Schizophrenia Research xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Frontal and temporal cortical volume, white matter tract integrity, and hemispheric asymmetry in schizotypal personality disorder

Chi C. Chan [a,b,*], Philip R. Szeszko [a,b], Edmund Wong [c], Cheuk Y. Tang [c], Caitlin Kelliher [b], Justin D. Penner [a,b], M. Mercedes Perez-Rodriguez [b], Daniel R. Rosell [b], Margaret McClure [b], Panos Roussos [a,b,d], Antonia S. New [b], Larry J. Siever [a,b], Erin A. Hazlett [a,b]

[a] VISN 2 Mental Illness Research, Education, and Clinical Center, James J. Peters Veterans Affairs Medical Center, Bronx, NY, USA
[b] Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[c] Translational and Molecular Imaging Institute, Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[d] Department of Genetics and Genomic Sciences and Institute for Genomics and Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

ARTICLE INFO

Article history:
Received 24 August 2017
Received in revised form 29 November 2017
Accepted 21 January 2018
Available online xxxx

Keywords:
Schizotypal personality disorder
Brain asymmetry
Magnetic resonance imaging
Fractional anisotropy
Diffusion tensor imaging

ABSTRACT

Abnormalities in temporal and frontal cortical volume, white matter tract integrity, and hemispheric asymmetry have been implicated in schizophrenia-spectrum disorders. Schizotypal personality disorder can provide insight into vulnerability and protective factors in these disorders without the confounds associated with chronic psychosis. However, multimodal imaging and asymmetry studies in SPD are sparse. Thirty-seven individuals with SPD and 29 healthy controls (HC) received clinical interviews and 3 T magnetic resonance T1-weighted and diffusion tensor imaging scans. Mixed ANOVAs were performed on gray matter volumes of the lateral temporal regions involved in auditory and language processing and dorsolateral prefrontal cortex involved in executive functioning, as well as fractional anisotropy (FA) of prominent white matter tracts that connect frontal and temporal lobes. In the temporal lobe regions, there were no group differences in volume, but SPD had reduced right > left middle temporal gyrus volume asymmetry compared to HC and lacked the right > left asymmetry in the inferior temporal gyrus volume seen in HC. In the frontal regions, there were no differences between groups on volume or asymmetry. In the white matter tracts, SPD had reduced FA in the left sagittal stratum and superior longitudinal fasciculus, and increased right > left asymmetry in sagittal stratum FA compared to HC. In the SPD group, lower left superior longitudinal fasciculus FA was associated with greater severity of disorganization symptoms. Findings suggest that abnormities in structure and asymmetry of temporal regions and frontotemporal white matter tract integrity are implicated in SPD pathology.

Published by Elsevier B.V.

1. Introduction

Schizotypal personality disorder (SPD) is a schizophrenia (SZ)-spectrum disorder characterized by pervasive interpersonal deficits, cognitive-perceptual distortions, and eccentric behavior resulting in impaired functioning (American Psychiatric Association, 2013). Individuals with SPD exhibit impairments in multiple cognitive domains, particularly working memory and processing speed (McClure et al., 2013; Mitropoulou et al., 2005). They are less likely to live independently and achieve a Bachelor's degree, and earn less income than nonpsychiatric controls (McClure et al., 2013). SPD shares genetic, phenomenological, and neurobiological features with SZ (Siever and Davis, 2004), but without the frank psychosis and more severe cognitive and functional impairments. Studying SPD provides insight into vulnerability and protective factors in the SZ-spectrum without confounds associated with SZ such as chronic psychosis, recurrent institutionalization, and long-term antipsychotic use.

Structural magnetic resonance imaging (MRI) studies in SZ-spectrum disorders have focused on abnormalities in temporal and frontal brain regions thought to underlie some of the most prominent clinical and cognitive symptoms in SZ. The neocortical temporal lobe involved in auditory and language processing, and the dorsolateral prefrontal cortex involved in executive functioning, are two regions that exhibit volume reduction in SZ (see reviews by Levitt et al., 2010 and Shenton et al., 2010). In SPD, one of the most robust finding is reduced gray matter volume in the superior temporal gyrus (STG; Asami et al., 2013; Dickey et al., 1999; Downhill et al., 2001; Goldstein et al., 2009; Kawasaki et al., 2004; Takahashi et al., 2006a, 2010) and its component parts including Heschl's gyrus (Dickey et al., 2002) and planum

* Corresponding author at: Mental Illness Research, Education, and Clinical Center, James J. Peters VA Medical Center, 130 West Kingsbridge Road, Room 6A-41G, Bronx, NY 10468, USA.
E-mail address: chi.chan@mssm.edu (C.C. Chan).

https://doi.org/10.1016/j.schres.2018.01.025
0920-9964/Published by Elsevier B.V.

temporale (Kawasaki et al., 2004; Takahashi et al., 2006a). The middle temporal gyrus (MTG) and inferior temporal gyrus (ITG) are also involved in auditory and language processing (Hickok and Poeppel, 2004), and studies in SPD have shown volume reduction in the MTG (Asami et al., 2013; Hazlett et al., 2008, 2014; Koo et al., 2006) and ITG (Asami et al., 2013; Downhill et al., 2001). Many of the findings reported are predominantly in the left hemisphere (see Fervaha and Remington, 2013; Hazlett et al., 2012) where language processing is localized. Indeed there is evidence that reduced temporal volumes are associated with odd speech (Downhill et al., 2001), and also with greater overall SPD symptom severity (Downhill et al., 2001) and negative symptoms (Asami et al., 2013).

In contrast to the temporal lobe findings in SZ, gray matter volume in the dorsolateral prefrontal cortex represented by the middle frontal gyrus has been reported to be normal in SPD compared with controls (Goldstein et al., 2009; Kawasaki et al., 2004). For example, in a study of SZ, SPD, and controls, Kawasaki et al. (2004) found SZ to have reduced temporal lobe and middle frontal gyrus volume, while SPD showed much milder temporal lobe volume reduction and normal middle frontal gyrus volume. In fact, Suzuki et al. (2005) found the middle temporal gyrus volume in SPD to be even larger than in controls, while SZ showed reduced volume in this area. The negative or reversed frontal lobe findings in SPD serve as the basis for the prominent theory that preserved frontal lobe is a protective factor against the development of psychosis (Siever and Davis, 2004).

Evidence also suggests that there is disrupted connectivity between temporal and frontal lobes in SZ. Diffusion tensor imaging (DTI) studies report lower fractional anisotropy (FA), a putative measure of white matter integrity, in some of the most prominent white matter tracts that traverse frontal and temporal lobes, including the uncinated fasciculus, inferior longitudinal fasciculus, and superior longitudinal fasciculus (see Kubicki et al., 2007; Wheeler and Voineskos, 2014). In SPD, lower FA has been reported in the uncinated fasciculus (UF; Gurrera et al., 2007; Nakamura et al., 2005) and inferior longitudinal fasciculus (ILF; Sun et al., 2016). One study showed a spectrum pattern in which ILF FA was highest in controls, intermediate in SPD, and lowest in SZ, particularly in the left hemisphere (Lener et al., 2015). These abnormalities may be associated with positive SPD symptoms and interpersonal difficulties (Lener et al., 2015; Nakamura et al., 2005; Sun et al., 2016).

Hemispheric effects have been frequently reported in neuroimaging studies of SZ-spectrum disorders (see Hazlett et al., 2012; Shenton et al., 2010). Normal asymmetry in the healthy brain is well documented and affected by evolutionary and developmental factors that shape brain laterality (Toga and Thompson, 2003). Crow et al. (1989) proposed that failure of genes to regulate normal development of cerebral asymmetry contributes to schizophrenia. Meta-analyses in SZ have shown reduced planum temporale asymmetry (Shapleske et al., 1999; Sommer et al., 2001) and asymmetry abnormalities in frontal and occipital lobes, Sylvian fissure, and posterior segment of the STG (Sommer et al., 2001). Indeed, structural asymmetry has been proposed as a biomarker for SZ (Oertel-Knochel et al., 2012). Studies have begun to examine temporal and frontal lobe asymmetry in SPD. Findings include lack of normal asymmetry in the anterior cingulate gyrus in female patients (Takahashi et al., 2002), increased asymmetry in the parahippocampal gyrus (Dickey et al., 1999), and normal MTG and ITG asymmetry (Takahashi et al., 2006b). However, paucity of asymmetry studies and inconsistent results warrant further research in SPD. For example, one study reported reduced left > right whole and caudal STG asymmetry compared with HC (Takahashi et al., 2006a) while another study found a trend toward greater left < right asymmetry in SPD (Dickey et al., 1999).

Although temporal and frontal structural anomalies are implicated in SZ-spectrum disorders, no study to our knowledge has examined structure and asymmetry of cortical volume and white matter tract integrity together in SPD. We used MRI and DTI to investigate temporal and frontal structure and asymmetry in SPD. To focus on brain regions implicated in the auditory processing (see Javitt and Sweet, 2015) and executive functioning impairments in SZ-spectrum disorders (see Eisenberg and Berman, 2010) and reduce Type I error, we specifically focused on lateral temporal regions, the dorsolateral prefrontal cortex, and prominent white matter tracts that traverse frontal and temporal lobes. We hypothesized that, in the temporal regions, individuals with SPD would show reduced gray matter volume and reduction of the normal asymmetry compared with healthy controls. Similarly, we predicted that individuals with SPD would exhibit lower FA and reduced asymmetry in the selected white matter tracts.

2. Methods

2.1. Participants

Appropriate Institutional Review Board approval and written informed consent were obtained. Thirty-seven individuals with SPD and 29 healthy controls (HC) were recruited through local medical centers and advertisements such as craigslist.org, local newspaper, and advertisement on the hospital website. Clinical psychologists administered the Structured Clinical Interview for DSM-IV Disorders (SCID-IV; First et al., 2002) and the Structured Interview for DSM-IV Personality Disorders (SIDP-IV; Pfohl et al., 1997). Exclusion criteria included pregnancy, a significant medical/neurological illness, substance abuse within the past three months, and positive urine toxicology on scan day. Patients had no history of any psychotic disorder. 62% of patients had a history of an Axis I disorder including 35% with depressive disorder, 46% with anxiety disorder, and 11% with some other Axis I disorder. All patients were unmedicated for at least six months prior to the scan and all but seven were psychoactive medication naïve. The majority of patients were not treatment seeking. HCs had no personal history of psychiatric disorders and no history of psychotic disorders in first-degree relatives. HCs were psychoactive medication naïve except for two who were medicated briefly for depressed mood more than three years prior to the study. HC had more education than SPD; groups were otherwise matched demographically (Table 1).

2.2. Symptom severity measure

The Schizotypal Personality Questionnaire (SPQ; Raine, 1991) is a widely used self-report questionnaire that assesses traits associated with SPD. It has good psychometric properties (Fonseca-Pedrero et al., 2014; Raine, 1991) including moderate to large test-retest reliability (Raine, 1991) and stability coefficients over two years (Geng et al., 2013; Stefanis et al., 2006). The SPQ subscale scores were calculated as the proportion of positive responses out of all valid responses and four factor scores (Cognitive-Perceptual, Paranoid, Negative, and Disorganization) were calculated by averaging the subscale scores in each factor (see Stefanis et al., 2004).

2.3. Magnetic resonance imaging

2.3.1. Image acquisition

All participants were scanned on a Siemens MAGNETOM Skyra 3 T scanner. A pulsed-gradient spin-echo sequence was used for DTI acquisition (TR = 3650 ms, TE = 87.0 ms, 74 slices, voxel size = 1.8 × 1.8 × 1.8 mm, matrix = 98 × 116, 128 gradient directions with b = 1500 s/mm^2). A high resolution 3-D T1-weighted MP-RAGE sequence was acquired with isotropic resolution of 0.8 mm × 0.8 mm × 0.8 mm (244 slices, matrix size = 320 × 320 × 224, FOV = 25.6 cm, TR = 2400 ms, TE = 2.07 ms and 8° flip angle).

2.3.2. Structural imaging methods

Cortical reconstruction and volumetric segmentation were performed on the MP-RAGE images using Freesurfer image analysis software (version 5.3.0). Regions of interest (ROIs) were segmented and

Please cite this article as: Chan, C.C., et al., Frontal and temporal cortical volume, white matter tract integrity, and hemispheric asymmetry in schizotypal personality disorder, Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.01.025