

# A longitudinal study on the effects of typical versus atypical antipsychotic drugs on hippocampal volume in schizophrenia

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## Abstract

**Background:** Previous studies have reported that hippocampal volumes correlate with symptom severity in schizophrenia. This longitudinal study measured changes in symptoms and hippocampal volume in patients switched from typical antipsychotics to olanzapine.

**Methods:** MRI scans were acquired from patients with chronic schizophrenia ( $n=10$ ) and healthy volunteers ( $n=20$ ). At baseline, patients were treated with typical antipsychotics for at least one year, then switched to olanzapine, and rescanned approximately one year later.

**Results:** Olanzapine treatment resulted in no significant change in right or left hippocampal volume. Individual changes in right hippocampal volume correlated significantly with changes in symptoms.

**Conclusions:** Hippocampal volume change may serve as a marker of symptom change in patients on olanzapine.

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**Keywords:** Antipsychotics; Hippocampus; Longitudinal study; Magnetic resonance imaging; Olanzapine; Schizophrenia

## 1. Introduction

Hippocampal dysfunction contributes to impaired information processing and psychotic symptoms (Antonova et al., 2004; Heckers and Konradi, 2002; Roberts,

1990). Reductions in hippocampal volume are amongst the more robust findings from neuroimaging studies of schizophrenia (Honea et al., 2005; Wright et al., 2000), and volumes correlate with symptom severity (Kuroki et al., 2006; Rajarethinam et al., 2001). The pathogenesis of hippocampal abnormalities in schizophrenia remains uncertain, although both antipsychotic drug treatment and the intrinsic disease process are factors (Chakos et al., 2005).

Multiple studies have demonstrated that antipsychotics induce consistent volumetric changes in brain areas that include the basal ganglia and thalamus (Khorram et al., 2006; Lang et al., 2006, 2004; Scherk and Falkai, 2006). However, data regarding the effects of typical and atypical

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antipsychotic medications on hippocampal volume are equivocal (Chakos et al., 2005; Velakoulis et al., 2006). To date, there are no longitudinal studies examining changes in hippocampal volume in response to switching from typical to atypical antipsychotics, or comparing changes in hippocampal size with changes in symptoms of schizophrenia.

To address these issues, we examined hippocampal volumes in a cohort of schizophrenia patients treated with typical antipsychotics at baseline and one year later after switching to olanzapine, and also compared them to healthy volunteers. We hypothesized that patients would have smaller hippocampal volumes at baseline and that these volumes would increase after switching to olanzapine. We also predicted that any increases in hippocampal volume would be related to decreased symptom severity.

## 2. Materials and methods

### 2.1. Participants

Subjects were patients with chronic schizophrenia (seven men, three women) and healthy volunteers (ten men, ten women). Schizophrenia was diagnosed according to DSM-IV criteria following interview and chart review (Khorram et al., 2006). Exclusion criteria were a history of significant head injury or loss of consciousness exceeding 5 min, a history of seizure disorder or a family history of psychotic disorders (healthy volunteers only), and presence of substance abuse according to DSM-IV criteria. The Dalhousie University Research Ethics Committee approved this study and all subjects provided written approval after a full explanation of the procedures.

### 2.2. Treatment and clinical measures

Clinical assessment included the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). At baseline, patients were previously treated with typical antipsychotic medications continuously for at least one year. After baseline clinical assessments were completed, patients were scanned, switched to olanzapine, and reassessed approximately one year later. Healthy subjects were scanned in parallel.

### 2.3. MRI acquisitions and measurement protocol

A coronal inversion recovery sequence, acquired perpendicular to the left Sylvian fissure to optimize hippocampal viewing, was obtained on a Siemens

Magnetom Vision 1.5T MRI scanner: TR/TE=2000/20 ms, field of view=200 cm, matrix size=168×256, pixel size=1.04×0.78 mm, slice thickness=4 mm, interslice gap=1 mm, and 18 slices total. Two raters (W.J.P. and G.N.S.), blind to diagnosis, gender, and time of scan, performed area and volumetric measures using interactive shareware (NIH Image, Version 1.62) (Rasband, 1997). Manual measurement of the hippocampus started at the first slice where the mamillary bodies were clearly visualized as per previously established protocols (Geuze et al., 2005a; Giedd et al., 1996). At this level the hippocampal alveus was reliably distinct and delineated the hippocampal–amygdala border. The subiculum and fimbria were included in the measurements. The white matter separating the hippocampus and parahippocampal gyrus defined the inferior border. The CSF of the uncus and ambient cisterns served as the medial border for the tracings. Temporal horns of the lateral ventricles or the temporal stem defined the lateral boundary of hippocampus. All of the above boundaries are common landmarks used in previous hippocampal volume studies (see Geuze et al., 2005a,b for review). Measurements continued posterior for a further three slices corresponding to a total length of 20 mm. The posterior tail of the hippocampus was not measured in this study.

Area measurement of each slice was the mean of four independent trials. The sum of the areas of each side was multiplied by 5 mm (4 mm slice thickness plus 1 mm interslice gap) to obtain right and left hippocampal volumes. Total brain volumes were manually measured from axial sequences (Lang et al., 2001). Inter-rater reliability for hippocampal (W.J.P. and G.N.S.) and total brain volumes (B.K. and D.J.L.) was high (ICC hippocampus=0.90, ICC total brain volume=0.99).

### 2.4. Data analysis

A repeated-measures analysis of variance (ANOVA) was used to determine whether hippocampal volume was smaller in subjects with schizophrenia, and whether hippocampal volume increased after olanzapine treatment. Group (schizophrenia, healthy) and gender were the between subject factors; age and total brain volume the covariates, and time (baseline, follow up) the within-subject factor. The effect size of differences was calculated using Cohen's *d*-statistic (mean control minus schizophrenia, divided by pooled standard deviation). Overall differences in PANSS scores between baseline and follow up were assessed using a paired *t*-test. We also conducted a partial correlation analysis to compare changes in

symptoms (percent change in PANSS scores, using 0–6 scoring) to change in hippocampal volumes, controlling for total brain volume and age.

### 3. Results

Subject demographic data was previously reported (Lang et al., 2004). Briefly, all subjects were right handed. Age differed between groups, with the schizophrenia group significantly older (35.3 years, SD 8.8 versus 23.5 years, SD 7.7:  $t=3.94$ ,  $df=28$ ,  $p=0.0005$ ). When a subset of the 10 older controls was compared with the 10 schizophrenia subjects, there was no significant difference in age ( $t=1.43$ ,  $df=18$ ,  $p=0.16$ ). The mean education of the schizophrenia group (11.7 years, SD 3.7) did not differ from controls (13.7 years, SD 3.8;  $t=1.38$ ,  $df=27$ ,  $p=0.18$ ). Educational data was missing on one volunteer.

At baseline, the total hippocampal volume in the age-matched subset of subjects was 3.9% smaller in the schizophrenia group (effect size  $-0.35$ ), with a greater

difference on the left (8.6% smaller, effect size  $-0.74$ ) than the right (0.6% larger, effect size  $=0.05$ ). In this small sample, neither difference was statistically significant. There was no statistically significant diagnosis-by-time interaction for either the left, or the right hippocampal volumes, disconfirming our hypothesis that hippocampal volumes would increase in the patient group after the switch to olanzapine (see Fig. 1A).

Subjects with schizophrenia were symptomatic but stable at baseline (mean total PANSS score=70), with no significant improvement in mean total or subscale PANSS scores at follow-up ( $p>0.20$ – $0.52$ ). However, closer inspection of the data revealed considerable individual variability in PANSS scores between evaluations. Interestingly, there was an association between change in individual hippocampal volume on the right and change in total PANSS score (Fig. 1B). This was not the case for volume changes on the left (data not shown). Partial correlation analysis between changes in volume on the right and total PANSS score was statistically significant (partial correlation  $-0.74$ ,

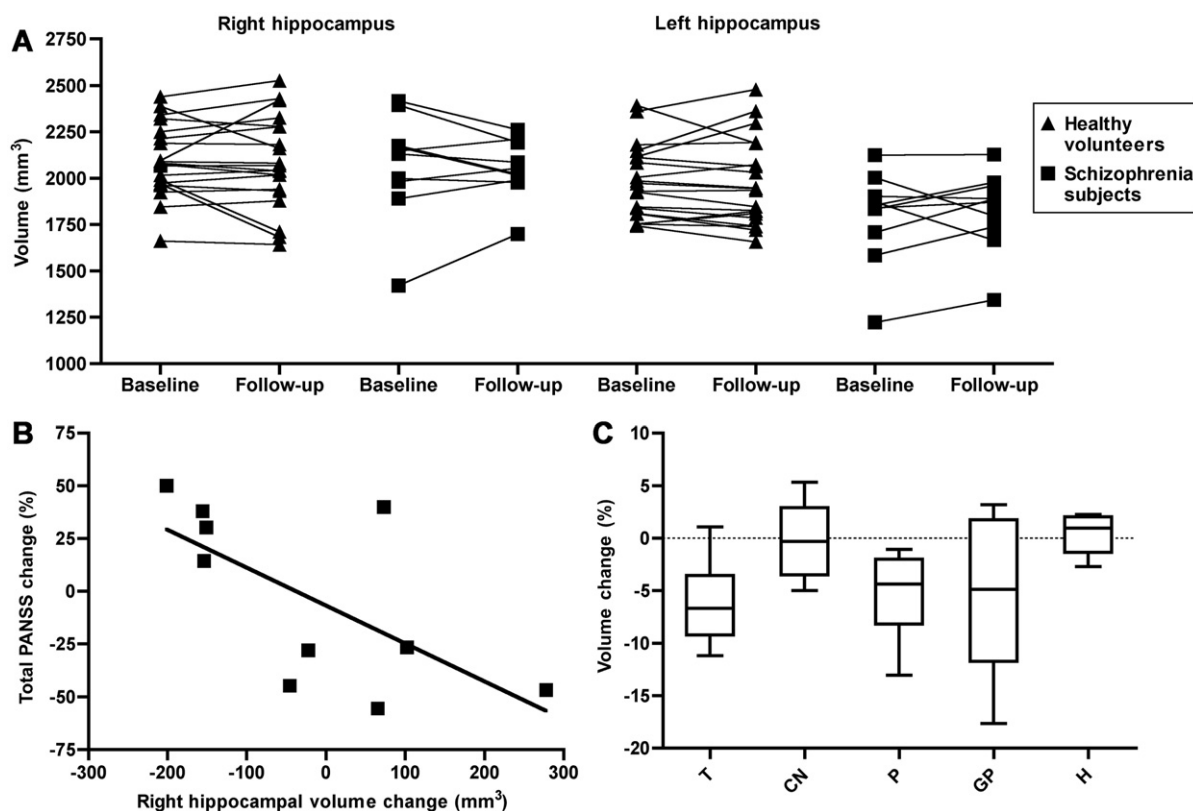


Fig. 1. (A) Baseline and follow-up hippocampal volumes of healthy volunteers and subjects with chronic schizophrenia. (B) Relationship between percent change in total PANSS and change in right hippocampal volume. (C) Percent change in volumes of various brain regions after olanzapine treatment (T, thalamus; CN, caudate nucleus; P, putamen; GP, globus pallidus; H, hippocampus).

$p=0.03$ ), controlling for age and total brain volume (Fig. 1B). Correlation coefficients for positive and negative symptom change and volume change were not statistically significant.

#### 4. Discussion

In this study, we assessed hippocampal volume in patients with schizophrenia who were switched from typical antipsychotics to olanzapine. Bilateral hippocampal volumes did not change significantly, disconfirming our hypothesis that hippocampal volume would increase after olanzapine treatment. Interestingly, there was a significant association between individual changes in right hippocampal volume and changes in symptoms. Decreases in right hippocampal volume were significantly correlated with worsening of symptoms, whereas increases in right hippocampal volume were associated with improvement.

The finding that treatment with olanzapine had no overall effect on hippocampal volume is consistent with a cross-sectional study, which reported no difference in hippocampal volume in schizophrenia subjects taking typical versus atypical antipsychotic drugs (Velakoulis et al., 2006). In another cross-sectional study (Chakos et al., 2005), patients with schizophrenia or schizophreniform disorder were subdivided into early illness and chronic groups. Atypical antipsychotics (olanzapine and risperidone) were associated with larger hippocampal volumes only in the early illness group. No effect was noted in the chronic patients, and neither study addressed the relationship of individual symptoms to hippocampal size.

The present finding of a significant association between right hippocampal volume change and symptomatology is novel. Decreases in right hippocampal volume may be progressive and parallel disease duration, while changes in left hippocampal volume tend to occur early in schizophrenia and thereafter remain stable (Geuze et al., 2005b; Velakoulis et al., 2006). This delayed reduction of right hippocampal volume may help explain the laterality of our findings. To our knowledge, only one other longitudinal medication switch study showed a relationship between volumetric changes of any brain region and symptom changes (Scheepers et al., 2001). After switching from typical antipsychotics to clozapine, significant reductions in left caudate volume were correlated with reduced symptoms (Scheepers et al., 2001).

We previously reported volumes of globus pallidus, putamen, and thalamus were significantly decreased, or “normalized”, after the olanzapine switch in the present

sample (Fig. 1C, see Lang et al., 2004; Khorram et al., 2006 for details). These brain regions all have a relatively high dopamine D<sub>2</sub> receptor density, compared to the hippocampus. Most studies indicate that antipsychotic drugs with a higher D<sub>2</sub> receptor affinity, which includes typical antipsychotics, are more likely to cause enlargement. By contrast, olanzapine causes no change, or a small decrease in volume, of these areas (Andersson et al., 2002; Lang et al., 2004). A D<sub>2</sub> receptor-dependent mechanism could account for the absence of hippocampal volume decreases. Hippocampal volume changes may be more related to the disease process rather than its treatment. Pathogenic factors could include glucocorticoids, as high levels of cortisol correlate with symptom severity (Tandon et al., 2000), and are hypothesized to contribute to hippocampal atrophy (Tata et al., 2006).

This study used scans acquired between 1995 and 2001, using a protocol for presurgical planning for refractory epilepsy. The 4mm MRI slice thickness, and the limited number of slices analyzed (four) may make our measurements more prone to errors from a single false estimate. These scans were not acquired for 3D analysis, and imposing this strategy would necessitate interpolation of data points, introducing a new source of error. The present study is also limited by small sample size, although it was adequately powered to detect significant differences in other brain regions (Fig. 1C) (Khorram et al., 2006; Lang et al., 2004). Future studies with larger patient cohorts and in different points in the illness are needed to extend these novel findings.

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#### Contributors

Authors W.G. Honer and L.C. Kopala designed the study and wrote the protocol. L.C. Kopala enrolled and followed the patients for clinical outcome. R.A. Vidorpe analyzed the MRI scans for suitability of inclusion (quality, presence of evident radiological abnormality). W.J. Panenka performed the measurements, managed the literature searches and wrote the first draft of the manuscript. G.N. Smith designed the measurement approach and performed reliability checks. B. Khorram, A.M. Barr and D.L. Lang managed and analyzed data. All authors contributed to and have approved the final manuscript.

### Conflict of Interest

Dr. Honer reports receiving consulting fees or sitting on paid advisory boards for In-silico, Wyeth, Janssen and AstraZeneca, receiving lecture fees from Janssen and AstraZeneca, and educational grant support from Janssen, Eli Lilly and AstraZeneca.

Dr. Kopala reports sitting on paid advisory boards for AstraZeneca and Pfizer and receiving lecture fees from Janssen, AstraZeneca, and Pfizer. No other authors report any potential conflicts of interest.

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