OFFICIAL ABSTRACT and CERTIFICATION

Exploring Parent-of-Origin Effects on Contextual and Cued Associative Threat Learning in Type III Neuregulin 1 Transmembrane Domain Mutant Mice

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Schizophrenia is believed to be a neural developmental disorder caused by complex interactions between genetic and environmental risk factors. One such genetic risk factor is Neuregulin 1 (Nrg1), which encodes a family of cell receptors that are essential for the development and function of the central nervous system. Type III Nrg1, an isoform of Nrg1, participates in bi-directional signaling during neuronal development. A valine to leucine mutation in the Nrg1 transmembrane domain impairs Type III Nrg1 back signaling and is associated with increased risk of psychosis, a key symptom of schizophrenia. This study sought to determine the behavioral consequence of the mutation in mice and to address the secondary question of whether behavioral phenotypes are influenced by the parent-of-origin of the mutation. In order to evaluate these questions, mice were tested in both a contextual and cued conditioned threat learning paradigm. The findings of this study indicate that the mutation affects associative learning, specifically contextual associative learning in male mice. Within female mice, the presentation of this learning phenotype was significantly influenced by the parent-of-origin of the mutant allele. These findings indicate that there are specific functions of Nrg1 that influence associative threat learning and require nuclear back signaling. Future studies should develop a complete behavioral profile for Nrg1 mice with a transmembrane mutation in order to determine the impact of back signaling on functional neural development. This study contributes to the wealth of investigations into the functions and mechanisms of Nrg1. Additionally, because genome databases do not contain parent-of-origin information, a parent-of- origin effect for Nrg1 would impact any Nrg1 genome wide association study (GWAS).

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