UNIVERSITY of GUELPH

COLLEGE of BIOLOGICAL SCIENCE

DEPARTMENT OF MOLECULAR AND CELLULAR BIOLOGY

Announcement:

All interested members of the university community are invited to attend the Final Oral Examination for the degree of ***Master of Science*** *of*

JOSHUA MANDUCA

on Monday, April 26, 2021 at 1:30 p.m. (online)

Thesis Title: **Transient dose-dependent effects of ketamine in neuronal oscillatory activity in Wistar Kyoto rats**

Examination Committee:

Dr. Joseph Yankulov, Molecular and Cellular Biology (Exam Chair)
Dr. Melissa Perreault, Dept. of Biomedical Sciences
Dr. Scott Ryan, Dept. of Molecular and Cellular Biology
Dr. Tariq Akhtar, Dept. of Molecular and Cellular Biology

Advisory Committee:
Dr. Melissa Perreault (Advisor)
Dr. Scott Ryan

Abstract: Ketamine is a promising therapeutic for treatment-resistant depression (TRD) but is associated with an array of short-term psychomimetic side-effects. These disparate drug effects may be elicited through the modulation of neural circuit activity. The purpose of this study was to therefore delineate dose- and time-dependent changes in ketamine-induced neural oscillatory patterns in regions of the brain implicated in depression. Wistar-Kyoto rats were used as a model system to study these aspects of TRD neuropathology whereas Wistar rats were used as a control strain. Animals received a low (10 mg/kg) or high (30 mg/kg) dose of ketamine and temporal changes in neural oscillatory activity recorded from the prefrontal cortex (PFC), cingulate cortex (Cg), and nucleus accumbens (NAc) for ninety minutes. Effects of each dose of ketamine on immobility in the forced swim test were also evaluated. High dose ketamine induced a transient increase in theta power in the PFC and Cg, as well as a dose-dependent increase in gamma power in these regions 10-min, but not 90-min, post-administration. In contrast, only low dose ketamine normalized innate deficits in fast gamma coherence between the NAc-Cg and PFC-Cg, an effect that persisted at 90-min post-injection. These low dose ketamine-induced oscillatory alterations were accompanied by a reduction in immobility time in the forced swim test. These results show that ketamine induces time-dependent effects on neural oscillations at specific frequencies. These drug-induced changes may differentially contribute to the psychomimetic and therapeutic effects of the drug.

Curriculum Vitae: Josh completed his Bachelor of Science (Honours) in Microbiology (co-op) at the University of Guelph in 2019 and started his M.Sc. under the supervision of Dr. Melissa Perreault in the same year.

Publications: (see next page)

Manduca JD, Thériault RK, Williams OF, Rasmussen D, and Perreault ML. 2020. Transient dose-dependent effects of ketamine on neural oscillatory activity in Wistar-Kyoto rats. *Neuroscience*. 441:161-175.

Manduca JD, Thériault RK, and Perreault ML. 2020. Glycogen synthase kinase-3: The missing link to abberant circuit function in disorders of cognitive dysfunction? *Pharmacol. Res.* 157:104819.

Thériault RK, Manduca JD, and Perreault ML. 2021. Sex differences in innate and adaptive neural oscillatory patterns link resilience and susceptibility to chronic stress in rats. *J. Psychiatry Neurosci*. 46(2):E258-E270.

Thériault RK, Manduca JD, Blight CR, Akhtar TA, and Perreault ML. 2020. Acute mitragynine administration supresses cortical oscillatory power and systems theta coherence in rats. *J. Psychopharmacol.* 34(7):759-770.

Foute Nelong MT, Manduca JD, Zonneveld PM, Perreault ML. 2019. Asenapine maleate normalizes low frequency delta coherence deficits in a neurodevelopmental model of schizophrenia. *Neurosci. Lett.*, 711: 134-404.

Hasbi A, Nguyen T, Rahal H, Manduca JD, Miksys S, Tyndale RF, Madras BM, Perreault ML, George SR. 2020. Sex difference in dopamine D1-D2 receptor complex expression and signaling affects anxiety- and depression-like behaviour. *Biol. Sex Diff.* 11(1):8.