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Subcortical neuromorphometry in schizophrenia spectrum and bipolar disorders

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ABSTRACT

Background: Disorders within the schizophrenia spectrum genetically overlap with bipolar disorder, yet questions remain about shared biological phenotypes. Investigation of brain structure in disease has been enhanced by developments in shape analysis methods that can identify subtle regional surface deformations. Our study aimed to identify brain structure surface deformations that were common across related psychiatric disorders, and characterize differences.

Methods: Using the automated FreeSurfer-initiated Large Deformation Diffeomorphic Metric Mapping, we examined volumes and shapes of seven brain structures: hippocampus, amygdala, caudate, nucleus accumbens, putamen, globus pallidus and thalamus. We compared findings in controls (CON; $n = 40$), and those with schizophrenia (SCZ; $n = 52$), schizotypal personality disorder (STP; $n = 12$), psychotic bipolar disorder (P-BP; $n = 49$) and nonpsychotic bipolar disorder (N-BP; $n = 24$), aged 15–35. Relationships between morphometric measures and positive, disorganized and negative symptoms were also investigated.

Results: Inward deformation was present in the posterior thalamus in SCZ, P-BP and N-BP; and in the subiculum of the hippocampus in SCZ and STP. Most brain structures however showed unique shape deformations across groups. Correcting for intracranial size resulted in volumetric group differences for caudate ($p < 0.001$), putamen ($p < 0.01$) and globus pallidus ($p < 0.001$). Shape analysis showed dispersed patterns of expansion on the basal ganglia in SCZ. Significant clinical relationships with hippocampal, amygdalar and thalamic volumes were observed.

Conclusions: Few similarities in surface deformation patterns were seen across groups, which may reflect differing neuropathologies. Posterior thalamic contraction in SCZ and BP suggest common genetic or environmental antecedents. Surface deformities in SCZ basal ganglia may have been due to antipsychotic drug effects.

1. Introduction

The term *schizophrenia spectrum disorder* has been used to describe a range of psychiatric conditions, including schizophrenia (SCZ), that share some genetic risk variants and clinical manifestations (Mamah and Barch, 2011). Among these, schizotypal personality disorder (STP) is the most commonly included in studies of the spectrum. This condition is typically not associated with florid psychotic symptoms of schizophrenia (such as hallucinations and bizarre delusions), but rather cognitive or perceptual distortions and eccentricities in everyday behavior. Bipolar disorder (BP) is not traditionally included among the schizophrenia spectrum disorders, despite the fact that genetic and familial overlap is present with SCZ (Cardno and Owen, 2014). Psychotic bipolar disorder (P-BP) has clinical similarities with SCZ and also has been reported to more closely overlap genetically with SCZ compared to nonpsychotic bipolar disorder (N-BP). Notwithstanding the relationship across these disorders, few studies have compared their brain structure (Mamah et al., 2009). Such studies would provide information on the extent of similarities between disorders, and help clarify the phenotypic manifestations of specific genetic profiles.

Volumetric analyses of structural brain imaging data have been a mainstay of brain structure investigations in psychiatry. In recent years, developments in shape analysis methodology have led to structural measures that can supplement data derived from volumetric analysis. In studies of disease, investigation of the three-dimensional surfaces of brain subcortical structures have been shown to identify group abnormalities where the volumetric analysis did not, indicating that subtle surface abnormalities are more sensitive to shape than size

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(Mamah et al., 2009). Since shape analysis enables the uncovering of localized deformations on the surface of a brain structure, it may more precisely identify impaired pathways within the brain. This is particularly important in the study of brain structures with explicit regional differentiation in function, such as the thalamus (Sherman and Guillery, 2013) or striatum (Verstynen et al., 2012; Draganski et al., 2008; Lehericy et al., 2004). Previous shape analyses have been conducted in psychiatric patients, including those with SCZ,(Mamah et al., 2009; Csernansky et al., 2004; Smith et al., 2011; Danivas et al., 2013; Kang et al., 2008; Csernansky et al., 2002; Mamah et al., 2012; Johnson et al., 2013; Qiu et al., 2010; Zierhut et al., 2013; Styner et al., 2004; Shenton et al., 2002; Mamah et al., 2008; Mamah et al., 2007; Ballmaier et al., 2008) BP(Qiu et al., 2013; Hwang et al., 2006; Womer et al., 2014; Ong et al., 2012; Liberg et al., 2014; Liberg et al., 2015) or STP,(Levitt et al., 2009; Levitt et al., 2004) often with varying results. However, studies are often conducted using differing recruitment criteria, scanners, imaging protocols and analyses methodology, which can significantly influence results. Thus, investigating various diagnostic patient groups in a single study, with identical protocol, is therefore necessary to obtain valid comparisons. Our shape analysis represents the most extensive investigation of its kind to our knowledge, comparing multiple subcortical brain structures across several diagnostic groups. We used an automated shape analysis methodology involving Large Deformation Diffeomorphic Metric Mapping (LDDMM) that has been validated and previous applied in the evaluation of disease (Khan et al., 2008; Ceyhan et al., 2011; Qiu et al., 2009).

In the current study, we investigated the volumes and shapes of seven subcortical structures simultaneously (i.e. the hippocampus, amygdala, caudate, putamen, globus pallidus, nucleus accumbens, and thalamus). We compared findings in healthy controls to those of individuals with SCZ, psychotic (P-BP) and nonpsychotic (N-BP) bipolar disorder, and STP, obtained using the same MRI scanner, imaging protocol and analysis methodology. We hypothesize that overlapping structural abnormalities will exist across these groups, with SCZ most affected. Abnormalities are expected to be largely trend toward shrinkage, and be best captured by shape analysis. Due to a probable past history of typical antipsychotic drug use, we hypothesize that the basal ganglia in SCZ will be enlarged.

2. Materials and methods

2.1. Participants

The study was approved by the Institutional Review Board of Washington University. Participant groups included: 1) healthy controls (CON; n = 40); 2) bipolar disorder (BP; n = 73); 3) schizophrenia (SCZ; n = 52); and 4) schizotypal personality disorder (STP; n = 12). Participants' ages ranged between 15 and 35 yrs. Participants were recruited through targeted advertisements in local psychiatric clinics, hospitals, and newspapers and through the Washington University volunteers for health recruitment system. All participants gave written informed consent for participation. SCZ and BP participants were all outpatients, and clinically stable for at least two weeks. They were diagnosed on the basis of a consensus between a research psychiatrist and a trained research assistant who used the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). The Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) was used to ascertain group diagnosis in STP participants. CON subjects were required to have no lifetime history of Axis I psychotic or mood disorders. Participants were excluded if they: (a) met DSM-IV criteria for substance dependence or severe/moderate abuse during the prior 6 months; (b) had a clinically unstable or severe general medical disorder; or (c) had a history of head injury with documented neurological sequelae or loss of consciousness. BP participants were subdivided into psychotic bipolar disorder (P-BP; N = 49) and nonpsychotic bipolar disorder (N-BP; N = 24) based on the presence or absence of a lifetime history of hallucinations and/or non-grandiose delusions using the SCID-I. Demographic data are shown in Table 1.

2.2. Clinical assessment

Psychopathology was assessed by trained Masters level research assistants using the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen et al., 1995). Specific subscale scores were summed to derive measures of positive symptoms (i.e. hallucination and delusion subscales), disorganization (i.e. formal thought disorder, bizarre behavior and attention subscales), and negative symptoms (i.e. flat affect, alogia, anhedonia and amotivation subscales).

2.3. Image acquisition and surface mapping

Magnetic Resonance (MR) scans were obtained using a Siemens (Erlangen, Germany) 3T Tim TRIO Scanner at Washington University Medical School. T1-weighted images were acquired using a sagittal MPRAGE 3D sequence (TR = 2400 ms, TE = 3.16 ms, flip = 8°; voxel size = 1 × 1 × 1 mm).

Surfaces of the hippocampus, amygdala, basal ganglia (i.e. caudate, nucleus accumbens, putamen and globus pallidus), and thalamus were automatically generated using FS + LDDMM, as previously described (Khan et al., 2008). In brief, this method combines a probabilistic voxel-based classification method of FreeSurfer (Desikan et al., 2006) and a deformable template-based method of large deformation diffeomorphic metric mapping (LDDMM) (Beg et al., 2005). The initial subcortical segmentations for the hippocampus, amygdala, basal ganglia and thalamus were obtained from FreeSurfer version 5.3.0, followed by image registration with LDDMM that produced smooth transformations for each region of interest (ROI). A previously-published template based on a healthy volunteer was used (Wang et al., 2008) to derive the segmentations and surfaces. Subcortical segmentations for the hippocampus and thalamus also included boundaries demarcating constituent subfields. Each ROI volume was calculated as the enclosed volume of the mapped surface. Intracranial volume, total gray matter volume and cortical white matter volume were obtained directly from the FreeSurfer pipeline output.

2.4. Statistical analyses

Statistical analyses (excluding shape) were done using SAS 9.4 (SAS Institute Inc., Cary, NC). Repeated measures ANCOVA (covaried for age and sex) were used to investigate volumetric group differences in subcortical brain regions, using hemisphere as the repeated measure. To

Table 1
Demographics table.

Characteristics	Control (n = 40)	SCZ (n = 52)	Schizotypal (n = 12)	PBP (n = 49)	NPBP (n = 24)
Age — Mean (SD)	24.9 (5.0)	26.1 (4.1)	22.4 (3.5)	25.2 (3.6)	26.2 (3.7)
Sex — N (%)					
Female	20 (50.0)	14 (26.9)	5 (45.5)	29 (59.2)	16 (66.7)
Male	20 (50.0)	38 (73.1)	6 (54.5)	20 (40.8)	8 (33.3)
Race (%)					
Asian	2 (5.0)	0	0	1 (2.0)	2 (8.3)
Black	21 (52.5)	27 (51.9)	3 (27.3)	13 (26.5)	2 (8.3)
Hispanic	0	0	0	3 (6.1)	0
White	17 (42.5)	25 (48.1)	8 (72.7)	30 (61.2)	18 (75.0)
Mixed/other	0	0	0	2 (4.1)	2 (8.3)
Handedness					
Right	36 (90.0)	50 (96.2)	9 (81.8)	45 (91.8)	21 (87.5)
Left	4 (10.0)	2 (3.8)	2 (18.2)	4 (8.2)	3 (12.5)