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# Preclinical Assessment of Psychoplastogens for Treatment of Psychiatric Symptoms and Neuroplasticity Deficits in Huntington Disease

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PRECLINICAL ASSESSMENT OF PSYCHOPLASTOGENS FOR TREATMENT OF  
PSYCHIATRIC SYMPTOMS AND NEUROPLASTICITY DEFICITS IN HUNTINGTON  
DISEASE

by

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B.S. University of Central Florida, 2020

A thesis submitted in partial fulfillment of the requirements  
for the degree of Master of Science  
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## **ABSTRACT**

Huntington disease (HD) is a neurodegenerative disorder caused by a CAG trinucleotide repeat expansion in the huntingtin (HTT) gene. HD manifests as a triad of psychiatric, cognitive, and motor symptoms, the latter of which defines symptomatic onset of the disease. Psychiatric symptoms including aggression and depression often emerge decades prior to motor symptom onset. Psychiatric disorders are closely linked with dysregulated neural plasticity, the ability of the brain to form new synaptic connections. Neural plasticity is impaired in HD, potentially playing a role in psychiatric symptoms. However, the association between plasticity and psychopathology in HD has yet to be thoroughly investigated. Psychoplastogens constitute a class of psychoactive compounds that induce neuroplasticity in key regions of emotional regulation, including the prefrontal cortex, hippocampus, and amygdala. In clinical settings, psychoplastogens promote lasting improvements in depression and anxiety scores following a single administration, suggesting an attractive therapeutic profile for HD-related psychopathology. Our lab has recently established the first preclinical model of HD-related aggression in Hu97/18 humanized HD model mice. This model further recapitulates other psychiatric-like aspects of HD, including depressive-like behavior, providing an opportunity to study mechanisms and explore therapeutic strategies for these psychiatric aspects of disease. In this study, we explore the behavioral response of Hu97/18 mice following treatment with psychoplastogens. A single hallucinogenic dose of psychoplastogens did not alter depressive-like behavior or aggression, though a trend towards reduced aggressive behaviors was observed. Encouragingly, psychoplastogens induced structural plasticity in the PFC, striatum, and hippocampus of Hu97/18 mice, suggesting that earlier intervention may be required for significant behavioral benefits. Our work furthers the investigation of interventions for HD psychopathology and expands our understanding of the relationship between plasticity and psychiatric symptoms in HD. This work implicates psychoplastogens as a potential therapeutic intervention for psychiatric dysfunction and impaired plasticity in HD.