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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 $\chi^2$/F (p) | Individual group comparisons $\chi^2$/F/t (p) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | | a. HC vs. SZ<br>b. HC vs. BP<br>c. HC vs. ADHD | d. SZ vs. BP<br>e. SZ vs. ADHD<br>f. BP vs. ADHD |
| Male:female | 24:29 | 45:55 | 37:12 | 76:24 | 27:19 | 59:41 | 21:20 | 51:49 | $\chi^2$ = 10.4 (0.015) | a. 9.68 (p = 0.002)<br>b. 1.88 (p = 0.183)<br>c. 0.326 (p = 0.568) | d. 3.05 (p = 0.081)<br>e. 5.75 (p = 0.017)<br>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 | $\chi^2$ = 13.5 (0.004) | a. 10.4 (p = 0.001)<br>b. 8.2 (p = 0.004)<br>c. 9.5 (p = 0.002) | d. 0.105 (p = 0.745)<br>e. 0.000 (p = 0.985)<br>f. 0.085 (p = 0.770) |

| | HC (N = 53) | | SZ (N = 49) | | BP (N = 46) | | ADHD (N = 41) | | All group comparison $\chi^2$/F (p) | Individual group comparisons $\chi^2$/F/t (p) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | | a. HC vs. SZ<br>b. HC vs. BP<br>c. HC vs. ADHD | d. SZ vs. BP<br>e. SZ vs. ADHD<br>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)<br>b. −2.26 (p = 0.026)<br>c. −1.08 (p = 0.281) | d. 0.667 (p = 0.506)<br>e. 1.52 (p = 0.132)<br>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)<br>b. 1.36 (p = 0.179)<br>c. 1.14 (p = 0.257) | d. −4.83 (p < 0.001)<br>e. −5.10 (p < 0.001)<br>f. 20.2 (p = 0.837) |

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

**Table 2**
Phenotype characteristics.

| | HC (N = 53) | | SZ (N = 49) | | BP (N = 46) | | ADHD (N = 41) | | All group comparison F (p) | Individual group comparisons t (p) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | | a. HC vs. SZ<br>b. HC vs. BP<br>c. HC vs. ADHD | d. SZ vs. BP<br>e. SZ vs. ADHD<br>f. BP vs. ADHD |
| SANS Composite | – | – | 28.1 | 16.3 | 16.5 | 11.3 | – | – | $F(1,93) = 16.1$ ($p < 0.001$) | a. –<br>b.–<br>c.– | d. 4.01 ($p < 0.001$)<br>e. –<br>f. – |
| SAPS Composite | – | – | 25.5 | 18.2 | 7.9 | 8.1 | – | – | $F(1,93) = 36.4$ ($p < 0.001$) | a. –<br>b. –<br>c. – | d. 6.03 ($p < 0.001$)<br>e. –<br>f. – |
| HMD-17 | – | – | 9.5 | 7.5 | 11.8 | 8.4 | 7.9 | 4.9 | $F(2,133) = 3.22$ ($p = 0.043$) | a. –<br>b.–<br>c.– | d. −1.41 ($p = 0.163$)<br>e. 1.15 ($p = 0.253$)<br>f. 2.58 ($p = 0.012$) |
| YMRS | – | – | 9.2 | 7.2 | 12.3 | 11.1 | 5.8 | 4.2 | $F(2,133) = 7.12$ ($p = 0.001$) | a. –<br>b. –<br>c. – | d. −1.64 ($p = 0.105$)<br>e. 2.69 ($p = 0.008$)<br>f. 3.57 ($p = 0.001$) |
| ACDS | – | – | 30.3 | 9.4 | 36.8 | 10.4 | 45.6 | 4.8 | $F(2,133) = 26.5$ ($p < 0.001$) | a. –<br>b. –<br>c. – | d. −3.20 ($p = 0.002$)<br>e. −9.42 ($p < 0.001$)<br>f. −4.93 ($p < 0.0001$) |

(Composite) score by summing SAPS items 1–6, 8–19, 21–24, and 26–33. The SAPS was collected on SZ and BP patients only.

Hamilton Depression Rating scale (HAM-D 17) (Hamilton, 1960) is a clinician-administered scale designed to assess depression symptom severity. Each item is rated on a 0–2 or 0–4 scale. Scores for each item are summed to create a total score. Scores of < 7 are considered normal. Scores in the 7–17 range indicate mild depression, 18–24 moderate depression, and over 24 indicate severe depression. This was collected for SZ, BP, and ADHD patients.

Young Mania Rating Scale (YMRS) (Young et al., 1978) is an 11-item clinician-administered instrument that was designed to measure the severity of manic episodes in patients with bipolar disorder. Scores range from 0 to 60 with a cutoff score of > 20 indicating the presence of manic symptoms.

Adult ADHD Clinical Diagnostic Scale (ACDS) (Adler and Cohen, 2004) is a semi-structured clinician-administered survey that assesses the 18 individual criteria for DSM criteria of ADHD, including the childhood presence of symptoms as well as current adult symptoms. Symptom severity is also rated by the clinician and can be used to create summary scores. Summary scores for adult total symptom count were used in the current study to confirm differences in attention deficit symptoms between those with ADHD, BP, and SZ.

### 2.4. Self-report instruments (collected on all patient groups and controls)

The Revised Physical Anhedonia Scale (RPAS) (Chapman et al., 1976) is a self-report measure, containing 61 True-False items, which assesses deficits in the ability to experience pleasure from typically pleasurable stimuli (for example, sex and food). The PAS yields scores between 0 and 61, with higher scores indicating more severe physical anhedonia.

The Revised Social Anhedonia Scale (RSAS) (Eckblad et al., 1982) is a self-report measure, containing 40 True-False items, which assesses deficits in the ability to experience pleasure from non-physical stimuli such as social interactions. Scores range from 0 to 40, with higher scores indicating more severe social anhedonia.

The RPAS and RSAS were originally developed in order to measure prodromal schizophrenia and have been validated as reliable predictors of schizophrenia spectrum disorders (Kwapil, 1998; Kuha et al., 2011). In our previous work, we chose these scales in order to better understand whether individual differences in anhedonia underlie OFC sulcogyral pattern variability in a cohort of individuals that did not have a psychiatric diagnosis (Zhang et al., 2016). Here, we include these scales in order to continue to explore the link between anhedonia and OFC sulcogyral patterns, as well as to illustrate any differences between patient groups.

The Hypomanic Personality Scale (HPS) (Eckblad and Chapman, 1986) is another Chapman Scale, designed to measure the overactive, gregarious style associated with episodes of hypomanic euphoria. This self-report measure consists of 48 True-False items, and scores range from 0 to 48, with higher scales indicating the presence of more features associated with a hypomanic personality. We include this scale to illustrate differences in mania symptoms between the groups.

Adult Attention Deficit Disorder Self-Report Scale (ASRS) (Kessler et al., 2005) is a self-report instrument that consists of the 18 DSM-IV criteria for Attention Deficit Disorder. Adults rate themselves on each criterion using a 5-point scale from Never to Very Often. Each question is scored with 0 points for “Never”, 1 point for “Rarely”, and so on, and then scores across all 18 questions are summed. We report this metric in order to confirm that adults in the ADHD subgroup have more attention deficits than other patient populations and controls.

### 2.5. Image acquisition

MRI scanning was conducted at two different locations, Ahmanson-Lovelace Brain Mapping Center and the Staglin Center for Cognitive Neuroscience, on a 3 T Siemens Trio scanner. High-resolution anatomical images (T1-weighted 3D MPRAGE) were collected for each participant with the following parameters: 1 $mm^3$ voxel size, 176 axial slices, 1 mm slice thickness, TR = 1.9 s, TE = 2.26 ms, FOV = 250, matrix = 256 × 256 sagittal plane. Although the publically available data set already excluded participants with excessive motion, we additionally excluded several individuals (N = 8) whose excessive motion caused noise in the OFC region of the structural image, thus limiting our ability to make accurate tracing classifications (SZ N = 1, BP N = 3, ADHD N = 1, Control N = 3). Control participants were primarily collected on one scanner, with the patient groups roughly split, with half of patients within each diagnosis being scanned on one scanner and half on the other (see Table 1). While data was collected in two locations, the same sequence was used for all subjects, regardless of imaging site. Recent work has confirmed that sulcal pattern characterization is a robust measure that is not influenced by scanner site (Chye et al., 2017). Thus, it is unlikely that sulcal pattern type would be influenced by scanner site. Nevertheless, we repeat all analyses using data from the one scanner site in order to confirm that results are not merely due to differences between scanners.

### 2.6. Data analysis

#### 2.6.1. Preprocessing

The anatomical images were normalized by first stripping non-brain tissue using FMRIB Software Library (FSL) Brain Extraction Tool (BET) (Smith, 2002), then aligned along the anterior commissure-posterior commissure plane to adjust for head tilt (using FMRIB Linear Image Registration Tool, FLIRT(Jenkinson and Smith, 2001; Jenkinson et al., 2002) after registration to an MNI template, and resampled into 1 mm cubic voxels. The fractional intensity threshold in BET was set to 0.3. This sometimes resulted in residual skull or brainstem being left in the image, but insured that we did not inadvertently remove portions of the brain surface. The OFC sulcal patterns were identified from the normalized images using the software ITK-SNAP (Yushkevich et al., 2006) and classified according to the criteria used in previous characterizations of OFC sulcogyral patterns (Lavoie et al., 2014; Ganella et al., 2015). The morphology of the orbitofrontal sulci was categorized into three main types (Type I, II, and III/IV) in each hemisphere based on the continuity of the medial and lateral orbital sulci (MOS and LOS respectively) (Chiavaras and Petrides, 2000). Type I consists of a discontinuous medial sulcus and continuous lateral sulcus, Type II a continuous medial and continuous lateral sulcus, and Type III a discontinuous medial and discontinuous lateral sulcus (see Fig. 1). Consistent with previous studies, all subjects with a hemisphere classified by the rare Type IV pattern (continuous medial and discontinuous lateral sulcus) were included with Type III patterns for group analysis (Bartholomeusz et al., 2013). Additional details on tracing procedure available in Supplementary Methods section. Each subject's bilateral OFC sulcal pattern was independently traced and classified by a tracer (M.P.) who was blind to diagnosis. A subset of 20 randomly selected brains (40 hemispheres) were also reviewed by V.T. to ensure classification validity. Interrater reliability between M.P. and V.T. was very good ($\kappa = 0.863$ (95% CI, 0.726 to 1), $p < 0.0005$). MP then re-characterized a subset of brains in order to obtain an intrarater reliability statistic. Intrarater reliability was also very good ($\kappa = 0.909$ (95% CI, 0.787 to 1), $p < 0.0005$).

### 2.7. Statistical analyses

Statistical analyses were performed using SPSS (IBM SPSS 23.0 for Mac, SPSS Inc., Chicago, Illinois). We first assessed whether there were any demographic differences across all groups in gender ratio and scanner site using $\chi^2$ statistics. We also assessed whether there were any differences in the demographic variables of age or education across all groups using an Analysis of Variance. In the case that this statistical test was significant across all groups, we followed up with independent sample *t*-tests in order to compare each group to another and establish which group differences were driving these effects. We also assessed whether there were any phenotypic differences between groups on quantitative psychometrics that are relevant to these populations. Similar to demographic analyses, we first assessed whether there were differences across all groups using an Analysis of Variance. These overall group comparisons were then followed-up with independent sample t-tests. Please note that analyses of demographic and phenotypic differences were not part of our main hypothesis, but were don't in order to confirm that patient populations and controls were different from each other in expected ways.

To test our main hypothesis regarding OFC sulcogyral pattern types, we established the inter-hemispheric distribution of OFC sulcogyral pattern types in the left and right hemisphere across each group relative to controls using $\chi^2$ statistics. Following these analyses, we explored what specific pattern type (I, II, or III) differentiates the groups. This was done by comparing frequency distributions within one pattern relative to all other patterns (i.e. proportion of Type I vs. not Type I, proportion of Type II vs. not Type II and so on) using $\chi^2$ statistics.

We then complete analyses to confirm whether previously identified phenotypic differences are related to sulcogyral patterns. These analyses were completed using a one-way ANOVA with left pattern type as the dependent variable and the relevant phenotypic trait (physical anhedonia scale or symptom severity scale) as the dependent variable.

We report all p-values and consider values of $p < 0.05$ as significant. However, it is important to point out that these results are not corrected for multiple comparisons. In particular, the large number of follow-up tests done in order to identify specific pattern types that differentiate the patient groups should be interpreted as tentative until corroborated, as these results may contain Type I errors.

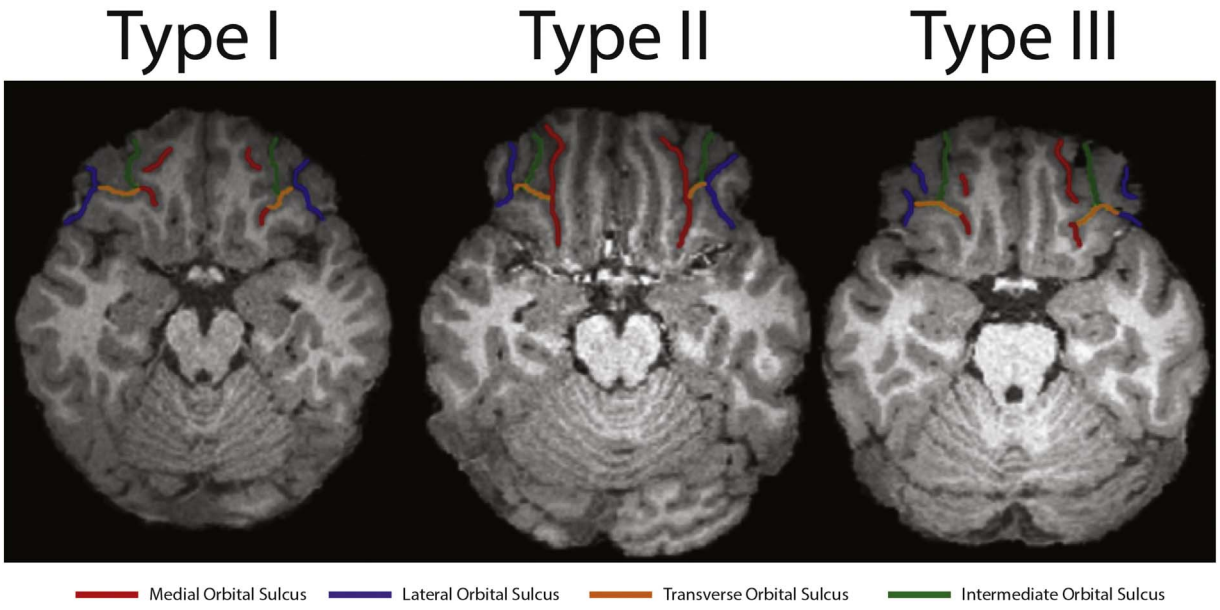


**Fig. 1. Examples of different H-sulcal pattern types.** Type I on the far left is distinguished by its discontinuous Medial Orbital Sulcus (MOS) and continuous Lateral Orbital Sulcus (LOS). Type II in the middle is distinguished by its continuous MOS and LOS. Type III on the right is distinguished by a discontinuous MOS and discontinuous LOS. Red line indicates MOS. Blue line indicates LOS. Orange line indicates Transverse Orbital Sulcus (TOS). Green line indicates Intermediate Orbital Sulcus (IOS). Important note: We chose examples that had the same pattern type on the left and right hemispheres for clarity of illustration. However, it is more common for an individual to have different patterns on the left and right.

**Table 3**
Sulcogyral pattern types.

| | HC (N = 53) | | SZ (N = 49) | | BP (N = 46) | | ADHD (N = 41) | | All group comparison $\chi^2$ (p) | Individual group comparisons $\chi^2$ (p) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | | a. HC vs. SZ<br>b. HC vs. BP<br>c. HC vs. ADHD | d. SZ vs. BP<br>e. SZ vs. ADHD<br>f. BP vs. ADHD |
| Left OFC pattern | | | | | | | | | $\chi^2$ = 26.1 (p < 0.001) | a. 17.6 (p < 0.001) | d. 0.461 (p = 0.794) |
| Type I | 42 | 79 | 19 | 39 | 17 | 37 | 25 | 61 | | b. 19.2 (p < 0.001) | e. 5.36 (p = 0.069) |
| Type II | 7 | 13 | 16 | 33 | 13 | 28 | 6 | 15 | | c. 5.52 (p = 0.063) | f. 5.22 (p = 0.074) |
| Type III/IV | 4 | 8 | 14 | 28 | 16 | 35 | 10 | 24 | | | |
| Right OFC pattern | | | | | | | | | $\chi^2$ = 8.13 (0.229) | a. 1.66 (p = 0.437) | d. 1.501 (p = 0.472) |
| Type I | 32 | 60 | 24 | 49 | 28 | 60 | 17 | 41.5 | | b. 0.024 (p = 0.988) | e. 1.68 (p = 0.432) |
| Type II | 10 | 19 | 14 | 29 | 9 | 20 | 17 | 41.5 | | c. 5.86 (p = 0.053) | f. 5.130 (p = 0.077) |
| Type III/IV | 11 | 21 | 11 | 22 | 9 | 20 | 7 | 17 | | | |

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

## 3. Results

### 3.1. Demographic differences

We first assessed any demographic differences between groups. We employed an Analysis of Variance with age as the dependent variable and diagnosis as the fixed factor. This analysis indicated a significant difference in age based on diagnosis ($F(3) = 3.13$, $p = 0.027$). Follow-up independent *t*-tests comparing each group to controls indicated that this effect was due to differences between the SZ and HC groups ($t(100) = -3.03$, $p = 0.003$) and BP and HC groups ($t(97) = -2.26$, $p = 0.026$), with both SZ and BP being slightly older. There was no difference in age between ADHD and HC groups ($t(92) = -1.08$, $p = 0.281$, NS). OFC patterns are thought to be stable throughout the lifespan and therefore this age difference should not impact our results. Nevertheless, we repeat all analyses with an optimized subsample that was created by removing the 5 oldest SZ subjects, 2 oldest BP subjects and the 8 youngest HC subjects and repeating analyses in order to confirm that sulcogyral pattern differences exist in the absence of age differences between diagnostic groups (see Supplemental Results).

We next assessed whether there were significant differences in the distributions of male and female subjects within each patient group by employing $\chi^2$ statistics. We find a significant difference in gender distribution between diagnostic groups ($\chi^2(3, N = 189) = 10.4$, $p = 0.015$). Follow-up $\chi^2$ tests between each group indicate that this was driven by a higher proportion of males in the SZ group relative to controls ($\chi^2(1, N = 102) = 9.68$, $p = 0.002$). Although there were significant differences in gender between the patient groups, there were no significant differences in the distribution of OFC pattern type based on gender ($\chi^2(3, N = 189) = 5.63$, $p = 0.131$, NS).

As mentioned in the Image Acquisition details of the Methods and materials section, the HC group was primarily scanned on one scanner while the patient groups were scanned on two scanners. Although OFC sulcogyral pattern type is a structural brain metric that should not be influenced by scanner, we complete all analyses using only data from patients that were ascertained on the same scanner as the majority of controls (see Supplemental Results). We also confirmed that the distribution of patients scanned on each scanner was not statistically significant by employing a chi-squared test. This test confirmed that there was not a significant difference in the distribution of patients scanned on one scanner vs. the other ($\chi^2(2, N = 144) = 0.279$, $p = 0.870$, NS).

### 3.2. Phenotype differences

We next assessed whether there were group differences between any of the clinician-interview or self-report instruments with an ANOVA to identify any group differences, with follow-up *t*-tests to determine specific differences between the patient groups. The SAPS and SANS were significantly higher in the SZ population relative to the BP group (SANS: $F(1,93) = 16.1$ ($p < 0.001$); SAPS: $F(1,93) = 36.4$ ($p < 0.001$)), indicating that both positive and negative symptoms of schizophrenia were present to a greater degree in the SZ population (see Table 2 for composite scores). Scores on the YMRS, ACDS, and HMD-17 all indicate significant differences between groups (YMRS: $F(2,133) = 7.12$ ($p = 0.001$); ACDS: $F(3,184) = 26.5$ ($p < 0.001$); HMD-17: $F(2,133) = 3.22$ ($p = 0.043$); see Table 2). Follow-up independent *t*-tests confirm that group differences were primarily driven by expected behavioral differences between diagnostic groups. For example, ACDS symptom count scores were significantly higher in ADHD relative to both SZ and BP groups (BP vs. ADHD: $t(85) = -3.20$, $p = 0.002$; SZ vs. ADHD: $t(88) = -9.42$, $p < 0.001$). However, these scores also suggest blurred diagnostic boundaries, with YMRS scores higher in BP patients relative to ADHD patients (BP vs. ADHD: $t(85) = -3.57$, $p = 0.001$), but no differences between SZ and BP groups (SZ vs. BP: $t(93) = -1.64$, $p = 0.105$, N.S.). For complete statistical comparisons, please see Table 2.

We also compared scores on the self-report questionnaires ascertained in all participants to illustrate differences between patients and controls (see Table 2 and Supplementary Results for all statistical comparisons). These results confirm that there are significant phenotypic differences between the control group and all patient groups and are largely consistent with phenotypic differences between these diagnostic categories (i.e. mean scores are highest in the ADHD group for the ASRS). However, results also indicate a phenotype continuum that crosses diagnostic boundaries when measuring quantitative differences in behavioral traits. This is consistent with the increasing recognition that these disorders are more related than distinct on a genetic and neurobiological level. We go on to describe the OFC sulcogyral analysis based on diagnostic groups and then return to potential influence of individual differences in these traits.

### 3.3. OFC pattern type distribution across groups

Table 3 contains the number of hemispheres identified with each pattern type in the right and left hemispheres, summarized by patient group. Within the left hemisphere, overall pattern type frequency for SZ ($\chi^2(2, N = 102) = 17.6$, $p < 0.001$) and BP ($\chi^2(2, N = 99) = 19.2$, $p < 0.001$) significantly differed from the control group. There were no significant differences in sulcal pattern frequency between BP ($\chi^2(2, N = 99) = 0.024$, $p = 0.988$, NS) and controls or between SZ and controls in the right hemisphere ($\chi^2(2, N = 102) = 1.66$ $p = 0.437$, NS). The ADHD group did not differ in overall sulcal pattern frequency from that of controls on the left ($\chi^2(2, N = 94) = 5.52$, $p = 0.063$, NS) or the right ($\chi^2(2, N = 94) = 5.86$, $p = 0.053$, NS) relative to controls, although results bilaterally do approach significance, a point we take up further in the discussion. See Fig. 2 for bar graphs pertaining to these

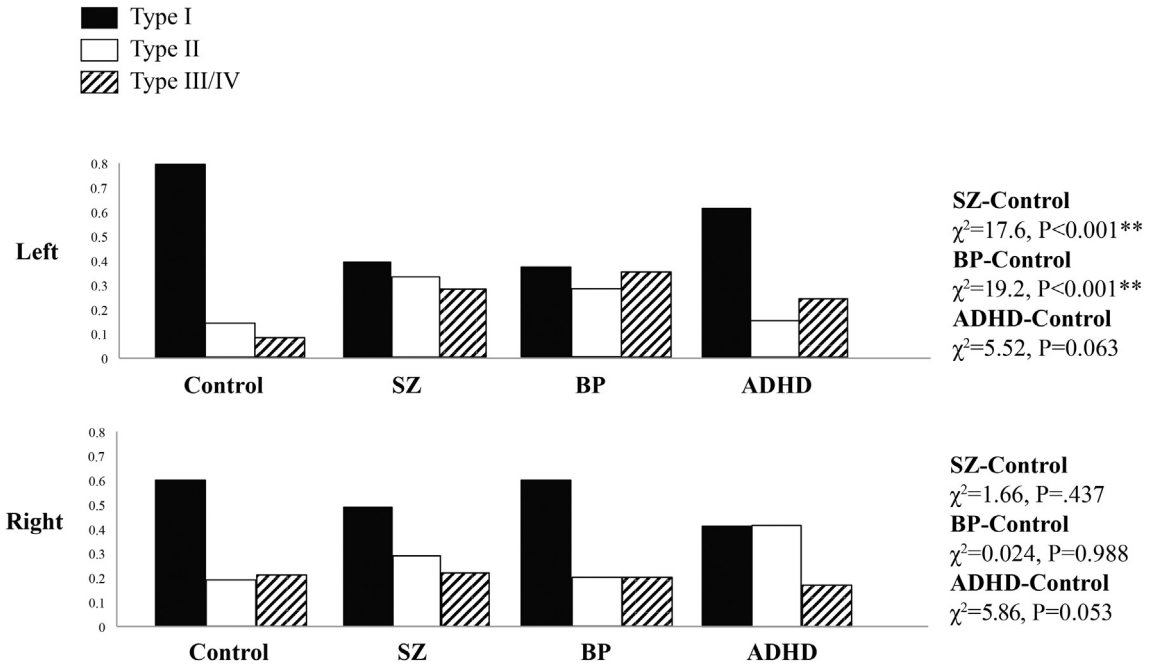


**Fig. 2. Sulcal pattern distribution of the H-sulcal pattern in orbitofrontal cortex.** Pattern frequencies plotted for each Type with diagnostic group clustered in columns. Note, frequencies of pattern type for each diagnosis group add up to a frequency of 1. Left-most column is control population. SZ, schizophrenia; BP, bipolar; ADHD, attention deficit hyperactivity disorder.

results.

Next, we explored what specific pattern types differentiated the groups. We focus on left lateralized comparisons, since there were no significant differences found in frequency distributions on the right. SZ patients had decreased Type I expression relative to the control group and the ADHD group (vs. controls ($\chi^2(2, N = 102) = 17.3$, $p < 0.001$); vs. ADHD ($\chi^2(2, N = 90) = 4.40$, $p = 0.036$). Similarly, BP patients had decreased Type I expression (vs. controls ($\chi^2(2, N = 99) = 18.3$, $p < 0.001$); vs. ADHD ($\chi^2(2, N = 87) = 5.01$, $p = 0.025$). There were no differences between the ADHD and control group in Type I expression ($\chi^2(2, N = 94) = 3.77$, $p = 0.052$, NS), nor between SZ and BP groups ($\chi^2(2, N = 95) = 0.03$, $p = 0.855$, NS). The SZ group had increased expression of Type II relative to the controls and ADHD group (vs. controls ($\chi^2(2, N = 102) = 5.51$, $p = 0.02$); vs. ADHD ($\chi^2(2, N = 90) = 3.92$, $p = 0.048$), but there were no other groups that showed differences in the Type II pattern expression (all $\chi^2 < 3.29$; all p's $> 0.07$). All three patient groups showed increased Type III prevalence on the left (SZ vs. Controls ($\chi^2(2, N = 102) = 7.74$, $p = 0.005$); BP vs. Controls ($\chi^2(2, N = 99) = 11.3$, $p < 0.001$); ADHD vs. Controls ($\chi^2(2, N = 94) = 5.17$, $p = 0.023$), but there were no differences between patient groups (all $\chi^2 < 1.12$; all p's $> 0.29$).

### 3.4. OFC pattern type and phenotypic variables

We next explored whether previously identified relationships between quantitative traits and sulcogyral patterns could be confirmed in our own population. Within controls, we assessed whether physical was related to left or right lateralized sulcogyral pattern differences. We have previously shown that individuals with high physical anhedonia scores showed decreased prevalence of Type I and increased prevalence of the Type II in the left hemisphere (Zhang et al., 2016). However, in the current study, we found no relationship between physical anhedonia and left hemisphere pattern type in this control population ($F(2,53) = 1.04$, $p = 0.362$, N.S.).

Based on previous findings of a relationship between SAP scores and sulcogyral pattern in patients with schizophrenia (Nishikawa et al., 2016), we also assessed whether the presence of positive or negative symptoms as measured using SANS/SAPS composite scores were related to atypical patterns seen in both the SZ and BP groups. We found no relationship between SANS or SAPS composite scores and sulcogyral pattern type in patients with SZ and BP (SANS: $F(2,92) = 2.527$, $p = 0.085$, N.S.; SAPS: $F(2,92) = 0.150$, $p = 0.861$, N.S.).

## 4. Discussion

Previous work has primarily linked atypical sulcogyral patterns within the H-sulcus to schizophrenia. Here, we show evidence that OFC sulcal patterns may also be linked to bipolar disorder. More recent genetic evidence has suggested similar underlying etiology for many disorders, including schizophrenia, bipolar disorder and autism, amongst other forms of developmental brain dysfunction (Moreno-De-Luca et al., 2013; Cardno and Owen, 2014). We find that sulcogyral pattern frequency in the left hemisphere is different in SZ and BP groups relative to controls. In addition, we find no significant differences in sulcogyral pattern frequency between the bipolar and schizophrenia patient groups. Although there are no significant differences between ADHD and control groups, frequency distribution differences between ADHD and controls did approach significance bilaterally. Further, analyses of between-group differences in individual pattern type presence showed increased Type III patterns in ADHD relative to controls. We were limited to analyzing the number of patients included in this publically available data set and are unsure as to why a smaller number of ADHD patients were recruited into this study. This finding should be replicated in a larger sample of patients with ADHD.

It is important to note that our original hypothesis was confirmed, in that both bipolar disorder and schizophrenia differed from controls, particularly within the left hemisphere. This hypothesis was based on the overlap in some symptomatology in bipolar and schizophrenia disorders (Maier et al., 2006), as well as more recent evidence suggesting similar underlying genetic etiology (Jackson et al., 2013; Cardno and Owen, 2014; Bramon and Sham, 2001; Lichtenstein et al., 2009). In conjunction with our previous work linking the quantitative trait of anhedonia to uncommon sulcogyral patterns in a control population (Zhang et al., 2016), disruption of common sulcogyral patterns may interfere more generally with the ability to experience pleasure, which is diminished in both schizophrenia and bipolar disorder.

Interestingly, anhedonia is also associated with other mood disorders, including unipolar depression. OFC sulcogyral patterns have been linked to depression in female adolescents (Whittle et al., 2014) and more recently, it has been suggested that the Type III pattern on the right may mediate the relationship between cannabis use and depressive symptoms (Chye et al., 2017). We were unable to confirm previous findings that link sulcogyral pattern type to quantitative traits. This may be due to differences in recruitment (college students vs. a community sample), exclusion criteria (drug screening in the current sample), or other unmeasured mediating factors. In our previous work, we did not confirm that our cohort was completely absent of any psychiatric diagnoses- thus previous results may be partially driven by a greater range of psychiatric symptoms in the sample. All patients and controls in the current study were required to pass a drug screen and therefore, were not illicit drug users. Because comorbid substance abuse and addiction are common in bipolar disorder and schizophrenia, it will be important to understand whether drug use is a mediator between OFC sulcogyral pattern, psychiatric diagnosis, and a particular quantitative symptom domain. Thus, future work should continue to explore how these patterns ultimately influence behavior and whether this is reflected in quantitative measurements of trait continuums.

The OFC has been broadly implicated in 'personality' and may be critical to a variety of cognitive skills that make us fundamentally human. Moreover, abnormalities within the OFC have been linked to a broad range of disorders (for review, see Jackowski et al., 2012). One reason that the OFC may be implicated in multiple disorders is the multifaceted nature of this cortical region. The OFC is parcellated into segments that exhibit distinct cellular architecture and connectivity (Kahnt et al., 2012; Brodmann, 1909; Walker, 1940; Ongür et al., 2003; Carmichael and Price, 1996; Uylings et al., 2010). These segments are densely interconnected with both subcortical and cortical structures, with reciprocal inputs to all sensory modalities. From this perspective, it is unsurprising that deviations from 'normal' cortical folding in the OFC would lead to multiple brain disorders. With regard to OFC sulcal patterns, the Type I pattern is likely a standard folding that represents an ideal spatial arrangement for efficient communication between and within brain regions. Deviations from this (Type II, III, and IV) likely result in suboptimal signaling that manifest as atypical cognitive traits and/or brain disorders. Original work that established OFC sulcogyral patterns found a left/right asymmetry in controls, with more Type I patterns appearing on the right. We find roughly equivalent frequencies on the left and right of our control population. Although several previous studies have found significant differences in right lateralized patterns in schizophrenia, other studies have shown left lateralized effects (Bartholomeusz et al., 2013). Thus, this analysis also adds to the growing body of knowledge that we have on the frequency of these patterns within the typical population.

In addition to the limitations noted above, we would like to note that our results are not corrected for multiple comparisons. We should continue to grow a database of OFC sulcogyral characterizations in multiple patient groups, in order to obtain the power necessary to perform rigorous statistical testing with multiple comparison correction. Another limitation is that this study and others show significant differences between control and patient populations on demographic variables, such as educational attainment, in addition to atypical sulcogyral pattern frequencies. It is known that individuals with severe mental illness are less likely to pursue higher education compared to individuals without mental illness (Eaton et al., 2008). Thus, it can be difficult to tease apart whether known differences in demographic variables are related to OFC sulcogyral pattern differences because psychiatric illness and education are highly associated. We do not believe these results are merely driven by differences in education level, as we find no significant difference in educational attainment between the BP and control groups, but still observe an increased rate of atypical sulcogyral patterns in BP. However, future work should address whether educational attainment is associated with OFC sulcogyral pattern type in a large, non-psychiatric control group that are matched on educational attainment. This particular issue is part of a larger problem in brain imaging studies of biased sampling due to non-representative sampling (LeWinn et al., 2017).

## 5. Conclusions

We find that atypical sulcal patterns are associated with bipolar disorder, rather than serving as a specific marker of schizophrenia. It is important to note that we do not believe this result diminishes the utility of OFC sulcal patterns on predicting disease susceptibility. Rather, we suggest that there is a more specific link between brain and behavior than brain and diagnosis, per se. This is consistent with recent findings of a common genetic source to multiple brain disorders (Moreno-De-Luca et al., 2013; The Lancet, 2013) and is in line with the research domain criteria (RDOC) framework put forward by the National Institutes of Mental Health, which emphasizes brain-behavior links rather than diagnostic categories. As we are beginning to realize the complexity of disorders that manifest from common genetic loci, this type of individualized brain metric (combined with genetic and behavioral data) could be useful in assessing individual disease risk. Ultimately, OFC sulcal pattern differences could assist in a more personalized approach for diagnosis and treatment of brain dysfunction.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2017.12.021.

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