European Neuropsychopharmacology (2019) 29, 1408–1418

www.elsevier.com/locate/euroneuro

The effect of second-generation antipsychotics on basal ganglia and thalamus in first-episode psychosis patients

Auria Albacete[a,b,c,d], Carolina Makowski[e,f], M. Mallar Chakravarty[e,g,h], Ridha Joober[a,e], Ashok K. Malla[a,e], Fernando Contreras[b,c,d], José Manuel Menchón[b,c,d], Martin Lepage[a,e,*]

[a] *PEPP-Montréal, Douglas Mental Health University Institute, Montréal, QC H4H 1R3, Canada*
[b] *Psychiatry Department, Bellvitge University Hospital-IDIBELL, Barcelona, Spain*
[c] *Department of Clinical Sciences, School of Medicine, University of Barcelona, Barcelona, Spain*
[d] *CIBERSAM (Centro de Investigación Biomédica en Red de Salud Mental), Madrid, Spain*
[e] *Department of Psychiatry, McGill University, Montréal, Canada*
[f] *McGill Centre for Integrative Neuroscience, McConnell Brain Imaging Centre, Montréal Neurological Institute, Montréal, Canada*
[g] *Department of Biological and Biomedical Engineering, McGill University, Montréal, Canada*
[h] *Brain Imaging Center, Douglas Mental Health University Institute, Montréal, Canada*

Received 27 November 2018; received in revised form 29 July 2019; accepted 15 October 2019

KEYWORDS
First episode psychosis;
Magnetic resonance imaging;
Globus pallidus;
Subcortical structures;
Antipsychotic medication;
Cognition

Abstract
Patients who have recently experienced a first of episode psychosis (FEP) exhibit considerable heterogeneity in subcortical brain volumes. These results become even more divergent when exploring the effect of antipsychotic medication among other clinical and cognitive features. We aimed to contrast volumetric measures in basal ganglia and thalamus in patients with a FEP treated with different second-generation antipsychotics. T1-weighted magnetic resonance images were obtained and subcortical structures were extracted with MAGeT-Brain. Relationships with cognitive functioning were also explored with a Global Cognitive Index obtained, on average, within one month from the scan. Subgroups included: risperidone ($n = 26$), aripiprazole ($n = 22$), olanzapine ($n = 19$) and controls ($n = 80$). The olanzapine subgroup displayed significant enlargement of the right globus pallidus volume compared with all other groups. More-

* Corresponding author at: PEPP-Montréal, Douglas Mental Health University Institute, Montréal, QC H4H 1R3, Canada.
E-mail address: martin.lepage@mcgill.ca (M. Lepage).

https://doi.org/10.1016/j.euroneuro.2019.10.004

over, despite not exhibiting poorer cognitive capacity than the rest of patients, results from a stepwise multiple-regression linear regression analysis identified a significant negative association between right globus pallidus volume and scores on the Global Cognitive Index among these patients. To our knowledge, this is the first study to associate treatment with olanzapine with an increase in globus pallidus volume in a sample of FEP patients with a relatively short time of antipsychotic monotherapy. Such enlargement was also found to be associated with poorer global cognitive functioning. Exploration of the biological underpinnings of this early medication-induced enlargement should be the focus of future investigations since it may lend insight towards achieving a better clinical outcome for these patients.

1. Introduction

Investigations of first episode of psychosis (FEP) patients are crucial to gain insight into the neurobiological and clinical course of psychotic spectrum disorders, including schizophrenia and bipolar disorder (Shenton et al., 2001). The study of subcortical structures, such as the basal ganglia and thalamus, has been of particular interest because they represent a main target for antipsychotic medications acting upon dopamine D_2 receptors, among other monoaminergic neurotransmitter systems (Guma et al., 2018; Howes and Kapur, 2009). Subcortical structures also play an important role in higher cognitive functions (Afifi, 2003; Van Der Werf et al., 2003), which have been widely reported to be impaired in psychosis (Levy et al., 1997).

Several magnetic resonance imaging (MRI) studies have demonstrated differences in subcortical structure in patients with schizophrenia and bipolar disorder as compared to controls (Rimol et al., 2010). In schizophrenia, results from a large meta-analysis exploring 2028 patients with schizophrenia and 2540 controls showed larger pallidum and lateral ventrical volumes, as well as smaller hippocampus, amygdala, thalamus, accumbens and intracranial volumes (Van Erp et al., 2016). However, among FEP patients including those with affective psychosis, results are more heterogeneous. When FEP patients are compared to healthy controls, some studies show a decrease in volumes of the caudate, the putamen and the thalamus (Crespo-Facorro et al., 2009), whereas others report increased volumes (Makowski et al., 2018), and even a lack of significant differences between groups (Lang et al., 2001). These results become even more contradictory when exploring the effect of antipsychotic medication (Ebdrup et al., 2011; Glenthoj et al., 2007), a factor that could significantly contribute to these heterogeneous findings.

Antipsychotics are reported to induce substantial and long-lasting alterations in subcortical structures. Such effects have been explained in the context of D_2-receptor blockade, causing a disruption of normal homeostatic mechanisms within target neurons (Andersson et al., 2002). This is believed to produce a number of compensatory changes, including increased blood flow in basal ganglia volume (Goozée et al., 2014). Thus, whereas typical agents have been widely related to basal ganglia enlargement (Chakos et al., 1994), atypical antipsychotics seem to have heterogeneous effects, suggesting a differential response as a function of the type of atypical agent and the dose taken (Andersson et al., 2002; Dazzan et al., 2004). In schizophrenia, volumetric changes in the basal ganglia do not occur in a linearly predictable fashion; a relevant review has shown that subcortical increases are specifically linked with olanzapine and risperidone treatment, rather than all atypical antipsychotics (Ebdrup et al., 2013). As mentioned, studies with FEP patient samples also suggest such relationships, further providing evidence that these changes can be observed with as little as 3–4 weeks of antipsychotic treatment (Chua et al., 2009). Such differential effects on brain volume might be supported by an antipsychotic's specific clinical profile. For instance, aripiprazole is a partial D_2-receptor agonist, a 5-HT_{2A}-receptor antagonist and a partial 5-HT_{1A}-receptor agonist, whereas risperidone and olanzapine are principally D_2- and 5-HT_{2A}-receptor antagonists, with olanzapine exhibiting lower affinity for dopamine D_2 than risperidone (Mauri et al., 2014). Studying relatively drug-naïve FEP patients offers a unique and valuable opportunity to explore the effects of different atypical antipsychotic medications as these patients undergo treatment.

On the other hand, it has been argued that cognitive deficits represent a core dimension of psychotic disorders (Milev et al., 2005). Such deficits may be strong predictors of patients' real-world functioning and already observable in the early stages of the disorder, even before the initiation of neuroleptic treatment (Lutgens et al., 2014). One possible avenue is to explore such deficits in relation to abnormalities of subcortical structures, especially taking into account the crucial roles that these structures play in cognitive and motor functioning through basal ganglia-thalamocortical feedback (Afifi, 2003; Van Der Werf et al., 2003). However, the relationship between subcortical volumes and cognitive deficits in FEP patients remains to be elucidated.

The primary aim of the present study was to extend previous MRI studies by investigating subcortical structural volume differences of the basal ganglia and thalamus in three subgroups of FEP patients taking different atypical antipsychotics (i.e. risperidone, olanzapine and aripiprazole) in comparison with a healthy control group. In addition, we also explored whether cognitive abilities relate to subcortical volumes differently across these three types of atypical antipsychotics.

2. Method

2.1. Participants

Sixty-two FEP patients and 80 controls were included in the current study. All patients were recruited from the Prevention and Early Intervention Program for Psychoses (PEPP-Montréal) at the Douglas Institute, and were part of a longitudinal naturalistic outcome

study. PEPP is a specialized early intervention service for individuals between the ages of 14 and 35 who are experiencing a FEP within a local catchment area of Southwest Montréal, Canada. Details are outlined elsewhere (Iyer et al., 2015). The program involves a comprehensive approach with low dose antipsychotic pharmacotherapy and a variety of psychosocial interventions provided within the context of a modified assertive case management model.

Inclusion criteria for patients included: age >18 years, diagnosis of affective or non-affective psychosis, IQ > 70, previous treatment with antipsychotic medication for a maximum of one month, no major medical disorders that could explain the psychotic symptoms, and having achieved sufficient clinical stability for both the scanning procedure and the neuropsychological evaluation. Baseline MRI scans were selected from a larger longitudinal neuroimaging study (see Makowski et al., 2016, 2017). Scans were acquired about 0.99 to 7.80 months after entry to PEPP. Controls were recruited through advertisements within the same local catchment area. In addition to exclusion criteria listed for FEP patients, controls were excluded if they had any current/past history of Axis I disorders, and/or a first-degree relative suffering from schizophrenia or a related spectrum disorder.

Of the 149 FEP patients and 95 controls with MRI scans acquired, 47 were removed due to: missing neuropsychological data ($n = 12$) and not meeting quality control standards (see *Section 2.6*) ($n = 35$). Patients were additionally removed due to: missing key pharmacological data ($n = 1$), medication adherence below 50% as defined by Cassidy et al. (2010) ($n = 23$), antipsychotics polypharmacy ($n = 13$) and insufficiently sized subgroups ($n = 13$; see Fig. 1).

Participants of this latter group were excluded as any results would have been uninterpretable due to small subgroup sizes. Final sample size was 67 FEP [risperidone ($n = 26$); aripiprazole ($n = 22$); olanzapine ($n = 19$)] and 80 controls. All participants provided written informed consent. Research protocol was approved by the Research Ethics Board of the Douglas Mental Health University Institute and that of the McGill University Faculty of Medicine.

2.2. Clinical assessment and demographic data

Diagnosis was made using the SCID-I for DSM-IV Axis I disorders First et al., 1997 performed by a trained interviewer and confirmed by a research psychiatrist. Symptoms and severity of illness were assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), the Calgary Depression Scale for Schizophrenia (Addington et al., 1990) and the Young Mania Rating Scale (Young et al., 1978). Parental socioeconomic status (Hollingshead, 1965), handedness (Oldfield, 1971) and full-scale IQ (Wechsler, 1999, 1997a) were assessed for all participants.

2.3. Antipsychotic treatment groups

Daily dose of antipsychotic medication was first converted to chlorpromazine equivalents according to Leucht et al. (2015), and then multiplied by percent medication adherence (Cassidy et al., 2010). As per treatment guidelines at PEPP-Montréal, all patients were offered an atypical antipsychotic at program entry. The antipsychotic treatment provided is determined by the treating psychiatrist while considering tolerability and side-effect profiles, and considering the preference that the patient may have. Medication adherence was determined using a validated protocol based on composite information collected from the patient, family members, and treating team, where medication adherence was classified as follows: 0 = =never (0%), 1 = =very infrequently (1-25%), 2 = =sometimes (26-50%), 3 = =quite often (51-75%), and 4 = =fully (76-100%) (Cassidy et al., 2010). Patients were then separated into subgroups based on the type of antipsychotic taken. As previously mentioned, to be considered for a subgroup, patients had to take one type of antipsychotic from entry to the clinic until their first scan with a monthly average adherence above 50%. Patients who outright refused antipsychotic treatment or had less than 50% adherence were categorized into the "refused-antipsychotics" subgroup. In the risperidone subgroup, 9 patients were being treated with long-acting injectable antipsychotic medication. Length of treatment prior to scanning after a patient experienced a FEP was calculated based on time elapsed between entry to the clinic and baseline MRI scan in order to explore the effect of exposure to medication on subcortical volume across the three subgroups of patients.

2.4. Neuropsychological evaluation

All patients were approached within one month prior to the MRI acquisition for a standardized neuropsychological evaluation ($M = 0.88$, SD = =2.30). As previously presented in Benoit et al. (2015), these assessments had been administered using two different neuropsychological batteries: (i) from 2003 to 2010 in pen and paper format, and (ii) from September 2010 in a computerized format by using the CogState Research Battery (Pietrzak et al., 2009). To explore cognitive domains, we included 6 of the 7 domains of the MATRICS battery (Green and Nuechterlein, 2004) - i.e., processing speed, attention, working memory, visual memory, verbal memory and executive function. Comparability of both batteries on FEP patients' performance has been empirically tested and published by our group (Benoit et al., 2015). Table 1 summarizes the corresponding tests for each battery. Testing with controls was done during the same time period with each battery. All of the test scores were transformed into standard equivalents (*z*-scores) using the mean and standard deviation of performance from the controls, such that higher values indicated better performance. An overall cognitive performance score (Global Cognitive Index, GCI) was explored by averaging scores over the six cognitive domains.

2.5. Magnetic resonance imaging acquisition

Scanning was carried out at the Montréal Neurological Institute (MNI) on a 1.5 T Siemens Sonata whole body MRI system. Structural T1 volumes were acquired for each participant using a three dimensional gradient echo pulse sequence with sagittal volume excitation (repetition time = =22 ms, echo time = =9.2 ms, flip angle = =30, 180 1 mm contiguous sagittal slices). The rectangular field of view (FOV) for the images was 204 mm (SI) 256 mm (AP).

2.6. Image processing and quality control procedures

Subcortical structures [striatum (including pre/postcommissural caudate and putamen, and nucleus accumbens), GP, thalamus] were extracted bilaterally using the Multiple Automatically Generated Templates (MAGeT)-Brain algorithm (Chakravarty et al., 2015; Pipitone et al., 2014) (https://github.com/CobraLab/MAGeTbrain) (Fig. S1). This method has previously been shown by our group to have high accuracy compared to other openly available segmentation toolboxes (Makowski et al., 2018). Atlases for the subcortical structures of interest were compiled from previous work, which reconstructed and warped a histological data set to an MRI-based template. This technique utilizes histological data described previously (Chakravarty et al., 2006) (https://github.com/CobraLab/atlases). Twenty-one templates were chosen based on recommended best practices for MAGeT (https://github.com/CobraLab/documentation/wiki/Best-Templates-for-MAGeT), where labels from the atlases were

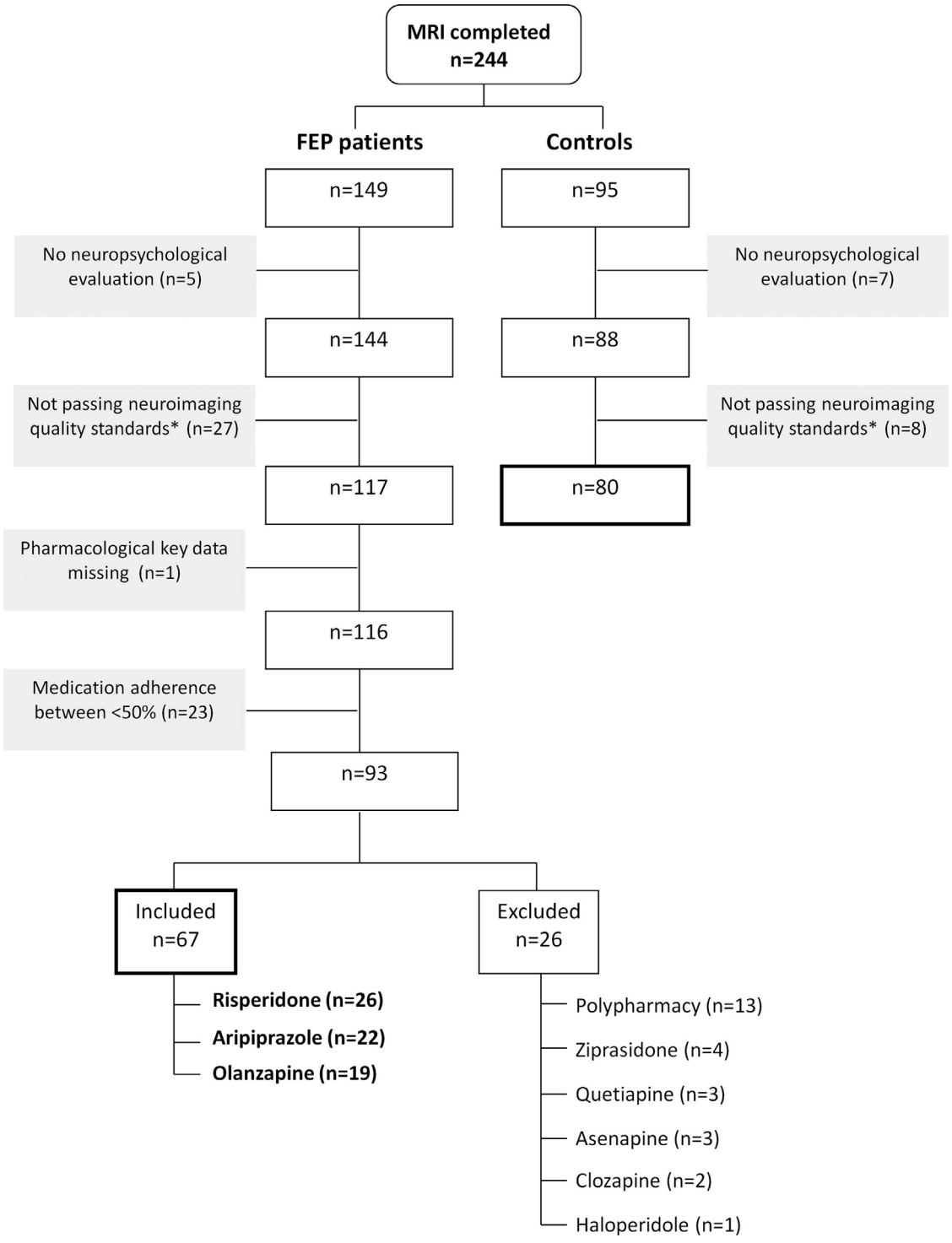

Fig. 1 Sample flow-chart. *Neuroimaging quality control standards are detailed in *Section 2.6* of the present article. *MRI: Magnetic Resonance Imaging; FEP: first episode of psychosis.*

registered to each individual subject, which acted as candidate templates. Each atlas label was then warped to the candidate templates, and the highest quality labels for 21 subjects, comprising 10 controls and 11 patients, were selected by an expert rater (CM). These 21 subjects were then used as the final templates in the MAGeT-Brain pipeline, a number shown to be optimal based on previous work (Pipitone et al., 2014). Customization of atlas labels to templates was conducted using a nonlinear registration where transformations were estimated with a version of Automatic Normalization Tools (ANTS) compatible with the *minctoolkit* (https://github.com/vfonov/mincANTS). Next, each template is used to segment each subject, yielding a total of 21 candidate labels followed by majority-vote label fusion (Collins and Pruessner, 2010).

Appendix S1 presents corresponding quality control and manual correction procedures, along with Kappa and Jaccard sim-

Table 1 Neuropsychological evaluation: batteries and tests descriptions.

Cognitive domain	Pen and paper battery		CogState research battery	
	Test	Outcome measure	Test	Outcome measure
Processing speed	Digit symbol[a]	*Number of correct symbols in 120s*	Groton maze chase test	*Average number of correct moves per second*
	Trail making test A[b]	*Completion time*	Detection task	*Average reaction time for correct responses*
	Stroop test: word[c]	*Number of correct words read in 1* min		
	Stroop test: color[c]	*Number of correct colors read in 1* min		
Attention	D2 test[d]	*Concentration performance*	Identification task	*Response accuracy*
	Stroop test: inhibition[c]	*Number of correct colors read in 1* min		
Working memory	Digit span	*Raw score*	One-back task two-back task	*Response accuracy*
	Corsi spatial span[e]	*Raw score*		
Visual memory	Visual reproduction: immediate recall[e]	*Raw score*	One-card learning task	*Response accuracy*
	Visual reproduction: delayed recall[e]	*Raw score*	Continuous paired associate	*Response accuracy*
			Groton maze learning task: delayed recall	*Total number of errors*
Verbal memory	Logical memory: immediate recall[e]	*Raw score*	International shopping list: immediate recall	*Total number of words recalled over 3 trials*
	Logical memory: delayed recall[e]	*Raw score*	International shopping list: delayed recall	*Total number of words recalled*
	Logical memory: recognition[e]	*Raw score*		
Executive functions	Block design[a]	*Raw score*	Groton maze learning task	*Total number of errors after 5 trials*
	Trail Making test B[b]	*Completion time*	Set-shifting task	*Response accuracy*

[a] Wechsler (1997a).
[b] Reitan (1992).
[c] Stroop (1935).
[d] Brikenkamp and Zillmer (1998).
[e] Wechsler (1997b).

ilarity indices calculations as previously reported by our group (Makowski et al., 2018).

2.7. Statistical analyses

Absolute and relative frequencies were calculated for categorical variables. Continuous variables were assessed using the mean (M) and standard deviation (SD) for normally distributed variables, and the median and interquartile range (IQR) for non-normally distributed variables. Sample characteristics and neuropsychological performance were analyzed by using one-way ANOVAs for continuous variables and Kruskall–Wallis *H*-tests for nominal variables. Subcortical structure volume differences were analyzed using a univariate general linear model including age at scan, total brain volume, and sex as covariates. The False Discovery Rate (FDR; Benjamini and Hochberg, 1995) was applied to account for multiple comparisons across the six structures explored (i.e., right and left striatum, thalamus and GP), and for individual striatal substructures as well. Post hoc comparisons were then calculated using a Bonferroni correction for the structures showing significant FDR-corrected differences.

The analysis above was used to inform which subcortical structures should be included in the next set of analyses. Pearson's product moment correlation coefficients were calculated between GCI and subcortical volumes (informed from analysis 1) with age at scan, total brain volume and sex as covariates. Stepwise multiple regression analyses were conducted to examine the associations between cognitive functioning and the subcortical structure volume that was significantly correlated. Possible confounding factors such as age, sex, total brain volume, antipsychotic chlorpromazine equivalents multiplied by percent medication adherence, and PANSS' positive and negative scales were included in the models. SPSS version 17.0 was used for statistical analyses. All statistical tests were two-tailed, and significance was determined at the 0.05 level.

3. Results

As presented in Table 2, there were no significant between-group differences for sex, age, parental socioeconomic status, or handedness. However, there were significant differences between patients and controls in education level, where controls completed more years of education and had

Table 2 General characteristics of the sample.

	Risperidone ($n=26$)	Aripiprazole ($n=22$)	Olanzapine ($n=19$)	Controls ($n=80$)	Statistic (p-value)	Post-hoc test
Female gender, *n (%)*	7 (26.90)	9 (40.90)	7 (36.80)	29 (36.30)	$X^2=1.144$ (0.766)	-
Age (years)	23.88 (3.63)	24.29 (4.88)	24.72 (3.31)	24.35 (3.36)	$F=0.202$ (0.895)	-
Educational level (years)	11.65 (2.40)	12.18 (2.50)	12.68 (2.58)	14.40 (2.43)	**$F=11.133$ (0.000)**	hc>r,o,a
Parental SES*	3.29 (1.12)	2.73 (0.88)	3.25 (0.86)	3.00 (1.03)	$X^2=4.067$ (0.254)	-
Handedness (right), *n (%)*	22 (84.60)	18 (81.80)	16 (84.20)	74 (92.50)	$X^2=2.679$ (0.444)	-
Premorbid IQ	98.27 (15.64)	99.82 (10.26)	99.42 (14.56)	110.76 (14.07)	**$F=8.562$ (0.000)**	hc>r,o,a
Clinical ratings						
Diagnosis, *n (%)*						
SSD	21 (80.80)	12 (54.50)	12 (63.20)			
Affective disorder	2 (7.70)	7 (31.80)	6 (31.60)			
Delusional disorder	0 (0.00)	1 (4.50)	0 (0.00)			
Psychosis NON	3 (11.50)	2 (9.10)	1 (5.30)			
GAF, median (IQR)	50 (39-60)	45 (36-68)	51 (40-61)	-	$F=0.032$ (0.968)	-
AP treatment	550.92 (538.41)	675.03 (656.75)	843.76 (576.41)	-	$F=0.181$ (0.835)	-
AP adherence rate, *(%)*	100 (92-100)	100 (89-100)	96.63%	-	$F=1.944$ (0.151)	-
Duration of AP treatment (weeks), median (IQR)	13.54 (7.87-21.41)	14.54 (7.91-20.03)	13.52 (7.32-19.40)	-	$F=0.002$ (0.998)	-
PANSS						
Positive symptoms	11.73 (4.47)	12.41 (5.51)	11.74 (4.50)	-	$F=0.144$ (0.866)	-
Negative symptoms	26.77 (8.80)	28.18 (11.75)	24.53 (7.41)	-	$F=0.756$ (0.474)	-
General psychopathology	27.18 (6.62)	30.05 (9.96)	26.42 (6.68)	-	$F=1.117$ (0.333)	-
Total score	66.31 (18.50)	70.64 (25.63)	62.68 (16.29)	-	$F=0.768$ (0.468)	-
CDSS, total score	3.46 (3.58)	4.68 (6.08)	3.11 (3.45)	-	$F=0.712$ (0.495)	-
YMRS, total score	2.58 (3.51)	2.64 (2.97)	2.63 (2.65)	-	$F=0.003$ (0.997)	-

Note. Values presented as means (standard deviation) unless otherwise specified. hc: healthy controls; r: risperidone subgroup; o: olanzapine subgroup; a: aripiprazole subgroup; IQ: Intelligence Quotient; SSD: Schizophrenia Spectrum Disorders; NOS: Not Otherwise Specified; GAF: Global Assessment of Functioning; AP: daily dose of antipsychotic treatment - milligrams per day of chlorpromazine equivalents; PANSS: Positive and Negative Syndrome Scale; YRMS: Young Rating Mania Scale; CDSS: Calgary Depression Scale for Schizophrenia; HAS: Hamilton Anxiety Scale. *Hollingshead parental Socio-Economic Status (SES): 1=high SES and 5=low SES.

higher premorbid IQ. Between the FEP subgroups, there were no significant differences in any of the clinical variables. GCI score was significantly different between the three subgroups of patients and the controls, with post-hoc analyses revealing that all subgroups of patients presented lower z-scores in comparison with the controls ($F=12.986$, $p<0.001$; Fig. 2).

3.1. Manual correction reliability of caudate/ventral striatum volumes

Comparison of intra-rater reliability for the two raters and inter-rater agreement for nine sets of labels (belonging to 6 controls and 3 FEP patients) that were manually corrected are outlined in Appendix S1. Dice kappa indices were high for all structures and for both raters, where κ ranged from 0.90 to 1.00.

3.2. Volume comparison of subcortical structures

After FDR correction, significant differences were only observed between groups in the right GP volume ($F=5.174$, $p=0.012$) and in the left GP volume ($F=3.652$, $p=0.042$), after covarying for total brain volume, age and sex. Bonferroni post-hoc analysis of GP volume differences between medication subgroups revealed that patients taking olanzapine had significantly greater right GP volume than the controls ($p=0.010$). No other significant between-groups differences were observed in the striatum or the thalamus (Table S1). Exploratory correlational analysis of sub-

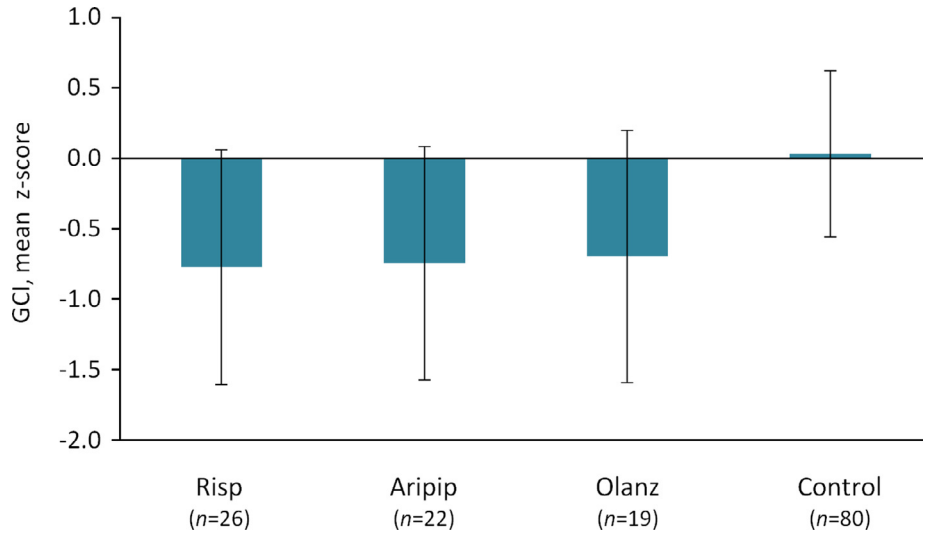

Fig. 2 Neuropsychological evaluation: differences between groups of study. *Risp: Risperidone; Aripip: Aripiprazole; Olanz: Olanzapine; GCI: Global Cognitive Index*. Note that the errors bars represent standard deviation.

Table 3 Results of the stepwise multiple linear regression analysis of selected variables predicting right GP volume in the Olanzapine subgroup.

	Unstandardized coefficients		95% confidence interval for B		Standardized coefficients Beta	*t*	Sig.
	B	Standard error	Lower bound	Upper bound			
Right GP							
TBV	0.795	0.146	0.485	1.106	0.791	5.461	<0.001
GCI	−60.299	24.124	−111.717	−8.880	−0.362	−2.500	0.025

TBV: Total Brain Volume; GCI: Global Cognitive Index.

cortical volumes and total length of antipsychotic exposure only revealed a statistically significant positive relationship between weeks of exposure and left precommissural caudate in the group of patients taking aripiprazole ($r = 0.541$, $p = 0.017$; partial correlation controlling for total brain volume, age and sex). The association did not remain significant after FDR correction ($p = 0.153$).

3.3. GP volumes and cognitive function

Given the significant results with GP volume, partial correlations controlling for total brain volume, age and sex, were calculated for each subgroup of patients between this structure and overall cognitive function. Significant negative correlations were observed in the olanzapine subgroup between right GP volume and z-scores on the GCI ($r = =-0.533$, $p = 0.041$). No significant results were found in the risperidone or the aripiprazole subgroups.

3.4. GP volumes and regression model

To better understand the different factors contributing to GP volumes, the following variables were included in a stepwise linear regression model: GCI, TBV, age, sex, medication, PANSS' positive scale and PANNS' negative scale scores. The final model identified two of the initial variables as predictors of the right GP volume in the subgroup of patients taking olanzapine: total brain volume and GCI (Table 3). The model provided a good fit to the data, as it predicted a large amount of the variability of the right GP volume ($F = 16.674$, $p = 0.025$; adjusted $R^2 = =0.648$). Breaking down the unique variance of each of these two variables on right GP volume, the semipartial correlation with TBV was 0.785 ($p < 0.001$), and −0.359 ($p = 0.025$) with GCI.

4. Discussion

The present study investigated how antipsychotic medication and cognitive capacity are associated with subcortical volumes in patients who have recently experienced a first episode of psychosis. Two key findings emerged: firstly, FEP patients taking olanzapine showed a significantly larger right GP volume than the other subgroups of patients and the controls; second, global neurocognitive functioning was negatively associated with right GP volume enlargement in the olanzapine subgroup. No other significant associations were observed in any of the other groups of study.

To our knowledge, this is the first study to report GP volume enlargement in a group of FEP patients taking olanzapine after a relatively short time of treatment. Present

results seem to be in line with those of previous studies that have positively associated basal ganglia volume with daily dose of antipsychotic medication in enduring schizophrenia (Ebdrup et al., 2013; Van Erp et al., 2016). However, although knowledge of the brain processes involved in the therapeutic effects of antipsychotic drugs is crucial for understanding the neurobiology of psychotic disorders, the underpinnings of basal ganglia volume increases induced by antipsychotics still remains poorly understood. Some authors have explained this volumetric increase in the context of dopamine-D_2 receptor blockade, a class of receptors highly expressed in the basal ganglia (Howes and Kapur, 2009). Intriguingly, other authors have associated basal ganglia volume change with increases in blood flow in these brain regions after antipsychotic treatment (Goozée et al., 2014). There is a need to streamline such analyses by comparing across multiple scales of evidence to build a mechanistic model of the impact of antipsychotic medication on brain structure. Our study represents findings at the macroscale level. The link to finer scales requires preclinical studies such as Guma et al. (2018) and Vernon et al. (2011), where the impact of different antipsychotic medications on brain structure can be further investigated at meso- and even micro-scale levels through histological analyses in the same animals.

The present study focused on the alterations in brain structure as a function of the exposure to different atypical antipsychotics, a topic that has elicited prior interest and investigation. A relevant systematic review (Ebdrup et al., 2013) has described how exposure to specific antipsychotic monotherapy is differentially related to volume increases in subcortical structures in patients with schizophrenia and non-affective psychosis. Although results with FEP patients seem to point in the same direction, these study designs are still rather scarce (Glenthoj et al., 2007). Despite the dearth of such studies in the literature, our results do seem to be consistent with previous research and also support the notion that individual medications might have their own unique pharmacological and side effect profiles (Leucht et al., 2009).

Indeed, the three antipsychotics included in this study have different pharmacodynamic properties; i.e., olanzapine has the highest affinity for 5-HT_{2A} but lower affinity for D_2 compared to aripiprazole and risperidone (Mauri et al., 2014). Thus, it could be possible that such differential pharmacological profiles of olanzapine and the other two antipsychotics may be contributing to the mechanism underlying our finding of increased GP volume at an early stage of the illness specific to the olanzapine group. Further studies are needed to better describe the effects of different neuroleptic agents and the specific neurochemical mechanisms involved.

Intriguingly, such volumetric enlargement seems to take place quickly in the first weeks of treatment – i.e., no relationship with duration of olanzapine exposure and GP volumes was found. This result provides some evidence to suggest that the observed group differences emerge very early after initiation of the treatment and plateau rapidly; a speculation that should be tested further with a longitudinal study design. Previous studies have also reported subcortical volume increases after a short time of atypical antipsychotics exposure (Chua et al., 2009), although more research is required to better understand the mechanisms of such rapid enlargement.

Moreover, such enlargement appears to be lateralized – i.e., patients taking olanzapine presented significantly greater volume in the right GP, but the same was not found for the left hemisphere. Indeed, previous studies have reported such lateralization in brain abnormalities in patients with schizophrenia and other psychotic disorders (for instance, see Lappin et al., 2006). However, it is possible that more subtle abnormalities are also present in the left GP, but were not detected in this study due to modest sample sizes.

Other variables known to influence subcortical structure, such as neurocognition, may also help inform the relationship between subcortical structure and antipsychotic medication exposure. Indeed, another key finding of this study was that increases in GP volumes in the olanzapine subgroup were significantly related to poorer global cognitive functioning. This significant relationship was not found to be associated with positive or negative symptom severity, and was not observed in the other FEP subgroups and controls. Surprisingly few studies have systematically examined this relationship in early psychosis. However, there are several reports of significant associations in schizophrenia and bipolar disorder between a higher degree of executive function deficits and abnormalities of subcortical structures (Hartberg et al., 2011). Our study adds to evidence supporting meaningful cognition-subcortical structure relationships in psychosis, specifically in patients exposed to olanzapine. This is consistent with previous research in non-clinical populations demonstrating the involvement of basal ganglia in higher cognitive function (Afifi, 2003). In addition, cognitive functioning has been proposed as an important predictor of everyday functioning in psychotic disorders (Kahn and Keefe, 2013); thus, the present results might be of particular relevance as they seem to reveal how short-term exposure to a specific antipsychotic might be differentially impacting cognitive abilities at a very early phase of the illness.

Present results are strengthened by the fact that our patients had a relatively limited exposure to antipsychotic medication, and were recruited from a well-defined catchment area with no competing clinical services and, therefore, are truly representative of people with FEP in the Montreal area with varying severity. Furthermore, we removed those who were taking multiple antipsychotics, antidepressants or mood stabilizers. However, there are a number of limitations to consider. Firstly, the sample size of each FEP subgroup was relatively small which may have limited the generalizability of our findings. It would be ideal to replicate present results with an independent sample. However, to date, our analysis represents the largest sized cross-sectional multigroup investigation of basal ganglia change among FEP patients in relation to exposure to specific atypical antipsychotic medications. Second, the present study has the limitations of a cross-sectional design; causal relationships between GP volumetric enlargement and cognitive impairment should be further explored with a longitudinal approach. Although a longitudinal randomized controlled trial (RCT) may be optimal to answer such a question, assigning FEP patients to a single antipsychotic medication and maintaining patients on one antipsychotic

in early phases of the illness comes with considerable challenges and limits feasibility; thus, preclinical studies, such as the recent investigation by Guma et al. (2018) assessing brain volume changes after different antipsychotic medication administration in a mouse model, are highly relevant and necessary to better understand the impact of these medications at the macroscale level. Third, the neuropsychological assessments were administered in two different formats which may have compromised the validity of the cognitive domains explored. It should also be noted that the olanzapine subgroup was entirely assessed by using only the pen and paper battery. However, care was taken to standardize scores against non-clinical controls for each neuropsychological test battery, and the two batteries have been found to be relatively comparable as shown previously by our group (Benoit et al., 2015). We also focused on a general cognitive index to overcome potential cognitive domain-specific limitations of battery. Fourth, although our patients demonstrated an overall medication adherence above 80% using a reliable and validated method (Cassidy et al., 2010), it was not possible to monitor the direct intake of medication. Further, the estimation of chlorpromazine equivalents based on converting medication doses across different antipsychotic classes is limited in the sense that individual differences in pharmacological response to these medications cannot be assessed; rather this conversion is more strongly based on clinical effects than objective measurement of individual biology. Future studies may consider employing long-acting injectables to ensure adherence or measure medication plasma levels as an objective method to confirm actual medication adherence and dosage. It should also be noted that some of the patients were previously exposed to antipsychotic medication prior to entry to the PEPP clinic (i.e. no more than 30 days of prior cumulative antipsychotic exposure), and this was not included in our duration of exposure estimation.

In conclusion, the current study found a significant difference between right GP volumes between FEP patients and controls, specifically within patients taking olanzapine. Among the subgroup of patients taking olanzapine, increases in pallidal volumes were significantly related to poorer global cognitive functioning. No other significant associations were found with any of the other antipsychotic agents included in this study in comparison with the controls. Present results suggest that particular attention should be given to subcortical regional brain volumes and pathophysiology of psychotic disorders, as they may be influenced by the type of antipsychotic medication taken. This may have direct implications for the choice of treatment in clinical settings.

Role of the funding source

The study is supported by operating grants from the Canadian Institutes of Health Research (CIHR, 68961, MCT-94189) and the Fonds de Recherche du Quebec – Santé (FRSQ, 202885). It also benefited from computational resources provided by SciNet (https://www.scinethpc.ca/). Salary awards include: Canadian Institutes for Health Research (CIHR; C.M., R.J., M.L.), Fonds de la Recherche en Santé du Québec (FRSQ; C.M., M.L., R.J.), funding from the Canada First Research Excellence Fund, awarded to McGill University for the Healthy Brains for Healthy Lives Initiative (C.M.), James McGill Professorship (M.L.) and Canada Research Chairs Programme (A.K.M.), Health University of Barcelona Campus (A.A.).

Contributors

A.A., C.M., A.K.M, R.J., and M.L. conceived and designed the study. A.K.M. and R.J. carried out clinical assessments. A.A. and C.M. undertook all statistical analyses. M.M.C., F.C., and J.J.M. provided technical support and additional statistical guidance. A.A. prepared the first draft of the manuscript. All authors contributed to subsequent drafts of the manuscript and have approved the final manuscript.

Conflict of interest

The authors disclose no conflict of interest.

Acknowledgments

We thank PEPP-Montréal research staff for their help with recruitment and for conducting the clinical assessments, and all participants in the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.10.004.

References

Addington, D., Addington, J., Schissel, B., 1990. A depression rating scale for schizophrenics. Schizophr. Res. 3, 247–251.

Afifi, A.K., 2003. The basal ganglia: a neural network with more than motor function. Semin. Pediatr. Neurol. 10, 3–10. doi:10.1016/S1071-9091(02)00003-7.

Andersson, C., Hamer, R.M., Lawler, C.P., Mailman, R.B., Lieberman, J.A., 2002. Striatal volume changes in the rat following long-term administration of typical and atypical antipsychotic drugs. Neuropsychopharmacology 27, 498. doi:10.1016/S0893-133X(02)00412-8.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. Stat. Soc. B doi:10.2307/2346101.

Benoit, A., Malla, A.K., Iyer, S.N., Joober, R., Bherer, L., Lepage, M., 2015. Cognitive deficits characterization using the CogState Research Battery in first-episode psychosis patients. Schizophr. Res. Cogn. 2, 140–145. doi:10.1016/j.scog.2015.03.006.

Brikenkamp, R., Zillmer, E., 1998. The d_2 Test of Attention. Hogrefe & Huber Publishers.

Cassidy, C.M., Rabinovitch, M., Schmitz, N., Joober, R., Malla, A., 2010. A comparison study of multiple measures of adherence to antipsychotic medication in first-episode psychosis. J. Clin. Psychopharmacol. 30, 64–67. doi:10.1097/JCP.0b013e3181ca03df.

Chakos, M., Lieberman, J., Bilder, R., Borenstein, M., Lerner, G., Bogerts, B., Wu, H., Kinon, B., Ashtari, M., 1994. Increase in caudate nuclei volumes of first-episode schizophrenic patients taking antipsychotic drugs. Am. J. Psychiatry 151, 1430–1436.

Chakravarty, M.M., Bertrand, G., Hodge, C.P., Sadikot, A.F., Collins, D.L., 2006. The creation of a brain atlas for image guided neurosurgery using serial histological data. Neuroimage 30, 359–376. doi:10.1016/j.neuroimage.2005.09.041.

Chakravarty, M.M., Rapoport, J.L., Giedd, J.N., Raznahan, A., Shaw, P., Collins, D.L., Lerch, J.P., Gogtay, N., 2015. Striatal shape abnormalities as novel neurodevelopmental endophenotypes in schizophrenia: a longitudinal study. Hum. Brain Mapp. 36, 1458–1469. doi:10.1002/hbm.22715.

Chua, S.E., Deng, Y., Chen, E.Y.H., Law, C.W., Chiu, C.P.Y., Cheung, C., Wong, J.C.H., Lienenkaëmper, N., Cheung, V., Suckling, J., McAlonan, G.M., 2009. Early striatal hypertrophy in first-episode psychosis within 3 weeks of initiating antipsychotic drug treatment. Psychol. Med. 39, 793–800. doi:10.1017/S0033291708004212.

Collins, D.L., Pruessner, J.C., 2010. Towards accurate, automatic segmentation of the hippocampus and amygdala from MRI by augmenting ANIMAL with a template library and label fusion. Neuroimage 52, 1355–1366. doi:10.1016/j.neuroimage.2010.04.193.

Crespo-Facorro, B., Roiz-Santiáñez, R., Pérez-Iglesias, R., Tordesillas-Gutiérrez, D., Mata, I., Rodríguez-Sánchez, J.M., de Lucas, E.M., Vázquez-Barquero, J.L., 2009. Specific brain structural abnormalities in first-episode schizophrenia. A comparative study with patients with schizophreniform disorder, non-schizophrenic non-affective psychoses and healthy volunteers. Schizophr. Res. 115, 191–201. doi:10.1016/j.schres.2009.09.007.

Dazzan, P., Morgan, K.D., Orr, K.G., Hutchinson, G., Chitnis, X., Suckling, J., Fearon, P., Salvo, J., McGuire, P.K., Mallett, R.M., Jones, P.B., Leff, J., Murray, R.M., 2004. The structural brain correlates of neurological soft signs in ÆSOP first-episode psychoses study. Brain 127, 143–153. doi:10.1093/brain/awh015.

Ebdrup, B.H., Nørbak, H., Borgwardt, S., Glenthøj, B., 2013. Volumetric changes in the basal ganglia after antipsychotic monotherapy: a systematic review. Curr. Med. Chem. 20, 438–447. doi:10.2174/0929867311320030015.

Ebdrup, B.H., Skimminge, A., Rasmussen, H., Aggernaes, B., Oranje, B., Lublin, H., Baaré, W., Glenthøj, B., 2011. Progressive striatal and hippocampal volume loss in initially antipsychotic-naive, first-episode schizophrenia patients treated with quetiapine: relationship to dose and symptoms. Int. J. Neuropsychopharmacol. 14, 69–82. doi:10.1017/S1461145710000817.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1997. Structured Clinical Interview for DSM-IV Axis I Disorders—Clinician Version (SCID-CV). American Psychiatric Press, Washington, D.C.

Glenthoj, A., Glenthoj, B.Y., Mackeprang, T., Pagsberg, A.K., Hemmingsen, R.P., Jernigan, T.L., Baaré, W.F.C., 2007. Basal ganglia volumes in drug-naive first-episode schizophrenia patients before and after short-term treatment with either a typical or an atypical antipsychotic drug. Psychiatry Res. - Neuroimaging 154, 199–208. doi:10.1016/j.pscychresns.2006.10.002.

Goozée, R., Handley, R., Kempton, M.J., Dazzan, P., 2014. A systematic review and meta-analysis of the effects of antipsychotic medications on regional cerebral blood flow (rCBF) in schizophrenia: association with response to treatment. Neurosci. Biobehav. Rev. 43, 118–136. doi:10.1016/j.neubiorev.2014.03.014.

Green, M.F., Nuechterlein, K.H., 2004. The MATRICS initiative: developing a consensus cognitive battery for clinical trials. Schizophr. Res. 72, 1–3. doi:10.1016/j.schres.2004.09.006.

Guma, E., Rocchetti, J., Devenyi, G.A., Tanti, A., Mathieu, A., Lerch, J.P., Elgbeili, G., Courcot, B., Mechawar, N., Chakravarty, M.M., Giros, B., 2018. Regional brain volume changes following chronic antipsychotic administration are mediated by the dopamine D2 receptor. Neuroimage 176, 226–238. doi:10.1016/j.neuroimage.2018.04.054.

Hartberg, C.B., Sundet, K., Rimol, L.M., Haukvik, U.K., Lange, E.H., Nesvåg, R., Melle, I., Andreassen, O.A., Agartz, I., 2011. Subcortical brain volumes relate to neurocognition in schizophrenia and bipolar disorder and healthy controls. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 35, 1122–1130. doi:10.1016/j.pnpbp.2011.03.014.

Hollingshead, A., 1965. Two Factor Index of Social Position. Yale University Press.

Howes, O.D., Kapur, S., 2009. The dopamine hypothesis of schizophrenia: version III – the final common pathway. Schizophr. Bull. 35, 549–562. doi:10.1093/schbul/sbp006.

Iyer, S., Jordan, G., Macdonald, K., Joober, R., Malla, A., 2015. Early intervention for psychosis: a Canadian perspective. J. Nerv. Ment. Dis. 203, 356–364. doi:10.1097/NMD.0000000000000288.

Kahn, R.S., Keefe, R.S.E., 2013. Schizophrenia is a cognitive illness: time for a change in focus. JAMA Psychiatry 70, 1107–1112. doi:10.1001/jamapsychiatry.2013.155.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale for schizophrenia. Schizophr. Bull. 13, 261–276. doi:10.1093/schbul/13.2.261.

Lang, D.J., Kopala, L.C., Vandorpe, R.A., Rui, Q., Smith, G.N., Goghari, V.M., Honer, W.G., 2001. An MRI study of basal ganglia volumes in first-episode schizophrenia patients treated with risperidone. Am. J. Psychiatry 158, 625–631. doi:10.1176/appi.ajp.158.4.625.

Lappin, J.M., Morgan, K., Morgan, C., Hutchison, G., Chitnis, X., Suckling, J., Fearon, P., McGuire, P.K., Jones, P.B., Leff, J., Murray, R.M., Dazzan, P., 2006. Gray matter abnormalities associated with duration of untreated psychosis. Schizophr. Res. 83 (2006), 145–153. doi:10.1016/j.schres.2005.11.018.

Leucht, S., Kissling, W., Davis, J.M., 2009. Second-generation antipsychotics for schizophrenia: can we resolve the conflict? Psychol. Med. 39, 1591–1602. doi:10.1017/S0033291709005455.

Leucht, S., Samara, M., Heres, S., Patel, M.X., Furukawa, T., Cipriani, A., Geddes, J., Davis, J.M., 2015. Dose equivalents for second-generation antipsychotic drugs: the classical mean dose method. Schizophr. Bull. 41, 1397–1402. doi:10.1093/schbul/sbv037.

Levy, R., Hazrati, L.N., Herrero, M.T., Vila, M., Hassani, O.K., Mouroux, M., Ruberg, M., Asensi, H., Agid, Y., Féger, J., Obeso, J.A., Parent, A., Hirsch, E.C., 1997. Re-evaluation of the functional anatomy of the basal ganglia in normal and Parkinsonian states. Neuroscience 76, 335–343. doi:10.1016/S0306-4522(96)00409-5.

Lutgens, D., Lepage, M., Iyer, S., Malla, A., 2014. Predictors of cognition in first episode psychosis. Schizophr. Res. 152, 164–169. doi:10.1016/j.schres.2013.10.044.

Makowski, C., Béland, S., Kostopoulos, P., Bhagwat, N., Devenyi, G.A., Malla, A.K., Joober, R., Lepage, M., Chakravarty, M.M., 2018. Evaluating accuracy of striatal, pallidal, and thalamic segmentation methods: comparing automated approaches to manual delineation. Neuroimage 170, 182–198. doi:10.1016/j.neuroimage.2017.02.069.

Makowski, C., Bodnar, M., Malla, A.K., Joober, R., Lepage, M., 2016. Age-related cortical thickness trajectories in first episode psychosis patients presenting with early persistent negative symptoms. npj Schizophr. 2, 16029. doi:10.1038/npjschz.2016.29.

Makowski, C., Bodnar, M., Shenker, J.J., Malla, A.K., Joober, R., Chakravarty, M.M., Lepage, M., 2017. Linking persistent negative symptoms to amygdala-hippocampus structure in first-episode psychosis. Transl. Psychiatry 7, e1195. doi:10.1038/tp.2017.168.

Mauri, M.C., Paletta, S., Maffini, M., Colasanti, A., Dragogna, F., Di Pace, C., Altamura, A.C., 2014. Clinical pharmacology of atypical antipsychotics: an update. EXCLI J. 13, 1163–1191.

Milev, P., Ho, B., Arndt, S., Andreasen, N.C., 2005. Predictive values of neurocognition and negative symptoms on functional outco .... Am. J. Psychiatry 162, 495–506. doi:10.1176/appi.ajp.162.3.495.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113. doi:10.1016/0028-3932(71)90067-4.

Pietrzak, R.H., Olver, J., Norman, T., Piskulic, D., Maruff, P., Snyder, P.J., 2009. A comparison of the CogState schizophrenia battery and the measurement and treatment research to improve cognition in schizophrenia (MATRICS) battery in assessing cognitive impairment in chronic schizophrenia. J. Clin. Exp. Neuropsychol. 31, 848–859. doi:10.1080/13803390802592458.

Pipitone, J., Park, M.T.M., Winterburn, J., Lett, T.A., Lerch, J.P., Pruessner, J.C., Lepage, M., Voineskos, A.N., Chakravarty, M.M.Alzheimer's Disease Neuroimaging, 2014. Multi-atlas segmentation of the whole hippocampus and subfields using multiple automatically generated templates. Neuroimage 101, 494–512.

Reitan, R.M., 1992. Trail Making Test: Manual for Administration and Scoring. Reitan Neuropsychology Laboratory.

Rimol, L.M., Hartberg, C.B., Nesvåg, R., Fennema-Notestine, C., Hagler, D.J., Pung, C.J., Jennings, R.G., Haukvik, U.K., Lange, E., Nakstad, P.H., Melle, I., Andreassen, O.A., Dale, A.M., Agartz, I., 2010. Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. Biol. Psychiatry 68, 41–50. doi:10.1016/j.biopsych.2010.03.036.

Shenton, M.E., Dickey, C.C., Frumin, M., McCarley, R.W., 2001. A review of MRI findings in schizophrenia. Schizophr. Res. 49, 1–52. doi:10.1016/S0920-9964(01)00163-3.

Stroop, J.R., 1935. Studies of interference in serial verbal reactions. J. Exp. Psychol. 18, 643–662. doi:10.1037/h0054651.

Van Der Werf, Y.D., Scheltens, P., Lindeboom, J., Witter, M.P., Uylings, H.B.M., Jolles, J., 2003. Deficits of memory, executive functioning and attention following infarction in the thalamus; a study of 22 cases with localised lesions. Neuropsychologia 41, 1330–1344. doi:10.1016/S0028-3932(03)00059-9.

Van Erp, T.G.M., Hibar, D.P., Rasmussen, J.M., Glahn, D.C., Pearlson, G.D., Andreassen, O.A., Agartz, I., Westlye, L.T., Haukvik, U.K., Dale, A.M., Melle, I., Hartberg, C.B., Gruber, O., Kraemer, B., Zilles, D., Donohoe, G., Kelly, S., McDonald, C., Morris, D.W., Cannon, D.M., Corvin, A., Machielsen, M.W.J., Koenders, L., De Haan, L., Veltman, D.J., Satterthwaite, T.D., Wolf, D.H., Gur, R.C., Gur, R.E., Potkin, S.G., Mathalon, D.H., Mueller, B.A., Preda, A., Macciardi, F., Ehrlich, S., Walton, E., Hass, J., Calhoun, V.D., Bockholt, H.J., Sponheim, S.R., Shoemaker, J.M., Van Haren, N.E.M., Pol, H.E.H., Ophoff, R.A., Kahn, R.S., Roiz-Santiaez, R., Crespo-Facorro, B., Wang, L., Alpert, K.I., Jönsson, E.G., Dimitrova, R., Bois, C., Whalley, H.C., McIntosh, A.M., Lawrie, S.M., Hashimoto, R., Thompson, P.M., Turner, J.A., 2016. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. Mol. Psychiatry 21, 547–553. doi:10.1038/mp.2015.63.

Vernon, A.C., Natesan, S., Modo, M., Kapur, S., 2011. Effect of chronic antipsychotic treatment on brain structure: a serial magnetic resonance imaging study with ex vivo and postmortem confirmation. Biol. Psychatry 69 (10), 936–944. doi:10.1016/j.biopsych.2010.11.010, May 15.

Wechsler, D., 1999. Wechsler Abbreviated Scale of Intelligence. The Psychological Corporation, San Antonio, TX.

Wechsler, D., 1997a. Adult Intelligence Scale, 3rd ed. The Psychological Corporation, San Antonio, TX.

Wechsler, D., 1997b. Wechsler Memory Scale, 3rd ed. The Psychological Corporation, New York.

Young, R., Biggs, J., Ziegler, V., Meyer, D., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 133, 429–435.