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Orbitofrontal sulcogyral morphology is a transdiagnostic indicator of brain dysfunction

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ABSTRACT

Atypical sulcogyral patterns in the orbitofrontal cortex (OFC) are associated with increased risk for schizophrenia, as well as with quantitative traits associated with schizophrenia, such as anhedonia. Here we conduct a cross-diagnostic comparison to assess whether atypical OFC sulcogyral patterns confer risk for multiple brain disorders. We examined structural images from 4 groups of adult participants (N = 189), including those diagnosed with schizophrenia (SZ; N = 49), bipolar disorder (BP; N = 46), attention deficit hyperactivity disorder (ADHD; N = 41), and controls (N = 53). OFC sulcogyral pattern types were determined based on the continuity of the medial and lateral orbitofrontal sulcus. Chi-square analysis was performed to compare the sulcogyral pattern frequency distributions between patient groups and controls. We find that both SZ and BP groups had atypical pattern distributions, with increased atypical pattern frequencies relative to controls in the left hemisphere, consistent with the overlapping clinical features and genetic etiology of these disorders (SZ: $\chi^2 = 17.6$; $p < 0.001$; BP: $\chi^2 = 19.2$, $p < 0.001$). The ADHD group distribution did not significantly differ from controls ($\chi^2 = 5.5$; $p = 0.06$, NS.). Similar sulcogyral pattern frequencies across BP and SZ suggest that the sulcogyral phenotype may map more directly to a trait that is transdiagnostic. These results suggest that sulcogyral patterns present a novel morphological indicator for increased susceptibility to multiple psychiatric diagnoses.

1. Introduction

Cortical surface morphology undergoes extensive changes during early brain development to form sulcal and gyral regions. Although the mechanism of this folding is unknown, it has been suggested that the crowding of neurons and axons causes physical tension that limits the expansion of the neocortex, thus causing it to fold (Essen, 1997). Given the complexity of this process, it is remarkable that there is a degree of regularity in the folding patterns, with a number of characteristic sulci that separate the four lobes of the brain and also form recognizable configurations within a given lobe. It is believed that individual sulcal morphology is established in neurodevelopment and remains stable throughout the life course (Armstrong et al., 1995). In the orbitofrontal cortex (OFC), the intersection of the medial, lateral, and transverse orbital sulci form one of four patterns and the collective pattern formed by these sulci is commonly referred to as the H-shaped sulcus. These patterns were first identified in both humans and monkeys (Chiavaras and Petrides, 2000), and pattern type was named according to the frequency with which it was observed (Type I being the most common). Subsequently, increased frequencies of the less common pattern types (Type II and Type III) were associated with schizophrenia (Chakirova et al., 2010; Takayanagi et al., 2010; Lavoie et al., 2014; Bartholomeusz et al., 2013). Thus, it is thought that the Type I pattern is somewhat protective against schizophrenia. More recently, we have associated the presence of less common OFC sulcal patterns with individual differences in anhedonia in a clinically normal population (Zhang et al., 2016). Atypical patterns have also been associated with depression symptoms in females, specifically, in a community sample of adolescents (Whittle et al., 2014). Because anhedonia is a symptom of several psychiatric disorders, it is unclear whether atypical OFC sulcal patterns indicate susceptibility to schizophrenia, specifically, or represent a risk factor for other brain disorders, more generally. Given the developmental temporality of OFC sulcal development to the manifestation of psychiatric symptomology, it should be emphasized that atypical configurations may predict later psychopathology, and are very unlikely the result of mental illness or psychiatric medications (Nakamura et al., 2007). In fact, one study evaluated sulcal patterns of individuals at high risk for developing schizophrenia (before onset of psychotic symptoms), and found that atypical patterns identified before disease onset were associated with psychotic features (Chakirova et al., 2010). Existing studies in clinical populations have only compared schizophrenia populations (or populations at risk for schizophrenia) to controls. Thus, no

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study to date has evaluated the frequencies of H-shaped sulcal patterns and compared distributions between several populations with distinct psychiatric or neurodevelopmental diagnoses. Although other groups have examined OFC sulcal patterns in populations other than schizophrenia and related disorders (Watanabe et al., 2014; Chye et al., 2017), our study is unique in our comparison of sulcal pattern frequencies across multiple psychiatric disorders. There is increasing evidence of overlap in the behavioral and genetic etiology of many psychiatric conditions and developmental disorders (Moreno-De-Luca et al., 2013; The Lancet, 2013). Considering the numerous behavioral and genetic similarities between schizophrenia (SZ) and bipolar disorder (BP) (Maier et al., 2006; Jackson et al., 2013; Cardno and Owen, 2014), we expected to observe a greater frequency of atypical patterns in these patient groups compared to attention deficit hyperactivity disorder (ADHD) and control populations.

2. Methods and materials

2.1. Participants

Structural images were obtained from the OpenfMRI database (accession number ds000030), a publically available and anonymized data set made accessible by the University of California Los Angeles Consortium for Neuropsychiatric Phenomics and can be obtained at: https://openfmri.org/dataset/ds000030/. All subjects gave written and informed consent to the Institutional Review Boards at UCLA and the Los Angeles County Department of Mental Health for their participation in the study. Participants included right-handed English- or Spanish-speaking controls, and patients with self-reported SZ, BP, or ADHD. These individuals were then assessed with the SCID-IV (First et al., 1995) to verify history and/or absence of psychopathology and a urine drug screen to assess for drug use (see Table 1 for demographic info). ADHD, BP, and SZ patients were recruited using a patient-oriented strategy involving outreach to local clinics and online portals, while healthy adults were recruited using advertisements in Los Angeles area newspapers. All candidates were screened via telephone and then in person. The Additional details regarding this cohort can be obtained at: https://web.archive.org/web/20151229081105/http://www.phenowiki.org/wiki/index.php/LA5C.

We only included controls from the larger cohort that had no Axis I diagnosis, as confirmed by the SCID (N = 56). In addition, we only included patients that had a diagnosis confirmed using the SCID for SZ (N = 50), BP (N = 49), and ADHD (N = 42).

2.2. Participant demographics and phenotype characterization

A complete list of all phenotype variables can be found at the study link above, some of which were acquired in the entire sample and others in specific disease groups. Relevant to the current investigation, we report age, gender, and clinician-interview instruments relevant to the phenotype of each clinical population. We also identified phenotype metrics that were commonly used to assess the phenotype in psychiatric-disorder specific groups in order to help describe the behavioral phenotype of these populations. Because the majority of the clinician interview instruments were not ascertained on the control population, we also report several self-report questionnaires that tap into similar psychometric domains as the clinician interview instruments. These metrics and the purpose for describing them in this analysis are reported below and average for each diagnostic group are reported in Table 2.

2.3. Clinician interview instruments (collected on patient-specific groups)

Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984a) is a clinician-administered scale that measures the negative symptoms of schizophrenia in five domains, including Affective Flattening, Alogia, Avolition, Anhedonia, and Attention. We calculated a SANS Total (Composite) score by summing SANS items 1–7, 9–12, 14–16, 18–21, and 23–24. The SANS was collected on SZ and BP patients only.

Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b) is a clinician-administered scale that measures the positive symptoms of schizophrenia, including hallucinations, delusions, bizarre behavior, and positive formal thought. We calculated a SANS Total

Table 1
Demographic characteristics.

	HC (N = 53)		SZ (N = 49)		BP (N = 46)		ADHD (N = 41)		All group comparison χ^2/F (p)	Individual group comparisons χ^2/F/t (p)	
	N	%	N	%	N	%	N	%		a. HC vs. SZ b. HC vs. BP c. HC vs. ADHD	d. SZ vs. BP e. SZ vs. ADHD f. BP vs. ADHD
Male:female	24:29	45:55	37:12	76:24	27:19	59:41	21:20	51:49	χ^2 = 10.4 (0.015)	a. 9.68 (p = 0.002) b. 1.88 (p = 0.183) c. 0.326 (p = 0.568)	d. 3.05 (p = 0.081) e. 5.75 (p = 0.017) f. 0.490 (p = 0.484)
Scanner site 1: scanner site 2	43:10	81:19	25:24	51:49	25:21	54:46	21:20	51:49	χ^2 = 13.5 (0.004)	a. 10.4 (p = 0.001) b. 8.2 (p = 0.004) c. 9.5 (p = 0.002)	d. 0.105 (p = 0.745) e. 0.000 (p = 0.985) f. 0.085 (p = 0.770)

	HC (N = 53)		SZ (N = 49)		BP (N = 46)		ADHD (N = 41)		All group comparison χ^2/F (p)	Individual group comparisons χ^2/F/t (p)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		a. HC vs. SZ b. HC vs. BP c. HC vs. ADHD	d. SZ vs. BP e. SZ vs. ADHD f. BP vs. ADHD
Age (years)	31.1	9.1	36.5	9.0	35.7	9.3	32.7	10.6	F(3,184) = 3.13 (p = 0.027)	a. −3.03 (p = 0.003) b. −2.26 (p = 0.026) c. −1.08 (p = 0.281)	d. 0.667 (p = 0.506) e. 1.52 (p = 0.132) f. 0.894 (p = 0.374)
Education (years)	15.0	1.7	12.7	1.8	14.5	1.9	14.6	1.8	F(3,184) = 16.5 (p < 0.001)	a. 6.69 (p ≤ 0.01) b. 1.36 (p = 0.179) c. 1.14 (p = 0.257)	d. −4.83 (p < 0.001) e. −5.10 (p < 0.001) f. 20.2 (p = 0.837)

HC = healthy controls; SZ = schizophrenia; BP = bipolar; ADHD = attention deficit hyperactivity disorder.