Investigating MK-801-Induced Changes on Electroencephalography and Cognition in Female Rats with and without 17β-Estradiol

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Schizophrenia affects 1% of the human population. Despite similar lifetime prevalence in males and females, >75% of patients diagnosed between 45-50 years of age are female, an age range that corresponds with the menopause transition. Additionally, perimenopausal and postmenopausal women exhibit heightened symptom severity, risk of relapse, and poorer treatment response to some antipsychotic medications including olanzapine. Because decreased circulating estrogen is a physiological change associated with menopause, this suggests a strong relationship between estrogen decline and schizophrenia. Administration of *N*-methyl-D-aspartate receptor (NMDAR) antagonists has emerged as a pharmacological model for symptoms of schizophrenia in animals. MK-801, an NMDAR antagonist, is frequently used to disrupt cognition and induce hyperlocomotion, modelling the cognitive and positive symptoms, respectively. Moreover, electroencephalography (EEG) studies provide a cross-species, translational biomarker to examine normal and aberrant brain function. MK-801 has been found to induce excessive increases in high frequency gamma power using EEG which corresponds with cognitive disruptions and positive symptoms. However, few preclinical studies using NMDAR antagonists examine the influence of hormones including 17β-estradiol (E2) that are known to impact symptomatology and treatment response. To directly test the hypothesis that E2 depletion influences NMDAR function, we are examining effects of MK-801 (0.03-0.18 mg/kg, sc) in 3 month old ovariectomized (Ovx; a rodent model of surgical menopause) female Sprague-Dawley rats using surface electrodes and wireless EEG transmitters. We are also investigating cognitive performance on a touchscreen paired-associates learning (PAL) task-- a highly translational task derived from the CANTAB battery to evaluate visual learning and working memory. Additionally, we are evaluating E2 through administration via implanted silastic capsules containing 25% E2 and 75% cholesterol, a well-established method of tonic delivery (Ovx+E rats). Preliminary EEG data suggests Ovx rats are more sensitive to MK-801-induced disruptions on gamma power compared to Ovx+E and ovary-intact rats. We hypothesize there will also be heightened sensitivity to MK-801-induced cognitive disruptions in Ovx rats. Moreover, we hypothesize that olanzapine, a current antipsychotic, will be less effective in attenuating these disruptions in Ovx rats. Ultimately, these studies aim to establish a relationship between estradiol, NMDAR function, and antipsychotic-like activity that inform menopause-related differences in patients with schizophrenia and can be pursued in the development novel antipsychotic medications.