



**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 **Doctor of Philosophy** of*

**Rachel Karson Thériault**

**on Monday, August 16, 2021 at 1:30 p.m.** (online)

**Thesis Title:** Sex differences in depression susceptibility are modulated by circuit function and Eph receptor signaling

**Examination Committee:**

Dr. Ray Lu, Dept. of Molecular and Cellular Biology (Exam Chair)  
Dr. Melissa Perreault, Dept. of Biomedical Sciences  
Dr. John Vessey, Dept. of Molecular and Cellular Biology  
Dr. Bettina Kalisch, Dept. of Biomedical Sciences  
Dr. Alexander McGirr, Dept. of Psychiatry, University of Calgary (External Examiner)

**Advisory Committee:**

Dr. Melissa Perreault (Adv)  
Dr. John Vessey  
Dr. Elena Choleris

**Abstract:** Major depressive disorder (MDD) is a debilitating affective syndrome that disproportionately affects women. Despite the known predominance of depression in women, most studies that have investigated the underlying pathogenesis have not employed sex as a factor. Consequently, the mechanisms that contribute to the increased vulnerability of females to depression remain poorly understood. Thus, using the chronic unpredictable stress (CUS) model of depression, we assessed sex differences in MDD pathology at the behavioural, electrophysiological and molecular levels. We first characterized the sex-specific neural oscillatory patterns associated with stress response in brain regions implicated in depression: prefrontal cortex (PFC), cingulate cortex (Cg), nucleus accumbens and hippocampus (HIP). Following stress exposure, stress-resilient females were characterized by increased HIP theta power and cortical gamma power, whereas stress-resilient males exhibited a widespread increase in high gamma coherence. In stress-susceptible animals, we observed a pattern of increased delta and reduced theta power; the changes were restricted to the Cg and HIP in males but occurred globally in females. To elucidate the molecular mechanisms associated with these sex-specific changes in circuit function, a proteomics analysis was performed on the HIP of CUS exposed male and female rats. We demonstrated that the majority of altered proteins induced by stress were distinct to each sex. Unique to female animals was a significant change in EphA2 receptor expression and its associated downstream effector proteins. Indeed, these findings were confirmed in both the HIP and PFC via immunoblotting, with a greater degree of upregulation observed in the PFC. The female-specific role of the EphA2 receptor in depression-like behaviours was subsequently confirmed. Following the infusion of a selective EphA2 receptor peptide ligand agonist into the PFC, only female rats exhibited despair- and anxiety-like

behaviours, as well as alterations in low frequency band oscillations that paralleled those induced by CUS exposure. Collectively, our results demonstrate that the molecular mechanisms and neural oscillatory patterns that underly the pathology of depression are sex specific. These findings begin to inform the use of oscillatory patterns as predictive biomarkers of depression and treatment response, as well as identify a potential female-specific molecular target for future antidepressant pharmacotherapies.

**Curriculum Vitae:** Karson obtained her B.Sc.(H), Biomedical Science at the University of Guelph followed by a M.Sc. Biomedical Sciences with a specialization in Neuroscience under the supervision of Dr. Kalisch and Dr. Leri. In the Fall of 2017, she began her Ph.D. in Molecular and Cellular Biology with a specialization in Neuroscience under the supervision of Dr. Perreault.

**Awards:** Dr. Donald Robert Phillips Molecular and Cellular Biology Scholarship (2021), Pharmacia Molecular and Cellular Biology Graduate Prize (2020), Vanier Canada Graduate Scholarship (2019), Queen Elizabeth II Graduate Scholarship in Science and Technology (2018), Ontario Graduate Scholarship (2017), Graduate Entrance Excellence Scholarship in Molecular and Cellular Biology (2017)

**Publications:** Thériault, R.K.<sup>1</sup>, St-Denis, M<sup>1</sup>., Hewitt, T., Khokhar, J. Y., Lalonde, J., Perreault, M.L. (2021). Sex differences in cannabidiol- and iloperidone-induced changes in cortical neuronal systems activity *in vitro* in the MAM model system of schizophrenia. *International Journal of Molecular Sciences* 22(11):5511.

Thériault, R.K., Manduca, J.D., and Perreault, M.L. (2021). Sex differences in innate and adaptive neural oscillatory patterns link resilience and susceptibility to chronic stress in rats. *Journal of Psychiatry and Neuroscience* 46(2):E258-E270.

Manduca, J.D.<sup>1</sup>, Thériault, R.K.<sup>1</sup>, Williams, O.F., Rasmussen, D.J., and Perreault, M.L. (2020). Transient dose-dependent effects of ketamine on neural oscillatory activity in Wistar-Kyoto rats. *Neuroscience* 441:161-175.

Manduca, J.D., Thériault, R.K., and Perreault, M.L. (2020). Glycogen synthase kinase-3: The missing link to aberrant circuit function in disorders of cognitive dysfunction? *Pharmacological Research*, 157:104819.

Thériault, R.K., Manduca, J.D., Blight, C.R., Khokhar, J.Y., Akhtar, T.A., and Perreault, M.L. (2020). Acute mitragynine administration suppresses cortical oscillatory power and systems theta coherence in rats. *Journal of Psychopharmacology* 34: 759-770.

Thériault, R.K., and Perreault, M.L. (2019). Hormonal regulation of circuit function: Sex, systems and depression. *Biology of Sex Differences*, 10(1):12.