


Volume and Asymmetry Abnormalities of Insula in Antipsychotic-Naive Schizophrenia: A 3-Tesla Magnetic Resonance Imaging Study

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ABSTRACT

Context: Insula, which is a vital brain region for self-awareness, empathy, and sensory stimuli processing, is critically implicated in schizophrenia pathogenesis. Existing studies on insula volume abnormalities report inconsistent findings potentially due to the evaluation of 'antipsychotic-treated' schizophrenia patients as well as suboptimal methodology. **Aim:** To understand the role of insula in schizophrenia. **Materials and Methods:** In this first-time 3-T magnetic resonance imaging study, we examined antipsychotic-naive schizophrenic patients ($N=30$) and age-, sex-, handedness- and education-matched healthy controls ($N=28$). Positive and negative symptoms were scored with good interrater reliability (intraclass correlation coefficient (ICC) >0.9) by using the scales for negative and positive symptoms. Gray matter volume of insula and its anterior/posterior subregions were measured by using a three-dimensional, interactive, semiautomated software based on the valid method with good interrater reliability (ICC >0.85). Intracranial volume was automatically measured by using the FreeSurfer software. **Results:** Patients had significantly deficient gray matter volumes of left ($F=33.4$; $P<0.00001$) and right ($F=11.9$; $P=0.001$) insula after controlling for the effects of age, sex, and intracranial volume. Patients with predominantly negative symptoms had a significantly deficient right posterior insula volume than those with predominantly positive symptoms ($F=6.3$; $P=0.02$). Asymmetry index analysis revealed anterior insular asymmetry to be significantly reversed (right $>$ left) in male patients in comparison with male controls (left $>$ right) ($t=2.7$; $P=0.01$). **Conclusions:** Robust insular volume deficits in antipsychotic-naive schizophrenia support intrinsic role for insula in pathogenesis of this disorder. The first-time demonstration of a relationship between right posterior insular deficit and negative symptoms is in tune with the background neurobiological literature. Another novel observation of sex-specific anterior insular asymmetry reversal in patients supports evolutionary postulates of schizophrenia pathogenesis.

Key words: *Insula, schizophrenia, volumetry*

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INTRODUCTION

Schizophrenia is among the most severe neuropsychiatric disorders that has been associated with deficits involving various brain regions.^[1] The defining features of schizophrenia involve disturbances in self-awareness, empathy, and sensory processing.^[2] Interestingly, insula – an important brain region in the limbic neuroanatomical

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circuit – is critically implicated to subserve self-awareness,^[3] empathy^[4] and sensory stimuli processing.^[5] It is divided into the anterior insula and the posterior insula with a central insular sulcus dividing the both. Both the anterior insula and the posterior insula have different cytoarchitectural appearance as well as function.

The anterior insula is made of agranular region with an adjacent dysgranular area. It has extensive connections with the limbic system and higher order visual areas. Functionally, it specializes in emotional processing of the interoceptive awareness,^[3] anticipation, and the evaluation of the emotional stimuli^[5] and self-awareness.^[6] The neurons in the anterior insula almost function like mirror neurons,^[7] which generate empathy and identification of the boundaries. The posterior insula encompasses granular region with the adjacent dysgranular area. It has an extensive connection with the higher order visual areas, auditory processing, and somatosensory areas.^[8,9] It specializes in the function of the directly experienced, multimodal sensory processing.^[4,5,10] It is reasonable to hypothesize that the many of the functional and the behavioral deficits that we observe in schizophrenia may involve insula considering its function and the connections with other areas.

Gray matter volume abnormalities of insula in schizophrenia have been examined by previous magnetic resonance imaging (MRI) studies with disparate findings. Some studies have noted that there is an overall decrease in the gray matter of insula.^[11-20] Similarly, deficits in gray matter specific to the anterior^[17] or posterior^[18] insula were also noted in schizophrenia. Among high-risk subjects, the insular volume is lower in people who develop psychosis subsequently;^[21,22] compared to people who did not develop schizophrenia. Negative correlation of insular volume with the positive symptoms has been reported,^[23-25] which could not be replicated in other studies;^[20,26] Hallucinations in schizophrenia were associated with a bilateral decrease in the insular volume.^[27] The inconsistent findings in the existing studies are potentially due to the evaluation of ‘antipsychotic-treated’ schizophrenic patients as well as suboptimal methodology. The need to look into the relationship between the insular volume and schizophrenia – especially in antipsychotic-naive patients – is very apt to the current context.

In this present study, to the best of our knowledge, we describe, for the first time, the 3-T MRI evaluation of insular gray matter volume with its subregions in antipsychotic-naive schizophrenia patients ($N=30$) in comparison with matched healthy controls ($N=28$). On the basis of background studies (as reviewed above), we hypothesized that the patients will have significantly deficient gray matter volume of insula.

MATERIALS AND METHODS

Subjects

The study sample consisted of 30 antipsychotic-naive schizophrenic patients and 28 age-, sex-, handedness-matched healthy controls. Patients meeting the Diagnostic and Statistical Manual of mental disorders – IV (DSM-IV) diagnostic criteria for schizophrenia were recruited from the clinical services of National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, Karnataka, India. Diagnosis was established by applying Mini International Neuropsychiatric Interview–Plus (MINI-Plus)^[28] and it was confirmed by another experienced psychiatrist through an independent clinical interview. The details related to the illness onset and antipsychotic-naive status were carefully ascertained by reliable information obtained from at least one first-degree relative. None of the patients were ever treated with any psychotropic medications including antipsychotics. Also, none had received electroconvulsive therapy previously. The psychopathology was assessed by using the Scale for the Assessment of Positive Symptoms (SAPS)^[29] and the Scale for the Assessment of Negative Symptoms (SANS)^[30] with good interrater reliability as assessed by the intraclass correlation coefficients greater than 0.9.

Healthy comparison subjects ($n=28$) were recruited with the contact help of friends and volunteers through ‘word of mouth’. Through these contacts, the healthy controls were chosen from different backgrounds to suit the varying sociodemographic status of the patients. Healthy controls were evaluated in detail to rule out history suggestive of psychiatric illness and were also screened by using MINI-Plus^[28] and comprehensive mental status examination. None of the control subjects had a family history of psychosis in any of their first-degree relatives.

Only right-handed subjects were included in the study and the left-handed subjects were excluded as ascertained by the Annett’s questionnaire.^[31] None of the subjects had any contraindication to MRI. None had any neurological/systemic illness, seizure disorder, and history suggestive of delayed developmental milestones or history of significant head injury. Neither the patients nor the controls had any clinically significant nutritionally deprived state. The substance-use history was carefully ascertained from the subject with corroboration by at least one first-degree relative. Patients and controls did not have current or past history of alcohol abuse or dependence. None used cannabis, opiates, stimulants, or any other illicit drugs of abuse. Female subjects neither were pregnant

nor were within the postpartum period. None of the subjects had dyskinesia [as assessed using the Abnormal Involuntary Movements Scale^[32] or parkinsonism [as assessed using the Simpson and Angus Scale.^[33] Clinical assessments and MRI acquisition were performed on the same day before starting antipsychotics. After a complete description of the study to the subjects (and care givers of patients), written informed consent was obtained. The institute's ethics committee approved the study.

MRI scanning protocol

MRI was done with a 3.0-T scanner. T1-weighted images (with capability for three-dimensional reconstruction) were acquired by using the following parameters: (repetition time) TR=8.1 ms, (echo time) TE=3.7 ms, nutation angle=8°, (field of view) FOV=256 mm, slice thickness=1 mm without interslice gap, (number of excitation pulses) NEX=1, matrix=256×256. The images were transferred onto a personal computer platform. The images were randomly coded and stored with coded identification to prevent any bias during the study.

Semiautomated volumetry of insula

Insula is a triangular structure folded deep in the lateral sulcus between the temporal and the frontal lobe covered by opercula. Circular sulcus outlines the insula. The apex of the insula is pointed toward anterior and inferior sides and the base of the triangle toward the superior side. Each insula is divided into the anterior insula and the posterior insula by the central insular sulcus.^[34]

The specific guidelines for insula volume measurement were compiled by the first author (H.S.V.) after exhaustive literature search to arrive at a set of validated steps that are described as below. The insula of both sides were measured with the open-source software 3D slicer (<http://www.slicer.org/>) by using methods followed previously.^[35] The tracing was done manually. The central insular sulcus was marked in the most prominently appearing slice by using the fiducial points in the sagittal section. The anterior and posterior points were also marked by using the fiducial points [Figure 1].

The tracing was done in coronal slices [Figure 2]. The most rostral slice containing the insular cortex and the slice containing the fusion of the superior and inferior insular sulcus were taken as the anterior and the posterior boundaries, respectively, following methods used previously.^[22]

All four subregions (right anterior insula, right posterior insula, left anterior insula, and left posterior insula) were traced separately and labeled. The tracing was

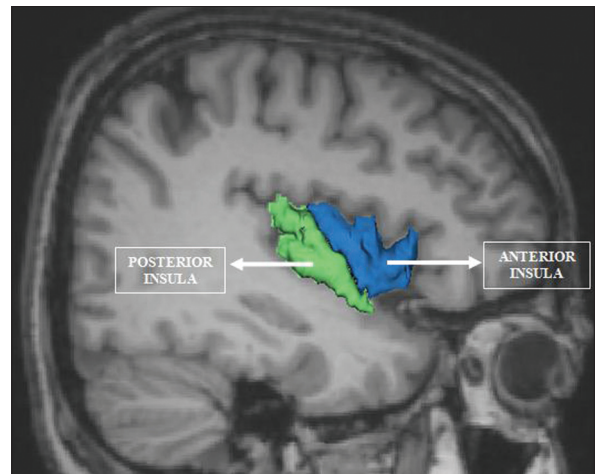


Figure 1: Sagittal section of MRI showing the 3D reconstruction of the anterior (blue) and posterior (green) subregions of insula, with the central insular sulcus dividing them

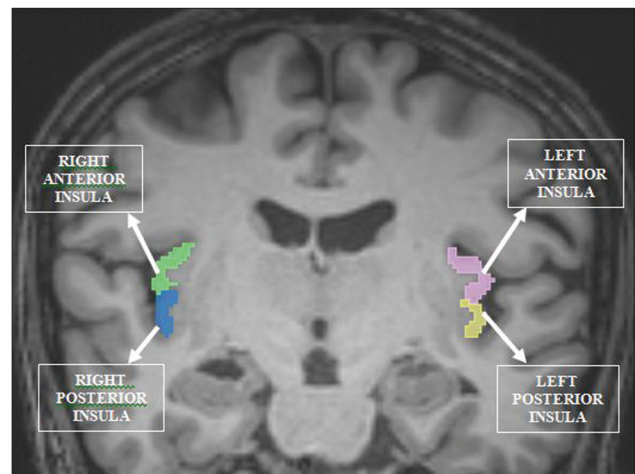


Figure 2: Coronal section of MRI showing the tracings of all four subregions of insula

checked and confirmed by viewing in the sagittal section for accuracy. The intracranial volume, which was used as a covariate in statistical analyses to control for the potential confounding effect of the global brain size, was automatically computed by using established methods with the FreeSurfer software.

The first author (H.S.V.) was trained for the tracing and the use of software by researchers with experience in neuroimaging research (G.V.S. and S.V.K.). The volume was measured by the first author by using coded MRI images; this ensured methodological rigorosity by keeping the rater blind to the subject status. The reliability of insular volume measurement was established by the first author along with another researcher, tracing five subjects with excellent concurrence as measured by the intraclass correlation (ICC). Five subjects were randomly chosen and traced by two raters (H.S.V. and V.S.) for interrater reliability (ICC>0.85).

Statistical analysis

The statistical analysis was performed by using the statistical package for social sciences, version 15.0. The sociodemographic data were analyzed by using the independent samples *t* test and the chi-square test. In addition to comparative analyses for volume deficits using the analysis of covariance (controlling for the potential confounding effects of age, sex, and intracranial volume), we performed two analyses examining (a) asymmetry of insula and (b) effect of predominant symptom status.^[36]

For the analysis of insula asymmetry, the insula asymmetry index was calculated separately for the anterior and posterior subregions by using the following formula:

$$\frac{\text{Left-side volume} - \text{Right-side volume}}{\text{Left-side volume} + \text{Right-side volume}}$$

The insula asymmetry index was subsequently compared between patients and controls by using the independent samples *t* test.

For the analysis of the effect of predominant symptom status, a ratio was obtained by dividing the total positive syndrome score by the total negative syndrome score with a priori definition of predominantly positive syndrome as having a ratio of >1 and predominantly negative syndrome having a ratio of <1.^[36] A comparative evaluation of the effect of predominant symptom status was done within the patients' group by using analysis of covariance controlling for the potential confounding effects of age and intracranial volume. Correlational analyses were performed to examine for any potential relationship between various clinical parameters (age at onset, duration of untreated psychosis, and symptom scores) and volumes of insular subregions.

RESULTS

Patients and controls were not significantly different in age and sex ratio [Table 1]. The clinical profile of patients (age at onset, duration of untreated psychosis, and symptom scores) is given in Table 1.

Insular volume analyses

Patients had significantly deficient gray matter volumes of the left insula ($F=33.4$; $P<0.00001$) as well as the right insula ($F=11.9$; $P=0.001$) than do healthy controls [Table 2, Figures 3 and 4]. The significance of deficits persisted in the left insula even in subregion analyses, whereas that in the right insula did not [Table 3].

Table 1: Clinical characteristics of study subjects

Variable	Patients (n=30)	Controls (n=28)	χ^2/t^*	P
Age (years)	29.7±7.3	27.5±7.1	t=1.1	0.6
Sex ratio (males/females)	16:14	14:14	$\chi^2=0.7$	0.8
Age at onset (years)	27.7±6.5	–	–	–
Duration of untreated psychosis (months)	38.1±34.6	–	–	–
Positive syndrome score	21.5±6.6	–	–	–
Negative syndrome score	27.1±15.9	–	–	–

* χ^2 , chi-squared test; *t*, independent sample *t*-test

Table 2: Comparisons of insular volume (in milliliters) between patients and controls

Brain region	Status	Mean ± SD	F*	P
Left insula	Patient	4.5±0.5	33.4	0.00001
	Control	4.9±0.6		
Right insula	Patient	4.6±0.5	11.9	0.001
	Control	4.9±0.7		

*ANCOVA: a statistic controlling the potential confounding effects of age, sex, and intracranial volume

Table 3: Volume (in milliliters) of insular subregions in patients and controls

Brain region	Mean±SD		F*	P
	Patients (n=30)	Controls (n=28)		
Left anterior insula	3.0±0.42	3.4±0.52	6.4	0.014
Left posterior insula	1.4±0.22	1.6±0.25	6.1	0.017
Right anterior insula	3.1±0.41	3.3±0.55	2.0	0.162
Right posterior insula	1.5±0.32	1.7±0.32	3.6	0.065

*ANCOVA: a statistic controlling the potential confounding effects of age, sex, and intracranial volume

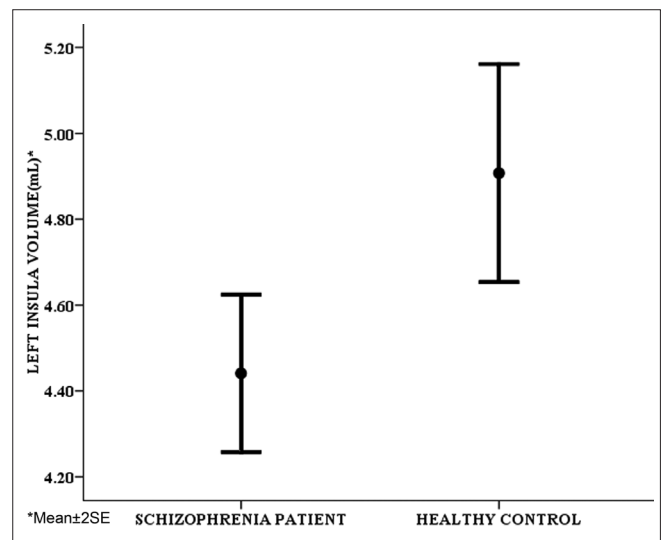


Figure 3: Left insular volume between patients and controls

Asymmetry index analysis

Asymmetry index analysis revealed anterior insular asymmetry to be significantly reversed (right>left) in male patients ($-0.01±0.03$) in comparison with male controls ($0.03±0.05$) (left>right) ($t=2.7$; $P=0.01$).

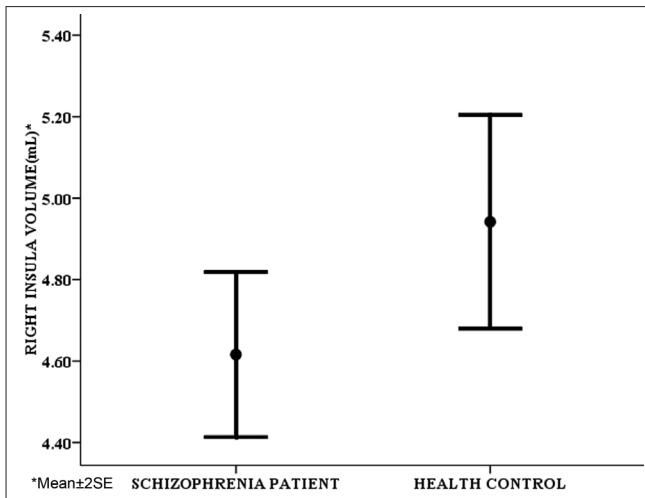


Figure 4: Right insular volume between patients and controls

Effect of predominant symptom status

Schizophrenic patients with predominantly negative symptoms ($N=21$) (1.5 ± 0.3) had significantly deficient gray matter volume of the right posterior insula in comparison with those of predominantly positive symptoms ($N=9$) (1.6 ± 0.2) ($F=6.3$; $P=0.02$) whereas other insular subregions did not differ significantly [Figure 5].

We did not observe any significant correlation between clinical parameters (age at onset, duration of untreated psychosis, and symptom scores) and volumes of insular subregions.

DISCUSSION

To the best of our knowledge, this is the first study to apply the high-resolution 3-T MRI to examine insular volumetry in antipsychotic-naive schizophrenic patients. Our study found statistically significant volumetric deficits in insula in patients with schizophrenia when compared to healthy controls. Patients with predominantly negative symptoms had significantly deficient right posterior insular volume than those with predominantly positive symptoms. Asymmetry index analysis revealed anterior insular asymmetry to be significantly reversed (right>left) in male patients in comparison with male controls (left>right).

As explained earlier, insula is a vital structure for processing the emotional stimuli, empathy, self-awareness, and identification of boundaries. It is essential that the insular volume is intact for the normal processing of the emotional and the sensory stimuli. It has been observed earlier that the left insula has larger volume than does the right insula. Within each insula, the anterior insula has larger volume compared to the

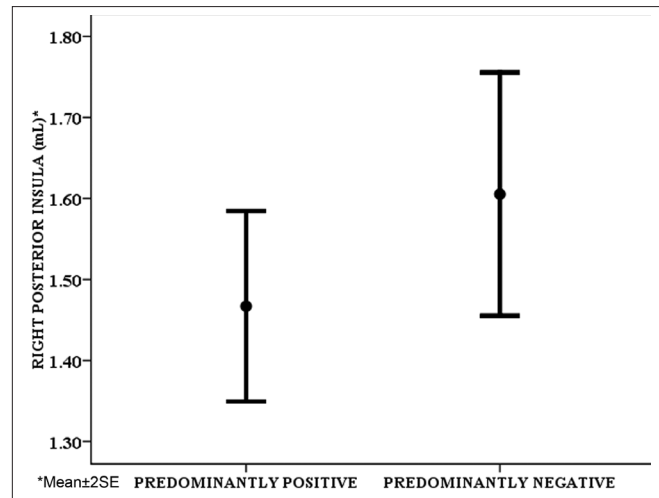


Figure 5: Right posterior insular volume comparison between predominantly positive, negative syndrome patients

posterior insula. There has been a difference in the volume of the insula in men and women, with insula in men being larger in volume.

This study observed a significant volume deficit of insula in schizophrenic patients. This might also explain the various symptom profiles of patients and the psychopathology, such as the loss of boundaries, lack of emotional reactivity, and poor empathy. The functions of the insula and the deficits in schizophrenia correlate well. This supports the earlier findings of insular volume deficits in patients with schizophrenia.^[11,12,19,37] The left-side involvement appears to be more severe than the right side; this finding in our study supports the earlier studies which have explained a similar trend.^[38]

We were able to demonstrate for the first time that right posterior insular volume had an inverse relation with negative symptoms, although no statistically significant relation was found between positive symptoms and insular volume. This novel finding of ours has not been evaluated in the previous studies even though there has been evidence regarding the association of the right posterior insula with poor insight.^[39] Any loss of gray matter volume in insula will lead to disturbance in its functions as explained earlier. It is reasonable to hypothesize that the loss in volume may lead to the genesis of negative symptoms; hence, the more the negative symptoms, the more is the loss of gray matter volume. Specifically, we were able to demonstrate significant volume deficits in right posterior insula in patients with predominantly negative symptoms [Table 2]. The role of the right posterior insula and its association with negative symptoms of schizophrenia needs further systematic exploration in future studies.

Another novel finding in our study is the reversal of

the asymmetry in the right–left insula in male patients. Male patients had larger right insular volume compared to left insular volume, which is contrary to the fact that the left insula is larger than the right insula in normal individuals.

The above reversal is not noted in female patients. Reversal has been explained to be a process of brain evolution where there has been a significant difference in the male and female brain architecture. Female sociality is more closely related to neocortex volume, but male sociality, which is more competitive and combative, is more closely related to subcortical units, notably those associated with emotional responses.^[40,41] Insula being the structure to process the emotional stimuli and also considered to be a part of the limbic system has a significant role in etiopathogenesis of schizophrenia. The left-sided insular volume deficits in male patients than in controls lead to the reversal of asymmetry. The reversal has also been noted in other brain structures in relation to schizophrenia and attributed to the anomalous brain asymmetry as an evolutionary concept.^[42,43]

Methodological issues

This is the first study to examine antipsychotic-naïve schizophrenic patients for neuroanatomical correlates of symptoms in schizophrenia and its association with insular volume by using 3-T MRI scans. Some of the other methodological advantages of the study include the following: (1) antipsychotic-naïve status of the patients during the assessments; (2) MINI-Plus to establish the diagnosis of the patients; (3) independent confirmation of the diagnosis by an experienced psychiatrist; (4) reliable methodology – good interrater reliability for insular cortex volume measurements; (5) measurements of subregions of insula; (6) age-, sex-, and handedness- matched controls; (7) use of 1-mm MRI slices with no interslice gap; and (8) first-time use of 3-T MRI scan in drug-naïve patients.

Implications

The findings of our study points toward the potential neural basis involving insula in the pathogenesis of schizophrenia. In addition to the previous evidences for the involvement of insula in schizophrenia, the association of the negative symptoms with more volume deficits in right posterior insula specifically emphasizes the need to look at the particular area in the insula in schizophrenia and its various symptom dimensions. This approach can potentially lead to better understanding of the biological basis of schizophrenia and its etiopathogenesis. Asymmetry is noted and this might point toward the evolutionary perspective and explain the origins of schizophrenia from a ‘distal etiological model’. The above findings can also be used to study the high-risk subjects for schizophrenia that

can be used in predicting the onset and progression as well as understanding its neurobiology.

CONCLUSION

Insular volume is significantly deficient in patients with schizophrenia, and especially right posterior volume deficits are noted in patients of schizophrenia with predominantly negative symptoms. Asymmetry of the insula on the right side, especially in men, is noted. The findings of our study support the involvement of the insula in schizophrenia and shed more light on the involvement of specific areas in negative symptoms that needs to be systematically studied in the future studies.

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