. Changes in the morphology, size and number of neurons affect GM size, which may be relevant to symptomatology. One suggestion is that microstructural changes are indicative of psychopathology. Thus, an evaluation of the GM using DTI, which has the sensitivity to detect microstructural changes, could prove to be a valuable approach.

The dorsal prefrontal cortex (DPFC) and temporal lobe have been a traditional focus of research for understanding the pathology of schizophrenia (John, 2009). The dorsal prefrontal area is primarily related to disorders of global cognitive function including executive function and thought disorder. The temporal region has been implicated in emotional problems and auditory hallucinations (John, 2009). One of our recent studies demonstrated that mind-related responses of the medial prefrontal–superior temporal network were attenuated during self-referential processing in schizophrenia patients, which may be related to the formation of their referential or persecutory delusions (Park et al., 2011). Progressive volume loss seems most pronounced in the frontal and temporal GM (reviewed in Hulshoff Pol and Kahn (2008)). Additionally, neuropathological examinations of post-mortem brain tissue from schizophrenia patients have shown consistent abnormalities in these two areas (Iritani, 2007). For example, quantitative abnormalities in the number, density, and size of neurons, disruption of neuronal arrangement and abnormality in pyramidal neuron arrangement have been observed in the temporal lobe. Further, decreased neuronal density, diminished size and a decrease in intermediate neurons have been observed in the frontal lobe (Harrison, 1999; Iritani, 2007). In light of these findings, we elected to measure DTI changes in brain cytoarchitecture in the dorsal prefrontal and temporal areas, where histological abnormalities are well established. To correlate symptoms with microstructural changes, we decided that the prefrontal and temporal cortices, which are important areas in schizophrenia pathology, should be investigated using various DTI parameters. In view of the thinness of the GM, we selected a large region of interest (ROI) such as the dorsal prefrontal cortex and temporal cortex to minimize susceptibility artifacts. In addition, to provide more information about GM and DTI measurements in an exploratory approach, we performed the second analysis using more additional areas, including the inferior frontal gyrus, anterior cingulate, superior temporal gyrus, and hippocampus.

The aim of this study was to determine whether DTI measurements would prove useful for detecting differences in the GM of schizophrenia patients and healthy controls, and whether symptom severity would be correlated with microstructural changes in the GM in schizophrenia. We hypothesized that DTI measurements reflect microstructural changes in the GM of frontal and temporal areas, and that these would be associated with the psychotic symptoms of schizophrenia. To obtain these measurements, we examined differences in FA and water diffusivity in schizophrenia patients and healthy controls. We also analyzed the correlation between DTI values and symptom severity in schizophrenia.