Schizophrenia Research xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Dorsal striatal volumes in never-treated patients with first-episode schizophrenia before and during acute treatment

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ARTICLE INFO

Article history:
Received 1 June 2015
Received in revised form 6 September 2015
Accepted 8 September 2015
Available online xxxx

Keywords:
Striatum
Caudate
Putamen
Antipsychotics
Schizophrenia

ABSTRACT

Background: Studies of pre-and post-treatment striatal volume in schizophrenia have reported conflicting results. *Materials and methods:* We assessed dorsal striatal (caudate and putamen) volumes bilaterally in 22 never-treated, non-substance-abusing patients with first-episode schizophrenia or schizophreniform disorder and 23 healthy controls matched for age, sex and educational status. Patients received either risperidone or flupenthixol long acting injection and were compared by structural MRI with controls at weeks 0, 4 and 13. T1-weighted data on a 3T MRI scanner were obtained and images were reconstructed using FreeSurfer. Treatment outcome was assessed by changes in psychopathology, insight, functionality, cognitive performance and motor symptoms. *Results:* Caudate, but not putamen volumes was significantly larger in patients bilaterally at baseline ($P = 0.01$). Linear mixed effects repeated measures found no significant group × time interactions for any of the regions. Caudate volume was not significantly associated with improvements in psychotic symptoms. Also, the findings of a regression model were inconsistent insofar as larger caudate volume was associated with less improvement in depression scores, greater improvement in functionality and greater improvement in verbal learning but less improvement in reasoning and problem solving (left caudate) and composite cognitive score (right caudate). *Conclusions:* The increased caudate volumes prior to treatment are contrary to previous reports in never-treated patients with first-episode schizophrenia, and together with our failure to demonstrate volume changes related to acute treatment, call into question previous proposals that enlarged caudate volume is a consequence of antipsychotic treatment.

1. Introduction

Striatal dysfunction is a fundamental component of the neurobiology of schizophrenia, with elevated striatal dopamine synthesis considered the best replicated dopaminergic abnormality in schizophrenia (Howes and Kapur, 2009). Structural imaging studies of striatal volume have however reported inconsistent results, although systematic reviews have concluded that striatal volume is likely decreased in unmedicated patients with first-episode schizophrenia, whereas studies in chronic, medicated samples mostly report striatal volume increases (Brandt and Bonelli, 2008; Ellison-Wright et al., 2008). Also, results from longitudinal studies suggest that antipsychotic treatment may be associated with striatal volume increases (Brandt and Bonelli, 2008; Haijma et al., 2013) although this is equivocal, and does not seem to be not specific to first generation antipsychotics, as originally proposed (Ebdrup et al., 2013).

In this study, we investigated dorsal striatal (caudate and putamen) volumes in a sample of 22 never-treated patients with first-episode schizophrenia at baseline, and after 4 and 13 weeks of antipsychotic treatment. A healthy control group ($n = 23$) matched for age, sex and educational status was included. We selected treatment naïve patients with a first-episode of schizophrenia to avoid the potential confounding influences of disease chronicity and previous antipsychotic usage. Moreover, by using depot antipsychotics we avoided the confounding effect of covert non-adherence. We also took care to exclude patients with substance abuse and comorbid psychiatric and general medical conditions. Based on previous literature, we hypothesised that patients would have smaller caudate volumes and normal putamen volumes at baseline and that these volumes would increase during the course of antipsychotic treatment. We further hypothesised that striatal volumes would be associated with changes in psychopathology, cognitive performance and functional outcome during the treatment period.

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http://dx.doi.org/10.1016/j.schres.2015.09.014
0920-9964/

2. Materials and methods

2.1. Study design

This was a single-site study conducted over 13 weeks of standardised treatment in antipsychotic-naive patients with a first-episode of schizophrenia. The study was initially conducted as a randomised, double-blinded, controlled trial to compare risperidone long acting injection and flupenthixol decanoate. However, no treatment x group effects were demonstrated in any of the MRI measures so treatment groups were pooled, and compared with the healthy controls for all of the subsequent analyses.

2.2. Participants

Patients were recruited from in- and outpatient facilities at Stikland and Tygerberg Hospitals and surrounding community clinics, in Cape Town, South Africa. They were carefully screened and those who met inclusion criteria were invited to participate in the study. Written, informed consent was obtained from participants and if available, from a family member after complete description of the study. In the case of minors, written assent was obtained as well as parental consent. Inclusion criteria were: male or female; in- or outpatients; aged 16 to 45 years; Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, text revision (DSM-IV) (American Psychiatric Association, 2000) diagnosis of schizophreniform disorder or schizophrenia; no previous exposure to antipsychotic medication; and right handedness. Exclusion criteria were: substance abuse in the previous 6 months (ascertained by patient and carer interrogation, or a positive urine test at baseline or any of the subsequent visits), significant general medical condition, and mental retardation (IQ < 70).

A group of healthy controls was also recruited for the MRI scans and cognitive testing. They were matched to the patients by age, sex, ethnicity and educational status. They were recruited from non-medical staff in the hospital and their relatives and acquaintances, and from independent sources in the community. They were excluded if they reported a history of mental illness, previous treatment with psychotropic medication or substance abuse, or were not right handed. The study was approved by the Committee for Human Research, Faculty of Health Sciences, University of Stellenbosch. The study was registered at the South African National Clinical Trials Register (DOH-27–0710–1808) and was conducted in accordance with International Conference on Harmonisation guidelines on good clinical practise (International Conference on Harmonization., 1996).

2.3. Assessments

Investigators were physicians who were trained in the use of the key assessment instruments, and inter-rater reliability testing was conducted periodically (intraclass correlation 0.7 or greater). Patients and controls were assessed by means of the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1994). Diagnosis was made by one of the psychiatrists and confirmed by consensus at regular team meetings including several experienced psychiatrists. Efficacy assessments included the PANSS (Kay et al., 1987), Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993), Social and Occupational Functioning Assessment Scale (SOFAS) (American Psychiatric Association, 2000), and the Birchwood Insight Scale (BIS) (Birchwood et al., 1994). For cognitive assessments, we used the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein and Green, 2006), which was administered by trained M-level psychologists. Motor side-effects were assessed by the Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard and Margolese, 2005). A physical examination was conducted at baseline and urine screening tests for amphetamines, cannabis and methaqualone were performed at each visit. Participants underwent imaging at weeks 0 (prior to antipsychotic administration), 4 and 13. PANSS, CGI, CDSS and ESRS were assessed at two-weekly intervals. SOFAS, and BIS were performed at weeks 0 and 13.

2.4. Treatment

Patients were randomised to either risperidone or flupenthixol treatment. There was a one week lead-in period of oral risperidone or flupenthixol 1 to 3 mg/day followed by long acting injections every 2 weeks for 12 weeks. Oral risperidone was continued for 3 weeks after the first injection due to its delayed time to attainment of therapeutic levels. The starting doses were 25 mg 2-weekly for long-acting risperidone and 10 mg 2-weekly for flupenthixol decanoate. Additional oral antipsychotic medication was permitted at the discretion of the investigator. Permitted concomitant treatment included medication for general medical conditions, lorazepam for sedation, orphenadrine or biperiden for extrapyramidal symptoms and propranolol for akathisia. No benzodiazepines, propranolol or anticholinergics were permitted in the 12 h prior to assessments. Medications not permitted included other antipsychotics, mood stabilisers and psychostimulants.

2.5. Imaging methods

2.5.1. MRI-acquisition

We acquired high-resolution T1-weighted data on a research-dedicated 3T Siemens Allegra MRI scanner (Erlangen, Germany) with the following acquisition parameters: MPRAGE sequence, 2080 ms repetition time; 4.88 ms echo time, Field of view: 230 mm, 176 slices, 0.9 mm X 0.9 mm X 1 mm voxel size. All of the scans were screened for intracranial pathology by a radiologist and inspected for motion artefacts.

2.5.2. MRI preprocessing

Scans were processed and analysed using FreeSurfer stable release version 5.1. (http://surfer.nmr.mgh.harvard.edu/) to measure a priori regions of interests (ROIs), namely left and right caudate and putamen volumes. Details of these procedures have been previously described (Dale et al., 1999). Briefly, slices were resampled to a three-dimensional image with 1 mm isotropic voxels. Non-uniform intensity normalisation was then performed and images were registered to the Montreal Neurological Institute space. A second normalisation step was performed with a different algorithm in which control points were automatically identified and normalised to a standard intensity value. This was followed by an automated skull strip procedure. Global brain anatomy was then delineated into cortical and subcortical labels. Reconstructions were performed with custom batching scripts, on the Centre for High Performance Computing, Rosebank, Cape Town, Sun Intel Nehalem cluster (http://www.chpc.ac.za/). All data were visually inspected for errors in Talairach transformation, skull strip, final segmentations as well as the within subject-registrations. We undertook detailed quality checking. Any errors were corrected manually and re-inspected.

2.6. Statistical methods

Analyses were performed on a modified intent-to-treat basis, meaning that participants were included in the analysis if they had a baseline and at least one post-baseline MRI measure. We employed linear mixed effect models for continuous repeated measures (MMRM) to compare changes in striatal volumes over time between the patients and controls. Visit-wise changes in caudate and putamen volumes bilaterally were compared between patients and controls using a model that included fixed terms of age, gender, intracranial volume, group, time and all interaction effects. Comparisons between patients and controls for baseline caudate and putamen volumes were derived from the post-hoc Fisher's Least Significant Difference (LSD) tests. We applied false discovery rate (FDR) adjustment of significance value according

Please cite this article as: Emsley, R., et al., Dorsal striatal volumes in never-treated patients with first-episode schizophrenia before and during acute treatment, Schizophr. Res. (2015), http://dx.doi.org/10.1016/j.schres.2015.09.014