

Contrasting effects of haloperidol and lithium on rat brain structure: a serial MRI study

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INTRODUCTION

• Chronic antipsychotic drug treatment may contribute to regional brain volume changes detected by magnetic resonance imaging (MRI) studies in Schizophrenia patients¹

• In contrast, MRI studies in Bipolar disorder suggest Lithium treatment is associated with increases in regional brain volumes²

HYPOTHESIS

Chronic treatment with antipsychotic drugs or lithium chloride results in contrasting effects on brain structure.

METHODS

Experimental design

To confirm this effect we implemented a model in rats combining serial *in vivo* MRI with clinically relevant drug doses.³ Haloperidol (HAL, 0.5 and 2 mg/kg/day), Lithium Chloride (2 mM equiv/kg/day) or common vehicle (β -hydroxypropylcyclodextrin, 20% wt/vol / ascorbic acid, pH 6) were continuously administered to male sprague-dawley rats (240-250 g, 9 weeks of age, $n=10$ per group) subcutaneously via osmotic mini-pumps for 8 weeks (wks). Animals then continued a further 8 wks without drug treatment to examine the effect of drug withdrawal on brain structure.

MRI (in vivo)

T₂W MR images (FSEMS: FOV: 30x30mm; matrix 128x128; TR = 4200 ms, TE = 60 ms), 4 averages; slice thickness 0.6 mm; 16 min) were acquired using a small horizontal bore 7.0 T MRI scanner (Varian, Oxford, UK). MR scans were acquired at baseline, after 8 wks drug treatment and 8 wks drug withdrawal, respectively.

Manual volumetry

Whole brain (WBV), total intracranial (TIV), cerebral cortex (CTX), corpus striatum (STR), lateral ventricle (LV) and hippocampus (HPC) volumes were manually segmented in JIM v5.0 software (Xinapse systems, UK) by two independent raters (ACV & SN) blinded to treatment group. (inter-rater reliability >0.9)

Post-mortem analysis

Serial coronal sections (40 μ m, interval 1/12) were cut on a freezing microtome, mounted on slides and nissl stained. The volume of the cortex and striatum were calculated using the Cavalieri probe method by a single operator (ACV) blinded to treatment group.

Data and statistical analysis

Statistics were performed using SPSS 19.0 software (SPSS Inc., Chicago, Illinois). Longitudinal assessment of variables was performed using two-way repeated measures analysis of variance (ANOVA) with one between-subject factor (treatment) and one within-subject factor (time) followed by *post hoc* Bonferroni evaluation.

RESULTS

Chronic HAL or lithium treatment results in contrasting, reversible region-specific effects on brain structure

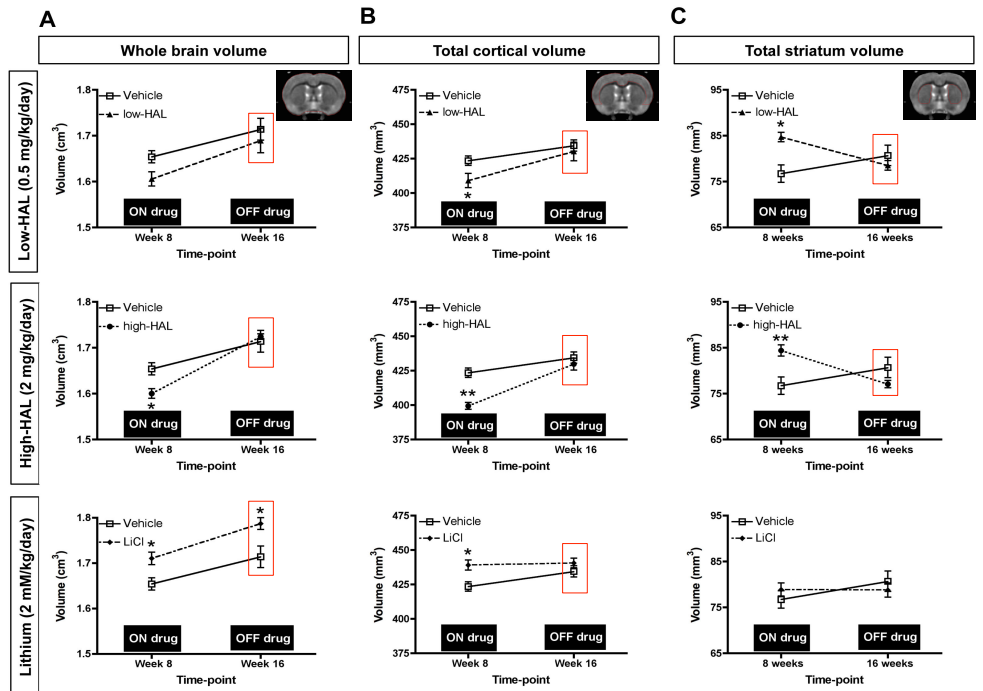


Figure 1. Contrasting effects of chronic HAL and Li treatment on whole brain, cortical and striatal volume. Before administration of drugs, there were no significant differences in brain volumes. Chronic HAL induced dose-dependent decreases in (A) the volume of the whole brain, (B) cortical volume, but induced hypertrophy of the striatum (C). (* $p<0.05$; ** $p<0.01$ HAL vs. vehicle). Brain volume changes induced by HAL were reversed on drug withdrawal. In contrast, chronic Li treatment induced an increase in (A) whole brain volume, (B) cortical volume, but had no effect on the striatum (C). Li-induced changes in whole brain volume were maintained after drug withdrawal whilst the cortical volume increase normalized. Neither drug affected TIV, HPC or LV volume (*data not shown*).

In vivo MRI data were confirmed histologically

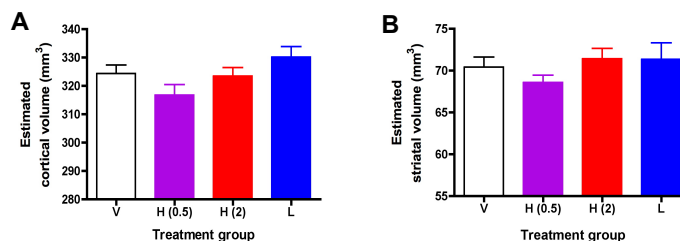


Figure 2. Cavalieri estimates of (A) cortex and (B) striatal volume confirm *in vivo* MRI data.

CONCLUSIONS

• Chronic treatment with clinically relevant doses of HAL and Li results in contrasting, region-specific effects on brain volume, consistent with data reported from clinical MRI studies. Psychotropic drug exposure may contribute to brain morphological changes in Schizophrenia and Bipolar disorder

• The effects of HAL appear to be reversible following drug withdrawal, whilst some, but not all, effects of Li persist

• This model offers a tractable system to investigate the neurobiology underlying brain volume changes induced by psychotropic drug treatment

REFERENCES 1. Ho et al., 2011. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first episode schizophrenia. *Arch Gen Psych*. 68(2): 128-37. 2. Hallahan et al., Structural magnetic resonance imaging in bipolar disorder: an international collaborative mega-analysis of individual adult patient data. *Biol. Psych*. 69(4):326-35. 3. Vernon et al., 2011. Effect of chronic antipsychotic treatment on brain structure: a serial magnetic resonance imaging study with *ex vivo* and *postmortem* confirmation. *Biol. Psych*. 69(10):936-44.