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Changes in brain regions associated with food-intake regulation, body mass and metabolic profiles during acute antipsychotic treatment in first-episode schizophrenia

Robin Emsley [a,*], Laila Asmal [a], Bonginkosi Chiliza [a], Stefan du Plessis [a], Jonathan Carr [b], Martin Kidd [c], Anil K Malhotra [d], Matthijs Vink [e], Rene S. Kahn [e]

[a] Department of Psychiatry, Faculty of Medicine and Health Sciences, Stellenbosch University, PO Box 19063, Tygerberg 7505, Cape Town, South Africa
[b] Division of Neurology, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, Cape Town, South Africa
[c] Centre for Statistical Consultation, Stellenbosch University, South Africa
[d] Division of Psychiatric Research, The Zucker Hillside Hospital, Glen Oaks, NY, USA
[e] Department of Psychiatry, University Medical Centre Utrecht, The Netherlands

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ABSTRACT

We investigated whether morphological brain changes occurred in brain regions associated with body-weight homeostasis during acute antipsychotic treatment, and if so, whether they were related to changes in body mass and metabolic profile. Twenty-two antipsychotic-naive patients with first-episode schizophrenia received either risperidone long acting injection or flupenthixol decanoate over 13 weeks and were compared by structural MRI with 23 matched healthy volunteers at weeks 0, 4 and 13. Images were reconstructed using freesurfer fully-automated *whole brain segmentation*. The ventral diencephalon and prefrontal cortex were selected to represent the homeostatic and hedonic food intake regulatory systems respectively. Body mass was measured at weeks 0, 7 and 13 and fasting glucose and lipid profiles at weeks 0 and 13. Linear mixed effect models indicated significant group*time interactions for the ventral diencephalon volumes bilaterally. Ventral diencephalon volume reduction was strongly correlated bilaterally with body mass increase and HDL-cholesterol reductions, and unilaterally with blood glucose elevation. There were no significant changes in prefrontal cortical thickness. These findings implicate the ventral diencephalon, of which the hypothalamus is the main component, in the acute adipogenic and dyslipidaemic effects of antipsychotic medication.

1. Introduction

Imaging studies have consistently demonstrated global and regional structural brain abnormalities in people with schizophrenia (Haijma et al., 2013). While some abnormalities are present at, and prior to the onset of first psychotic symptoms, longitudinal studies have established that progressive changes also occur (Olabi et al., 2011). These changes may represent illness progression (Lieberman et al., 2001), although some evidence suggests that they are related to antipsychotic treatment per se (Ho et al., 2011; Andreasen et al., 2013; Fusar-Poli et al., 2013). A few studies have investigated the acute treatment effects in first-episode samples, and although the findings are inconsistent they report regional brain morphological changes during this period (Massana et al., 2005; Lieberman et al., 2005; Girgis et al., 2006; Glenthoj et al., 2007; Li et al., 2012; Szeszko et al., 2014). A direct relationship to antipsychotic treatment is suggested by the finding that some of these changes were significantly correlated with antipsychotic efficacy, with improvements in psychopathology being associated with increased volumes in several brain regions (Lieberman et al., 2005; Li et al., 2012; Goghari et al., 2013), a finding which is contrary to longer term studies describing reductions in brain volumes.

Just as some brain changes are related to efficacy, it is possible that others are related to the adverse effects of antipsychotic medication. Of particular interest here is the well-recognized adipogenic effect of antipsychotic medication. Weight gain is evident in the first few weeks of antipsychotic treatment and continues during the following months (Tarricone et al., 2010). While the pathogenesis of weight gain associated with antipsychotic treatment is poorly understood, weight gain per se generally results from an imbalance between energy intake and expenditure. The brain plays a fundamental role in regulating food intake by means of two major systems, the homeostatic and the non-homeostatic, or hedonic

* Correspoding author: Fax: +27 21 9389738.

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systems. The homeostatic system controls appetite and the hypothalamus, located in the ventral diencephalon, has been identified as a critical anatomical site with cells able to monitor changes in energy status and trigger appropriate responses. The hedonic system comprises mesocorticolimbic pathways including the prefrontal cortex, and is important for the cognitive and motivational aspects of eating such as prior experience with food, reward and emotion, and the social and environmental context of eating (Berthoud and Morrison, 2008; Marques-Iturria et al., 2013). Significant associations between brain volume and body mass are well described, with cortical and subcortical gray matter reductions having been associated with increased BMI (Taki et al., 2008). While some studies report widespread cortical thinning in obesity (Taki et al., 2008), the majority point to reduced frontal cortical gray matter volumes being specifically associated with increased BMI, thereby implicating the hedonic regulatory system (Walther et al., 2010; Marques-Iturria et al., 2013; Kurth et al., 2013; Brooks et al., 2013). For subcortical regions, several studies conducted in obese and non-obese healthy subjects found an association between increased body mass and reduced hypothalamic or ventral diencephalic (DC) volume, suggesting involvement of the homeostatic system (Marques-Iturria et al., 2013; Kurth et al., 2013; Ha et al., 2013).

We investigated whether morphological changes occurred in brain regions associated with homeostatic and hedonic food intake regulation during acute antipsychotic treatment, and if so, whether they were related to changes in body weight and metabolic profiles. We hypothesized that volume reductions would occur in brain regions related to these systems, and that the reductions would be associated with weight gain and changes in metabolic profiles.

2. Method

This single-site study was conducted over 13 weeks of standardised treatment in antipsychotic-naive patients with the first-episode of schizophrenia. The study was originally conducted as a randomised, double-blinded, controlled trial. We planned to compare the acute brain morphological changes associated with treatment with a first generation vs. a second generation antipsychotic. Because weight-gain and metabolic dysregulation has been associated more with the latter agents it would be expected that changes in brain regions associated with food intake would be more prominent in this group. We selected risperidone long acting injection and flupenthixol decanoate as what we regarded as the best representatives of these groups that were available in long-acting injection formulations at the time of the study. Using depots meant that the confounding effect of covert non-adherence was removed. There was a significant group*time effect for weight ($F(2, 35)=6.0760$, $p=0.005$), with risperidone treated patients gaining relatively more weight. However, no treatment group effects were demonstrated for any of the metabolic indices or any of the MRI measures. Therefore, the results from both groups were pooled and compared to a matched group of healthy volunteers for this post-hoc analysis. The study was approved by the Committee for Human Research, Faculty of Health Sciences, University of Stellenbosch and was registered at the South African National Clinical Trials Register (DOH-27-0710-1808)

URL: www.sanctr.gov.za/SAClinicalTrials/tabid/169/Default.aspx

2.1. Participants

Patients were recruited from in- and outpatient facilities at Stikland and Tygerberg Hospitals and surrounding community clinics in Cape Town, South Africa between January 2009 and March 2011. 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 where appropriate, from a family member. 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 (DSM-IV) diagnosis of schizophreniform disorder or schizophrenia; no previous exposure to antipsychotic medication; right handedness. Exclusion criteria were: Substance abuse in the previous 6 months, significant general medical condition and mental retardation.

A group of healthy controls, matched to the patients by age, sex, ethnicity and educational status, was also recruited for the MRI scans. These controls were recruited from non-medical staff in the hospitals 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, substance abuse or were not right handed.

2.2. Assessments

A physical examination was conducted at the start and completion of the study. For body mass measurements patients removed all surplus clothing including their shoes and socks and were weighed on an electronic scale that was regularly calibrated throughout the study. Height was measured with a prefixed, wall-mounted measuring tape. Laboratory tests comprised fasting glucose, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides, and total cholesterol. For these tests patients fasted for at least 8 h overnight and rested for 10 min prior to venipuncture. Laboratory tests were performed by a single laboratory. Patients and controls underwent imaging at weeks 0, 4 and 13. For the patients, weight was measured at week 0, 7 and 13 and laboratory tests were performed at weeks 0 and 13. Patients were also comprehensively assessed for psychopathology (including the Positive and Negative syndrome Scale (PANSS) (Kay et al., 1987)), cognitive and functional outcomes. These results will be reported separately.

2.3. Treatment

Patients were randomised to either risperidone or flupenthixol treatment. There was a one week lead-in period of oral risperidone or flupenthixol 1–3 mg/day followed by two-weekly long acting injections for 12 weeks. Oral risperidone was continued for a further 3 weeks due to the delayed onset of action of long-acting risperidone. The starting doses were 25 mg IMI 2-weekly for long-acting risperidone and 10 mg IMI 2-weekly for flupenthixol decanoate. Additional oral risperidone or flupenthixol was prescribed 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 taken in the 12 h prior to assessments. Medications not permitted included other antipsychotics, mood stabilizers and psychostimulants.

2.4. Imaging methods

2.4.1. MRI-acquisition

We acquired high-resolution T1-weighted data on a 3 T 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, $0.9 \times 0.9 \times 1$ mm^3 voxel size. All of the scans were screened for intracranial pathology by a radiologist and inspected for motion artefacts.