Neural structure and social dysfunction in individuals at clinical high risk for psychosis

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ABSTRACT

Individuals at a clinical high risk (CHR) for psychosis have gray matter volume (GMV) abnormalities that are similar to, though less severe than, those in individuals with schizophrenia. Less GMV in schizophrenia is related to worse social cognition and social functioning, but the relationship between GMV and social functioning in CHR individuals has yet to be investigated. The aim of this study was to (1) investigate differences in GMV between healthy controls (HC) and CHR individuals, and (2) evaluate the relationship between GMV and social functioning in these two groups. Participants comprised 22 CHR and 21 HC individuals who completed a structural magnetic resonance imaging (MRI) scan as well as self-reported and interviewer-rated measures of social functioning. Processing and analysis of structural images were completed using voxel based morphometry (VBM). Results showed that the CHR group had less GMV in the left postcentral gyrus, bilateral parahippocampual gyri, and left anterior cingulate cortex. Reduced GMV in the postcentral gyrus and the anterior cingulate was related to self-reported social impairment across the whole group. This study has implications for the neurobiological basis of social dysfunction present before the onset of psychosis.

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1. Introduction

Abnormalities in neural structure, particularly reductions in gray matter volume (GMV), are well documented in schizophrenia-spectrum populations (Borgwardt et al., 2011; Jung et al., 2012). Individuals at clinical high risk (CHR) for psychosis are characterized by attenuated positive symptoms, brief psychotic episodes that do not meet diagnostic criteria for schizophrenia, or a combination of genetic vulnerability and functional decline. These individuals have similar, though less severe, GMV reductions in regions consistent with those seen in individuals with schizophrenia (Fusar-Poli et al., 2012b). Importantly, among CHR individuals, those with more severe GMV reductions are more likely to develop schizophrenia or another psychotic disorder (for review, see Pantelis et al., 2005; Smieskova et al., 2010). These findings have prompted the proposal that GMV deficits are a biomarker of schizophrenia and could facilitate early detection and intervention.

However, schizophrenia is a heterogeneous disorder characterized by psychological symptoms and behavioral problems in multiple domains (Harvey et al., 2007). Given that neural structures and functions map onto single behaviors more accurately than diagnostic categories, structural deficits in a single brain region are unlikely to predict the heterogeneous collection of symptoms associated with schizophrenia. An alternative and, potentially, more reliable approach for identifying biomarkers would be to investigate the relationship between GMV and specific behaviors associated with schizophrenia (Cuthbert and Insel, 2010). This approach would not only benefit from established basic research on brain-behavior relationships, but might also provide personally relevant clinical information since individuals at risk for or with the disorder have different symptom profiles.

Research with CHR individuals has examined GMV and its relationship to cognitive deficits (Koutsouleris et al., 2012) and clinical symptoms (Cullen et al., 2013), but not the relationship between GMV and social functioning. Yet, social functioning may be an even more important factor to investigate in relation to GMV as it exists earlier than the onset of psychotic symptoms (Addington et al., 2008; Tarbox and Pogue-Geile, 2008; Cornblatt et al., 2012), persists as a problem in individuals who do not transition to psychosis (Cornblatt et al., 2012), and is a main cause of functional disability and poor outcome in individuals who do transition to psychosis (Bellack et al., 1990; Hooley, 2010).

The current study looks at the relationship between GMV and social functioning as a way of better understanding the specific relationship between the neurobiological deficits underlying the disorder and functional impairment. Behavioral data indicate that CHR individuals have social cognitive deficits (Amminger et al., 2012; Bora and Pantelis, 2013), and poorer performance on social cognitive

tasks is associated with transition to psychosis (Kim et al., 2011). Social cognitive processing and associated social behaviors are supported by a network of brain regions, including the medial prefrontal cortex (MPFC), anterior cingulate cortex (ACC), superior temporal cortex (including superior temporal sulcus (STS) and superior temporal gyrus (STG)), amygdala, and somatosensory related cortices (including postcentral gyrus, supramarginal gyrus, and anterior insula) (Adolphs, 2009).

Individuals with schizophrenia have GMV deficits in regions supporting social cognition, and these abnormalities predict social functioning (Hooker et al., 2011; Tully et al., 2014). Previous research with CHR individuals has shown abnormal neural structure in multiple brain regions, including regions related to social and emotional processing, such as the ACC, STG, ventral and dorsal MPFC, orbital frontal cortex (OFC), postcentral gyrus, supramarginal gyrus, and insula (Meisenzahl et al., 2008; Fusar-Poli et al., 2011; Dazzan et al., 2012). CHR individuals also have structural abnormalities in medial temporal lobe regions associated with memory, cognitive-control, and other core cognitive functions; these regions include the superior, middle and inferior frontal gyri, parahippocampal gyri, and hippocampus (Pantelis et al., 2003; Meisenzahl et al., 2008; Witthaus et al., 2009). Longitudinal studies have shown that less volume in these regions (supporting both social cognition and cognition) is associated with greater risk of psychosis conversion (Borgwardt et al., 2007, 2008; Takahashi et al., 2009). Given the observed structural abnormalities in regions that process social and emotional information, such as the ACC, STG, MPFC, insula, postcentral gyrus, OFC, and supramarginal gyrus, it may be useful to investigate the relationship between GMV in the above-referenced regions and social functioning, as abnormalities in these areas may be a specific biomarker for social dysfunction in psychotic disorders.

The aims of this study are twofold: (1) investigate differences in GMV between CHR and matched healthy control group, and (2) identify the relationship between GMV and social functioning in these groups. We hypothesize that CHR individuals will have reduced GMV relative to HC individuals in the following regions associated with social and emotional processing: STG, STS, ACC, MPFC, and somatosensory related cortices, including the postcentral gyrus and the supramarginal gyrus. To identify this relationship, we use self-report and interviewer-rated measures that assess daily functioning in social contexts, including interpersonal relationships as well as work and/or school. We expect to see a relationship between GMV and social functioning, such that greater volume in these regions will relate to better social outcomes. Although other regions, not part of the social cognitive network, may differ in volume between groups, we do not expect these non-social regions to relate to social functioning. Since structure and function of these social and emotional brain regions are known to correlate with social behaviors in healthy adults (Adolphs, 2003a, 2003b), we expect a continuous relationship between GMV and social functioning across all individuals.

2. Methods

2.1. CHR group

Participants include 22 individuals, 15–35 years of age, who met CHR status due to the presence of attenuated positive symptoms as defined by a score of 3 or greater on one of five positive symptom clusters (unusual thought content, paranoid ideation, grandiosity, perceptual aberrations and disorganized speech) assessed by the Structured Interview for Prodromal Syndromes (SIPS) (McGlashan, 2001). Participants' symptoms did not have to meet duration (within the last year) and frequency (4 times per month) criteria for the prodromal syndrome to be included in the study. CHR participants were excluded for past or current Axis I psychotic disorder (including mood disorder with psychosis). However, CHR participants were not excluded for other Axis I or II disorders unless those disorders

could explain their prodromal symptoms. Many CHR individuals have co-occurring disorders (Salokangas et al., 2012; Hui et al., 2013); thus, the goal of this recruitment strategy was to maintain the external validity of our CHR sample. For example, a recent meta-analysis by Fusar-Poli and colleagues (2014) showed that the majority of CHR individuals have comorbid depressive and/or anxiety disorders (Fusar-Poli et al., 2014), suggesting that symptoms of other Axis I disorders may be part of the prodromal state and not separate from the emerging psychotic process. Our final sample included one participant with current social anxiety disorder and a history of panic disorder; and one participant who had Eating Disorder-Not Otherwise Specified (with mild severity). Only one CHR participant was excluded for co-occurring psychopathology; this participant had post-traumatic stress disorder (PTSD), and her prodromal paranoid symptoms only occurred within the context of PTSD symptoms. Exclusion criteria for all participants (CHR and HC) included an IQ < 70, history of neurological problems, head injury, loss of consciousness > 20 min, current or past substance dependence, or MRI incompatibility.

2.2. HC group

Twenty-one healthy, age-matched controls were recruited. In addition to the exclusion criteria listed above, healthy participants were excluded for past or current Axis I/II disorders or psychotic-like symptoms rated 2 or higher on the positive symptom scales of the SIPS.

2.3. Clinical measures

All participants were screened for psychopathology using the Structured Clinical Interview for DSM IV (SCID) I (First et al., 1996) and II (First, 1997). Full-scale IQ scores were obtained from the Wechsler Abbreviated Intelligence Scale (Wechsler, 1999). Social functioning was assessed with the Social Adjustment Scale (SAS) (Weissman et al., 1978; Sasaki et al., 2014) and the Global Functioning (GF): Social and Role scales (Cornblatt et al., 2007). These social functioning measures were chosen because of their good psychometric properties and validation for use with adolescents and young adults. The SAS is a self-report measure assessing multiple aspects of functioning. The Social and Leisure subscale of the SAS was our primary interest, as it specifically assesses the social aspects of day-to-day functioning, including social motivation and social activities. Standardized t scores are reported; higher scores indicate lower functioning. The Social and Leisure subscale was chosen because every participant completed this scale, whereas other subscales were not completed by all participants. The Work subscale, for instance, failed to capture the role functioning of unemployed individuals. The GF: Social and Role interviews were specifically created for the psychosis prodrome population. Scales are rated 1 to 10 (10=highest). The GF: Social interview assesses social motivation/initiative and the number and quality of interpersonal relationships. The GF: Role interview assesses functioning in occupational, educational, and/or homemaker roles. Ratings for both scales incorporate environmental context (e.g., level of educational support) and developmental stage (e.g., age-appropriate interest in romantic relationships). The use of both self-report and interview-based measures is methodologically rigorous, as converging evidence from two different sources and types of measures for the same construct provides stronger support for the validity of the data.

2.4. Image acquisition

Structural images were acquired on a 3.0 T Siemens Tim Trio scanner using a 32-channel head coil. A three-dimensional anatomical T1-weighted scan (MEMPRAGE) was acquired with the following parameters: 176 axial slices, $1 \times 1 \times 1$ mm^3 voxels, echo time (TE)1(multi-echo): 1.64 ms, TE2: 3.5 ms, TE3: 5.36 ms, TE4: 7.22 ms; repetition time (TR): 2530 ms; flip angle=7°; field of view=256 mm $\times$ 256 mm.

2.5. Image processing

Structural analysis was done using voxel-based morphometry (VBM) with Statistical Parametric Mapping (SPM8; http://www.fil.ion.ucl.ac.uk/spm/software/spm8). Structural images were preprocessed using the DARTEL SPM8 toolbox, which has been shown to improve normalization in the VBM process (Ashburner, 2007). After alignment to the DARTEL-generated template, images were spatially normalized to Montreal Neurological Institute (MNI) space and smoothed with an 8-mm Gaussian kernel.

2.6. Statistical analysis

For the whole brain analysis, an analysis of covariance (ANCOVA) was performed to detect differences in GMV between HC and CHR groups. Total intracranial volume (TIV) (sum of gray matter, white matter, and cerebrospinal fluid) was a covariate of no interest. Given the inherent risk of missing true CHR abnormalities when using a conservative statistical threshold, we sought to balance