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At the boundary of the self: The insular cortex in patients with childhood-onset schizophrenia, their healthy siblings, and normal volunteers

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ABSTRACT

The insular cortex (insula), whose normal function involves delineating the boundary between self and non-self stimuli, has been implicated in the pathophysiology of the positive symptoms of schizophrenia, including hallucinations and delusions. Childhood-onset schizophrenia (COS), that includes the onset of psychosis before age 13, is a severe and continuous form of the illness which shows profound and global progressive cortical brain abnormalities during adolescence which merge in the adult pattern with age. Using prospectively acquired anatomic brain magnetic resonance imaging (MRI) scans, a matched sample of COS patients, their nonpsychotic full siblings and healthy volunteers, we measured insular volume using the FreeSurfer automated software. COS patients ($n = 98$; 234 scans) had significantly lower right ($p = 0.003$), left ($p < 0.001$), and total ($p < 0.001$) insular volumes than healthy volunteers ($n = 100$; 248 scans). Right insular volume negatively correlated with positive symptoms as measured by the Scale for the Assessment of Positive Symptoms (SAPS) ($p = 0.02$), while both left ($p = 0.01$) and right ($p = 0.006$) insula volumes were positively correlated with overall functioning, as measured by the Children's Global Assessment Scale (CGAS) scores. COS siblings ($n = 71$; 153 scans), on the other hand, did not differ significantly from normal volunteers suggesting that the insular deficits are more related to the illness state than a familial endophenotype. These results also highlight the salience of the insula in positive symptoms of schizophrenia perhaps resulting from the inability to discriminate between self from the non-self in COS. Further work to connect insular deficits to other neurocircuitries is warranted.

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1. Introduction

A disabling hallmark of schizophrenia is the suite of positive symptoms that include hallucinations and delusions. Of prime importance in the search for improved treatment for schizophrenia is determining the biological basis of such psychotic features (Weinberger, 1997). A large body of evidence has indicated that patients with schizophrenia display widespread brain abnormalities, both structurally and functionally (Chua and McKenna, 1995; Gur and Gur, 2010; Karlsgodt et al., 2010), but sifting through these findings and connecting them to illness characteristics remain challenging. One such region implicated in the positive symptoms of schizophrenia is the insular cortex (insula) (Wylie and Tregellas, 2010).

The insula, which is folded within the lateral sulcus of the cerebral cortex, is located between the temporal and frontal lobes, with wide connections. It has been functionally implicated in the discrimination of sensory stimuli between self and non-self, as well other functions such as physiological interoception of heat (Strigo et al., 2012), heart rate (Critchley et al., 2004), pain, to perception of thoughts (Ochsner et al., 2008) and emotions, that are essential for social engagement and communication. Thus a failure of this construct, of self vs. non-self, could be easily tied to the possible rise of psychotic symptoms in schizophrenia. This is supported by many reports of insular pathology in schizophrenia that range from deficits in insular gray matter (Honea et al., 2005), cortical thickness (Roiz-Santianez et al., 2010), and protein expression (Pennington et al., 2008), to blunted activity while viewing social stimuli (Seiferth et al., 2009). Lesion studies involving the insula have also provided evidence that its functioning is crucial for the integration of body and mind awareness (Jones et al., 2010). The

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range of insula deficits seen in the schizophrenia population and their relationship to disruption of social (Giuliani et al., 2011) and cognitive behaviors lead to the hypothesis that positive symptoms, primarily hallucinations, may involve insula activity. Recent meta-analyses have even pointed out that the insula is a common site of cortical activation during auditory verbal hallucinations (Jardri et al., 2011).

Childhood-onset schizophrenia (COS) is a rare, severe, and continuous form of the disorder where the onset of psychosis is before age 13 (McKenna et al., 1994). COS patient show a much greater incidence of positive symptoms compared to adult onset populations, which makes this cohort an ideal sample to explore insular pathology. In a recent analysis, of the 111 COS probands studied, 94.9% exhibited auditory hallucinations, and 80.3% experienced visual hallucinations, and COS patients had higher rates of hallucinations across all modalities (David et al., 2011).

Along with COS patients, their full nonpsychotic siblings are also prospectively studied with anatomic brain MRI scans and these provide a contrast to examine whether the observed brain changes are disease related or likely to be trait markers (endophenotypes). The purpose of this study was to examine insula volume in patients with COS, their nonpsychotic siblings, and unrelated healthy volunteers. Given the findings linking the insula to the boundary of the self and positive schizophrenia symptomology, and the high rate of positive symptoms in patients with COS, we hypothesized that COS patients would exhibit significantly lower insula volumes compared to their siblings and healthy volunteers, and that within COS patients, insula volume would correlate with positive symptoms. Additionally, as has been documented in other brain regions (Gogtay et al., 2012), we hypothesized that COS sibling insula volume would be greater than their ill siblings, but significantly reduced compared to healthy volunteers, indicating an endophenotype. Our basis for the sibling-aspect of this hypothesis is documented brain abnormalities in siblings of patients with COS from prospective neuroimaging studies (Gogtay et al., 2003), including replication from a non-overlapping sample (Raznahan et al., 2011).

2. Materials and methods

2.1. COS patients

COS patients ($n = 98$, 234 scans) were recruited nationwide and diagnosed after inpatient observation that included a medication washout. Exclusionary criteria included medical or neurological illness, substance abuse, or IQ below 70 prior to onset of psychotic symptoms; details are described elsewhere (McKenna et al., 1994). In this study all patients and their full biological siblings were clinically followed and rescanned at two-year intervals.

2.2. Siblings

Siblings ($n = 71$, 153 scans) were assessed using structured psychiatric interviews for Axis I (using either the Schedule for Affective Disorders and Schizophrenia [SADS] (Endicott and Spitzer, 1987) or the Schedule for Affective Disorders and Schizophrenia for School-Age Children [K-SADS] (Kaufman et al., 1997) and Axis II (using the Structured Interview for the *DSM-III* Personality Disorders [SIDP] (McKenna et al., 1994; Stangl et al., 1985) diagnoses. Siblings were considered "healthy" if they were free of any schizophrenia spectrum diagnoses (which include schizophrenia and schizoaffective disorder, any psychotic illness on Axis I, or paranoid, schizotypal, schizoid, or avoidant personality disorders on Axis II) (Asarnow et al., 2001).

2.3. Normal volunteers

($n = 100$, 248 scans) were selected from a larger prospective study of normal brain development and matched for age, sex and scan interval to the COS patients and their siblings. Only normal volunteers with two or more successive scans were used. As with siblings, control subjects were free of lifetime medical or psychiatric disorders as determined by means of clinical examination and standardized interview. Psychiatric illness in a first-degree relative was also exclusionary. Further details are described elsewhere (Giedd et al., 1999).

2.4. Imaging processing and analysis

T1-weighted images with contiguous 1.5-mm slices in the axial plane were obtained using a 3-dimensional spoiled gradient recalled echo sequence in the steady state. Imaging parameters were echo time of 5 ms, repetition time of 24 ms, flip angle of 45°, acquisition matrix of 256°—192, number of excitations equaled 1, and a 24-cm field of view. Head placement was standardized as previously described (Castellanos et al., 2001).

The DICOM image files were transferred to a Linux workstation for analysis. Subcortical volumes were measured automatically with the FreeSurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). Individual scans were visually reviewed by a trained rater, blind to the diagnosis. Each scan was rated on a 1–5 scale of quality in terms of artifacts (1 being the highest quality). Scans receiving a score of 4 or 5 were excluded. The automated procedures for subcortical volumetric, area, and thickness measurements of different brain structures have been described previously (Fischl et al., 2002, 2004; Lerch and Evans, 2005).

The procedure automatically provides segments and labels for many brain structures by assigning a neuroanatomic label to each voxel in an MR imaging volume on the basis of probabilistic information estimated automatically from a manually labeled training set. Briefly, this processing includes motion correction and averaging of multiple volumetric T1 weighted images (when more than one is available), removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles) (Fischl et al., 2002, 2004), intensity normalization, tessellation of the gray matter white matter boundary, automated topology correction (Fischl et al., 2001; Segonne et al., 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines a transition to the other tissue class.

Standardized image processing techniques are listed in greater detail elsewhere (Fischl et al., 2002; Han et al., 2006). Regardless, all segmentations were visually inspected for accuracy prior to inclusion in the group analysis. Total insula gyrus volume was calculated as the sum of left and right insula measurement for each study participant.

2.5. Statistical analysis

Demographic differences between groups (Table 1) were tested using ANOVA for continuous variables and chi-square tests of independence for categorical variables

Table 1
Participant demographics. Following abbreviations are employed: Intelligence Quotient (IQ), socio-economic status (SES), and standard deviation (SD).

	cos ($N = 98$)	Healthy siblings ($N = 71$)	NV ($N = 100$)	Statistic (df)	p value
Sex	41 F; 57 M	38 F; 33 M	41 F; 59 M	$X^2_{(2)} = 3.11$	0.21
Race	5 A; 27 B; 8 H; 9 O; 49 W	1 A; 14 B; 6 H; 9 O; 41 W	4 A; 26 B;8 H;6 O; 56 W	$X^2_{(8)} = 5.27$	0.73
Handedness	4 M; 14 L; 80 R	5 M; 4 L; 62 R	5 M; 4 L; 91 R	$X^2_{(4)} = 8.38$	0.08
IQ, mean (SD)	74.8 (17.5)	–	111.6 (11.8)	$f(1,178) = 279$	**<0.01**
SES, mean (SD)	62.8 (29.9)	54.1 (26.6)	40.8 (20.0)	$f(2,261) = 17.8$	**<0.01**
Mean age scan 1 (SD)	14.6 (2.4) ($N = 98$)	15.7 (5.3) ($N = 71$)	14.6 (4.4) ($N = 100$)	$f(2,266) = 2.17$	0.12
Mean age scan 2 (SD)	17.1 (2.8) ($N = 66$)	17.7 (4.6) ($N = 41$)	16.8 (3.8) ($N = 70$)	$f(2,174) = 0.87$	0.42
Mean age scan 3 (SD)	19.7 (3.1) ($N = 43$)	20.0 (4.7) ($N = 28$)	19.1 (3.4) ($N = 42$)	$f(2,110) = 0.59$	0.55
Mean age scan 4 (SD)	22.2 (2.9) ($N = 17$)	21.4 (2.7) ($N = 9$)	22.1 (2.9) ($N = 24$)	$f(2,47) = 0.22$	0.80
Mean age scan 5 (SD)	24.5 (2.8) ($N = 6$)	23.6 (2.6) ($N = 4$)	24.0 (2.2) ($N = 9$)	$f(2,16) = 0.17$	0.85
Mean age scan 6 (SD)	25.9 (1.6) ($N = 4$)	–	26.0 (1.6) ($N = 3$)	$f(1,5) = 0.01$	0.92
Mean age overall (SD)	17.2 (4.0) ($N = 234$)	17.6 (5.2) ($N = 153$)	17.2 (4.8) ($N = 248$)	$f(2,632) = 0.44$	0.64

Bold values are the p-values that are below 0.05, and statistically significant.