



Bold Research Projects for Advancing Women's Mental Health

BASICS OF BETTER MENTAL HEALTH PROGRAM GRANTS 2024

Mental health conditions affect women differently than men. For example, women are more likely than men to develop anxiety, depression, and traumatic stress-related disorders. Yet only 3% of neuroscience studies are focused on women, and only about 5% include sex in the study design in a way that allows scientists to make comparisons between sexes.

Like much health research, neuroscience research has historically focused on male subjects, materials, and participants, biasing results toward the male body and men's experiences.

This has led to ongoing deficits in evidence regarding sex and gender-related dynamics in brain health and disease in females, women, and gender-diverse people.

To help address this gap, Women's Brain Health Initiative (WBHI), Brain Canada, and the Krembil Foundation, with the support of The Erika Legacy Foundation and Power Corporation of Canada, recently awarded \$3.3 million in the Basics of Better Mental Health Program to three recipients and their research teams.

Basic science aims to expand knowledge and understanding, laying the groundwork for future clinical research. Each team received \$1.1 million for their three-year basic science projects to investigate and discover new insights into sex-related factors or differences in mental health conditions.

"Emphasizing sex-specific factors or differences is essential for advancing our understanding and treatment of mental health conditions, ultimately paving the way for more effective interventions tailored to the unique needs of women. These studies are taking bold strides toward promoting women's brain health and well-being," said Lynn Posluns, Founder and President of WBHI.

"As Canada's leading research funder focused specifically on the brain, we are seizing this opportunity and committing to advancing the field of sex and gender brain science. The inclusion of sex-specific biological considerations is instrumental in understanding the biological roots of mental health conditions," said Dr. Viviane Poupon, President and CEO of Brain Canada.

"We take great pride in supporting these three recipients who are at the forefront of addressing sex gaps in brain research."

Mind Over Matter® met with the principal investigator from each winning team to learn more about their projects aimed at advancing knowledge about sex-specific factors or differences in depression, anxiety, and postpartum depression.

DOES INSULIN RESISTANCE PLAY A ROLE IN DEPRESSION ASSOCIATED WITH OBESITY?


Depression and anxiety diagnoses in people with obesity are approximately double in women compared to men. While social factors such as stigma and the challenges of living with obesity can lead to depression, emerging science reveals obesity-related brain changes are also contributing factors.

Dr. Stephanie Borgland, a professor of physiology and pharmacology at the University of Calgary's Hotchkiss Brain Institute, and her research team are investigating whether sex-related differences in insulin resistance might explain this disparity. "There is an urgent unmet need for new treatment strategies for depression given that most current medications lead to weight gain," she said.

Her lab studies insulin signals in a midbrain structure called the ventral tegmental area (VTA). For this project, Dr. Borgland and her team are exploring whether insulin resistance impairs the brain circuit involved in motivating responses, known as the mesolimbic system, in obese mice compared to lean mice.

The mesolimbic system involves neurons in the VTA that reach into another area of the brain, the nucleus accumbens, where they release dopamine, the brain chemical responsible for reward-motivated behaviour.

“We predict that in the context of obesity and Type 2 diabetes, insulin is no longer properly regulating dopamine-releasing neurons, and that may be contributing to the development of depression and anxiety.”

An essential part of Dr. Borgland's project is developing a new biosensor that measures brain insulin levels in mouse models of depression and anxiety in real time. "If successful, 

this first-ever brain insulin biosensor will allow us to measure insulin levels in specific brain areas and observe how they change during daily activities," she said. "This new technology could reveal important insights we might never learn from analyzing postmortem tissue."

Dr. Borgland and colleagues will also explore whether restoring abnormal dopamine signalling increases insulin sensitivity and improves anxious and depressive behaviour in mice.

The research team includes Drs. Marie-Ève Paquet and Rochelin Dalangin at the Université de Laval, Stéphanie Fulton at the Université de Montréal, Carrie Ferrario at the University of Michigan, and Xiaochen Bai at the University of Texas Southwestern Medical Center.

WHAT BRAIN CHANGES TAKE PLACE DURING POSTPARTUM DEPRESSION, AND HOW DO THEY INFLUENCE THE PREDISPOSITION FOR MENTAL HEALTH CONDITIONS IN OFFSPRING?

The postpartum period is the time of highest risk for new-onset depression and other psychiatric disorders in birthing parents. Up to 20% of birthing parents experience postpartum depression, which affects their health and also affects their children's brain development and mental health risk.

Similar to other forms of depression, symptoms of postpartum depression include intense sadness, lethargy, loss of interest in daily activities, and memory and thinking problems.

However, the specific timing of new-onset depression during this time gives clues to how depression arises at other time periods.

"The postpartum period is a time of huge fluctuations in hormone levels, brain chemistry, and the immune system. We also see some of those same changes with psychiatric disorders, such as depression, so it's not surprising these are times of great risk. But very few studies to date have investigated exactly what transpires in the brain," said Dr. Liisa Galea, senior scientist, the inaugural womenmind Treliving Family Chair in Women's Mental Health, and head of the Women's Health Research Cluster at the Centre for Addiction and Mental Health (CAMH) in Toronto.

Dr. Galea's lab studies how sex hormones influence brain health, with a focus on dementia and stress-related psychiatric conditions and developing tailored treatments for both women and men.

Her lab was the first in the world to create animal models of postpartum depression.

For this project, Dr. Galea and her team will explore brain areas implicated in depression using advanced technologies called spatial genomics and spatial transcriptomics. These technologies will allow them to map how brain cells change relative to other cells, such as immune cells. They will compare differences between mice during the natural pregnancy and postpartum periods with mouse models of postpartum depression.

"Our experiments seek to reveal how, when, and where postpartum depression develops in birthing parents and how, when, and where their offspring develop susceptibility to developing anxiety or depression during childhood, adolescence, and early adulthood," said Dr. Galea. "We hypothesize that mental health issues will arise in adolescence for female mice and during early childhood for male mice, similar to human patterns of mental illness."

Part of this grant involves identifying biological signals, or biomarkers, that will help researchers determine whether new postpartum depression approaches may improve responses.

This is important as there are currently only two drugs for treating postpartum depression available in the United States.

The intravenous drug Zulresso (brexanolone) must be administered in a hospital setting and requires a hospital stay of at least 60 hours. The most recently approved

drug, Zurzuvae (zuranolone), is an oral medication that can significantly improve depressive symptoms but does have some serious side effects. It is not known if either drug will be approved in Canada.

Dr. Galea and her team will evaluate potential treatments, including a novel drug called Kineret (anakinra), an approved anti-inflammatory medication used to treat rheumatoid arthritis. Their preliminary work suggests this drug may be effective in blocking certain postpartum depression processes.

The research team includes Drs. Brian Kalish at the Hospital for Sick Children and Shreejoy Tripathy at CAMH in Toronto.

WILL INSIGHTS INTO A DOPAMINE RECEPTOR COMPLEX IN THE BRAIN ADVANCE DRUG DISCOVERY FOR DEPRESSION?

The incidence of major depressive disorder is two to three times higher for women than men. Yet, there are no treatments targeted to women, and current therapies are ineffective for many people.

Dr. Susan George is a physician and consultant in endocrinology at Toronto General Hospital, University Health Network, and a professor of medicine and pharmacology and toxicology at the University of Toronto. She and members of her lab discovered a unique dopamine receptor complex in an area of the brain implicated in mood and anxiety. This receptor complex occurs with a two- to three-fold greater density in female brains than in male brains.

“The complex is found in neurons targeted by dopamine neurons within the nucleus accumbens,” said Dr. George. “We were excited about this discovery and then surprised to learn that rather than boosting reward responses, it mediates aversion, generating a ceiling on reward processes.”

DR. GEORGE AND COLLEAGUES HYPOTHESIZE THIS DOPAMINE RECEPTOR COMPLEX BECOMES OVERACTIVE IN MAJOR DEPRESSION.

They found that activating the complex in rats increased anxiety- and depression-related behaviours, and especially so in females. They were able to reverse these effects by blocking the complex with a small protein called a peptide, which they developed.

For their project, Dr. George's research team will validate their preliminary findings about sex-related differences in the dopamine receptor complex in female and male rat models of anxiety and depression. They will compare their insights with postmortem human brain tissue from male and female individuals with and without depression.

Dr. George and colleagues will also create a new imaging tool that will allow them to examine how the dopamine receptor complex behaves in live animals. “We anticipate this new tool will inform the future development of brain imaging technology for monitoring the complex in humans, with potential to be a biomarker and prognostic indicator,” said Dr. George. “At the same time, it will help advance the discovery of new drugs for treating depression and anxiety.”

The research team includes Drs. Martin Beaulieu at the University of Toronto and Junchao Tong and Isabelle Boileau at CAMH in Toronto.

SUPPORT WOMEN'S BRAIN HEALTH RESEARCH

All three investigators credited the Basics of Better Mental Health Program with allowing them to continue advancing women's brain health research.

The Basics of Better Mental Health Program has been made possible by the Canada Brain Research Fund (CBRF), an innovative arrangement between the Government of Canada (through Health Canada) and Brain Canada Foundation. Brain Canada matches the federal government's investment with contributions from its partners and donors, doubling the government's impact on brain research and ultimately improving the quality of life for people living in Canada.

To learn more about Brain Canada's mission to accelerate, amplify, and fund brain research across Canada, visit braincanada.ca.

Learn more about WBHI's research initiatives at womensbrainhealth.org/research.

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