Psychiatry Research: Neuroimaging 223 (2014) 75–83

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Basal ganglia and thalamic morphology in schizophrenia and bipolar disorder

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ARTICLE INFO

Article history:
Received 31 May 2013
Received in revised form
15 May 2014
Accepted 27 May 2014
Available online 6 June 2014

Keywords:
Structural magnetic resonance imaging
Morphometry
Basal ganglia
Thalamus

ABSTRACT

In this study, we examined the morphology of the basal ganglia and thalamus in bipolar disorder (BP), schizophrenia-spectrum disorders (SCZ-S), and healthy controls (HC) with particular interest in differences related to the absence or presence of psychosis. Volumetric and shape analyses of the basal ganglia and thalamus were performed in 33 BP individuals [12 without history of psychotic features (NPBP) and 21 with history of psychotic features (PBP)], 32 SCZ-S individuals [28 with SCZ and 4 with schizoaffective disorder], and 27 HC using FreeSurfer-initiated large deformation diffeomorphic metric mapping. Significant volume differences were found in the caudate and globus pallidus, with volumes smallest in the NPBP group. Shape abnormalities showing inward deformation of superior regions of the caudate were observed in BP (and especially in NPBP) compared with HC. Shape differences were also found in the globus pallidus and putamen when comparing BP and SCZ-S groups. No significant differences were seen in the nucleus accumbens and thalamus. In summary, structural abnormalities in the caudate and globus pallidus are present in BP and SCZ-S. Differences were more apparent in the NPBP subgroup. The findings herein highlight the potential importance of separately examining BP subgroups in neuroimaging studies.

1. Introduction

Differentiating bipolar disorder (BP) and schizophrenia (SCZ) is challenging, particularly with their overlap in symptomatology such as psychosis. Neuroimaging studies, including those that directly compare BP and SCZ, indicate both overlapping and disparate abnormalities between BP and SCZ; however, identification of biomarkers that clearly differentiate between the two disorders remains elusive due to complicating factors such as varying medication exposure and clinical heterogeneity (McIntosh et al., 2008a, 2008b; Arnone et al., 2009; Hamilton et al., 2009; Ellison-wright and Bullmore, 2010; Hall et al., 2010; Ongür et al., 2010; Rimol et al., 2010; Brown et al., 2011; Sui et al., 2011).

Studying brain structure in non-psychotic and psychotic subgroups of BP individuals may mitigate challenges related to clinical heterogeneity in BP, and could elucidate underlying mechanisms of psychosis when these BP subgroups are compared with SCZ. However, studies comparing psychotic and non-psychotic BP subgroups with SCZ are scarce (Strasser et al., 2005). Yet, preliminary evidence does support the potential for such approaches to enhance our understanding of psychosis. Recent studies suggest unique and shared abnormalities among affective psychosis and schizophrenia-spectrum disorders (SCZ-S) (De Castro-Manglano et al., 2011; Ivleva et al., 2012). Differences in brain structure and function, as well as dopamine receptor density and ventricular volume, have been found between non-psychotic and psychotic affective disorders (Pearlson et al., 1995; Wang and Ketter, 2000; Strasser et al., 2005; Garrett et al., 2011; Busatto, 2013).

Potential key regions involved in psychosis include the basal ganglia and thalamus. Both these regions have been increasingly implicated in emotional and cognitive processing, particularly via cortico-basal ganglia and cortico-thalamic circuits, and appear to play important roles in executive functions that are commonly impaired in psychotic conditions (Byne et al., 2009; Haber and Calzavara, 2009; Marchand and Yurgelun-Todd, 2010). Moreover, the basal ganglia and thalamus are rich in dopaminergic innervation (Byne et al., 2009), which are significant in light of the evidence implicating the critical

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http://dx.doi.org/10.1016/j.pscychresns.2014.05.017
0925-4927/

role of dopamine in psychosis (Howes and Kapur, 2009). Structural abnormalities in the basal ganglia and thalamus have been observed in psychosis (Brandt and Bonelli, 2008; Byne et al., 2009; Smith et al., 2011). Volume abnormalities in the basal ganglia and thalamus have been more consistently found in SCZ than BP, when compared with controls (Byne et al., 2009; Ellison-Wright and Bullmore, 2010; Marchand and Yurgelun-Todd, 2010; Radenbach et al., 2010). Most studies have found increased basal ganglia and decreased thalamic volumes in SCZ, whereas findings have been quite variable in BP. The inconsistencies in BP may possibly relate to clinical heterogeneity within samples (e.g., inclusion of BP individuals with and without psychotic features).

Shape analysis of specific brain regions could provide more refined discrimination of structural differences between groups and localize structural abnormalities within a brain region, thus complementing volumetric analyses (Csernansky et al., 1998; Csernansky et al., 2002; Csernansky et al., 2004). Shape abnormalities in the basal ganglia and thalamus have been found in BP and SCZ, although such studies are limited and have largely focused on SCZ (Harms et al., 2007; Mamah et al., 2007; Coscia et al., 2009; Smith et al., 2011; Ong et al., 2012). We are not aware of any morphometric neuroimaging studies directly comparing BP and SCZ in the basal ganglia and thalamus.

In this study, we examined the volume and shape of basal ganglia structures and the thalamus in BP, SCZ-S, and healthy controls (HC) using FreeSurfer-initiated large deformation diffeomorphic metric mapping (FS+LDDMM), a fully automated brain-segmentation methodology (Khan et al., 2008). We hypothesized that structural abnormalities in these regions would vary across clinical subgroups as follows: (1) for basal ganglia volumes, SCZ-S > bipolar disorder with psychotic features (PBP) > bipolar disorder without psychotic features (NPBP) and healthy controls (HC); (2) for thalamic volume, HC and NPBP > PBP > SCZ-S; and (3) shape abnormalities in the basal ganglia and thalamus would be most prominent in SCZ-S and intermediate in PBP.

2. Methods

2.1. Participants

Written informed consent was obtained from all participants in accordance with the institutional review boards at Washington University School of Medicine and Northwestern University Feinberg School of Medicine.

Participants included 33 adults with BP [12 without history of psychotic features (NPBP) and 21 with history of psychotic features (PBP)], 32 adults with SCZ-S [28 with SCZ and 4 with schizoaffective disorder (SAD)], and 27 healthy controls (HC). Participants were recruited at two sites, Washington University (St. Louis, MO) [WU] and Northwestern University (Chicago, IL) [NU], through advertisements in the community and mental health centers/clinics, and through research participant registries. The BP participants were recruited at WU. The SCZ-S and HC participants were selected to match in age, gender, and race with the BP participants from a larger study sample recruited at WU and NU. For the SCZ-S group, 18 participants were recruited at WU, and 14 were recruited at NU. For the HC group, eight participants were recruited at WU, and 19 were recruited at NU. For each participant at his or her respective sites, DSM-IV Axis I diagnoses were determined through consensus between a research psychiatrist and trained research clinicians using the Structured Clinical Interview for DSM-IV Axis I Diagnoses (SCID) and an independent psychiatric evaluation by a research psychiatrist. Individuals were excluded if they had neurological disorders, unstable medical disorders, head injury with loss of consciousness, or contraindication to magnetic resonance imaging (e.g., metal implant or claustrophobia). In addition, to minimize clinical heterogeneity within the BP group, only participants with a history of euphoric mania (versus mania characterized by primarily irritable mood) were included in the study.

Demographic and clinical characteristics of the participants are detailed in Table 1. The SCID was used to identify participants with lifetime substance use disorders for alcohol, cannabis, cocaine, stimulants, hallucinogens, sedatives, and opioids. Substance use disorders were defined as meeting lifetime DSM-IV-TR criteria for abuse or dependence. Participants did not have a history of substance dependence within past 6 months, except for one BP participant with cannabis dependence. Results were unchanged when volume analyses were performed excluding the BP

Table 1
Participant demographic profiles and characteristics.

	Control ($n=27$)	SCZ-S ($n=32$)	BP ($n=33$)	NPBP ($n=12$)	PBP ($n=21$)	F/χ^a	p^a	F/χ^b	p^b
*Mean age**	25.5 (4.3)	25.8 (4.1)	25.5 (3.9)	27.0 (3.8)	24.6 (3.7)	0.1	0.9	1.0	0.4
Gender						0.2	0.9	2.6	0.5
Female	14 (51.9)	17 (53.1)	16 (48.5)	8 (66.7)	8 (38.1)				
Male	13 (48.1)	15 (46.9)	17 (51.5)	4 (33.3)	13 (61.9)				
Race						3.0	0.5	6.7	0.4
Black	6 (22.2)	11 (34.4)	9 (27.3)	1 (8.3) 10	8 (38.1)				
Caucasian	15 (55.6)	17 (53.1)	21 (63.6)	(83.3) 1	11 (52.4)				
Other	6 (22.2)	4 (12.5)	3 (9.1)	(8.3)	2 (9.5)				
Handedness						0.2	0.9	4.4	0.2
Right	26 (96.3)	30 (93.8)	31 (93.9)	10 (83.3)	21 (100)				
Left	1 (3.7)	2 (6.3)	2 (6.1)	2 (16.7)	0 (0)				
Lifetime substance use									
Alcohol	0 (0)	10 (31.2)	18 (54.6)	5 (41.7)	13 (61.9)	20.9	< 0.0001	22.3	< 0.0001
Cannabis	0 (0)	16 (50.0)	12 (36.4)	2 (16.7)	10 (47.6)	18.1	0.0001	21.6	< 0.0001
Cocaine	0 (0)	5 (15.6)	3 (9.1)	1 (8.33)	2 (9.5)	4.5	0.1	4.5	0.2
Stimulant	0 (0)	4 (12.5)	0 (0)	0 (0)	0 (0)	7.8	0.01	7.8	0.05
Sedative	0 (0)	0 (0.0)	2 (6.1)	0 (0)	2 (9.5)	3.6	0.2	6.9	0.07
Hallucinogen	0 (0)	1 (3.1)	3 (9.1)	0 (0)	3 (14.3)	3.1	0.2	6.6	0.07
Opiate	0 (0)	0 (0)	3 (9.1)	0 (0)	3 (14.3)	5.5	0.06	10.5	0.01
*Antipsychotic use in past 2 years***						0.02*	0.9*	0.6*	0.7*
FGA only	N/A	0 (0)	0 (0)	0 (0)	0 (0)				
SGA only	N/A	26 (81.2)	22 (66.7)	5 (41.7)	15 (71.4)				
Both FGA+SGA	N/A	3 (9.4)	2 (6.1)	0 (0.0)	2 (9.5)				

SCZ: Schizophrenia-spectrum disorders; BP: Bipolar disorder; NPBP: Non-psychotic bipolar disorder; PBP: Psychotic bipolar disorder.
Values are given as number of participants (percentages), unless stated otherwise.

[a] *F* statistic, chi-square statistic or *p* Value for 3-group analysis comparing control, SCZ-S, and BP
[b] *F* statistic, chi-square statistic or *p* Value for 4-group analysis comparing control, SCZ-S, NPBP, and PBP
* Mean age is expressed in years with standard deviation in parentheses.
** For antipsychotic use, controls were excluded from the analysis.