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Research paper

Basal ganglia volumetric changes in psychotic spectrum disorders

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ABSTRACT

Background: Basal ganglia are particularly important for understanding the pathobiology of psychosis given their key roles in dopaminergic neurotransmission which are associated with psychotic symptoms and one of the target sites of antipsychotic drugs. Psychotic symptoms are prevalent in both schizophrenia (SZ) and bipolar disorder (BD). Although the components of basal ganglia are implicated in psychosis, comparative structural changes of components of the basal ganglia between SZ and BD are less clear after disentanglement of clinical effects of antipsychotic dose, duration and severity of illness.

Methods: In this study, we examined the morphology of the basal ganglia in 326 subjects comprising of 45 patients of BD type I with psychotic symptoms, 97 first-episode SZ (FE-SZ) patients, 86 non-first-episode chronic SZ (NFE-SZ) patients, in comparison with 98 healthy controls (HC).

Results: Results showed increased volumes in subregions of caudate, putamen, and pallidum in chronic SZ patients compared with HC after controlling for age, gender, and total intracranial volume. No change was found between FE-SZ patients, psychotic BD patients, and HC. Furthermore, hierarchical regressions showed that the dosage of antipsychotics had a significant contribution to basal ganglia volumetric enlargement in NFE-SZ after controlling for the effects of age, gender, total intracranial volume, age at illness onset, as well as illness duration and severity.

Limitations: Lack of information about the cumulative history of exposure to medication for all the three groups of patients is a major limitation in our study.

Conclusions: There are distinct basal ganglia structural changes in SZ and psychotic BD. Basal ganglia are enlarged in chronic SZ but not in FE-SZ and BD and this enlargement is significantly associated with antipsychotic dosage over and beyond the effects of illness duration and severity.

1. Introduction

There is some overlap between schizophrenia (SZ) and bipolar disorder (BD) in terms of shared psychotic features (Jabben et al., 2009), comparable neurocognitive deficits (Kuswanto et al., 2013), and common genetic determinants (Lichtenstein et al., 2009). So far there are no specific brain biomarkers that can reliably distinguish these two disorders which is further confounded by the clinical heterogeneity and impact of treatment including psychotropic medications (De Peri et al., 2012; Rimol et al., 2010; Womer et al., 2014). One important clinical confound that needs attention is the illness subtype BD with and without psychosis. Accumulating evidence indicates that psychotic and nonpsychotic BD have distinct neural mechanisms, which suggests these two subtypes may differ in pathophysiology and should be examined separately (Altamura et al., 2017; Ekman et al., 2017). For instance, psychotic BD but not nonpsychotic BD patients have been reported to have similar brain abnormalities with SZ, which may be due to clinical similarities in psychotic BD and SZ (Mamah et al., 2016; Strasser et al., 2005). Therefore, directly comparing SZ with psychotic BD rather than a single BD group would help clarify the underlying mechanisms of psychosis in these disorders, which may shed light on the diagnosis and treatment of these disorders.

Basal ganglia are particularly important with regards to psychosis. Dopamine hypothesis, one of the most influential theories explaining the neurobiological mechanisms of psychosis in schizophrenia, postulates that psychosis is the result of dopaminergic dysfunction (Howes

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and Kapur, 2009; Pankow et al., 2012; Toda and Abi-Dargham, 2007). Basal ganglia, particularly dorsal striatum and ventral striatum, are important input areas of the neurotransmitter dopamine from midbrain. There is evidence that increased firing of dopamine neurotransmitters involving basal ganglia is associated with the positive symptoms including hallucinations and delusions of SZ (Abi-Dargham, 2004; Laruelle and Abi-Dargham, 1999; Seeman and Kapur, 2000). Correspondingly, antipsychotic drugs are dopamine D2 receptor antagonists which aim at blocking the dopamine receptors including at basal ganglia to alleviate the psychotic symptoms (Creese et al., 1976). Of note, such striatal dopaminergic elevation is not restricted to psychosis in SZ, but it is also observed in other disorders such as BD and Alzheimer disease that involve psychotic symptoms (Cousins et al., 2009; Howes and Kapur, 2009; Reeves et al., 2009). Together, the involvement of dopaminergic neurotransmission in these conditions implicate the basal ganglia in psychosis.

In addition to the link to positive symptoms of psychosis in SZ, basal ganglia play a potential role in the negative symptoms such as apathy and lack of motivation and cognitive dysfunctions such as deficits in attention, working memory, and executive function (Simpson et al., 2010). A recent meta-analysis of functional imaging data demonstrates that SZ patients show markedly decreased activation of basal ganglia in emotional and cognitive processing (Bernard et al., 2017). In contrast, BD patients show broadly increased activation of basal ganglia in emotional and cognitive tasks (Marchand and Yurgelun-Todd, 2010). Given basal ganglia's key role in psychosis and differential functional activity in basal ganglia in SZ and BD, it is important to further delineate pathophysiological patterns of basal ganglia across the psychosis spectrum.

Structural abnormalities of basal ganglia have been observed in SZ in many studies (see review, Brandt and Bonelli, 2008). Most structural magnetic resonance imaging (MRI) studies found volumetric increases in distinct basal ganglia structures (Levitt et al., 2013; Mamah et al., 2007; Oertel-Knöchel et al., 2012; van Erp et al., 2016). Accumulating evidence suggests that such basal ganglia enlargements are most likely due to antipsychotic medication. For example, longitudinal studies comparing schizophrenic patients before and after treatment indicate significant basal ganglia volume increase after treatment (Li et al., 2012; Mh, 1994). However, the exact mechanism of basal ganglia enlargement associated with antipsychotic medication remains unclear. One possibility is that antipsychotics which block D2 receptors in basal ganglia may induce cell proliferation (Hashimoto et al., 2018). Another possibility is that administration of antipsychotic drugs may lead to the increment of striatal blood flow (Handley et al., 2013).

Previous research about the antipsychotic effect on basal ganglia volumes could be confounded by factors such as duration and severity of psychosis. Indeed, basal ganglia volume changes in psychotic disorders are related to a combination of multiple factors such as illness progression and severity, in addition to medication effects (Haijma et al., 2012). For example, research has shown positive associations between putamen and pallidum volumes and duration of illness in SZ (van Erp et al., 2016) as well as between putamen volume increase and positive symptom reduction in SZ after 6 weeks treatment (Li et al., 2012). In fact, clinical features of illness duration and severity as well as the impact of medication are highly correlated with each other. Generally, the more severe patients tend to receive a higher dosage of medication and the longer the duration of illness, the greater the cumulative effects of antipsychotic medications. Given the significant correlation between medication and illness, findings of association between clinical variables and brain structural variations should be interpreted cautiously (van Erp et al., 2016). To better untangle the relationships of illness duration, severity, and antipsychotics with basal ganglia volume changes in psychotic disorders, it is important to dissociate the effect of one factor from the other two to examine their specific contributions to volumetric changes.

Structural differences in basal ganglia are also seen in BD. Studies have shown larger basal ganglia structures in patients with BD (Aylward et al., 1994; Strakowski et al., 2002) while many others have reported no volumetric changes (Brambilla et al., 2001; Hibar et al., 2016; López-Jaramillo et al., 2017; Sanches et al., 2005). To note, findings of basal ganglia structures are inconsistent overall in BD and the pattern is still not clearly defined. The inconsistencies may possibly relate to clinical heterogeneity within samples, such as the inclusion of BD individuals with and without psychotic features and no differentiation between BD I and BD II types (Altamura et al., 2017).

Together, based on previous observations, the first aim of this study was to compare the basal ganglia volumes (e.g., caudate, putamen, pallidum, and nucleus accumbens) among psychotic BD type I (BD-I), first-episode SZ (FE-SZ) with minimal exposure to antipsychotics, non-first-episode SZ (NFE-SZ) with long-term treatment, and healthy controls (HC). The second objective is to dissociate the effect of daily dose of antipsychotics, duration of illness, and illness severity from each other to examine their specific contributions to basal ganglia volumetric changes.

2. Methods

2.1. Participants

Three hundred and twenty-six subjects (comprising of 97 FE-SZ patients, 86 NFE-SZ patients, 45 BD-I patients with psychotic features, and 98 healthy controls) were recruited at the Institute of Mental Health (IMH), Singapore as well as the local community through advertisements. The diagnosis evaluation of mental disorders was performed by a board-certificated psychiatrist (K.S.) using the information obtained from the clinical history, mental status examination, existing medical records, interviews with significant others, as well as the administration of the Structural Clinical Interview for DSM-IV (diagnostic and statistical manual of mental disorders, 4th edition, revised) disorders-Patients Version (SCID-P). Patients and comparison subjects were excluded if they had any of the following characteristics: (1) A history of any significant neurological illness such as brain trauma, epilepsy, or cerebral vascular accident and (2) met DSM-IV criteria for current and past alcohol or other substance abuse. The healthy controls were additionally screened for family history of mental illness: participants with a first-degree relative suffering from a mental illness were excluded in this study. The institutional review board of the hospital had approved the study and all participants provided signed, written informed consent prior to any study procedures.

At the time of scanning, all SZ patients and 38 BD patients were regularly receiving antipsychotic medication and had no changes to their medications for the last 4 weeks. Most of the BD patients were euthymic at the time of the scan. In Table 1, we present the detailed demographics and clinical characteristics of the participants. The antipsychotic medication dosage was converted to daily chlorpromazine (CPZ) milligram equivalents. The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) and Global Assessment of Functioning (GAF; American Psychiatric Association, 1994) were used to rate and assess the severity of symptoms and level of psychosocial functioning respectively.

2.2. MRI acquisition and image processing

High-resolution T1-weighted brain images were acquired on a 3-T whole-body scanner (Philips Achieva, Philip Medical System, Eindhoven, the Netherlands). Prior to the scanning, participants were instructed to keep still and remain as motionless as possible. During the data acquisition, participants lay supine with the head snugly fixed by foam pads provided by the scanner manufacturer to further minimize head motion. Images were collected by means of a T1-weighted magnetization-prepared rapid gradient recalled sequence (repetition time [TR] = 7.2 s; echo time [TE] = 3.3 ms; flip angle = 8; slice

Table 1
Demographic and clinical data.

	HC (N = 98)	BD (N = 45)	FE-SZ (N = 97)	NFE-SZ (N = 86)	F/χ^2	p
Demographic variables						
Age (years)	32.67 (9.79)	34.70 (10.74)	30.55 (7.77)	36.70 (9.26)	7.23	< 0.001
Sex (male/female)	60/38	18/27	58/39	62/24	12.81	< 0.01
Handedness (right/left/ambidextrous)	91/7/0	43/2/0	89/7/1	78/8/0	3.41	> 0.5
Education (years)	14.18 (2.04)	12.03 (2.39)	11.58 (2.66)	11.58 (2.49)	25.44	< 0.001
Clinical variables						
Age at onset (years)		29.84 (10.42)	27.25 (7.80)	24.53 (7.22)	6.55	< 0.01
Duration of illness (years)		3.86 (4.72)	2.81 (3.05)	11.54 (7.95)	59.15	< 0.001
Duration of untreated psychosis (years)		0.30 (0.52)	2.03 (2.99)	1.15 (1.48)	10.41	< 0.001
PANSS						
Positive symptoms		8.60 (2.83)	11.05 (3.98)	10.47 (3.59)	7.07	< 0.01
Negative symptoms		7.07 (0.33)	9.15 (2.98)	9.58 (3.91)	10.30	< 0.001
General psychopathology		17.87 (1.87)	21.10 (4.31)	20.19 (3.68)	11.73	< 0.001
Total score		33.53 (4.20)	41.31 (8.71)	40.23 (8.51)	15.54	< 0.001
GAF		64.56 (20.58)	53.06 (18.18)	50.14 (14.95)	10.33	< 0.001
YMRS		3.64 (4.88)				
Medication		N = 45	N = 97	N = 83 (3 missing for CPZ)		
Antipsychotics						
Typical		8 (17.8%)	36 (37.1%)	34 (40.5%)		
Atypical		27 (60.05)	52 (53.6%)	24 (28.6%)		
Both typical and atypical		3 (6.7%)	9 (9.3%)	26 (31.0%)		
CPZ (mg)		166.05 (151.81)	166.29 (155.91)	272.26 (209.83)	9.19	< 0.001
Mood stabilizers						
Lithium		14 (31.1%)	1 (1.0%)	4 (4.8%)		
Valproate		20 (44.4%)	7 (7.2%)	19 (22.6%)		
Both lithium and valproate		3 (6.7%)	0	0		
Anticholinergics		0	29 (29.9%)	51 (60.7%)		
Antidepressants		7 (15.6%)	21 (21.6%)	20 (23.8%)		
Benzodiazepines		9 (20.0%)	5 (5.2%)	33 (39.3%)		

Abbreviations: HC, healthy controls; BD: bipolar disorder; FE-SZ, first-episode schizophrenia; NFE-SZ, non-first-episode schizophrenia; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; YMRS, Young Mania Rating Scale; CPZ, daily chlorpromazine equivalent dose. All values are mean (SD) unless otherwise indicated.
For demographic variables, F statistic or chi-square statistic was used for 4-group analysis comparing HC, BD, FE-SZ, and NFE-SZ, as appropriate. For clinical variables, F statistic or chi-square statistic was used for 3-group analysis comparing BD, FE-SZ, and NFE-SZ.

number = 180; thickness = 0.9 mm; field of view [FOV] = 230 × 230 mm^2; acquisition matrix = 256 × 256; in-plane resolution = 0.9 × 0.9 mm^2) in the direction of the anterior-posterior commissures.

After all scans were visually inspected to be valid, cortical and subcortical reconstruction and volumetric segmentation were performed using the open-source Freesurfer pipeline (software version 5.3, http://surfer.nmr.mgh.harvard.edu). The whole procedure included motion correction, intensity normalization, automated topology corrections, and automatic segmentations of cortical and subcortical regions. The regions labeled as left and right caudate, putamen, pallidum, and accumbens areas were extracted, and the corresponding volumes were calculated (Fischl et al., 2002).

2.3. Statistical analysis

Demographic and clinical characteristics across groups were compared using univariate analyses of variance (ANOVA) and chi-square test, as appropriate. A general linear model (GLM) was used to compare basal ganglia volumes in four regions (caudate, putamen, pallidum, and accumbens) between the four groups of participants. Specifically, the brain volume was treated as the dependent variable and diagnosis (FE-SZ vs. NFE-SZ vs. BD-I vs. HC) as the between-subject factor. Brain volumes laterality (left and right) was set up as a within-subject variable, and age, gender, and the estimated total intracranial volume were entered into the model as covariates.

Furthermore, hierarchical regression was conducted to disentangle the contributions of duration of illness, illness severity, and antipsychotic dose respectively to basal ganglia volumetric changes. Here, illness severity was assessed using PANSS positive scores and antipsychotic dose was assessed using the daily chlorpromazine equivalent (CPZ) dosage. Specifically, for the effect of antipsychotics, a two-stage hierarchical multiple regression was conducted with basal ganglia volume as the dependent variable. Age, sex, total intracranial volume, age at onset, duration of illness, and PANSS positive, negative, and general scores were entered as predictors at stage one of the regression. CPZ dosage was entered as the predictor at stage two.

Relationships between basal ganglia volumes and antipsychotics dosages were explored across three patient groups using partial correlation, controlling for age, sex, total intracranial volume, age at onset, duration of illness, and PANSS positive, negative, and general scores. All statistical analyses were performed using IBM SPSS Statistics (Version 23.0). The threshold of statistical significance was set at $p < 0.05$. Bonferroni correction for multiple comparisons was performed across the four diagnostic groups for *post hoc* tests, when applied.

3. Results

Demographic and clinical characteristics of participants are presented in Table 1. In terms of clinical characteristics, patients with BD had a significantly older age of onset than patients with NFE-SZ; patients with NFE-SZ had a longer duration of illness than patients with FE-SZ or BD; and patients with FE-SZ had a longer duration of untreated psychosis than patients with NFE-SZ or BD. Patients with FE-SZ or NFE-SZ had more severe psychotic psychopathology, and poorer level of psychosocial functioning, indicated by lower GAF scores, compared to the BD group. There was no difference between FE-SZ and NFE-SZ groups. Patients with NFE-SZ had greater antipsychotic dose (in daily chlorpromazine milligram equivalents, CPZ) than patients with FE-SZ or BD. The CPZ dose was not available for three NFE-SZ patients, leaving 83 patients for further analyses. In BD, seven patients didn't

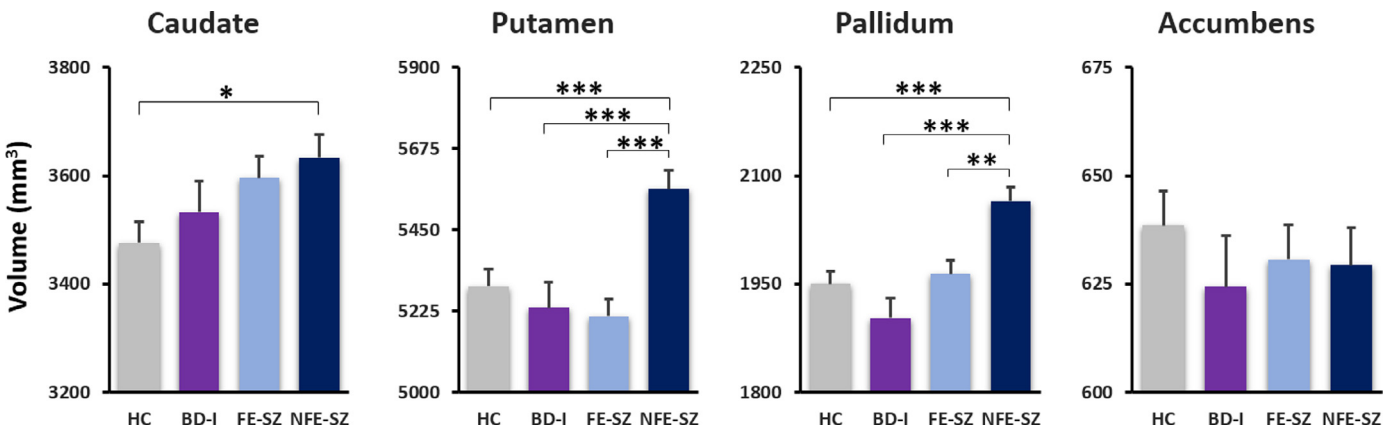

Fig. 1. Basal ganglia volume differences across groups of psychotic bipolar disorder I (BD-I), first-episode schizophrenia (FE-SZ), non-first-episode schizophrenia (NFE-SZ), and healthy controls (HC). * represents $p < 0.05$, ** represents $p < 0.01$, and *** represents $p < 0.001$.

take any antipsychotics, leaving 38 patients for further analyses involving CPZ dose.

Specifically, the repeated measures analysis comparing the left and right caudate volume across groups of BD, FE-SZ, NFE-SZ, and HC yielded a significant main effect of group [$F(3319) = 3.036$, $p = 0.029$, partial $\eta^2 = 0.028$], but no significant effect of laterality [$F(1319) = 3.149$, $p = 0.077$, partial $\eta^2 = 0.010$] and no interaction between group and laterality [$F(3319) = 0.462$, $p = 0.709$, partial $\eta^2 = 0.004$]. Pairwise comparisons showed that caudate volume was significantly larger in NFE-SZ group than HC group, $p = 0.036$ (Fig. 1); there were no other significant differences between groups (p values > 0.1). The specific basal ganglia volumes are shown in Table S1.

Putamen volume analysis revealed a main effect of group [$F(3319) = 9.370$, $p < 0.001$, partial $\eta^2 = 0.081$], but no main effect of laterality [$F(1319) = 3.460$, $p = 0.064$, partial $\eta^2 = 0.011$] and no interaction between group and laterality [$F(3319) = 2.012$, $p = 0.112$, partial $\eta^2 = 0.019$]. Pairwise comparisons showed that, across groups, the putamen volume was significantly greater in NFE-SZ group than other groups [NFE-SZ vs. HC: $p = 0.001$; NFE-SZ vs. FE-SZ: $p < 0.001$; NFE-SZ vs. BD: $p = 0.001$]; there were no significant differences among FE-SZ group, BD group, and HC group (p values > 0.9).

For pallidum volume, there was also a main effect of group [$F(3319) = 9.516$, $p < 0.001$, partial $\eta^2 = 0.082$], and no main effect of laterality [$F(1319) = 0.256$, $p = 0.613$, partial $\eta^2 = 0.001$] and no interaction between group and laterality [$F(3319) = 0.417$, $p = 0.741$, partial $\eta^2 = 0.004$]. Pairwise comparisons showed a significantly greater pallidum volume in NFE-SZ group than other groups [NFE-SZ vs. HC: $p < 0.001$; NFE-SZ vs. FE-SZ: $p = 0.003$; NFE-SZ vs. BD: $p < 0.001$]; there were no significant differences among FE-SZ group, BD group, and HC group (p values > 0.4).

No significant differences were seen in the nucleus accumbens. The main effect of group [$F(3319) = 0.413$, $p = 0.744$, partial $\eta^2 = 0.004$], the main effect of laterality [$F(1319) = 0.941$, $p = 0.333$, partial $\eta^2 = 0.003$], and the interaction between group and laterality [$F(3319) = 0.888$, $p = 0.448$, partial $\eta^2 = 0.008$] were all not significant.

Of note, we also divided the BD patients into FE-BD group ($n = 31$) and NFE-BD group ($n = 14$) and found no basal ganglia volume differences between these two groups (caudate: $t_{43} = 0.955$, $p = 0.345$; putamen: $t_{43} = 0.858$, $p = 0.395$; pallidum: $t_{43} = 0.205$, $p = 0.839$; accumbens: $t_{43} = 0.339$, $p = 0.736$). Given the small number of patients in NFE-BD group, we combined both first-episode and non-first-episode patients as the BD group. To further explore the possible effect of antipsychotic medication on basal ganglia in SZ, we compared the basal ganglia volumes according to type of antipsychotics, namely, typical vs. atypical antipsychotics. Results showed that typical and atypical antipsychotics had no differential effect in terms of basal ganglia volume changes.

In general, we found significantly enlarged brain volumes in caudate, putamen, and pallidum in NFE-SZ patients than FE-SZ patients, BD patients, and healthy controls after controlling for age, gender, and the estimated total intracranial volume (Fig. 1). There were no significant volumetric differences among FE-SZ patients, BD patients, and healthy controls.

Given that no laterality effect was observed in brain volumes, we computed the average of left and right basal ganglia volumes for further analysis. The finding of the overall enlarged basal ganglia volume in NFE-SZ group compared with FE-SZ group may suggest an antipsychotic effect on basal ganglia in NFE-SZ patients. Partial correlation analysis showed that higher dose of antipsychotic medication was associated with larger volume of caudate ($r = 0.242$, $p = 0.037$) and putamen ($r = 0.236$, $p = 0.041$) in NFE-SZ patients, after controlling for age, sex, total intracranial volume, age at onset, duration of illness, and PANSS positive, negative and general scores. There was no such partial correlation between antipsychotic dosage and basal ganglia volume in FE-SZ patients. In BD, however, dose of antipsychotic medication was negatively associated with volume of caudate ($r = -0.391$, $p = 0.033$), putamen ($r = -0.482$, $p = 0.007$). There was no correlation between antipsychotic dosages and basal ganglia volumes after pooling all patients together.

Hierarchical regression was carried out to investigate the specific contribution of antipsychotic medication to enlarged caudate in NFE-SZ patients after regressing out the effects of illness duration and illness severity (Table 2). In the first step of regression, seven predictors were entered: age, sex, total intracranial volume, age at onset, duration of illness, and PANSS positive, negative and general scores. This model was statistically significant ($F(8,74) = 4.971$, $p < 0.001$), and explained 35% of variance in caudate volume. At stage 2, adding CPZ dosage to the regression model explained an additional 4% of the variation in caudate volume and this change in R^2 was significant, $F(1,73) = 4.535$, $p < 0.05$.

Similar hierarchical regression was performed to investigate the specific contribution of antipsychotics to enlarged putamen in NFE-SZ patients (Table 3). Results revealed that the first model was significant ($F(8,74) = 3.341$, $p < 0.01$) and explained 27% of variance in putamen volume. The entry of CPZ dosage at stage 2 explained an additional 4% of the variation in putamen volume and this change in R^2 was significant, $F(1,73) = 4.317$, $p < 0.05$. Hierarchical regressions on pallidum and accumbens in NFE-SZ patients revealed no significant contribution of daily antipsychotic dosage. Moreover, to explore the specific contribution of duration of illness to basal ganglia volumes, similar hierarchical regressions were carried out controlling for illness severity and CPZ dosage. Results revealed no significant effect of illness duration. Controlling for illness duration and CPZ dosage also revealed

Table 2
Summary of hierarchical regression analysis for variables predicting caudate volumetric alteration in chronic schizophrenia patients. * represents $p < 0.05$, *** represents $p < 0.001$.

Variable	Beta	*t*	R^2	ΔR^2	F change	(df1, df2)	*p*
Step 1			0.349		5.751	7, 75	***
Age	−0.267	−2.074*					
Sex	0.093	0.736					
Total intracranial volume	0.559	4.420***					
Illness duration	−0.093	−0.738					
PANSS positive	−0.177	−1.413					
PANSS negative	0.192	1.777					
PANSS general	0.061	0.463					
Step 2			0.387	0.038	4.615	1, 74	*
Age	−0.181	−1.372					
Sex	0.047	0.377					
Total intracranial volume	0.533	4.300***					
Illness duration	−0.182	−1.400					
PANSS positive	−0.243	−1.929					
PANSS negative	0.195	1.852					
PANSS general	0.099	0.759					
CPZ dosage	0.213	2.148*					

no significant contribution of illness severity to basal ganglia volumes in NFE-SZ patients.

Taken together, these results indicate a role of antipsychotic medication with regards to basal ganglia enlargement in NFE-SZ, controlling for illness duration and severity. Lastly, we also examined the other medication effects on basal ganglia volumes. Comparing patients administered with and without drugs (lithium, valproate, anticholinergics, antidepressants, and benzodiazepines, respectively) revealed no significant basal ganglia volume differences in three patient groups, after controlling for age, gender, and total brain volume.

4. Discussion

In this study, we found significantly enlarged brain volumes in caudate, putamen, and pallidum in chronic schizophrenia patients compared with first-episode schizophrenia patients, psychotic bipolar disorder patients, and healthy controls, after controlling for age, sex, and total intracranial volume. Of note, there were no significant differences among these three latter groups. Antipsychotics had a significant contribution to basal ganglia volumetric enlargement in chronic schizophrenia, especially caudate nucleus and putamen after controlling for the effects of illness duration and severity. Neither duration of illness nor severity had such a pure effect on basal ganglia in chronic schizophrenia.

In this study, direct comparisons between SZ and psychotic BD with the same control group revealed enlarged basal ganglia in NFE-SZ and no significant differences among FE-SZ, BD, and healthy controls. Only a few studies directly compared these two disorders with the same control group regarding basal ganglia volumes. Among these, Swayze II et al. (1992) observed significant enlargement in the putamen and caudate in male SZ patients and found no basal ganglia volume deviations in BD compared to healthy controls. In their study, however, information about patients' duration of illness and history of psychosis in BD were not reported. Some others found reduced basal ganglia volumes in SZ which was in contrast with our findings, whereas psychotic BD patients with the similar illness duration had no significant basal ganglia abnormality which was in agreement with our findings (McDonald et al., 2005; Molina et al., 2011). Of note, a recent meta-analysis study showed overall decreased caudate volume in antipsychotic-naive SZ patients ($n = 771$), suggesting a neurodevelopmental process of the disease (Haijma et al., 2012). In our study, the finding of no basal ganglia changes in medicated FE-SZ might be caused by the antipsychotic treatment, even with a short treatment duration and a small dosage, given the evidence showing that antipsychotic medication attenuates volume loss (Haijma et al., 2012). With regard to chronic SZ, a relatively stable pattern of basal ganglia enlargement has been observed in chronic SZ patients with antipsychotic treatment, in line with our findings (Mamah et al., 2016).

Table 3
Summary of hierarchical regression analysis for variables predicting putamen volumetric alteration in chronic schizophrenia patients. * represents $p < 0.05$, *** represents $p < 0.001$.

Variable	Beta	*t*	R^2	ΔR^2	F change	(df1, df2)	*p*
Step 1			0.265		3.854	7, 75	***
Age	−0.296	−2.159*					
Sex	0.178	1.315					
Total intracranial volume	0.584	4.350***					
Illness duration	0.073	0.540					
PANSS positive	−0.032	−0.241					
PANSS negative	0.054	0.469					
PANSS general	0.032	0.228					
Step 2			0.305	0.041	4.330	1, 74	*
Age	−0.207	−1.471					
Sex	0.130	0.971					
Total intracranial volume	0.558	4.228***					
Illness duration	−0.019	−0.138					
PANSS positive	−0.101	−0.749					
PANSS negative	0.057	0.511					
PANSS general	0.071	0.511					
CPZ dosage	0.220	2.081*					

Findings of basal ganglia morphology are relatively equivocal. Overall, basal ganglia volume changes seem to be subtle in BD as most studies and meta-analyses found no differences of basal ganglia volumes between BD and HC (Kempton et al., 2008; McDonald et al., 2004; Ong et al., 2012; Quigley et al., 2015). A recent large study with 1710 BD patients and 2594 healthy controls also found no basal ganglia volume differences between the two groups (Hibar et al., 2016). However, several earlier studies reported both increased (Aylward et al., 1994; Strakowski et al., 2002) and decreased (Abramovic et al., 2016; Beyer et al., 2004) basal ganglia volumes in BD. In Aylward et al. (1994) study, the finding of enlarged basal ganglia in male BD patients may be confounded with the effects of comorbidity or medication. Beyer et al. (2004) found volumetric reduction particularly in old patients which may suggest an interact between age and illness progression. Taken together, basal ganglia variations in BD may be confounded and interacted with clinical and demographic variables. Overall, our results of no basal ganglia changes in BD are consistent with most previous findings and meta-analyses. Our findings suggest that volumetric enlargement in basal ganglia structure might be one of the hallmarks of chronic SZ and is less impaired in BD.

The finding of the specific contribution of antipsychotics after controlling for the effects of illness duration and severity in chronic SZ validates its role underlying basal ganglia volumetric alterations, consistent with previous findings from both cross-sectional studies and longitudinal studies. Direct comparison between antipsychotic-naïve SZ patients and medicated SZ showed that medicated patients had an increased volume in the putamen and pallidum (Brandt and Bonelli, 2008; Gur et al., 1998). Earlier longitudinal studies comparing SZ patients before and after treatment found significant basal ganglia volume increase after treatment (Zampieri et al., 2014). Indeed, Gur et al. (1998) also showed that a higher dose of typical neuroleptic was associated with higher caudate and putamen volumes in treated SZ. This positive association between dosage of antipsychotics and basal ganglia volumes may be due to dopaminergic neuroplasticity in basal ganglia which adapts to receptor blockade by antipsychotics (Konradi and Heckers, 2001). Furthermore, the finding of no basal ganglia volume changes and no associations between basal ganglia volumes and antipsychotic dosages in FE-SZ suggests that the influence of antipsychotics is progressive.

Considering the antipsychotic effect in BD, however, there was no basal ganglia enlargement even though 84% of BD patients have taken antipsychotic drugs. Giving that the antipsychotic dose in BD was significantly less than in chronic SZ patients in the current study, it is conceivable that the lower antipsychotic dose may be inadequate to produce an significant increment of basal ganglia volume. Interestingly, we found negative correlations between the dose of antipsychotics and basal ganglia volumes in BD while previous research has shown that associations between antipsychotic medication and brain volume are subtle and less pronounced in BD. Indeed, the possibility of the antipsychotic effect on basal ganglia of BD patients cannot be fully ruled out, considering the finding of the negative association between the dose and basal ganglia volumes. This finding highlights the complex relationship between basal ganglia volume changes and antipsychotics. It suggests that intrinsic illness factors may underlie differential basal ganglia changes in SZ and BD (Abramovic et al., 2016). Further research is needed to explore the differential antipsychotic effect on basal ganglia in BD as well as in comparison with SZ.

To note, medication effect is one of the most debated sources in terms of brain morphological changes in BD (Hibar et al., 2016). It is difficult to distinguish medication effects on brain volumes given that patients are commonly prescribed various medicines typically including lithium, valproate, antipsychotics, antidepressants, and benzodiazepines. These medications may interact with each other and the medication effect may also interact with clinical and demographic variables. Longitudinal studies with tightly monitored medication history and rich clinical information would help to elucidate the medication effects.

Several strengths support our study. First, this study was a cross-diagnostic comparison between SZ and BD with the same control group. Second, the sample size was relatively large, especially in schizophrenia group which allow us to compare the patients with minimal antipsychotics and with long-term treatment. A third strength is the high homogeneity of the clinical features with regard to psychosis across disorders. In the current study, BD patients were with psychotic symptoms, and directly comparing SZ with psychotic BD rather than a single BD group gave us good chance at clarifying the underlying mechanisms of psychosis across distinct disorders. Lastly, age, gender, and total brain volumes were all controlled for analyses which yielded robust statistic power. Importantly, hierarchical regression analyses were used to distinguish between the highly intercorrelated clinical variables of illness duration, severity, and antipsychotic dose taken. Together, cross-sectional comparisons with a large sample size, high homogeneity of the clinical feature of psychosis, and also a strict control for potential confounding variables in the current study ensure relatively reliable results.

There were several limitations in this study. First, we did not have the information about the exact previous history of antipsychotic medication, so our findings are limited to the effect of current antipsychotic dosages, which may be state-dependent. Further characterization of antipsychotic exposure is needed in future studies to better understand the relationship between antipsychotics and basal ganglia structure. Second, there were relatively fewer patients with bipolar disorder in our sample which does not permit the comparison between FE- and NFE-BD. Third, our FE-SZ patients were defined as SZ patients without clinical treatment. These patients may still have medication before seeing doctors. The finding that only chronic SZ but not FE-SZ patients showed structural changes in basal ganglia suggests that the influence of antipsychotic drugs is progressive, and brief treatment has no influence on brain volume changes in bfasal ganglia (Chakos et al., 1994; Li et al., 2012). Fourth, the current study mainly focused on the basal ganglia structure. Indeed, the basal ganglia are highly connected with prefrontal cortex and other brain regions (Hélie et al., 2015). Further investigation of basal ganglia connectivity with other regions at a brain network level may refine the contribution of basal ganglia to the pathophysiology of a range of psychiatric disorders. Fifth, we did not assess how the structural changes of basal ganglia interact with cognitive dysfunctions in patients. Future research is encouraged to link structural changes with cognitive functions in patients.

5. Conclusion

This study provides evidence that SZ and BD are characterized by distinct abnormalities of basal ganglia even though there is a high overlap of psychotic symptoms in the two illnesses. Chronic SZ was associated with basal ganglia enlargement involving the caudate, putamen, and pallidum, after controlling for age, gender, and total intracranial volume.

Whether basal ganglia volume changes are a result of the disease process progresses itself or are a result of antipsychotic effect is an important question with respect to the diagnosis and treatment of the disorders. The findings of the significant positive association of basal ganglia volume (caudate and putamen) with daily antipsychotic dose rather than with severity of the disorder (PANSS score) and duration of illness in chronic SZ further highlight the importance of the effect of antipsychotic medication on these basal ganglia components in SZ. The finding of negative association between basal ganglia volume and antipsychotic dose in BD may suggest a differential impact of antipsychotics across psychotic spectrum conditions.

Competing interests

The authors declare no competing interests.

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Supplementary materials

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