Changes in brain volume in response to estradiol replacement, amphetamine sensitization and haloperidol treatment in awake female rats

Dan Madularu1, Praveen Kulkarni, Craig F. Ferris, & Wayne G. Brake

1 Department of Psychology and Center for Studies in Behavioural Neurobiology, Concordia University, Montreal, QC
2 Brain Imaging Centre, Department of Psychiatry, McGill University, Montreal, QC
3 Department of Psychology and Center for Translational Neuro-imaging, Northeastern University, Boston, MA

Background

Sex differences in schizophrenia are well established, implicating gonadal hormones in schizophrenia pathophysiology. In addition, women differ in symptom severity depending on phase of menstrual cycle. We have recently shown that blood-oxygen-level dependent (BOLD) activity in response to amphetamine (AMPH) is mediated by estradiol (E2) levels in sensitized rats, with high E2 rats showing the largest activation. Similarly, Sarvari et al. (2014) showed an increased BOLD response in the prefrontal cortex (PFC) and ventral tegmental area (VTA) in ovariectomized female rats receiving estrogen receptor agonist replacement compared to control. Finally, hippocampal volume changes throughout the estrous cycle have been reported, with proestrus (a period of high levels of estrogen), mice showing increased volume compared to estrous mice, when estrogen levels are low.

We hypothesized that repeated exposure to AMPH would increase the volumes of select regions of interest (ROIs), such as the hippocampal formation as well as components of the DA mesocortical circuit. Furthermore, we expected the highest volumetric increases in animals receiving high E2 replacement, however based on clinical findings. The third goal of this study was to investigate the effects of acute and chronic haloperidol (HAL) on brain volume in AMPH-sensitized rats, and its possible interactions with E2. Based on clinical findings showing HAL to be associated with gray matter volume reduction, we expected HAL treatment to result in a decrease in brain volume. In order to address these hypotheses, OVX female rats receiving no, low or high E2 showed increased volume compared to estrous mice, when estrogen levels are low.

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Methods

A series of experiments were conducted to investigate the effects of acute and chronic haloperidol treatment in female rats. All rats were scanned awake, in order to avoid any possible confounding effect of anesthesia (alone or in interaction with E2, HAL or AMPH) on brain morphology.

Results

Changes in brain volume with E2 replacement, AMPH sensitization and HAL treatment were observed. In order to address these hypotheses, OVX female rats receiving no, low or high E2 showed increased volume compared to estrous mice, when estrogen levels are low.

Summary

The overarching aim of this study was to investigate the effects of the possible E2-HAL interaction on brain volume changes in AMPH-sensitized, awake female rats. Specifically, we expected that, a) hippocampal volumes would differ as a function of hormonal status (Bartzokis et al., 2000; Chang et al., 2004; Qiu et al., 2013), b) repeated exposure to AMPH would result in an overall reduction in brain volume and (Madularu et al., 2015), and c) antipsychotic treatment would further reduce brain volume (Lieberman et al., 2005; for review, see Moncrieff and Leo, 2010).

Conclusion

These findings add to the literature supporting the approach of controlling for hormonal status when female animals are used. As indicated by our previous findings (Madularu et al., 2015) and those of others, brain shape (Qiu et al., 2013) and function (Sarvari et al., 2014), as well as responsiveness to drugs is strongly influenced by ovarian hormones. As such, hormonal status should be at least considered, if not controlled for throughout clinical and preclinical studies, leading the way to understanding which brain areas may be important to study when investigating the combined effects of estrogen and antipsychotics in the brain.

Selected references


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