Schizophrenia Research 208 (2019) 114–123

Contents lists available at ScienceDirect

Schizophrenia Research

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

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

Alessia Di Sero [a,b,c,1], Kjetil N. Jørgensen [a,c,*,1], Stener Nerland [a,c], Ingrid Melle [c,d], Ole A. Andreassen [c,d], Jorge Jovicich [b], Ingrid Agartz [a,c,e]

[a] Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway
[b] Center for Mind and Brain Sciences, University of Trento, Trento, Italy
[c] Norwegian Centre for Research on Mental Disorders, K.G. Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Norway
[d] Norwegian Centre for Research on Mental Disorders, K.G. Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway
[e] Department of Clinical Neuroscience, Centre for Psychiatric Research, Karolinska Institutet, Stockholm, Sweden

ARTICLE INFO

Article history:
Received 11 December 2018
Received in revised form 27 March 2019
Accepted 2 April 2019
Available online 18 April 2019

Keywords:
Magnetic resonance imaging
Brain
Psychotic disorders
Corpus striatum
Dopamine

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

* Corresponding author at: Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway.
E-mail address: k.n.jorgensen@medisin.uio.no (K.N. Jørgensen).
[1] These authors contributed equally to the work.

https://doi.org/10.1016/j.schres.2019.04.002
0920-9964/

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