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RESEARCH ARTICLE

Voxel-Based Morphometry in Individuals at Genetic High Risk for Schizophrenia and Patients with Schizophrenia during Their First Episode of Psychosis

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Abstract

Understanding morphologic changes in vulnerable and early disease state of schizophrenia (SZ) may provide further insight into the development of psychosis.

Method

Whole brain voxel-based morphometry was performed to identify gray matter (GM) regional differences in 60 individuals with SZ during their first psychotic episode (FE-SZ), 31 individuals at genetic high risk for SZ (GHR-SZ) individuals, and 71 healthy controls.

Results

Significant differences were found in several regions including the prefrontal cortex, parietal lobe, temporal lobe, hippocampus, occipital lobe, and cerebellum among the three groups (p<0.05, corrected). Compared to the HC group, the FE-SZ group had significantly decreased GM volumes in several regions including the cerebellum, hippocampus, fusiform gyrus, lingual gyrus, supramarginal gyrus, and superior, middle, and inferior temporal gyri and significantly increased GM volumes in the middle frontal gyrus and inferior operculum. The GHR-SZ group had significant decreases in GM volumes in the supramarginal gyrus, precentral gyrus, and Rolandic operculum and significant increases in GM volumes in the cerebellum, fusiform gyrus, middle frontal gyrus, inferior operculum, frontal gyrus, and superior, middle, and inferior temporal gyrus when compared to the HC group (p<0.05). Compared to the GHR-SZ group, the FE-SZ group had significant...
decreases in GM volumes in several regions including the cerebellum, fusiform gyrus, supramarginal gyrus, and superior, middle, and inferior temporal gyri (p<0.05).

Conclusions
The findings herein implicate the involvement of multisensory integration in SZ development and pathophysiology. Additionally, the patterns of observed differences suggest possible indicators of disease, vulnerability, and resiliency in SZ.

Introduction
Neural abnormalities develop and progress long before the onset of the clinical hallmarks of schizophrenia (SZ) [1]. This challenges efforts to implement effective treatment that substantially improve the clinical outcomes of affected individuals, pushing earlier identification and intervention in SZ to the forefront in psychiatric research. There are many questions as to the markers of SZ development, the appropriate timing and targets of such interventions, and potential resiliency factors. Understanding the neural underpinnings of SZ particularly during the vulnerability period and initial stages of the illness is critical in the search for answers to these questions.

Structural and functional abnormalities in multiple brain regions, including the prefrontal cortex, anterior cingulate cortex, hippocampus, thalamus, and cerebellum, have been observed in both SZ and high risk populations, implicating disruptions in various neural networks in the development and pathophysiology of SZ [1–4]. While studies have increasingly focused on neural alterations in individuals at high risk for (HR-SZ), studies comparing high-risk individuals and those during early stages of SZ are relatively limited. Such studies would provide direct comparison between high-risk and disease populations with less confounding effects from psychotropic medications and illness chronicity. Moreover, they could implicate candidate markers of vulnerability and progression to SZ, as well as potential markers for resiliency to the disorder. Prior studies in HR-SZ suggest that abnormalities in the prefrontal cortex (PFC) and temporal cortex are involved in conversion to psychosis and that other regions such as the parietal cortex, anterior cingulate cortex, and hippocampus may also confer vulnerability to SZ [3, 5]. However, interpretation of findings from these studies is complicated by the varying criteria used to define HR-SZ, including those based on clinical symptoms or family history. Differences in altered regions have been observed when comparing individuals at clinical high-risk for SZ (CHR-SZ) and those at genetic high risk (GHR-SZ) [5, 6]. Studies have reported up to 30–35% conversion to psychosis during multi-year follow-up in CHR-SZ, however these results may be partly attributed to sampling strategies and reflect the magnitude of subsyndromal symptoms that are already present within these populations [7]. Furthermore, there is still significant debate regarding which clinical symptoms or features would be more specific and predictive of psychosis conversion in CHR-SZ. Criteria for individuals at genetic high risk for SZ (GHR-SZ) can be more clearly defined. SZ is highly heritable with estimated heritability rate of 81% [8]. Recent genome-wide association studies suggest that some specific genes such as NRGN, CACNA1C and ZNF804A have been identified risk loci for SZ, which associated with brain structure and function, and illness development in SZ [9–11]. Nevertheless, genetic factors appear to have substantial influence on brain structure and function, and illness development in SZ. A recent study by Nenadic et al. compared two high risk groups- those with GHR and those with high but sub-clinical psychotic symptom profiles. Their findings suggest
that GHR-SZ is more similar to individuals during their first episode of SZ (FE-SZ) in brain
morphologic changes than CHR-SZ to FE-SZ [6]. Subsequently, studies of GHR-SZ may more
reliably yield potential neural markers of SZ development and resiliency.

In this study, we examined structural brain alterations in GHR-SZ and FE-SZ using whole
brain voxel-based morphometry (VBM). GHR-SZ was defined as offspring of at least one par-
ent with schizophrenia.

Methods
Participants
Participants in this study included 60 FE-SZ and 31 GHR-SZ individuals, and 71 healthy con-
trols (HC). FE-SZ and GHR-SZ participants were recruited from the outpatient clinics of the
Department of Psychiatry, First Affiliated Hospital of China Medical University, Shenyang,
China, and HC participants were recruited from Shenyang, China by advertisement. The
absence or presence of Axis I disorders were independently assessed by 2 trained psychiatrists
using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) for participants
over 18 years old and the Schedule for Affective Disorders and Schizophrenia for School-Age
Children--present and Lifetime Version (K-SADS-PL) for participants under 18 years old.
FE-SZ participants met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
(DSM-IV) diagnostic criteria for schizophrenia, schizophreniform disorder, or schizoaffective
disorder, and no other Axis I disorders. GHR-SZ participants were offspring of individuals
with schizophrenia (at least one parent with SZ and were not related to the FE-SZ participants)
who were within the peak period for illness onset (late adolescence to 30 years old) but did not
meet criteria for psychotic disorder or any other DSM-IV Axis diagnoses. HC participants did
not have current or lifetime Axis I disorder or history of psychotic, mood, or other Axis I disor-
ders in first-degree relatives (as determined detailed family history). For all participant groups,
individuals were excluded for history of substance or alcohol abuse or dependence, head injury,
neurologic or comorbid major medical disorder, and any MRI contraindications for MRI.
This study was approved by the Institutional Review Board of China Medical University, and
all participants provided written informed consent after detailed description of the study.

Symptom measures using the Brief Psychiatric Rating Scale (BPRS) and medication history
were obtained in the FE-SZ and GHR-SZ groups. In the FE-SZ group, 27 were taking atypical
antipsychotics including clozapine, risperidone, olanzapine, aripiprazole and quetiapine, 1 was
taking perphenazine, and 32 were not taking any psychotropic medication at the time of scan.
Only 1 GHR-SZ participant had prior exposure to sertraline for 1 month for social phobia
symptoms but was not taking any psychotropic medications at the time of scan. All antipsy-
chotic doses were converted to chlorpromazine equivalents using standard procedures [12]
(Table 1).

Image Acquisition
MRI was performed on a GE Signa HDX 3.0T magnetic resonance (MR) scanner using a
T1-weighted, 3D fast spoiled gradient-echo (FSPGR) sequence with the following parameters:
TR/TE = 7.2/3.2ms, Flip = angle 13°, field of view (FOV) = 240×240mm², 176 slices, voxel
size = 1mm³.

Data processing
Processing was performed using the DARTEL algorithm Statistical Parametric Mapping soft-
ware (SPM8, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) under the MATLAB R2010b
platform (Mathworks, Sherborn, MA, USA). Briefly, the segmentation function was used to divide the regions into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using the ‘new segment’ tool implemented in SPM8. During spatial normalization, inter-subject registration was achieved using respective registration based on group assignment. A modulation step was used to ensure that the overall amount of tissue in a class was unaltered. The segmented images were normalized to the Montreal Neurological Institute (MNI) template and were smoothed with an 8-mm full width at half-maximum (FWHM) Gaussian filter. The voxel size of data acquisition was 1mm\(^3\) and the voxel size of normalized data was 1.5mm\(^3\).

Statistical analysis

Statistical analyses for demographic and clinical characteristics were performed using IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY, USA). (Table 1)

Whole brain GM volumetric comparisons among the diagnostic groups were performed using a full-factorial design, with age and gender as covariates, using SPM8 (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Statistical significance was determined by a voxel-level statistical threshold (p<0.01) with AlphaSim correction for multiple comparisons (minimum cluster size of 444 voxels). AlphaSim correction was performed using DPABI software (DPABI_V1.2_141101, http://rfmri.org/dpabi). Post hoc comparisons between groups were performed for significant GM regions. Values were extracted from all significant regions in the three group analysis and analyzed in pair-wise two sample t-tests (HC vs. SZ, HC vs. GHR-SZ, GHR-SZ vs. SZ) using SPSS. Statistical significance was determined by p<0.05. Analyses were also performed to test for effects of demographic and clinical variables on GM volumes for significant regions from the three-group comparison (S1 File).

Results

Demographics and clinical characteristics

Demographic and clinical characteristics for all groups are presented in Table 1. Age significantly differed among the diagnostic groups [Degrees of freedom (df) = 2, F = 9.52, p<0.001] with post-hoc comparisons showing that the GHR-SZ and FE-SZ groups were significantly younger than the HC group. There were also significant differences in gender among the groups (df = 2, \(\chi^2 = 27.66\), p<0.05). Subsequently, all analyses were controlled for age and gender.

BPRS scores were significantly different between the GHR-SZ and FE-SZ groups (df = 1, \(t = 51.75\), p<0.001) with higher mean score in the FE-SZ group, as expected. Medication
exposure was also significantly different between these two groups (df = 1, $\chi^2 = 17.76$, $p < 0.001$) with a higher percentage of FE-SZ participants (53%) taking psychotropic medications compared to the GHR-SZ group (3%). Results from subsequent analyses, as reported below, remained unchanged with inclusion of BPRS scores and medication exposure.

Whole brain GM VBM analyses

**Three group comparison.** Significant differences were found in several regions including the prefrontal cortex, parietal lobe, temporal lobe, hippocampus, occipital lobe, and cerebellum among the three groups (df = 2, $p < 0.05$, corrected). *(Table 2 and Fig 1)*

**FE-SZ and HC.** The FE-SZ group had significantly decreased GM volumes in the left cerebellum posterior lobe, vermis, bilateral hippocampi, bilateral parahippocampal gyri, bilateral fusiform gyri, left lingual gyrus, left inferior occipital gyrus, right middle temporal gyrus, bilateral superior temporal gyrus, right rolandic operculum, left inferior parietal lobule, left

| Cortical Regions | BA | Cluster Size | MNI Coordinates | F Values |
|------------------|----|--------------|-----------------|---------|
|                  |    | X Y Z        |                 |         |
| A R Cerebellum Anterior Lobe | 37 | 589 | 40 -49 -25 | 7 |
| R Cerebellum Posterior Lobe | 505 | 198 |
| R Fusiform Gyrus | 20 |
| R Inferior Temporal Gyrus | 456 | 3 -61 -28 | 6.77 |
| B L Cerebellum Posterior Lobe | 149 | |
| C R Hippocampus | 28/36/20/3 | 267 | 37 -24 -18 | 6.56 |
| R ParaHippocampal Gyrus | 147 |
| R Fusiform Gyrus | 43 |
| D L Fusiform Gyrus | 18/19 | 317 | -21 -79 -10 | 7.81 |
| L Lingual Gyrus | 188 |
| L Inferior Occipital Gyrus | 113 |
| E L Hippocampus | 37/19/28/36/34/35 | 291 | -30 -39 -7 | 7.63 |
| L ParaHippocampal Gyrus | 212 |
| L Fusiform Gyrus | 151 |
| L Lingual Gyrus | 15 |
| F L Middle Temporal Gyrus | 22/21 | 658 | -57 -28 -1 | 5.63 |
| L superior Temporal Gyrus | 134 |
| G R superior Temporal Gyrus | 22/42/41/21/40/13/43 | 1535 | 55 -28 7 | 6.51 |
| R Middle Temporal Gyrus | 2/6/4/3/40/43/1/44 | 266 |
| H R Supra Maginal Gyrus | 40/2/3/1/42/4 | 392 | 55 -3 18 | 8.86 |
| R Precentral Gyrus | 230 |
| I L Superior Parietal Lobule | 747 | -51 -34 34 | 9.38 |
| L Supra Marginal Gyrus | 9/8 | 717 |
| L Postcentral Gyrus | 80 |
| L Superior Temporal Gyrus | 21 |
| J R Middle Frontal Gyrus | 252 | 34 16 43 | 9.2 |

GHR-SZ: genetic high-risk schizophrenia; FE-SZ: first-episode schizophrenia; HC: healthy controls. Letters represent clusters of significant difference in the three group analysis, which are shown in Fig 1. BA: Brodmann Area. MNI: Montreal Neurological Institute.

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postcentral gyrus, and left supramarginal gyrus and significantly increased GM volumes in the right middle frontal gyrus and inferior operculum frontal gyrus, compared to the HC group (df = 1, p < 0.05). (Fig 2)

**GHR-SZ and HC.** When compared to the HC group, the GHR-SZ group demonstrated significant decreases in GM volumes in the right supramarginal gyrus, right precentral gyrus, and right rolandic operculum and significant increases in GM volumes in the right cerebellum anterior lobe, right cerebellum posterior lobe, right fusiform gyrus, right inferior temporal gyrus, left middle temporal gyrus, superior temporal gyrus, right middle frontal gyrus, and right inferior operculum frontal gyrus (df = 1, p < 0.05). (Fig 2)

**FE-SZ and GHR-SZ.** Significant decreases in GM volumes were observed in bilateral cerebellum posterior lobe, right cerebellum anterior lobe, vermis, right fusiform gyrus, right inferior temporal gyrus, right middle temporal gyrus, right superior temporal gyrus, right rolandic operculum, bilateral supramarginal gyri, bilateral precentral gyri, left inferior parietal lobule,
and left superior temporal gyrus in the FE-SZ group compared to the GHR-SZ group (df = 1, p < 0.05). (Fig 2)

There were no significant effects of demographic and clinical variables on GM volumes (S1 and S2 Tables).

Discussion

Consistent with the converging view of SZ as a disorder with widespread neural disruptions, multiple regions including the prefrontal, temporal, and parietal cortices, hippocampus, and cerebellum were found to have significant differences when comparing GHR-SZ, FE-SZ, and HC individuals in this study [1, 5, 13]. Post-hoc comparisons of these regions with significant differences suggest potential indicators of disease, vulnerability, and resiliency or compensatory mechanisms in SZ, although these interpretations are tentative and warrant further investigation. The FE-SZ group demonstrated significantly decreased GM volumes in the cerebellar vermis, right superior temporal gyrus, right middle temporal gyrus, right operculum rolandic, left inferior parietal lobule, and left postcentral gyrus when compared to the GHR-SZ and HC groups, suggesting that these are altered regions in the disease state. The FE-SZ group also
showed significantly decreased GM volumes in the bilateral hippocampus, bilateral parahippocampal gyri, bilateral fusiform gyri, left lingual gyrus, and left inferior occipital gyrus when compared to the HC group but not to the GHR-SZ group. These regions were not significantly different between the GHR-SZ and HC groups, and GM volumes for these regions in the GHR-SZ group appeared intermediate to the FE-SZ and HC groups. This may reflect changes related to disease vulnerability that progress with disease onset. Significant increases in GM volumes were observed in the right middle frontal gyrus and right inferior operculum frontal gyrus in the FE-SZ and GHR-SZ group, compared to the HC group. These may be markers of vulnerability to SZ and possibly reflect neuroinflammation, which may be present during vulnerability and early disease states in SZ [4, 14]. Significantly increased GM volumes were also found in the right cerebellum anterior and posterior lobes, right fusiform gyrus, right inferior temporal gyrus, right supramarginal gyrus, right precentral gyrus, and right operculum rolindic in the GHR-SZ group when compared to the FE-SZ and HC groups. These increases could reflect resiliency or compensatory mechanisms against SZ development, as well as neuroinflammation with disease vulnerability. The implications for the significantly decreased GM volumes in the left superior and middle temporal gyri in the GHR-SZ group compared to the HC group are less clear. GM volumes of these regions in FE-SZ were intermediate to the HC and GHR-SZ group though no significant differences were observed compared to either the HC or GHR-SZ groups. It is possible that we were underpowered to detect significant differences between the HC and FE-SZ groups in these regions. Additionally, there may be multiple or more complex processes underlying these findings, such as the interaction between neuroprotection and neural dysfunction. The mechanism underlying this finding remains incompletely understood and warrants further investigation.

The findings in this study are consistent with those from prior studies of HR-SZ and FE-SZ, including direct comparisons of these groups, particularly with observations of altered fronto-temporal and parietal regions in these samples; however there are some discrepancies involving regions such as the cingulate cortex, thalamus, and basal ganglia and in hemispheric lateralization that may be attributed to differences in ethnic background, sample size, definition of HR-SZ, medication exposure, and methodological techniques [3, 5, 6, 13, 15–20]. In general, our findings indicate abnormalities in frontal, temporal, and parietal regions involved in language, sensory processing, and somatosensory integration in SZ, as well as alterations in the cerebellum, for which there is mounting evidence of its role in cognitive processes in SZ in addition to its known roles in motor coordination and sensory integration [21–24]. This is of particular interest as prior studies suggest impaired multisensory integration (MSI) involving these regions in the development and pathophysiology of SZ[25–28]. Individuals with SZ appear to have selective deficits in audiovisual integration of linguistic stimuli, and the severity of MSI deficits may correspond with the modalities of hallucinations in SZ [25, 27, 29]. Postural sway, which reflects cerebellar function and integration of proprioceptive, vestibular, and visual inputs, has been shown to be increased in SZ and HR-SZ, and appears to correlate with negative symptoms in HR-SZ [26, 30, 31]. These findings regarding MSI in SZ, while limited, are not surprising given the convergent evidence for the central role of structural and functional dysconnectivity in the disorder [13, 32, 33].

There are limitations to the present study. The study was cross-sectional and could not examine changes related to psychosis conversion in GHR-SZ. Such observations would better elucidate neural markers that predict psychotic onset and differentiate from alterations reflecting vulnerability but not necessarily progression to disease onset in this population. Clinical characterization was limited in this study, and we were unable to correlate our findings with specific clinical variables. BPRS scores did not appear to have significant effects on the findings. Future investigations should include more extensive clinical and behavioral data including cognitive...
testing. Potential confounding effects by medication exposure and illness duration were mini-
mized in the study; however 47% of the FE-SZ participants received antipsychotics prior to scan-
ning. The mean duration of illness was 8 months in the FE-SZ group. Additional analyses did 
not reveal significant effects of medication and illness duration within each patient group on 
regional brain volume (S2 Table). However, we did not collect patient data regarding duration of 
medication exposure, which may be an important characteristic for future studies. Moreover, age 
and gender are key variables showing between-group differences across the clinical groups. Age 
and gender could therefore be related to brain maturity and confound observed across-group 
clinical differences. We therefore performed analysis to to test for interactions between age and 
group and gender and group for effects in regions identified in our three-group comparison anal-
yses. We did find that there were significant interaction effects in the vermis and bilateral mid-
dle/superior temporal gyri for the group×age interaction and vermis for group×gender 
interaction, which previous studies have also reported [34–36] (S1 Table). Although most regions 
did not show significant interaction effects, future experiments that explicitly control for demo-
graphic within the same cross-sectional designs are needed to validate the present finds.

In summary, significant differences were found in multiple brain regions including the fron-
tal, temporal, and parietal cortices as well as the hippocampus, occipital cortex, and cerebellum in 
comparison of GHR-SZ, FE-SZ, and HC groups in this study. Potential markers of vulnera-
bility, disease, and resiliency or compensatory mechanisms could be inferred based on the pat-
tern of observed differences, however further studies are needed for more definitive 
conclusions. Additionally, our findings in GHR-SZ and FE-SZ support implications from other 
studies of impaired MSI in SZ vulnerability and development. If MSI indeed is importantly 
involved in progression to SZ onset, studies of MSI in SZ may lead to novel and promising 
strategies for prevention and early intervention in high risk and affected individuals such as 
cognitive remediation or enhancement therapy targeting sensory integration[37].

Supporting Information

S1 Fig. Clusters showing significant differences in the three-group analysis (GHR-SZ, 
FE-SZ, and HC). p<0.001, cluster size = 218 (p<0.05 corrected). GHR-SZ: genetic high-risk 
schizophrenia; FE-SZ: first-episode schizophrenia; HC: healthy controls. Number labels repre-
sent clusters of significant difference in the three-group analysis and correspond to regions 
listed in S1 Table.

S1 File. Supporting Information. Part 1: Relationship between gray matter volume and clini-
cal information. Part 2: Detailed on narrowing threshold of whole brain GM VBM analyses.

S1 Table. The effects of age and gender on GM in healthy control, genetic high risk for 
schizophrenia and first episode schizophrenia groups. T value (P value). Results considered 
statistically significant at p<0.05 corrected. *p < 0.05 false discovery rate corrected. GM: Gray 
matter.

S2 Table. Correlations between clinical characteristics and GM volume in healthy control, 
genetic high risk for schizophrenia and first episode schizophrenia groups. T value(P value). *p< 0.05 false discovery rate corrected. GM = Gray matter; HC: healthy control; 
GHR-SZ: genetic high risk for schizophrenia; FE-SZ: first episode schizophrenia BPRS = Brief 
Psychiatric Rating Scale.
S3 Table. Clusters and corresponding regions showing significant differences between GHR-SZ, FE-SZ, and HC groups. GHR-SZ: genetic high-risk schizophrenia; FE-SZ: first-episode schizophrenia; HC: healthy controls. BA: Brodmann Area. MNI: Montreal Neurological Institute.

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Conceptualization: FW.
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Methodology: FW.
Project administration: FW YT.
Resources: QZ SW XJ HG YZ YT.
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Supervision: MC FYW FW.
Validation: MC FW.
Visualization: MC FYW FW.
Writing – original draft: MC FYW.
Writing – review & editing: MC FYW FW.

References
1. Bois C, Whalley HC, McIntosh AM, Lawrie SM. Structural magnetic resonance imaging markers of susceptibility and transition to schizophrenia: a review of familial and clinical high risk population studies. J Psychopharmacol. 2015; 29(2):144–54. doi: 10.1177/0269881114541015 PMID: 25049260.
2. Rubinov M, Bullmore E. Schizophrenia and abnormal brain network hubs. Dialogues Clin Neurosci. 2013; 15(3):339–49. PMID: 24174905; PubMed Central PMCID: PMCPMC3811105.
3. Thermenos HW, Keshavan MS, Juelich RJ, Molokots E, Whitfield-Gabrieli S, Brent BK, et al. A review of neuroimaging studies of young relatives of individuals with schizophrenia: a developmental perspective from schizotypia to schizophrenia. Am J Med Genet B Neuropsychiatr Genet. 2013; 162B(7):604–35. doi: 10.1002/ajmg.b.32170 PMID: 24132894.
4. Chung Y, Cannon TD. Brain imaging during the transition from psychosis prodrome to schizophrenia. J Nerv Ment Dis. 2015; 203(5):336–41. doi: 10.1097/NMD.0000000000000286 PMID: 25900551; PubMed Central PMCID: PMCPMC4414922.
5. Brent BK, Thermenos HW, Keshavan MS, Seidman LJ. Gray matter alterations in schizophrenia high-risk youth and early-onset schizophrenia: a review of structural MRI findings. Child Adolesc Psychiatr Clin N Am. 2013; 22(4):689–714. doi: 10.1016/j.chc.2013.06.003 PMID: 24012081; PubMed Central PMCID: PMCPMC3767930.
6. Nenadic I, Dietzek M, Schonfeld N, Lorenz C, Gussaw A, Reichenbach JR, et al. Brain structure in people at ultra-high risk of psychosis, patients with first-episode schizophrenia, and healthy controls: a
7. Lindgren M, Manninen M, Kalska H, Mustonen U, Laajasalo T, Moilanen K, et al. Predicting psychosis in a general adolescent psychiatric sample. Schizophr Res. 2014; 158(1–3):1–6. doi: 10.1016/j.schres.2014.06.028 PMID: 25015028.

8. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry. 2003; 60(12):1187–92. doi: 10.1001/archpsyc.60.12.1187 PMID: 14662550.

9. Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D, et al. Common variants conferring risk of schizophrenia. Nature. 2009; 460(7256):744–7. doi: 10.1038/nature08186 PMID: 19571808; PubMed Central PMCID: PMCPMC3077530.

10. Ripke S, O'Dushlaine C, Chambert K, Moran JL, Kahler AK, Akterin S, et al. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat Genet. 2013; 45(10):1150–9. doi: 10.1038/ng.2742 PMID: 23974872; PubMed Central PMCID: PMCPMC3828797.

11. Gurung R, Prata DP. What is the impact of genome-wide supported risk variants for schizophrenia and bipolar disorder on brain structure and function? A systematic review. Psychol Med. 2015; 45(12):2461–80. doi: 10.1017/S0033291715000537 PMID: 25858580.

12. Andreassen NC, Pressler M, Nopoulos P, Miller D, Ho BC. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. Biol Psychiatry. 2010; 67(3):255–62. doi: 10.1016/j.biopsych.2009.08.040 PMID: 19897178; PubMed Central PMCID: PMCPMC4668042.

13. Wheeler AL, Voineskos AN. A review of structural neuroimaging in schizophrenia: from connectivity to connectomics. Front Hum Neurosci. 2014; 8:653. doi: 10.3389/fnhum.2014.00653 PMID: 25202257; PubMed Central PMCID: PMCPMC4142355.

14. Parestrem O, Kubicki M, Shenton ME. In vivo imaging of neuroinflammation in schizophrenia. Schizophr Res. 2016; 173(3):200–12. doi: 10.1016/j.schres.2015.05.034 PMID: 26048294; PubMed Central PMCID: PMCPMC4668243.

15. Witthaus H, Kaufmann C, Bohner G, Ozgurdal S, Gudowski Y, Gallinat J, et al. Gray matter abnormalities in subjects at ultra-high risk for schizophrenia and first-episode schizophrenic patients compared to healthy controls. Psychiatry Res. 2009; 173(3):163–9. doi: 10.1016/j.psychres.2008.08.002 PMID: 19616415.

16. Chan RC, Di X, McAlonan GM, Gong QY. Brain anatomical abnormalities in high-risk individuals, first-episode, and chronic schizophrenia: an activation likelihood estimation meta-analysis of illness progression. Schizophr Bull. 2011; 37(1):177–88. doi: 10.1093/schbul/sbp073 PMID: 19633214; PubMed Central PMCID: PMCPMC3004195.

17. Nakamura K, Takahashi T, Nemoto K, Furuichi A, Nishiya S, Nakamura Y, et al. Gray matter changes in subjects at high risk for developing psychosis and first-episode schizophrenic patients compared to healthy controls. Psychiatry Res. 2009; 173(3):163–9. doi: 10.1016/j.psychres.2008.08.002 PMID: 19616415.

18. Chang EF, Raygor KP, Berger MS. Contemporary model of language organization: an overview for neurosurgeons. J Neurosurg. 2015; 122(2):250–61. doi: 10.3171/2014.10.JNS132647 PMID: 25423277.
24. Wynn JK, Jahshan C, Green MF. Multisensory integration in schizophrenia: a behavioural and event-related potential study. Cogn Neuropsychiatry. 2014; 19(4):319–36. doi: 10.1080/13546805.2013.866892 PMID: 24397786; PubMed Central PMCID: PMCPMC4103881.

25. Williams LE, Light GA, Braff DL, Ramachandran VS. Reduced multisensory integration in patients with schizophrenia on a target detection task. Neuropsychologia. 2010; 48(10):3128–36. doi: 10.1016/j.neuropsychologia.2010.06.028 PMID: 20600181; PubMed Central PMCID: PMCPMC2915827.

26. Bernard JA, Dean DJ, Kent JS, Orr JM, Pelletier-Baldelli A, Lunsford-Avery JR, et al. Cerebellar networks in individuals at ultra high-risk of psychosis: impact on postural sway and symptom severity. Hum Brain Mapp. 2014; 35(8):4064–78. doi: 10.1002/hbm.22458 PMID: 24464473; PubMed Central PMCID: PMCPMC4103881.

27. Tseng HH, Bossong MG, Modinos G, Chen KM, McGuire P, Allen P. A systematic review of multisensory cognitive-affective integration in schizophrenia. Neurosci Biobehav Rev. 2015; 55:444–52. doi: 10.1016/j.neubiorev.2015.04.019 PMID: 25956248.

28. Ronconi L, Casartelli L, Carna S, Molteni M, Arrigoni F, Borgatti R. When one is Enough: Impaired Multisensory Integration in Cerebellar Agenesia. Cereb Cortex. 2016. doi: 10.1093/ercor/bhw049 PMID: 26946125.

29. Mayer AR, Hanlon FM, Teshiba TM, Klimaj SD, Ling JM, Dodd AB, et al. An fMRI study of multimodal selective attention in schizophrenia. Br J Psychiatry. 2015; 207(5):420–8. doi: 10.1192/bjp.bp.114.155499 PMID: 26382953; PubMed Central PMCID: PMCPMC4629072.

30. Kent JS, Hong SL, Bolbecker AR, Klaunig MJ, Forsth JK, O'Donnell BF, et al. Motor deficits in schizophrenia quantified by nonlinear analysis of postural sway. PLoS One. 2012; 7(8):e41808. doi: 10.1371/journal.pone.0041808 PMID: 22870250; PubMed Central PMCID: PMCPMC3411581.

31. Dean DJ, Kent JS, Bernard JA, Orr JM, Gupta T, Pelletier-Baldelli A, et al. Increased postural sway predicts negative symptom progression in youth at ultrahigh risk for psychosis. Schizophr Res. 2015; 162(1–3):86–9. doi: 10.1016/j.schres.2014.12.039 PMID: 25601361; PubMed Central PMCID: PMCPMC4339540.

32. van den Heuvel MP, Fornito A. Brain networks in schizophrenia. Neuropsychol Rev. 2014; 24(1):32–48. doi: 10.1007/s11065-014-9248-7 PMID: 24500505.

33. Li T, Wang Q, Zhang J, Rolls ET, Yang W, Palaniyappan L, et al. Brain-Wide Analysis of Functional Connectivity in First-Episode and Chronic Stages of Schizophrenia. Schizophr Bull. 2016. doi: 10.1093/schbul/sbw099 PMID: 27445261.

34. Raz N, Gunning-Dixon F, Head D, Williamson A, Acker JD. Age and sex differences in the cerebellum and the ventral pons: a prospective MR study of healthy adults. AJNR Am J Neuroradiol. 2001; 22(6):1161–7. PMID: 11415913.

35. Torii Y, Iritani S, Sekiguchi H, Habuchi C, Hagikura M, Arai T, et al. Effects of aging on the morphologies of Heschl’s gyrus and the superior temporal gyrus in schizophrenia: a postmortem study. Schizophr Res. 2012; 134(2–3):137–42. doi: 10.1016/j.schres.2011.10.024 PMID: 22115995.

36. Womer FY, Tang Y, Harms MP, Bai C, Chang M, Jiang X, et al. Sexual dimorphism of the cerebellar vermis in schizophrenia. Schizophr Res. 2016. doi: 10.1016/j.schres.2016.06.028 PMID: 27401530.

37. Thorsen AL, Johansson K, Loberg EM. Neurobiology of cognitive remediation therapy for schizophrenia: a systematic review. Front Psychiatry. 2014; 5:103. doi: 10.3389/fpsyt.2014.00103 PMID: 25177300; PubMed Central PMCID: PMCPMC4133649.