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# EEG studies reveal estradiol-dependent differences in GluN2A-containing NMDAR function

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Estrogen decline during menopause is a risk factor for the onset of schizophrenia as over 75% of patients diagnosed between 45-50 years of age are female. Compared to premenopausal women, postmenopausal women display more severe positive symptoms and worsened treatment response. However, the underlying mechanisms contributing to this increased risk are not understood. *N*-methyl-D-aspartate receptor (NMDAR) hypofunction is hypothesized to be a major contributor to schizophrenia pathology. Administration of NMDAR antagonists (i.e. MK-801) have thus been used in preclinical models to induce hyperlocomotion, social withdrawal, and cognitive impairment modelling positive, negative, and cognitive symptoms, respectively. However, efforts to identify subpopulation-specific therapeutic approaches have been met with a high failure rate in part due to limited translational screening tools sensitive to individual differences. Assessing brain waveforms using electroencephalography (EEG) represents a translational approach to identify targetable biomarkers and detect changes in neuronal activity. Abnormalities in EEG waveforms have been identified in patients with schizophrenia, including aberrant elevations in resting-state gamma power, corresponding to psychosis and cognitive impairment. Importantly, gamma power reflects cortical glutamate and GABA signaling and, thus, is sensitive NMDAR antagonists which also induce aberrant increases. These increases are hypothesized to be attributed to inhibition of NMDARs on cortical parvalbumin (PV)-containing interneurons, which leads to disinhibition of pyramidal neurons and hyperexcitability. NMDARs are heterotetrameric, comprised of two obligatory GluN1 subunits and two GluN2 or GluN3 subunits, with GluN2 splice variants including GluN2A-D. Interestingly, GluN2A, not GluN2B, antagonists increased gamma power in male rats. Further, post-mortem studies reported reduced GluN2A mRNA expression in PV-containing interneurons in patients with schizophrenia compared to healthy tissue. This may suggest GluN2A hypofunction contributes to aberrant elevations in gamma power. However, few studies have examined how hormones including 17β-estradiol (E2) influence NMDAR antagonist-induced changes in gamma power or if these changes are subunit-specific. We tested the hypothesis that E2 depletion reduces NMDAR function in an GluN2A-dependent manner. MK-801 (0.03-0.18 mg/kg, sc) was administered to 3-month-old female rats implanted with wireless EEG transmitters who remained ovary-intact (O-I) or were ovariectomized (Ovx) and implanted with an empty capsule (Ovx) or a capsule containing E2, a method of chronic delivery (Ovx+E). Data suggest, while there were no significant baseline differences, Ovx rats were more sensitive to MK-801-induced changes in gamma power compared to O-I and Ovx+E rats. Further, PEAQX (10-30 mg/kg, SC) and CP-101,606 (3-30 mg/kg, SC), a GluN2A-preferring and GluN2B-selective antagonist, respectively, were tested. Ovx rats were more sensitive to PEAQX-induced changes in gamma power; CP-101,606 produced no effect in either group. Ongoing studies are assessing differences in GluN2A, and GluN2B expression in cortical synaptoneurosomes. Ultimately, studies aim to establish a relationship between E2 and NMDAR function using gamma power as a translational biomarker to inform subpopulation-specific therapeutic approaches.

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