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Antipsychotic treatment and basal ganglia volumes: Exploring the role of receptor occupancy, dosage and remission status

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ABSTRACT

Antipsychotic treatment may affect brain morphology, and enlargement of the basal ganglia (BG) is a replicated finding. Here we investigated associations between antipsychotic treatment and BG volumes in patients with psychotic and bipolar disorders. We hypothesized that current treatment and, among those medicated, higher dosage, estimated D2R occupancy and being in remission would predict larger BG volumes. Structural covariance analysis was performed to examine if correlations between BG volumes and cortical thickness differed by treatment status.

224 patients treated with antipsychotics; 26 previously treated, 29 never treated and 301 healthy controls (HC) were included from the TOP study cohort (NORMENT, Norway). T1-weighted MR images were processed using FreeSurfer. D2R occupancy was estimated based on serum concentration measurements for patients receiving stable monotherapy. Statistical analyses were adjusted for age, gender and estimated intracranial volume (ICV). We found larger right ($p < 0.003$) and left putamen ($p < 0.02$) and right globus pallidus (GP) ($p < 0.03$) in currently medicated patients compared to HC. Bilateral regional cortical thinning was also observed in currently and previously medicated patients compared to HC. In medicated patients, higher chlorpromazine equivalent dose (CPZ) was associated with larger left GP ($p < 0.04$). There was no association with estimated D2R occupancy ($n = 47$) or remission status. Lower positive correlation between left putamen volume and cortical thickness of the left lateral occipital cortex was found in medicated patients compared to HC.

We replicated the BG enlargement in medicated patients, but found no association with estimated D2R occupancy. Further studies are needed to clarify the underlying mechanisms.

1. Introduction

1.1. Antipsychotic drugs and effects on subcortical structures

In the last two decades, the role of antipsychotic medication for the observed alterations of brain morphology in patients with psychotic disorders has been a frequent topic of study. Structural magnetic resonance imaging (sMRI) studies revealed increased volumes of the basal ganglia (BG) after treatment in patients with schizophrenia (Chakos et al., 1994; Gur et al., 1998; Keshavan et al., 1994). These changes were proposed to reflect striatal hypertrophy as a compensatory response to the neuroleptic antagonism to dopamine receptors, the main targets of most antipsychotics (Stahl, 2013).

Enlargements of the BG during or after antipsychotic medication use have since been replicated in several studies. Lieberman et al. (2005) conducted the first randomized longitudinal study in 161 first-episode patients showing a differential pattern of volume change in the caudate nucleus in patients treated with haloperidol, a first-generation antipsychotic (FGA), compared patients treated with olanzapine, a second-generation antipsychotic (SGA). Additionally, the patients treated with haloperidol showed significant longitudinal decrease in gray matter volume in frontal regions while the patients treated with olanzapine did not (Lieberman et al., 2005). Corson and co-authors reported longitudinal increase of BG volumes during a 2-year follow-up in patients with schizophrenia treated with FGA, and decreased volumes in patients treated with SGA (Corson et al., 1999). However, SGA treatment has in other studies been associated with volumetric increase of the BG, and

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a recent critical review found little support for a clear distinction between the two drug classes (Ebdrup et al., 2013). In a study conducted by our own research group (Jorgensen et al., 2016b), patients treated with FGA and non-clozapine SGA both showed larger BG volumes compared to healthy control subjects, whereas clozapine users showed no increase.

1.2. Relationship between BG volume increases and dopamine D_2 receptor occupancy, dosage and treatment response

This research literature raises the question of how the pharmacological properties of antipsychotics relate to the observed BG volume changes. The striatum has a high density of dopamine D_2 receptors (D2R) (Palacios et al., 1988) and a recent study using DRD2 knockout mice and wild type mice indicated that these receptors are necessary for the volumetric changes to occur (Guma et al., 2018). For clinical efficacy, positron emission tomography (PET) studies have indicated a therapeutic window where D2R occupancy between 60% and 78% is associated with a favorable treatment response while exceeding the 78% threshold increases the likelihood of neurological side effects (Farde et al., 1992; Nyberg et al., 1995); this was corroborated by a pooled meta-analysis (Uchida et al., 2011a). However, no similar relationship with BG enlargement has been demonstrated (Ebdrup et al., 2013), although the absence of volumetric increase after clozapine treatment could suggest its existence, since clozapine shows lower D2R occupancy compared to other antipsychotics (Seeman, 2014; Uchida et al., 2011b). To our knowledge, this has not been directly tested.

Uchida and co-authors developed a method that allows estimation of D2R occupancy with high accuracy based on plasma concentrations measurements (Uchida et al., 2011b). Based on data from a pooled analysis of PET studies where both drug plasma concentrations for five different antipsychotic drug types and D2R occupancy was measured, they derived formulas to predict D2R occupancy on an individual basis. This method has been used to examine associations between estimated D2R occupancy and side effects (Tsuboi et al., 2013; Yoshida et al., 2014), cognitive impairment (Sakurai et al., 2013), and remission (Moriguchi et al., 2013) in data from the CATIE trial, but to our knowledge not associations with brain structure measurements.

Moreover, it is also unclear if the effects of antipsychotics on the BG are dose-dependent. In the Iowa longitudinal study, associations between higher doses of antipsychotic treatment over time and enlargements of putamen and caudate were found (Ho et al., 2011). Similarly, in a recent large-scale cross-sectional study, higher antipsychotic dosage was associated with larger left globus pallidus (GP) volume (Hashimoto et al., 2018). However, longitudinal studies on associations between BG volume change and antipsychotic dosage have not been consistent as some studies do not find a dose-response relationship (Ebdrup et al., 2013).

Further, previous studies have suggested that enlarged BG volumes are related to treatment outcome in schizophrenia (Buchsbaum et al., 2003; Li et al., 2012). In one study, increased putamen volume was associated with symptom reduction in the initial treatment period in patients predominantly treated with SGA (Li et al., 2012). Consistent with this, Buchsbaum et al. found increased mean volumes of the left and right putamen in long-term treated patients with a favorable outcome compared to poor outcome patients (Buchsbaum et al., 2003). However, a number of studies have also reported no association between BG volume increase and symptoms (Crespo-Facorro et al., 2008; Ebdrup et al., 2013).

To summarize, while brain plasticity in the basal ganglia as a response to antipsychotic treatment has been corroborated in several studies, less is known about the pharmacological properties leading to this effect and how it relates to the clinical outcome of treatment.

1.3. A relationship with cortical thickness?

Whether antipsychotic-induced BG volume increases are region-specific or are part of a shared effect on a larger brain circuitry is also not known. The BG are hub regions in the cortico-striato-thalamic circuitry where four distinct functional circuits have been identified. These project from the cerebral cortex to the BG, from the BG to the thalamus and back to the cortex and are, hence, described as 're-entrant loops' (Redgrave et al., 2011). They include the motor loop, involved in movement selection and control; the cognitive or associative circuit, involved in decision making and cognitive control; the limbic loop, which plays a central role in reward learning, and the oculomotor loop which is involved in saccadic movements (Alexander et al., 1986; Haber, 2016).

Given this, it is natural to ask whether the mechanisms leading to BG enlargement may also affect the macrostructure of the cerebral cortex. A number of studies have shown associations between antipsychotic treatment and cortical GM (Dorph-Petersen et al., 2005; Ho et al., 2011; Huhtaniska et al., 2017), although findings are less consistent: both increased and decreased volumes as well as no change after treatment have been reported (Huhtaniska et al., 2017; Vita et al., 2015). However, in two recent meta-analyses (Huhtaniska et al., 2017; van Erp et al., 2018), use of antipsychotic medication was associated with regional reductions of cortical GM.

Structural covariance methods are increasingly applied to examine patterns of correlation between brain regions (Bassett et al., 2008). While brain volume alterations are often treated as regionally independent using traditional analysis methods, emerging evidence suggests structural interconnected networks are affected in schizophrenia (Palaniyappan et al., 2019). For example, reduced correlations between left frontal and bilateral subcortical gray matter (GM) have been found in patients compared to healthy controls (Collin et al., 2013), suggesting impaired integrity of large-scale brain networks. The cortico-striatal brain circuitry is functionally altered in psychosis (Horga et al., 2016) and is modulated by dopamine (Haber, 2014). Yet, how antipsychotics may affect the structural covariance patterns between the BG and the cerebral cortex has not been studied.

1.3.1. Aims and hypothesis

The core aim of this study was to do a thorough investigation of contributions from three potential factors for BG volume increases in antipsychotic-treated psychotic patients. We first aimed to replicate associations between antipsychotic treatment status and BG volumes, hypothesizing that current treatment would be associated with larger volumes. We then hypothesized that (1) higher estimated D2R occupancy, (2) higher dosage, and (3) being in remission, a proxy measure for treatment response, would all be associated with BG enlargements in patients. Lastly, we aimed to examine the hypothesis that medication status is linked to differences in structural covariance patterns between cortical thickness and BG volumes.

2. Materials and methods

2.1. Subjects

2.1.1. Inclusion criteria

Patients and healthy controls (HC) were recruited from the same catchment area as part of the ongoing Thematically Organized Psychosis (TOP) project, conducted by the Norwegian Centre for Research on Mental Disorders (NORMENT).

Patients aged 18–65 years, with a diagnosis of a psychotic or bipolar disorder, were included from hospitals in the Oslo region. Diagnostic interviews were performed by trained medical doctors and clinical psychologists using the Structural Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Participants were excluded if they had IQ < 70, a history of moderate head injury or had been diagnosed with a neurological

disorder. HC were screened with the Primary Care Evaluation of Mental Disorders (PRIME-MD) and interviewed to ensure no illicit substance use or alcohol abuse and no history of severe mental disorders. All participants gave informed written consent. The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

To avoid potential confounding by the effect of mood-stabilizers, patients using lithium and/or anticonvulsants were excluded from this specific study sample (Germana et al., 2010).

2.2. Demographic, clinical and psychopharmacological data

Demographic and clinical data are presented in Table 1. The sample included 580 subjects in total. Of the 279 patients in the sample, 224 were medicated at time of inclusion, 26 subjects had been treated with antipsychotic medication before time of inclusion and 29 subjects had never received any antipsychotic treatment. 159 patients had diagnosis of schizophrenia spectrum disorders (SCZ), 38 of bipolar disorder (BD) and 82 of other psychotic disorders. 301 HC were selected as a comparison group.

In the currently medicated group 179 patients were treated with the same antipsychotic drug type from time of inclusion to MRI scan.

Table 2 presents psychopharmacological data: currently medicated patients received mostly SGA medication (77.2%); while FGA were used by fewer patients (2.7%) and with lower doses. Among those who had received antipsychotic treatment only before inclusion to the study, treatment with more than one type of drug, including both SGA and FGA, was common. We used remission status as a proxy variable for treatment effect among medicated patients. Being in remission was defined as having a rating of <4 on the positive and negative symptoms scale (PANSS) items P1, P3, P5, P6 and G9 for more than one week (Kay et al., 1987).

2.3. MRI acquisition and processing

Participants underwent structural MRI using a 1.5 T Siemens Magnetom Sonata scanner located at Ullevål University Hospital and equipped with a standard head coil. Two T1-weighted structural images were obtained during the same scan session using a Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence (TE = 3.93 ms, TR = 2730 ms, TI = 1000 ms, flip angle = 7°; FOV = 24 cm, voxel size = $1.33 \times 0.94 \times 1$ mm^3, number of partitions = 160).

The FreeSurfer software package version 5.3.0 (https://surfer.nmr.mgh.harvard.edu) (Fischl, 2012) was used to obtain estimated intracranial volume (ICV) and automatic subcortical segmentations, previously demonstrated to be reliable measures (Jovicich et al., 2009). The two T1-weighted volumes acquired were averaged in post-processing to increase signal-to-noise ratio (SNR). All scans received a quality control of surface reconstruction and subcortical segmentations, including manual editing performed by trained assistants. The manual editing followed standard FreeSurfer procedures, as described in McCarthy et al. (2015). Data from the same cohort was previously used in studies examining other research questions (Jorgensen et al., 2016a; Jorgensen et al., 2015; Lange et al., 2016; Morch-Johnsen et al., 2015; Morch-Johnsen et al., 2017; Rimol et al., 2012).

In the present study, volumes of the caudate, putamen and GP were analyzed, and for structural covariance analyses vertex-wise cortical thickness across the cortical surface was used (Fischl and Dale, 2000). Individual surfaces were mapped to a common template using spherical co-registration and cortical thickness maps were smoothed with a kernel of 15 mm (FWHM).

2.4. Medication and blood samples

Information on type of antipsychotics used and dosage was collected by interview and chart review at the time of inclusion and an additional interview at the day of MRI scan. Blood serum samples were obtained in conjunction with a medical examination as part of the study protocol. The patients were fasting and instructed not to take their morning medication dose prior to blood sampling.

For all drug types, serum concentrations were determined in approved laboratories using liquid chromatography tandem-mass spectroscopy (LC-MS/MS). Detailed information about the analysis methods for risperidone and olanzapine has previously been provided in Steen et al. (2017).

Using the method developed by Uchida and co-authors, described in the introduction (Uchida et al., 2011b), D2R occupancy could be estimated based on serum concentration measurements for patients receiving monotherapy with four different antipsychotics used in the sample: Olanzapine, Clozapine, Risperidone and Ziprasidone (Uchida et al., 2011b). For this analysis, we selected subjects who had used the same antipsychotic medication type and dose from the time of inclusion to MR scanning, and where this period did not exceed one year. To obtain representative serum concentration measurements, we also excluded subjects who had changed their daily dosage less than two weeks before the blood test. A flowchart illustrating eligible subjects for this analysis is found in Fig. 1.

In order to quantify treatment exposure across different antipsychotic drugs, we converted doses into chlorpromazine equivalents

Table 1
Demographic and clinical data across the three patient groups and healthy controls.

	Current medicated	Previously medicated	Never medicated	Healthy controls	Tests
	N = 224	N = 26	N = 29	N = 301	F $\tilde{\chi}^2$ p
Age at MRI (yrs)	31.4 (9.0)	34.3 (11.7)	31.9 (11.3)	35.5 (9.7)	F = 8.2; p < 0.01
Duration of treatment (yrs)	1.6 (2.3)	–	–	–	
Diagnosis subgroup	N (%)	N (%)	N (%)	N (%)	
Schizophrenia	132 (63.4)	10 (38.5)	7 (24.1)	–	ns
Bipolar disorder	26 (11.6)	5 (19.2)	7 (24.1)	–	$\tilde{\chi}^2$=20.2; p < 0.01
Other psychotic disorder	56 (25.0)	11 (42.3)	15 (51.7)	–	ns
Gender					
Male	138 (61.6)	13 (50)	13 (44.8)	158 (52.5)	ns
Female	86 (38.4)	13 (50)	16 (55.2)	143 (47.5)	ns
Remission	84 (38.9)	11 (42.3)	6 (20.7)	–	ns
Not in remission	132 (61.1)	14 (53.8)	23 (79.3)	–	ns

The values in each cell represent means and standard deviations except for the rows of Gender, Diagnosis subgroup and Remission status. Between-groups difference in demographic and clinical data was determined by standard analysis of variance (ANOVA) and chi-square test, where appropriate.
Duration of treatment was defined as time between patients started using their current medication type until the MRI scan. Duration of treatment data was missing for 13 subjects for current medicated patients due to changed medication type between inclusion and MRI date.
Remission status was used as a proxy variable for treatment effect among medicated patients. Being in remission was defined as having a rating of <4 on the positive and negative symptoms scale (PANSS) items P1, P3, P5, P6 and G9 for more than one week.

Table 2
Psychopharmacological data.

	Currently medicated patients		
Current antipsychotic drug	N (%)	Dosage at MRI day (mg) Mean (SD)	Estimated D_2 occupancy Mean (SD) (N = 47)
AP monotherapy	179 (80.0)		
SGA total	173 (77.2)		
Risperidone	19 (8.5)	3.04 (1.6)	77 (5.8) (N = 7)
Olanzapine	70 (31.3)	11.4 (6.1)	78.4 (7.2) (N = 36)
Ziprasidone	10 (4.5)	71.0 (37.3)	62.5 (9.8) (N = 3)
Clozapine	4 (1.8)	412.5 (165.2)	57.3 (N = 1)
Aripirazole	26 (11.6)	14.5 (4.8)	N/A
Quetiapine	41 (18.3)	439.4 (408.0)	N/A
Amisulpride	2 (0.9)	800	N/A
Sertindole	1 (0.4)	16	N/A
FGA total	6 (2.7)		
Levomepromazine	1 (0.4)	N/A	
Zuclopenthixol	1 (0.4)	N/A	
Perphenazine	3 (1.3)	9.5 (9.8)	
Chlorprotixene	1 (0.4)	100	
Polypharmacy	45 (20.1)		
Current total dose		CPZ	
CPZ at MRI day		318.5 (284.6)	

N, number of users; AP, antipsychotic; FGA, first-generation antipsychotic; SGA, second-generation antipsychotic; monotherapy was defined as the use of only one AP type from time of inclusion to MRI scan; CPZ, chlorpromazine-mg equivalent.
In currently medicated group 179 patients were on monotherapy while 45 were on polypharmacy, meaning they were concurrently using multiple AP drugs.
Mean and SD are reported for dosage at MRI day and estimated receptor occupancy of patients treated with AP. Estimated receptor binding to dopamine D_2, based on serum concentration measurements, was calculated only for patients (N = 47) receiving Olanzapine, Clozapine, Risperidone and Ziprasidone.
Dosage data for patients treated with Levomepromazine and Zuclopenthixol was missing.
Current CPZ data was also missing for three subjects.

(CPZ; 1 mg chlorpromazine as reference) following Andreasen et al. (2010).

2.5. Statistical analysis

2.5.1. Subcortical and cortical thickness analysis

In order to assess group differences across demographical data, analysis of variance (ANOVA) and chi-square test for categorical data were performed. ANOVA was used to examine the total and general subscales of PANSS scores, while Kruskal-Wallis test was used to examine positive and negative symptoms subscales since they were not normally distributed.

In the main group analyses, analysis of covariance (ANCOVA) was first performed to assess group differences between four groups: currently medicated, previously medicated, never treated patients and HC. Covariates in the model were age, gender and estimated total ICV. Group differences in cortical thickness were tested using general linear models adjusted for age and gender. Pairwise comparisons between groups were performed using the least significant difference method, without correction for multiple comparisons. We also calculated the effect size (Cohen's *d*) to determine the magnitude of effects.

Additional background analyses were performed to assess brain volumetric differences between the three diagnostic subcategories in the sample (SCZ, BD and other psychotic disorders).

Statistical analysis was performed with SPSS version 22.0.0.0.

2.5.2. Regression analysis

Further, to evaluate the contributions of three potential factors on BG volume increases in psychotic patients, we fitted separate linear regression models with estimated D2R occupancy, current CPZ and remission status as independent variables and volumes of BG and mean cerebral cortical thickness as dependent variables. To account for potential non-linear effects, a squared term was added to the model and a secondary analysis using median split was applied to compare patients with high and low estimated occupancy. For all models, age and gender were included as covariates; for analysis of subcortical volumes, ICV was also included. Dosage was converted to current CPZ equivalent and ln-transformed since it was not normally distributed. In line with the explorative aim of the study, results are reported without correction for multiple testing.

To reduce the potential influence of diagnostic heterogeneity, the analyses were repeated in patients with SCZ only. To further reduce pharmacological heterogeneity, the analyses of estimated D2R occupancy were also restricted to patients currently using the same antipsychotic agent, olanzapine.

2.5.3. Structural covariance analysis

To investigate the anatomical relationship between subcortical structures and cortical thickness, a seed-based approach was used, examining the structural covariance between each BG volume and cortical thickness at each vertex of the cortical surface. This was done by fitting two separate general linear models (GLM) to the smoothed cortical thickness maps. The first models were used to adjust for the effects of age, gender and ICV before the final analyses. In order to compare structural covariance across groups, the second GLMs were constructed as seed-based structural covariance models where residualized values for the volume of each BG structure obtained from using the first models were correlated with residualized vertex-wise cortical thickness in the same hemisphere. We used three categorical predictors: medicated patients, unmedicated patients and healthy controls. Contrasts were created to test the slopes and, therefore, main effects and interactions, adjusted for the effects of age and gender.

This analysis allowed us to identify differences in the positive or negative associations between cortical and subcortical structures, i.e. if higher volume of GM in the seed region was associated with thicker cortex at the vertex, or conversely, if higher volume of GM in the seed region was associated with thinner cortex at the vertex. Partial correlation coefficients were used to assess the strength of structural covariance between the structures.

Cluster-wise correction for multiple comparisons was performed in FreeSurfer, using a cluster-forming threshold of $p < 0.001$ and where clusters with $p < 0.05$ were considered significant. Null distributions were based on precomputed Monte Carlo simulations with 10,000 permutations, and we used two-tailed *t*-tests on cortical surfaces with ~150,000 vertices in each hemisphere (Hagler Jr. et al., 2006).

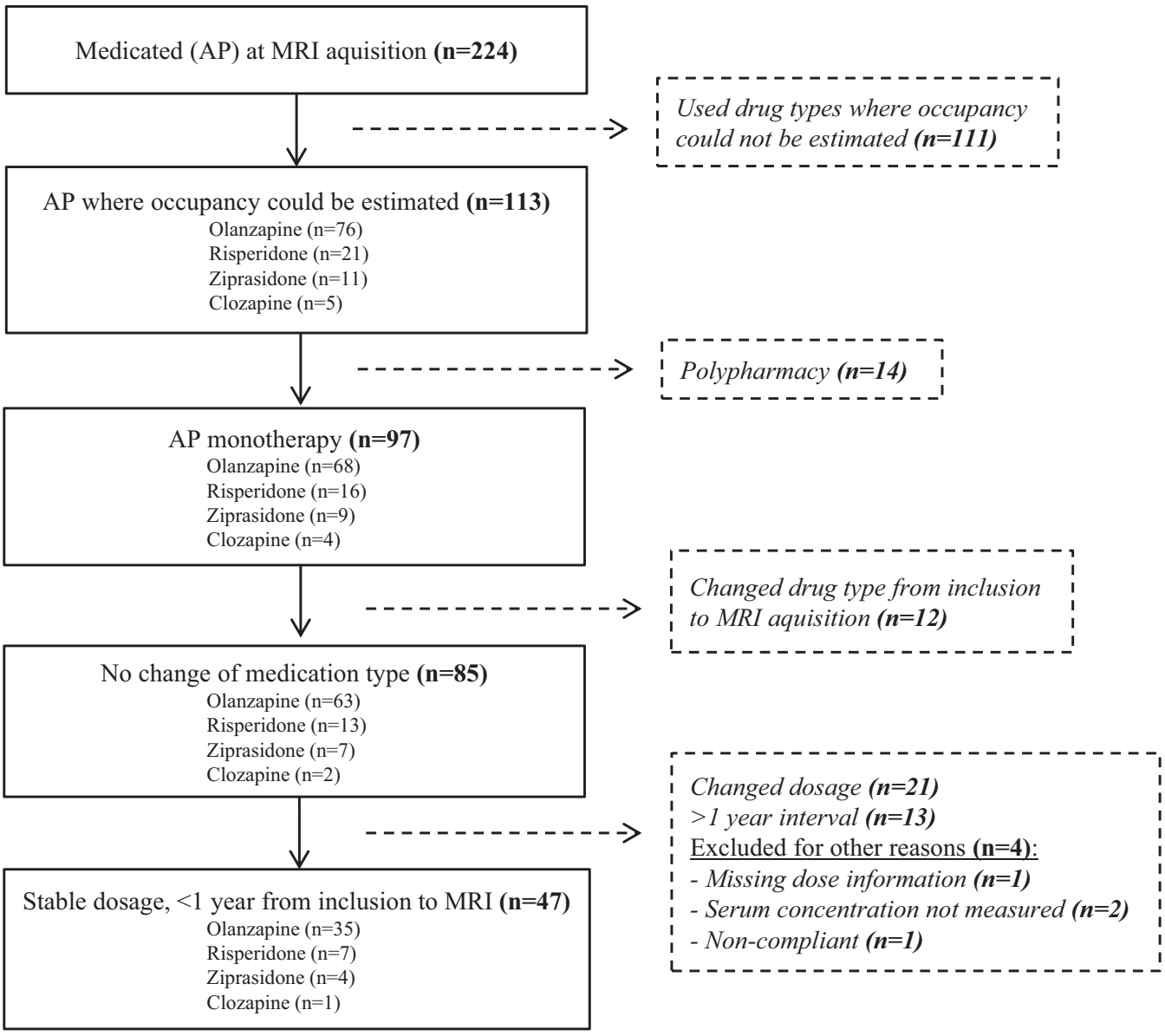

Fig. 1. Selection of eligible subjects for analysis of estimated receptor occupancy.

3. Results

3.1. Demographic, clinical and psychopharmacological data

There was a small age difference between currently medicated patients (31.4 years) and HC (35.5 years) (Table 1). Among patients there were significant differences in proportion of bipolar disorder diagnosis between currently medicated and previously medicated patients ($\tilde{\chi}^2$=20.2 p < 0.01). There were no significant gender differences between the three groups and no significant differences in remission status between the patient groups.

3.2. Subcortical brain volume differences between currently medicated, previously medicated, never treated patients and healthy controls

Results for the between-group comparisons (currently medicated, previously medicated, never treated, and HC) showed statistical significant differences in the left and right pallidum (F = 3.28, p = 0.02 and F = 2.93, p = 0.03, respectively), in the right putamen (F = 4.71, p = 0.003) and in the total BG volume, derived by the sum of bilateral subcortical structures under analysis (F = 3.7, p = 0.01) (Table 3).

Specifically, pairwise contrast analyses showed larger volumes of the globus pallidus bilaterally, the right putamen and total BG volume in currently medicated patients compared to HC (Table 3). Cohen's effect sizes [37] in the comparison of currently medicated group and HC were slightly below medium in left and right pallidum (d = 0.26; d = 0.25) and medium in right putamen (d = 0.32).

3.3. Regional cortical thickness differences

Significant differences were found in the between-group comparison of left (LH) and right (RH) hemisphere average cortical thickness between all three groups (LH: F = 19.0, p = 0.0001; RH: F = 17.1, p = 0.0001). The pairwise contrast analysis showed significantly thinner cortex in the left hemisphere in the currently medicated group compared to HC (p = 0.0001), and in the currently medicated group compared to never treated (p = 0.002).

Thinner cortex was also detected in the right hemisphere between current medicated compared to never treated (p = 0.001) and HC (p

Table 3
BG volume differences between currently medicated patients, previously medicated patients, never treated patients and healthy controls.

	Currently medicated mm^3 (SE)	Previously medicated mm^3 (SE)	Never treated mm^3 (SE)	Healthy controls mm^3 (SE)	F	p	Pairwaise comparisons
	N = 224	N = 26	N = 29	N = 301			
L. Caudate	3660.9 (24.9)	3701.0 (71.5)	3660.9 (67.6)	3624.3 (21.1)	0.65	0.58	
R. Caudate	3932.8 (25.0)	4017.5 (72.0)	3940.4 (68.0)	3892.0 (21.3)	1.26	0.29	
L. Pallidum	1582.7 (16.5)	1542.6 (47.4)	1495.5 (44.7)	1518.9 (14.0)	3.28	**0.02**	Currently med > HC **p = 0.004**
R. Pallidum	1610.2 (10.1)	1573.6 (29.2)	1567.7 (27.5)	1572.4 (8.6)	2.93	**0.03**	Currently med > HC **p = 0.005**
L. Putamen	5909.5 (38.2)	6020.2 (109.6)	5822.2 (103.6)	5806.4 (32.4)	2.2	0.09	
R. Putamen	5764.3 (32.0)	5789.4 (92.1)	5719.3 (87.0)	5613.9 (27.2)	4.71	**0.003**	Currently med > HC **p = 0.0004**
Corpus striatum	22,459.5 (106.9)	22,664.3 (307.1)	22,206.2 (290.1)	22,027.9 (90.7)	3.7	**0.01**	Currently med > HC **p = 0.002**
Cerebrum cortical thickness (lh)	2.28 (0.01)	2.32 (0.02)	2.35 (0.02)	2.35 (0.01)	19.0	<**0.0001**	Currently med < HC **p = 0.0001** Currently med < Never treated **p = 0.002**
Cerebrum cortical thickness (rh)	2.28 (0.01)	2.30 (0.02)	2.35 (0.02)	2.35 (0.01)	17.1	<**0.0001**	Currently med < HC **p = 0.0001** Currently med < Never treated **p = 0.001** Previously med < HC **p = 0.03**

BG, basal ganglia; L., lh, left; R., rh, right; SE, standard errors; Currently med, currently medicated patients; HC, healthy controls; Previously med, previously medicated patients.
Estimated marginal means of BG volumes and cortical thickness are reported. Analysis of covariance (ANCOVA) was performed to assess group differences between four groups: currently medicated, previously medicated, never treated and HC. BG differences were calculated with age, gender and estimated total intracranial volume (ICV) as covariates. Cortical thickness differences were calculated adjusting for age and gender.
Pairwaise comparisons were performed using the least significant difference method (LSD).
Volumes of subcortical structures and mean thickness were obtained from FreeSurfer and general linear models fitted in the SPSS software.
Bold: $p < 0.05$.

= 0.0001), and previously medicated patients also had thinner cortex compared to HC (p = 0.03) (Table 3). Cohen's d of left and right cortical thickness showed large negative effects between currently medicated and HC (LH: $d = -0.66$; RH: $d = -0.62$).

Finally, vertex-wise cluster analysis revealed eight regions of cortical thinning in the currently medicated group compared to HC in the left and right superior frontal cortex, left inferior parietal cortex, left and right precuneus, and right inferior temporal and post-central cortex. The currently medicated group exhibited significant thinning in lateral occipital, superior frontal and rostral middle frontal cortex in the left hemisphere and in the pars opercularis cortex in the right hemisphere compared to the unmedicated group (previously treated and AP-naïve subjects).

3.4. Differences between diagnostic subgroups in the sample

In the globus pallidus, patients with SCZ and other psychotic disorders showed larger volumes compared to HC. No differences between diagnostic subgroups were found in other BG volumes.

For mean cortical thickness, patients with SCZ showed thinner cortex bilaterally compared to patients with other psychotic disorders and, in the right hemisphere, compared with patients with bipolar disorders. Results from these analyses are found in Supplementary Table 1.

3.5. Relationship between brain measures and estimated receptor occupancy, current CPZ and remission status among medicated patients

Of the n = 224 currently medicated patients, n = 47 were eligible for analysis of estimated D2R occupancy (Fig. 1). Among these patients, there were no significant associations between estimated D2R occupancy and cortical and subcortical GM (Table 4). Similarly, when the sample was restricted to patients with SCZ treated with olanzapine monotherapy only (n = 18), no association was found (Supplementary Table 2).

Higher current CPZ (n = 221) was associated with larger left pallidum volume (p = 0.049); this association was also present in patients with SCZ only (n = 140, p = 0.02). Furthermore, higher CPZ

Table 4
Regression table of association between estimated receptor occupancy, remission status, dosage in CPZ (independent variables) and BG and cortical thickness (dependent variables) in currently medicated patients.

	Estimated receptor occupancy (N = 47)			Remission status (N = 216)			Current CPZ (N = 221)		
	B	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
L. Caudate	−2.32	6.84	0.04	20.9	56.1	0.02	−21.7	34.2	−0.04
R. Caudate	−0.98	7.31	−0.01	49.7	54.7	0.05	−2.5	33.4	−0.00
L. Pallidum	2.02	4.18	0.06	17.5	35.7	0.03	43.1	21.7	**0.12****
R. Pallidum	−0.94	2.36	−0.04	−17.0	21.1	−0.04	8.7	13.0	0.03
L. Putamen	−2.50	9.36	−0.02	−18.8	79.2	−0.01	11.6	48.7	0.01
R. Putamen	0.46	8.11	0.00	3.9	64.4	0.00	−7.3	40.3	−0.01
Corpus striatum	0.37	27.83	0.00	56.2	220.6	0.01	31.8	136.1	−0.01
Cortical thickness (lh)	−0.00	0.00	−0.08	−0.02	0.02	−0.07	−0.03	0.009	**−0.18*****
Cortical thickness (rh)	0.00	0.00	−0.08	−0.02	0.01	−0.06	−0.03	0.009	**−0.19****

*p < 0.05; **p < 0.01; ***p < 0.001.
Separated linear regression models were performed including age and gender as covariates. For BG volumes estimated total intracranial volume (ICV) has been also included. Dosages converted to current chlorpromazine equivalent and ln-transformed.
Remission data was missing for eight subjects.
Current CPZ data was missing for three subjects.
Bold: p < 0.05.

was associated with lower left average cortical thickness ($p = 0.004$) and right average cortical thickness ($p = 0.001$) among medicated patients; however, this did not remain significant in patients with SCZ only (Supplementary Table 2).

Remission status ($n = 221$; SCZ only: $n = 137$) was not associated with differences in any of the volumes under study.

3.6. Patterns of covariance between cortical and subcortical GM

In one cluster, lower positive structural covariance between the left putamen and left lateral occipital cortex (mm^2 306.73; $p = 0.03$) was found in medicated patients compared to HC (Fig. 2). There were no other differences in structural covariance patterns.

4. Discussion

4.1. Main findings

In this cross-sectional study of $n = 580$ patients and healthy controls, four principal findings emerged: first, BG volumes were larger in patients treated predominantly with SGA, replicating previous findings (Jorgensen et al., 2016b). Second, within the medicated patients there were dose-dependent associations with increased GP volume and decreased cortical thickness. Third, the data did not support the hypothesis that estimated D2R occupancy predicts volumetric enlargement in the BG. Fourth, the data suggested a difference in the pattern of covariance between left putamen and left lateral occipital cortex in medicated patients compared to healthy controls, whereas no other cortical regions showed differential patterns of correlation with BG volumes.

4.2. Antipsychotics and associated cortical and subcortical GM

We found larger putamen and GP in patients receiving mostly SGA, consistent with other studies showing that BG volume increases also emerge after treatment with SGA (Ebdrup et al., 2013; Jorgensen et al., 2016b). Given the consistent lack of larger volumes in medication-naïve patients in the previous literature, this finding is likely to represent an effect of treatment in accordance with our hypothesis. However, in the caudate nucleus, no group differences were observed. This contrasts with some previous studies (Ho et al., 2011; Jorgensen et al., 2016b), but the literature has not been consistent (Huhtaniska et al., 2017). The caudate nucleus may be measured with acceptable reliability

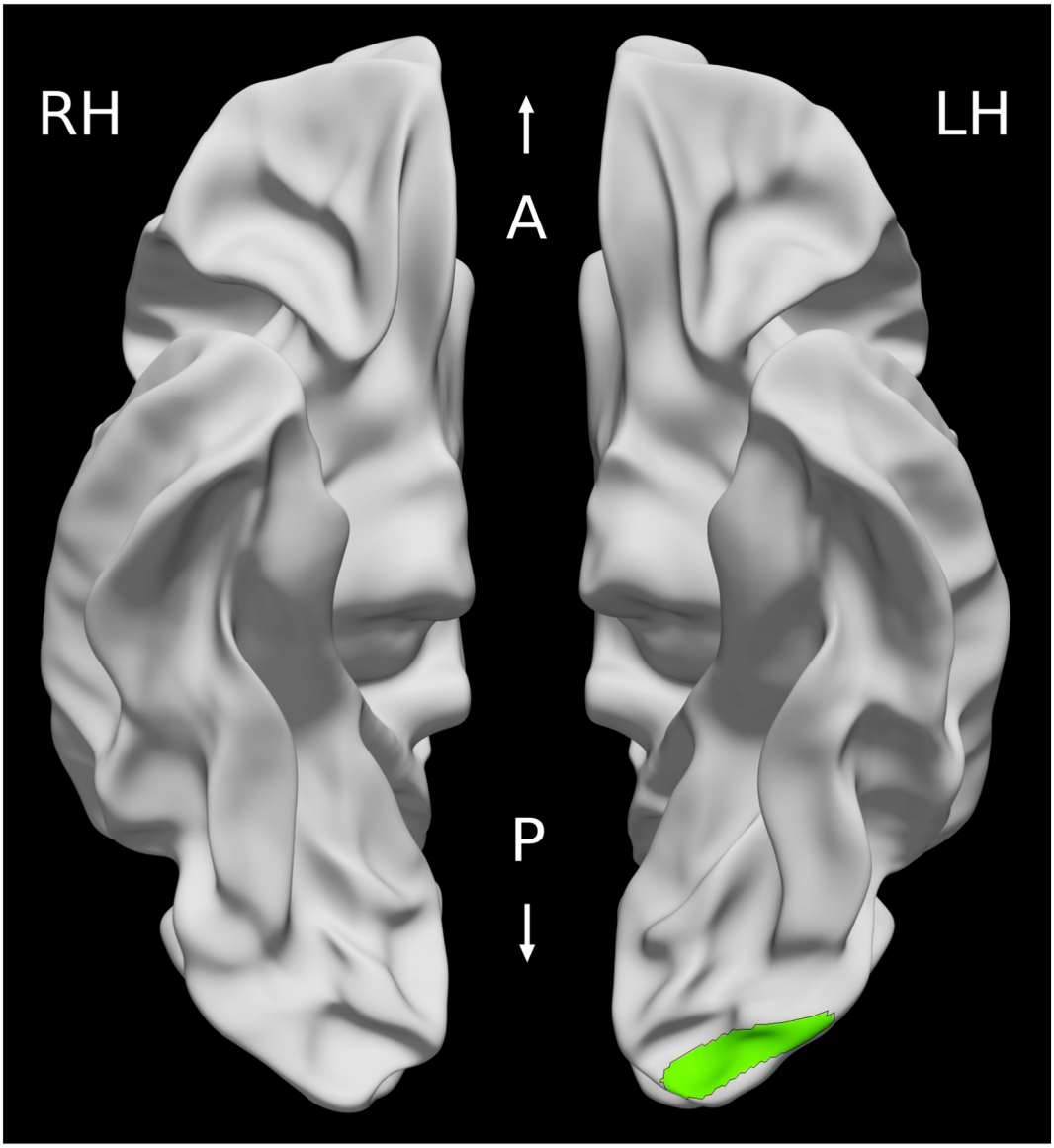

Fig. 2. Significant cluster of lower positive correlation between left putamen and left later occipital cortex in current medicated patients compared to healthy controls.

(Jovicich et al., 2009), rendering technical variability a less likely explanation for this source of heterogeneity than clinical variability. In one meta-analysis, reduced caudate volumes were found in antipsychotic-naïve patients with schizophrenia (Haijma et al., 2013). This raises the possibility of a complex interplay between the primary illness mechanisms of psychosis and the effects of antipsychotic medication in the caudate nucleus, although no significant volume reduction was found in the unmedicated group in this study.

We also found significant regional differences in cortical thickness in currently medicated patients compared to both controls and unmedicated patients. Eight distinct cortical clusters of thinning were identified in the currently medicated patients compared to controls. Reduced cortical thickness has also been shown to be related to several indices of illness severity in psychotic disorders, including symptom severity (Morch-Johnsen et al., 2015; Morch-Johnsen et al., 2017) and cognitive functioning (Hartberg et al., 2010), although not in all studies (Crespo-Facorro et al., 2011). In previous studies, significant negative correlations between typical antipsychotics and cortical thickness were found while significant positive correlations were found between atypical antipsychotics and cortex (van Haren et al., 2011). However, in a recent large-scale study from the ENIGMA Schizophrenia Working Group demonstrating widespread significantly thinner cortex in SCZ compared to HC, the effect sizes indicated thinner cortex in both SGA and FGA users compared to unmedicated patients, with larger effect sizes when on FGA (van Erp et al., 2018). Therefore, further research is necessary to disentangle the complex interplay between the illness and medication use influencing cortical thickness in psychotic disorders.

4.3. Receptor occupancy and dosage effects on cortical and subcortical GM

We found a small, but significant positive correlation between left pallidum and current CPZ equivalents. This finding is in close accordance with a recent study by Hashimoto et al. (2018), where daily dosage of antipsychotic treatment was reported to be associated with left GP volume. Moreover, we found a negative association between cortical thickness in both hemispheres and current CPZ equivalents.

Previous works suggested that brain morphology changes such as an increase in striatal volume might occur even after a very short period of antipsychotic treatment indicating a dynamic effect (Chua et al., 2009). Here we investigated brain volumes in both patients with psychotic disorders who received AP treatment from the time of inclusion to the study and patients who have been treated before the time of inclusion.

As demonstrated in SPECT studies, one hypothesis to explain the volumetric differences in the BG would be that chronic D2R antagonism influences receptor proliferation, caused by an up-regulation of these receptors densely found in the striatum, leading to increased metabolism, blood flow and neural size in corpus striatum (Corson et al., 2002; Hawkins et al., 2018; Miller et al., 1997; Scherk and Falkai, 2006). It is noteworthy, however, that the GP also showed a dose-dependent volumetric increase both within medicated patients as a whole and patients with schizophrenia. This is likely related to downstream effects, as the GP has lower density of D2R but receives highly convergent GABA-ergic projections from the striatum (Kita and Jaeger, 2016). However, more research is warranted to clarify the mechanisms of plasticity within the GP.

In the previous scientific literature, the effects of antipsychotic treatment on the cerebral cortex have not been fully clarified as some cross-sectional studies have not found evidence of dose or type of antipsychotic causing alteration in cortical thickness (Nesvag et al., 2008) while, in contrast, a recent meta-analysis (Fusar-Poli et al., 2013) suggested that some of the cortical brain changes in patients may be influenced by antipsychotic dosage.

4.4. Structural covariance

We found a different pattern of correlation between left putamen and left lateral occipital cortex in the currently medicated group compared to healthy control subjects. Healthy controls showed positive correlation between left putamen volume and cortical thickness in this region, while medicated patients showed less positive correlation.

The lack of previous studies on the topic limits the interpretation of this result, but it is worth noting that for other regions the patterns of correlation between BG volumes and cortical thickness were remarkably similar across groups, possibly suggesting that medication use has only limited influence on the normal anatomical patterns of structural covariance.

4.5. Strength and limitations

The main strengths of this study include the comprehensive medication data, with detailed information about antipsychotic medication use and serum samples enabling the estimation of D2R occupancy, and the substantial number of patients and healthy controls who underwent a standardized and detailed clinical assessment. Moreover, all participants were scanned on the same MR equipment and a well-tested processing software, FreeSurfer, was used for data analysis.

However, certain limitations need to be considered: first, since the study is naturalistic and observational, we did not have control over third variables, such as illness severity, that might have impacted our results. Further, we were not able to study the time course of antipsychotic-induced BG volume changes. Previous studies have indicated that volumetric increase may occur early in treatment (Chua et al., 2009), but it is unknown whether these are progressive or reach a plateau. Longitudinal data with no or minimal medication at baseline would be ideal to study this further.

Second, dopamine D2 receptor occupancy was not measured in the study, but estimated from individual serum concentration measurements on the basis of a meta-analysis of previous PET data (Uchida et al., 2011b). While this method was shown to have acceptable accuracy, it does assume generalizability across samples. In this context, age and gender distributions were similar and while a more restricted diagnostic spectrum (i.e., schizophrenia spectrum disorders only) was included in the meta-analysis compared to our sample, we restricted the sample to SCZ only in a secondary analysis. However, measuring dopamine D2 receptor occupancy using PET in conjunction with structural MRI may, although challenging, be necessary to overcome this limitation entirely.

Third, the calculation of chlorpromazine equivalent dosage is not straight-forward since it assumes that antipsychotics have similar mechanisms of action. It is possible that the choice of investigating antipsychotics as a broad class could mask potential between-type differences. Despite shared properties of commonly used antipsychotic drugs with respect to dopamine D_2 receptor occupancy and the particular relevance of this receptor being supported by empirical data (Guma et al., 2018), other receptor systems including the dopamine D_1 receptor which is also densely found in the striatum (Levey et al., 1993) could also be involved in BG volume change.

An additional limitation is that blood samples for serum concentration measurements were not drawn at the same day as MRI acquisition. Although stable antipsychotic treatment was ascertained, we cannot rule out the possibility that serum concentration measurements could vary over time, affecting the ability to detect a correlation with estimated D2R occupancy. Further, although compliance to treatment was assured in the receptor occupancy analysis, longitudinal compliance could not be assessed.

Finally, the PANSS scores could have been altered by the medication itself, and thus the remission status, since we would expect a reduction of positive symptoms. Therefore, considering other measures related to illness severity, such as number of hospital admissions and time spent in

acute psychosis, persistent negative symptoms or apathy, or cognitive decline, may be more exhaustive.

4.6. Conclusions

The present study replicates findings of larger volume in the GP and putamen in patients treated with antipsychotics compared to HC, but the hypothesis of an association between BG volumes and estimated D2R occupancy was not supported. However, we observed a dose-response relationship between CPZ and GP volume. Moreover, there was a lower positive correlation indicating less structural covariance between the left putamen and left lateral occipital cortex in the antipsychotic-treated patients while there were no effects on structural covariance patterns in other regions.

Further research is warranted to elucidate how the pharmacological properties of antipsychotics relate to the observed brain structural changes and the underlying physiological mechanisms.

Conflict of interest

Author OAA has received speaker honorarium from Lundbeck. Authors KNJ, AD, SN, IM, JJ and IA report no conflict of interest.

Contributors

AD, KNJ, IA and JJ planned and designed the study. AD and KNJ analyzed the data, with support from SN, and were responsible for the integrity of analyses and interpretation of results. AD and KNJ drafted the first version of the manuscript. OAA and IM contributed with data and interpretation of results. JJ, IA and KNJ supervised the project. All authors contributed to the writing of the manuscript and have approved the final version.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.04.002.

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