Insular Cortex Abnormalities in Schizophrenia: Relationship to Symptoms and Typical Neuroleptic Exposure

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Background: *The insular cortex is a limbic integration region engaged in emotional and cognitive functions. Previously, we found that neuroleptic-naïve subjects had abnormally small insular volumes compared with control subjects, with volume directly related to severity of psychotic symptoms.*

Methods: *To further investigate insular cortex abnormalities and their functional correlates, we measured insular gray matter volume and cortical surface size, using magnetic resonance images among 30 patients with schizophrenia and a matched control group. The sample was designed to represent a variety of phenomenologic profiles to provide sufficient variance in multiple measures, including severity of illness and exposure to neuroleptics (typical only).*

Results: *There were no significant differences in morphology between patients and control subjects; however, among patients, psychotic symptoms were inversely correlated with insular volume, replicating our previous finding in neuroleptic-naïve subjects. Neuroleptic exposure had a specific effect on insular morphology: increasing drug exposure (measured in dose-years) correlated with larger insular volume.*

Conclusions: *This effect of neuroleptic exposure might account for the lack of difference in structural measures in this more chronic sample, whereas the initial study on neuroleptic-naïve subjects showed group differences. Further research is needed to investigate the potential relationship between changes in insula volume from neuroleptic exposure and clinical outcome.*

Key Words: Schizophrenia, brain, insula, gray matter, tomography

The insular cortex has been associated with the integration of sensory phenomena specifically mediating temporally defined auditory-visual interaction at an early stage of cortical processing (Bushara et al 2001; Calvert 2001). As such, the insular cortex promises to be a fertile area of investigation into the psychotic symptoms of schizophrenia, which have been linked to the misinterpretation and confusion of internal and external perceptions (Brebion et al 1998; Frith and Dolan 1997). Additionally, allocortical and mesocortical regions, especially those within the limbic system, are involved in emotional and cognitive functions relevant to schizophrenia (Mega et al 1997).

Structural imaging studies have shown the insula to have morphologic abnormalities in subjects with schizophrenia. Goldstein et al (1999) reported volumetric reduction of insular cortex in structural imaging studies with chronic medicated schizophrenic patients. In a previous study (Crespo-Facorro et al 2000), we found marked deficits in left insular cortical surface area and volume of drug-naïve first-episode schizophrenic patients as compared with control subjects. Moreover, these structural abnormalities were directly related to the severity of psychosis. We also found decreased blood flow in the right insula on positron emission tomography studies in patients with chronic schizophrenia (Kim et al 2000). More recently, with a single photon emission computed tomography technique, patients with major depression with psychotic features were found to have a focus of decreased regional cerebral blood flow in the right inferior frontal cortex compared with nonpsychotic depressed patients, with the voxel of maximal significance in the insula (Skaf et al 2002). This finding suggests that the insula might be involved in psychotic symptoms that are not specific to schizophrenia. Finally, in a unique structural study, Shapleske et al (2002) used automated voxel-wise analyses to compare hallucinating and nonhallucinating patients with schizophrenia and found a single region of reduced gray matter tissue proportion affecting the left insula and adjacent temporal lobe.

Changes in brain structure and blood flow in response to neuroleptic exposure have been well documented for the basal ganglia (Corson et al 1999, 2002). In addition, recent studies from our group have shown regions of the superior-temporal plane and the anterior cingulate gyrus to have similar effects (i.e., cortical volume changes in response to typical neuroleptics [Crespo-Facorro, in press; Kopelman et al, in press]). To date, no study has evaluated morphologic change in the insular cortex in relation to neuroleptic exposure.

The current study was designed to expand on our previous report of insular morphologic abnormalities in a neuroleptic-naïve sample by looking at a different sample that included medication exposure. Morphology of the insula was evaluated in a separate sample of male patients with schizophrenia, designed to represent a wide variety of phenomenologic variables, including neuroleptic exposure. Morphologic measures were compared with those from a matched healthy control sample, and the relationship of structure to clinical variables was explored through correlation analysis.

Methods and Materials

Subjects

All patients (n = 30) were inpatients at the Mental Health Clinical Research Center at the University of Iowa Hospitals and Clinics. Exclusion criteria included a history of seizure disorder, severe head trauma resulting in loss of consciousness, brain surgery, and mental retardation. Because structural symmetry of

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cortical structures has been shown to be affected by gender and handedness, the sample was restricted to right-handed men. In addition, because atypical neuroleptics have been shown to have a different effect on the morphology of brain tissue compared with typical neuroleptics (Corson et al 1999), subjects who had been treated with typical neuroleptics only were included. That is, none of them had ever received such atypical neuroleptics as clozapine, risperidone, olanzapine, or quetiapine fumarate. Currently, the vast majority of patients with schizophrenia are treated with atypical neuroleptics. It is important to note that the patients in the current study were assessed in the early to mid-1990s, when atypical neuroleptics were just being introduced. Therefore, at the time, these patients were a representative sample of the patient population as a whole.

Of the 30 patients, 6 were "first episode" (defined as first psychiatric hospitalization), 11 were "recent onset" (first hospitalization within the last 5 years), and the remaining 13 were "chronic" (more than 5 years since the first hospitalization). There is no overlap in patient samples between our previously reported study of insular morphology (Crespo-Facorro et al 2000) and the present study.

All patients met DSM-III-R criteria for schizophrenia and were evaluated with the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al 1992). Clinical symptoms were rated with the Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1983) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen 1984). On the basis of prior longitudinal factor analysis (Arndt et al 1995), summary scores for three dimensions of symptoms (psychotic, negative, and disorganized) were calculated according to sums of global scores from the SANS/SAPS. The psychotic symptom dimension was the sum of global scores for hallucinations and delusions. The negative symptom dimension score was the sum of global scores for alogia, affective flattening, avolition-apathy, and anhedonia-asociality. The disorganized symptom dimension comprised the global scores of positive formal thought disorder, disorganized/bizarre behavior, and inappropriate affect.

The "dose-year" formula (Miller et al 1995) was used to measure neuroleptic exposure. This required conversion of neuroleptic medication to chlorpromazine equivalents (Davis 1974). Exposure was calculated over time and weighted for dose with this formula: X milligrams - Y years/100. All subjects had been exposed to neuroleptics at the time of scanning. Exposure ranged from .5 to 650 "dose-years."

The control subjects consisted of 30 healthy men, individually matched with the patients for age and handedness. Control subjects were recruited from the community through a newspaper advertisement. They had no current or past history of psychiatric, neurologic, or general medical illness, including substance abuse, as determined through an abbreviated version of the CASH. All subjects gave written informed consent, in accordance with the Human Subjects Institutional Review Board of the University of Iowa. Table 1 summarizes the demographic characteristics of the two groups.

There were no significant differences between groups in age, height, or parental socioeconomic status. As expected, there was a significant difference in education between groups, as measured in years [control subjects = 14.30 (2.07); patients = 12.83 (2.42); $t(58) = 2.52$; $p < .02$].

Table 1. Demographic and Clinical Characteristics in Patients with Schizophrenia Compared with Healthy Volunteers

	Patients ($n = 30$)	Control Subjects ($n = 30$)
Age (y)	33.5 (10.6)	33.7 (7.9)
Height (cm)	175.9 (9.9)	177.9 (7.6)
Parental Socioeconomic Status	2.97 (.77)	2.93 (.52)
Subjects Educational Level (y)[a]	12.83 (2.42)	14.30 (2.07)
Duration of Illness (wk)	109.4 (112.9)	N/A
Dose-Years	29.55 (45.08)	N/A
Symptoms		
Negative symptoms (Scale, 1–20)	11.43 (3.86)	N/A
Disorganized symptoms (Scale, 1–15)	6.63 (2.86)	N/A
Positive symptoms (Scale, 1–10)	4.87 (3.31)	N/A
Global severity (Scale, 1–45)	22.9 (7.55)	N/A

Values given as mean (SD).
[a]df = 58; $p \leq .05$.

MRI Acquisition

All multimodal magnetic resonance imaging (MRI) scans were obtained at the University of Iowa Hospitals and Clinics with a 1.5-Tesla General Electric SIGNA System (GE Medical Systems, Milwaukee, Wisconsin). Three-dimensional T1-weighted images, with a spoiled grass sequence, were acquired in the coronal plane with the following parameters: echo time (TE) = 5 msec, repetition time (TR) = 24 msec, numbers of excitations (NEX) = 2, rotation angle = 45°, field of view (FOV) = 26 × 24 × 18.8 cm, and a matrix of 256 × 192 × 124. Two-dimensional PD and T2 sequences were acquired as follows: 3.0- or 4.0-mm-thick coronal slices, TR = 3000 msec, TE = 36 msec (for PD) and 96 msec (for T2), NEX = 1, FOV = 26 × 26 cm, matrix = 256 × 192.

Image Processing

Magnetic resonance data were processed using computational resources at the Iowa image processing laboratory along with our locally developed software, BRAINS (Andreasen et al 1992). The T1-weighted images were spatially normalized and resampled to 1.0-mm3 voxels so that the anterior-posterior axis of the brain was realigned parallel to the anterior commissure-posterior commissure line and the interhemispheric fissure aligned on the other two axes. The T2- and PD-weighted images were aligned to the spatially normalized T1-weighted image (Woods et al 1992). The data sets were then segmented with the multispectral data and a discriminant analysis method based on automated training class selection (Harris et al 1999). The tissue-classified image was then used to generate a triangle-based iso-surface with a threshold of 130 representing pure gray matter, which corresponds to the parametric center of the cortex (Magnotta et al 1999). This triangulated surface was used as the basis for our calculations of cortical areas and volumes.

ROI Definition and Reliability

On the coronal view, the insular cortex is clearly defined by the superior (SCIS) and inferior circular insular sulci (ICIS). The fusion of the SCIS and the ICIS within the fundus of the Sylvian fissure constitutes the caudal end of the insula. Because the ICIS does not extend rostral to the limen insulae, there is no well-defined boundary between the anterior insula and the orbitofrontal cortex. The orbitoinsular sulcus is considered the topographic boundary between the anterior insula and the adjacent orbitofrontal cortex (see Figure 1) (Mesulam and Mufson 1985; Türe et al 1999). Two-dimensional, hand-traced regions of interest were made on coronal slices of the MRI, following these parameters. Intersections between the tracings and the previ-