

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



Sarah Hope Lincoln*, Christine l'Lee Hooker

Department of Psychology, Harvard University, William James Hall 1008, Cambridge, MA 02138, USA

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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 parahippocampal 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

* Corresponding author. Tel.: +1 617 496 7095; fax: +1 617 495 3728.

E-mail addresses: sarahhope.lincoln@gmail.com, slincoln@fas.harvard.edu (S.H. Lincoln).

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 interviewer-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, $1 \times 1 \times 1$ mm³ 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 × 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

the probability of Type I and Type II errors (Lieberman and Cunningham, 2009) by using a two-step statistical approach as follows: first using a less stringent threshold ($p < 0.001$) for the whole brain analysis, and then correcting for multiple comparisons within regions of interest (ROIs). First, we report between-group differences exceeding a statistical threshold of $p < 0.001$ (uncorrected for multiple comparisons) and cluster size (k) of 10 voxels. We then correct for multiple comparisons within hypothesized anatomical ROIs using the Small Volume Correction (SVC) toolbox in SPM. Clusters that are significant at $p < 0.05$ with family-wise error (FWE) correction are designated with an asterisk (*). This two-step approach is recommended for new research areas, since whole-brain multiple test correction is a conservative threshold with high probability of Type II error. Thus, at this early stage of CHR research, Type II error (i.e., missing true CHR abnormalities) could impede progress by restricting the scope of future investigations. Marsbar toolbox (<http://marsbar.sourceforge.net>) was used to extract GMV from regions that were significantly different between HC and CHR groups in the whole brain ANCOVA. These volumes were correlated with social and role functioning measures using Pearson product-moment correlations, at $p < 0.05$ (two-tailed test).

3. Results

3.1. Clinical and demographic characteristics

The two groups did not differ in age, gender, or years of education, but the CHR group had lower average IQ than the HC group. As expected, the CHR group had higher psychotic-like symptom SIPS scores and worse social and role functioning (Table 1).

3.2. GMV analysis

3.2.1. Regional differences in GMV: HC > CHR

CHR participants had less GMV than HC participants in the left (L) ventral ACC, right (R) postcentral gyrus, the midbrain, and

Table 1
Demographic and clinical details.

	High risk subjects <i>n</i> =22	Control subjects <i>n</i> =21	Differences between groups
Age: mean (S.D.)	22.05 (4.48)	22.22 (3.04)	$t(37)=0.140, p=0.89$
Education: mean (S.D.)	14.10 (2.40)	15.28 (1.32)	$t(30.09)=1.90, p=0.07$
IQ: mean (S.D.)	108.10 (17.29)	118.11 (9.44)	$t(31.79)=2.29, p=0.03$
SIPS Scale: mean (S.D.)			
Positive	12.38 (4.79)	0.47 (1.01)	$t(22.16)=11.10, p=0.000$
Negative	6.57 (5.25)	0.65 (1.22)	$t(22.64)=5.01, p=0.000$
Disorganized	2.76 (1.70)	0.41 (0.62)	$t(26.20)=5.87, p=0.000$
General	4.43 (3.96)	0.18 (0.53)	$t(20.88)=4.87, p=0.000$
Global Functioning Scale (scale 1–10; higher scores reflect better functioning)			
Social	7.38 (1.63)	9.17 (0.99)	$t(33.55)=4.21, p=0.000$
Role	6.81 (1.44)	9.00 (0.686)	$t(29.60)=6.21, p=0.000$
Social Adjustment Scale ^a (scale 1–100; lower score reflects better functioning)			
Social and Leisure	62.00 (9.88)	48.75 (5.92)	$t(31.77)=4.98, p=0.000$

^a Data reported are T scores, which are standardized scores with mean=50 and S.D.=10.

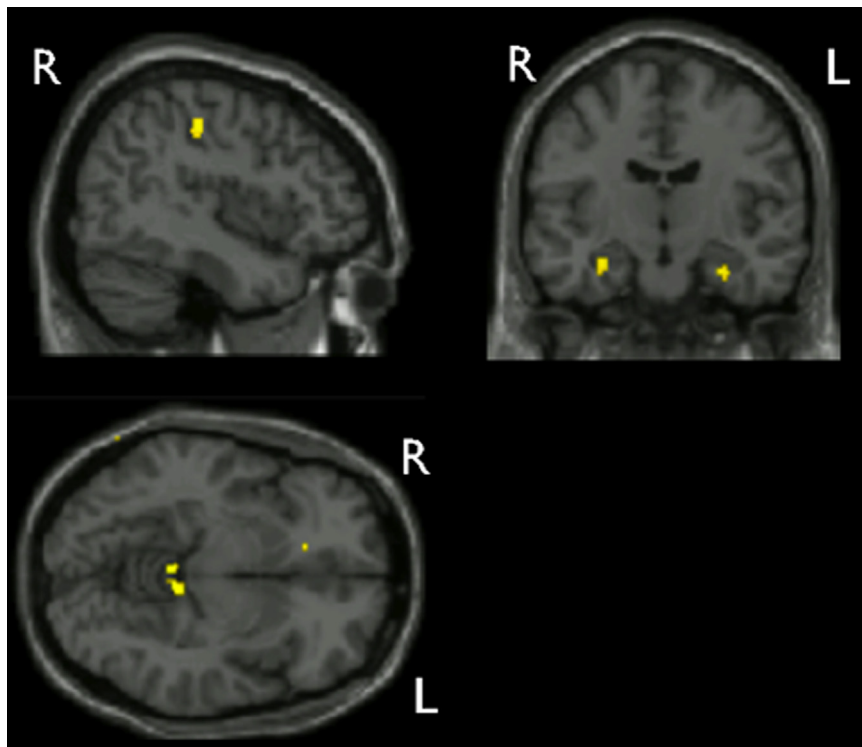


Fig. 1. A whole brain ANCOVA for between group differences, controlling for TIV was conducted. These results demonstrate regions where GMV:HC > CHR, $p < 0.001$ (uncorrected), $k=10$.

Table 2
Between-group differences in gray matter volume at threshold of $p < 0.001$ (uncorrected) and cluster size ≥ 10 voxels. Coordinates are in MNI space.

Anatomical region	R/L	BA	Voxels	x	y	z	t-value
HC > CHR							
Cerebellum	R	27	216	6	-39	-5	5.69
Parahippocampal gyrus	L	20	68	-30	-13	-21	4.08
Postcentral gyrus*	R	2, 3	163	48	-25	46	3.98
Anterior cingulate gyrus	L	11	12	-12	30	-8	3.72
Parahippocampal gyrus	R	20	46	30	-13	-26	3.70
Postcentral gyrus	R	3, 4	21	51	-16	33	3.54
CHR > HC							
Superior frontal gyrus	L	10	20	-19	51	24	3.70
Middle frontal gyrus	L	46	12	-31	51	27	3.63
Rolandic operculum	L	44	12	-43	6	15	3.63
Middle frontal gyrus	L	45, 46	12	-39	41	19	3.56

* Significant with small volume correction at FWE, $p < 0.05$.

the bilateral parahippocampal gyri (PHG) (Fig. 1, Table 2). Reduced GMV values in CHR relative to HC participants in the ACC and postcentral gyrus are consistent with our hypotheses. Thus, small volume correction was conducted in the ACC and postcentral gyrus. The postcentral gyrus was significant after correction for multiple tests ($p < 0.05$, FWE). To ensure that the two CHR participants with a co-occurring Axis I disorder were not skewing results, the between-group ANCOVA was conducted again with these two participants removed from the sample. Results are similar to findings from the full sample (Supplemental Table 1).

3.2.2. Regional differences in GMV: CHR > HC

Compared with HC participants, CHR participants had more GMV in the L superior frontal gyrus, L middle frontal gyrus, and L Rolandic operculum (Table 2).

Table 3
Correlations between gray matter volume and social functioning.

	ACC	Left PHG	Postcentral gyrus (x=51)	Right PHG	Postcentral gyrus (x=48)	Cerebellum
Whole group (n=39)						
GFS_Social	0.18	0.10	0.12	0.19	0.13	0.21
GFS_Role	0.34*	0.10	0.21	0.18	0.25	0.16
SAS_Social Leisure (Higher scores equal greater impairment)	-0.39*	-0.06	-0.45**	-0.010	-0.35*	-0.32

* $p < 0.05$.

** $p < 0.01$.

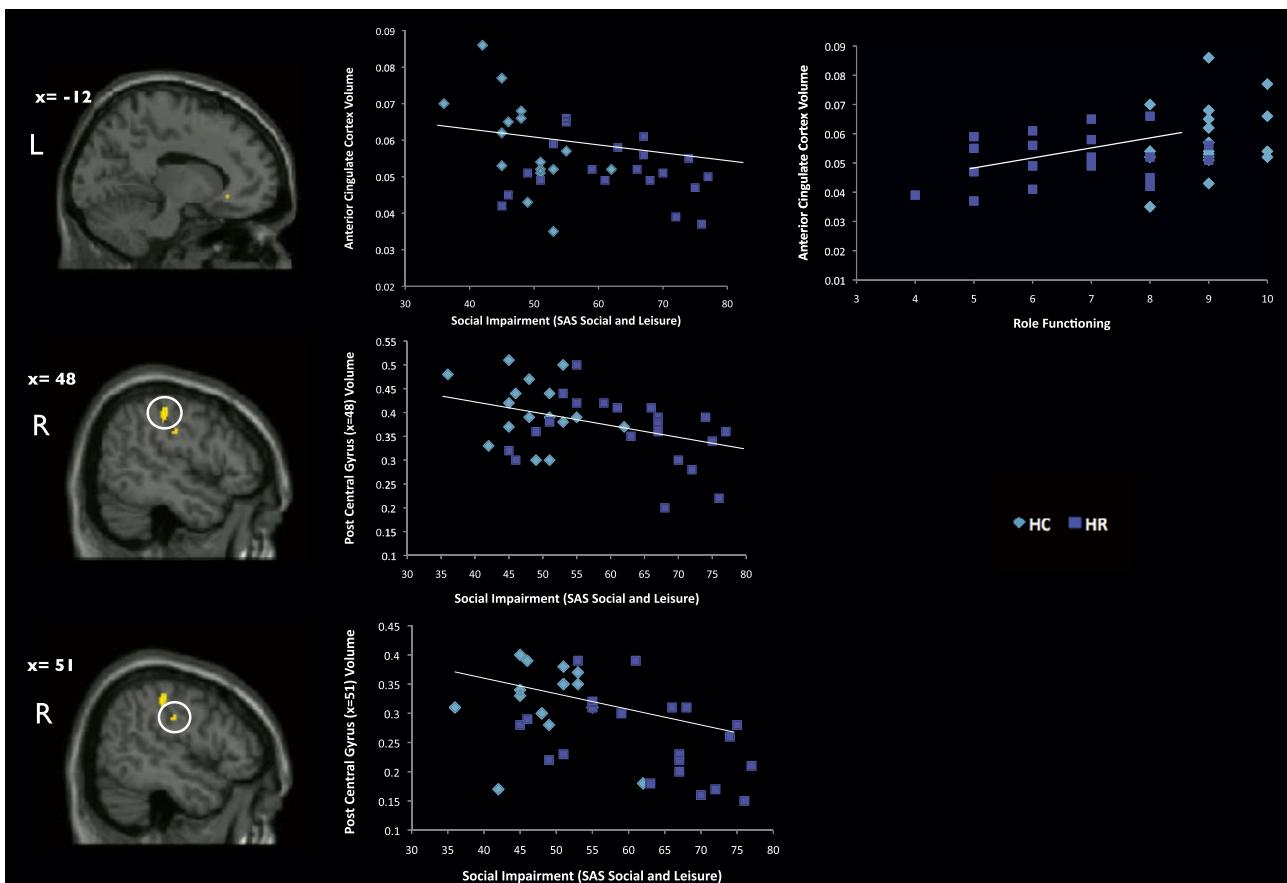


Fig. 2. Volume from regions of interest identified in the whole brain ANCOVA HC > HR was correlated with social impairment and role functioning.

3.2.3. Relationship between GMV and social functioning

GMV for each participant was extracted from the regions that were significant in the whole-brain group analysis of CHR < HC groups. We correlated social and role measures with each of these regions (Table 3).

As hypothesized, regions associated with social and emotional processing, the ACC and the postcentral gyrus, correlated with measures of social and role functioning. Specifically, across the whole group, there was a significant relationship between ACC GMV and GF: Role as well as SAS: Social and Leisure subscale scores, such that greater volume in the ACC was related to better interview-rated role functioning and self-reported social functioning. Greater volume in postcentral gyrus regions was related to the Social and Leisure subscale of the SAS (Fig. 2, Table 3). As expected, regions that are not primarily involved with supporting social and emotional processes, such as the parahippocampal gyri and the cerebellum, did not correlate with measures of social functioning.

4. Discussion

This study found that, compared with healthy participants, CHR individuals had less GMV in the ventral ACC, PHG, postcentral gyrus, and midbrain. Correlational analyses revealed a significant relationship between GMV in the ACC and social and role functioning, as well as GMV in the postcentral gyrus and social functioning. Regions not involved in social and emotional processing, such as the cerebellum, which showed differential volume between groups, did not, as expected, show significant correlations with measures of social functioning. These findings suggest that structural abnormalities in social and emotional regions are related to social functioning deficits in CHR individuals.

The regions identified as having reduced GMV in CHR individuals are consistent with earlier studies in schizophrenia and CHR groups. Differences in PHG structure (Job et al., 2005; Mechelli et al., 2011) have consistently been reported in the literature for CHR relative to HC individuals. Moreover, even greater reductions in GMV in the PHG have been found in CHR individuals who transition to a psychotic disorder relative to CHR individuals who do not transition to psychosis (Mechelli et al., 2011).

A decrease in volume in the postcentral gyrus in CHR relative to HC individuals is consistent with previous research (Meisenzahl et al., 2008). Dazzan and colleagues (2012) found that CHR individuals who transitioned to a psychotic disorder had less GMV in the postcentral gyrus than those who did not transition, implicating this region as a risk marker for the disorder (Dazzan et al., 2012).

Previous research also shows reduced GMV of the ACC in CHR individuals (Job et al., 2005; Meisenzahl et al., 2008; Mechelli et al., 2011). Our findings replicate these previous studies. Additionally, work by Smieskova and colleagues (2010) shows that decreased GMV in the cingulate cortex was predictive of individuals at risk who transitioned to psychosis versus at-risk individuals who did not transition (Smieskova et al., 2010).

In addition to between-group GMV differences, we found ACC volume was related to social and role functioning and postcentral gyrus volume correlated with social functioning. The ACC is known to play a role in emotion and social behaviors (Adolphs, 2001); is critical for social cognitive processes such as person perception, theory of mind, and thinking about the self (Amodio and Frith, 2006); and has been implicated in deficits in social cognition in patients with schizophrenia (Hooker et al., 2011; Dodell-Feder et al., 2013; Tully et al., 2014). Additionally, cortical thickness in the ACC in CHR individuals is negatively correlated with negative symptoms, indicating a relationship between this area and social engagement (Fornito et al., 2008). Building on this work, our

results demonstrate that reduced ACC volume is related to poorer social functioning. Given that the ACC is a region involved in the integration of social and emotional processing, these structural abnormalities in CHR indicate that the ACC may be part of the neurobiological explanation for social dysfunction in CHR individuals.

Findings from this study also indicate that reduced postcentral gyrus volume relates to social dysfunction. Research shows that the postcentral gyrus and related somatosensory areas are important for social cognition, particularly emotion recognition (Adolphs et al., 2000) and affective mentalizing/ToM (Hooker et al., 2008). Given the importance of the somatosensory cortex and related areas in social and emotional processing, a reduction in GMV in the postcentral gyrus in CHR individuals may indicate a deficit in processes necessary for effective social cognition and social interactions.

Although we had no a priori hypotheses of greater GMV in CHR relative to HC individuals, we found significantly greater GMV in the lateral prefrontal cortex (LPFC). While these findings should be interpreted cautiously, it is notable that abnormalities in the LPFC, particularly dorsal (D)LPFC, structure and function are often observed in CHR individuals as well as those in both early and chronic phases of schizophrenia. A study looking at GMV in monozygotic twins discordant for schizophrenia, found that twins with schizophrenia had less GMV in the DLPFC than non-affected twins (Cannon et al., 2002). This finding has led some researchers to suggest that changes in cortical gray matter in the DLPFC may be a result of the progression and/or onset of the disease (Cannon et al., 2002; Sun et al., 2009). Given that our sample is an early stage of clinical risk and the majority of these individuals will not go on to develop a psychotic disorder (Fusar-Poli et al., 2012a), it may be that greater GMV in the DLPFC is a protective factor.

Several limitations are worth noting. First, the groups were not matched for IQ. We anticipated this difference, as a decline in IQ is part of the disorder (Woodberry et al., 2010). Additionally, we did not use whole-brain correction for multiple comparisons due to our concern regarding Type II error at conservative thresholds; while this approach is warranted for initial investigations, future research should verify these initial findings with larger samples and more stringent statistical thresholds (Lieberman and Cunningham, 2009). Although we limited our focus to social and role functioning, these are global constructs, and the scores on our functioning measures undoubtedly reflect the cumulative influence of many social and cultural variables that were not examined in the study. Thus, to fully understand social dysfunction in CHR individuals, it will be important to investigate the relative contribution of GMV as well as other factors, such as socioeconomic status, that are known to influence functional outcome. Moreover, the influence of GMV on social functioning is, most likely, mediated by specific social cognitive processes, such as emotion recognition and ToM (Gibson et al., 2010; Dodell-Feder et al., 2013). Previous research has found relationships between clinical symptoms and social functioning in CHR groups (Corcoran et al., 2011) as well as neurocognition and social functioning (Niendam et al., 2007), and social cognition and social functioning outcomes (Pinkham and Penn, 2006). Next steps include looking at the relationship between GMV, social cognition and social functioning in CHR individuals.

By focusing on a CHR group, we are able to study potential biomarkers of schizophrenia-spectrum characteristics, in individuals who experience, at a lesser degree of severity, clinical, social, occupational, and cognitive difficulties similar to those experienced by patients with schizophrenia. Our research demonstrates that structural abnormalities are present in adolescents/young adults with attenuated positive symptoms who may or may not develop psychosis, and these differences are related to social

dysfunction, a symptom also evident before the onset of a psychotic disorder (Cornblatt et al., 2012). These findings suggest that structural abnormalities, particularly in neural regions involved in social and emotional processing, may underlie the social dysfunction seen in CHR individuals, and could be a potential biomarker of functional outcome.

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Appendix A. Supporting information

Supplementary data associated with this paper can be found in the online version at <http://dx.doi.org/10.1016/j.psychres.2014.08.008>.

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