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The insula–claustrum region and delusions in schizophrenia

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ABSTRACT

Objective: We examined the relationship between cerebral gray matter (GM) volume and severity of delusions and hallucinations in adults with schizophrenia.
Method: MRI scans in 43 patients with schizophrenia were acquired. Correlations were computed between GM volume and clinician ratings of hallucinations and delusions.
Results: The analysis revealed significant inverse correlations between ratings of the severity of delusions and volumes of the left claustrum and right insula. Significant correlations were not observed between cerebral GM volume and ratings of hallucinations.
Conclusion: The insula/claustrum region may be critical to the experience of delusions and more careful scrutiny of the claustrum in relation to schizophrenia appears warranted.

1. Introduction

Schizophrenia (SZ) is characterized by three partially overlapping domains of symptoms. These include positive, negative and disorganized symptoms. With the advent of neuroimaging techniques, attempts have been made to correlate symptoms of schizophrenia with brain structure and function in order to better characterize the pathophysiology of SZ. Using voxel-based morphometry or VBM (Ashburner and Friston, 2000), investigators have correlated regional cerebral gray matter (GM) volume or concentration with schizophrenia subtypes, global ratings of positive symptoms, as well as specific positive symptoms (McCarley et al., 1999; Ha et al., 2004; Pressler et al., 2005; Koutsouleris et al., 2008; Cascella et al., 2010; Nenadic et al., 2010a, 2010b). Imaging studies using region-of-interest (ROI) measurements have also found associations between volume changes in the temporal cortex (superior temporal gyrus and middle temporal lobe) and positive symptoms in schizophrenia, including hallucinations, delusions, and thought disorder (Barta et al., 1990, 1997; Shenton et al., 1992; Bogerts et al., 1993; McCarley et al., 1993; Flaum et al., 1995).

Applications of current VBM techniques have confirmed correlations of positive symptoms with temporal structures, as well as the prefrontal cortex and subcortical structures, such as the thalamus and the basal ganglia (Wright et al., 1995; Gaser et al., 2004; Koutsouleris et al., 2008; Nenadic et al., 2010b). As a follow-up to our earlier report of structural brain abnormalities associated with prominent negative symptoms of SZ, i.e., patients with the deficit syndrome (Cascella et al., 2010), the goal of this study was to extend our investigation of GM abnormalities associated with the presence and the severity of positive symptoms, specifically, hallucinations and delusions.

2. Method

2.1. Participants

Forty-seven adults with SZ were recruited primarily from outpatient clinics of the Johns Hopkins and Sheppard Enoch Pratt hospitals in Baltimore, Maryland, and 3 were recruited as inpatients and assessed immediately prior to discharge. All participants were 19 to 56 years of age, and met *DSM-IV* (American Psychiatric Association, 1994) criteria for schizophrenia, as assessed by a psychiatrist. Exclusion criteria included substance abuse within 6 months prior to entering the study or substance dependence within 12 months prior to entering the study; intellectual disability; and/or a history of neurological disorder or traumatic brain injury with >1 h loss of consciousness. Seven participants refused brain MRI scanning or produced unusable imaging data. Thus, 43 participants had complete neuropsychological, psychiatric, and imaging data. Only one participant in the present study also participated in our previous study (Cascella et al., 2010) from which we are extending our findings. This study was approved by the Johns Hopkins Medicine IRB. All participants gave written informed consent to participate.

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2.2. Clinical assessment

All diagnostic interviews and symptom ratings were conducted by a board-certified psychiatrist (N.G.C.) with extensive experience assessing and diagnosing schizophrenia. Positive and negative symptoms associated with schizophrenia were assessed using Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS; Andreasen and Olsen, 1982), and this assessment was completed within 48 h of the MRI for all participants.

Additionally, participants completed a comprehensive neuropsychological assessment. We used scores on the Hopkins Adult Reading Test (HART; Schretlen et al., 2009) to estimate premorbid full scale IQ. No other neuropsychological data were used for this paper.

2.3. Imaging methods

Structural magnetic resonance imaging (MRI) brain scans were obtained with a Philips Achieva 3.0 T machine. We obtained 3D magnetization prepared rapid gradient echo (MPRAGE) images with sensitive encoding (SENSE). T1-weighted images in contiguous 1.0 mm thick slices were acquired in the coronal plane for each participant. Given variability in head and brain size among participants, the number of slices acquired varied somewhat, but it did not exceed 200 contiguous slices. The acquisition parameters were TR/TE = 7.9/3.7 ms, flip angle = 8°, FOV = 200 × 200 mm, voxel size of $1 \times 1 \times 1$ mm^3 and in-plane matrix of 256 × 256.

The whole brain images were preprocessed with Statistical Parametric Mapping (SPM5; http://www.fil.ion.ucl.ac.uk/spm/software/spm5/) software. We then implemented voxel-based morphometry (Ashburner and Friston, 2000) with a Dell workstation using Matlab version 7.9 (The MathWorks, Natick, MA), following the unified segmentation method of SPM5 (Ashburner and Friston, 2005). Non-brain regions were removed from the normalized images using MRIcro (http://www.mricro.com). The normalized images were then segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) probability maps. Segmentation was based on a cluster analysis to identify each voxel's signal intensity, together with *a priori* information about the spatial distribution of these tissue segments in normal adults derived from probability maps. The GM images were smoothed using an 8 mm full width at half-maximum isotropic Gaussian kernel. Modulating GM images removes the effect of non-linear transformation of the images on local tissue volumes—applying the Jacobian determinants of the transformation parameters yields corresponding changes of voxel values in areas that were increased or decreased by the transformation. These modulated images were used for statistical analyses of GM volumetric differences. MNI coordinates were generated by SPM5 and Talairach labels by Talairach Client (Lancaster et al., 2000) after conversion of MNI coordinates to Talairach coordinates by the mni2tal algorithm (Lancaster et al., 2007) implemented within GingerALE (Laird et al., 2005).

2.4. Statistical analysis

Descriptive statistics were performed to characterize the demographic and clinical characteristics of this sample. The images were analyzed with the general linear model executed in SPM5 to evaluate the relationship between GM volume and ratings on the SAPS Hallucinations and Delusions subscales, as well as SAPS Global Rating. Given the demographics of our sample, we controlled for race, age, and total intracranial volume (TICV) in the analyses. TICV was calculated as the sum of GM, WM, and cerebrospinal fluid (CSF). Furthermore, TICV was used as a covariate in place of sex, as it allowed us to simultaneously control for individual and sex-related differences in TICV. We did not apply an extent threshold for these analyses, but do not report any clusters containing fewer than 50 voxels. A false discovery rate (FDR) error correction method was used to maintain a Type I error rate of $p < 0.05$ for all positive findings relating GM volume to positive symptom ratings. An atlas-based method was utilized in order to identify any specific brain areas that significantly correlated with SAPS scores.

3. Results

Descriptive statistics classifying the demographic and clinical characteristics of the study sample are presented in Table 1.

Based on assessment of positive symptoms, 49% of participants in our sample were suffering from hallucinations (predominantly auditory) and 70% from delusions at the time of their MRI scans. The expression of hallucinations and delusions in our sample is similar to that reported in previous imaging studies that used the SAPS to assess severity of hallucinations and delusions (Goldstein et al., 1999; Crespo-Facorro et al., 2000). This study sample included a statistically significant preponderance of male patients (chi-square $(1, 43) = 8.40$; $p = 0.04$). Mean age ± SD of the participants was 39.6 ± 10.7. The sample consisted of 22 African–Americans, 17 Caucasians and 4 Asians. All patients participating in this study were being treated with antipsychotic medications (76% with atypical antipsychotics and 36% with typical antipsychotics). In addition to antipsychotic medications 25% of the participants were also taking an antidepressant, and 12% of the participants were also taking an anticonvulsant medication at the time of study.

3.1. Gray matter volume and positive symptoms

The SAPS Delusion subscale was inversely correlated with left claustrum and right insula GM volume after correcting for multiple comparisons ($p < 0.05$). No significant correlations were found between GM volumes and the SAPS Global Rating score or the SAPS Global Rating Hallucinations subscale after correcting for multiple comparisons.

The lack of significant correlations between GM volumes and the SAPS Global Rating score or the SAPS Global Rating Hallucinations subscale was discrepant from previous findings in the literature (Goldstein et al., 1999; Crespo-Facorro et al., 2000; Paillere-Martinot et al., 2001). We explored possible reasons for this discrepancy by conducting some additional analyses to better characterize our sample and further explore our initial findings.

Table 1
Demographic, clinical and CNS volumetric characteristics of the patients.

Characteristic	SZ ($n = 43$)
Age, years ($M \pm SD$)	39.6 ± 10.7
Sex, male/female (%)[1]	72:28
Race, white/black/other (%)	40:51:9
Education, years ($M \pm SD$)	12.4 ± 2.3
Est. premorbid IQ ($M \pm SD$)	96.2 ± 11.3
Age at onset, years ($M \pm SD$)	21.7 ± 6.7
# Hospitalizations ($M \pm SD$)	4.6 ± 4.2
Duration of illness ($M \pm SD$)	18.7 + 10.2
SANS sum ($M \pm SD$)	7.8 ± 4.2
SAPS sum ($M \pm SD$)	4.5 ± 3.6
SAPS Hallucinations ($M \pm SD$)	1.6 ± 1.9
SAPS Delusions ($M \pm SD$)	2.0 ± 1.6
Typical neuroleptics (%)	36.4
Atypical neuroleptics (%)	75.8
Any antidepressant (%)	25.0
Lithium (%)	3.0
Any anticonvulsant (%)	12.1
Gray matter volume mm^3 ($M \pm SD$)	598 ± 68
White matter volume mm^3 ($M \pm SD$)	492 ± 51

Note: Estimated premorbid IQ based on the HART.