Healthy Brains for Healthy Lives
Strategic Research Plan

The Healthy Brains for Healthy Lives (HBHL) initiative is a high profile, high priority multidisciplinary and cross-sectoral initiative located at McGill University made possible with support from the Canada First Research Excellence Fund (CFREF).

Vision

The central vision of the HBHL initiative is to reduce the human and socio-economic burden of psychiatric and neurological illnesses, and improve the mental health, quality of life, and productivity of Canadians and people around the world. This will be done by elucidating how the individual brain functions in health, in disease, and throughout our lives using world-leading neuroinformatics integrating genetic, epigenetic, neurophysiological, imaging, behavioural, clinical, social and environmental data.

Goals

HBHL's overall goals cover four domains:

- **Research**: Encourage interdisciplinary and novel approaches to research across fields linked by neuroinformatics to: understand the individual brain in health and disease, improve brain disease and mental health diagnosis and treatment, and generate new preventative measures and social programs for brain health.
- **Talent**: Train and support young researchers in neuroscience and interdisciplinary approaches to the brain in health and illness. This includes recruiting 21 new McGill faculty focused on HBHL key disciplines.
- **Innovation**: Foster international collaboration, and support early stage commercialization and knowledge mobilization of HBHL supported discoveries.
- **Infrastructure**: Develop novel technologies and support core facilities that are key to achieving HBHL's goals.

Deliverables

HBHL's main deliverables are the following:

- NeuroHub, an open-access platform for neuroinformatics and big data analysis.
- Commercially valuable products, tools, services, licenses and start-ups.
- Collaborations with partner institutions (Western University, Université de Montréal and the University of British Columbia.), as well as with national and international researchers and initiatives.
- Major scientific advances (publications, presentations, etc.)
- Training of highly qualified personnel.
- Leveraged funding from other sources.
- Work towards a *Canadian Framework for Brain Health* that translates our research into evidence-based clinical best practices, guidelines and policies for health care funders, providers, and users.

Research Priorities

HBHL's strategic research priorities are anchored to neuroinformatics, the development and use of analytical tools and computational models that can combine neuroscience data across all scales and levels to better understand the brain in health and disease. Neuroinformatics tools can acquire, store, share, publish, analyze, model, visualize or simulate neuroscience data. Neuroinformatics is central to HBHL's four Research Themes:

1. **Neuroinformatics and Computational Modelling** (leader: Alan Evans)

a. Background: The core of HBHL will be the application of a novel advanced analytic platform for brain research, NeuroHub, which will enable the development of new models to improve understanding of normal development, enhanced classification of disorders, and better understanding of clinical outcomes for individual patients. These goals will be accomplished through the integration of information from large-scale, complex data sets through a secure data-sharing platform, by leveraging state-of-the-art mathematical and computational modelling methods, and by ensuring a close interaction of research groups with a broad range of expertise in neuroscience, computer science, clinical research, and social science.

b. Research Priorities:

- Development and deployment of new analytical methods that simultaneously take into account multiple dimensions (e.g. genetics, imaging, behaviour), multiple modalities (e.g. morphology, structure, electromagnetic activity, haemodynamics), and multiple scales (e.g. protein structure, microscopy, calcium imaging, single-cell recordings, electro- and magnetoencephalography, magnetic resonance imaging and positron emission tomography).
- Provide new software platforms for curation, integration and analysis of multimodal data.
- Development of prediction-based analytic frameworks to understand and predict individual differences in learning and performance, as well as disease vulnerability and progression
- Develop analytic methods and strategies as part of a common analytic framework that directly benefits other HBHL research themes.
- Encourage contribution to the principles of Open Science recently adopted by the Montreal Neurological Institute, including sharing of data, methods and open access to published work.

2. **Mechanistic Models of Neurodegenerative Disorders** (leader: Guy Rouleau)

a. Background: The main goal of this Research Theme is to develop research programs that will focus on understanding, detecting, diagnosing, measuring, modelling and treating human neurodegenerative diseases. Neurodegenerative diseases are diseases that usually affect the brain after it has developed. Their hallmark is the progressive death of neurons. Typically, they are diseases of adulthood and old-age (e.g. Alzheimer's disease, Parkinson's disease, ALS, FTD, rarer genetic diseases) but this category may also include neurodegenerative diseases of early life (e.g. schizophrenia, leukodystrophies, ataxias). Research into neurodegenerative aspects of diseases not typically considered primarily degenerative, such as epilepsy and MS, may also be considered.

b. Research Priorities:

- Protein misfolding / propagation
- Autophagy, synaptic, mitochondrial and lysosomal dysfunction
- Functional and anatomical brain imaging
- Genetically unique individuals or commonalities across disease categories; study of rare disease.
- Early diagnosis and investigation of prodromal syndromes
- Neuroengineering (e.g. microfluidics and scaffolds for neural cell and tissue growth, neural organoids, brain/neuron:machine interfaces, wearable and implantable devices)

- Therapeutics, including biomarker development, gene editing (CRISPR), drug screening, risk factor identification and modification, personalized medicine.
- Gene-environment interactions as causes of neurodegenerative disease
- Enrollment and characterization of patient cohorts, with an emphasis on data sharing and open science.

3. Applied Cognitive Neuroscience of Brain Plasticity (leader: Robert Zatorre)

a. Background: The goal of this theme is to promote research to address both basic-science questions pertaining to the mechanisms underlying plasticity, as well as their application to health, disorders, and other related domains, considering mechanisms that may stretch from genes to socio-cultural influences, and that apply across the lifespan from early development, through adolescence to aging. The theme emphasizes plasticity within the context of human cognitive neuroscience (i.e. the neural basis of human thought and behavior), given the importance placed within HBHL on developing tools and treatments relevant for human application. Animal models can also play a key role in developing better understanding of basic neural plasticity mechanisms or to test the consequences of certain types of interventions. Research supported via this theme will focus on two principal axes: a) Learning and Performance, and b) Resilience.

b. Research Priorities:

- Characterize the neural changes associated with plasticity, whether adaptive or maladaptive, using multi-modal and interdisciplinary approaches
- Improve cognitive, perceptual or motor performance in healthy individuals, including aging or other vulnerable populations, and in educational or workplace settings
- Promote recovery from neural dysfunction, damage, sensory loss, or from behavioral/mental health disorders
- Promote resilience by preventing or delaying functional impairment from disease or aging, and by predicting individual outcomes
- Develop tools, procedures, products, software, devices, etc. that enable optimization of plasticity in the above contexts

4. Population Neuroscience and Brain Health (leader: Michael Meaney)

a. Background: Canada faces dynamic changes in its economy and society owing to globalization and mass migration, and ongoing economic and health disparities between urban, rural, migrant, Indigenous, and non-indigenous populations. There are increasing pressures to establish an inclusive, knowledge-based economy that addresses these disparities and is competitive on the global level. Success depends on promoting brain health and functional capacity across the population. The goals of this research theme are to: 1) understand the forces that shape individual and population differences in brain health and function across the developmental continuum; 2) increase capacity to conduct neuroscience-based research programs that address major societal issues to inform evidence-based public policy; 3) better integrate findings from neuroscience and social science research to promote wellbeing in the lives of all Canadians in family, workplace, educational and community environments; 4) target under-served and more disadvantaged Canadian communities; and 5) emphasize the promotion of brain health in Canadian youth.

b. Research Priorities:

- Brain health in a multicultural and Canadian context, e.g. population neuroscience and brain health projects that integrate cultural and ethnic diversity as a major theme.
- Brain health of mothers, caregivers, children, and adolescents, e.g. research targeting the determinants of women's brain health with an emphasis on the pre-conception and pregnancy periods of reproduction when the influence on offspring neuro-development is profound and intervention may be most successful.

- Brain health and function in the workplace and educational environments, e.g. prevention of mental health issues and promotion of resilience, creativity and intellectual capabilities in the classroom and workplace.
- Socio-economic determinants of brain health, productivity and treatment outcomes, e.g. the development of interdisciplinary projects that examine the social determinants of brain health, including the influence of economic inequality, racism and discrimination, and that can lead to evidence-based intervention and prevention programs, including those focused on the determinants of individual differences in resilience and susceptibility as well as on the mechanisms (at all levels of analysis) that mediate the links between socio-economic and other contextual factors and brain health.
- Brain health in Indigenous peoples, e.g. by building the relations and establishing participatory models for brain health research with First Nations, leading to culturally-appropriate prevention and intervention programs.
- 'Big Data' approaches to the study of determinants of resilience/ susceptibility and capacity. This involves high-dimensional analyses of large data sets that reflect biological (genetic/epigenetic) and social contextual or environmental (family, culture, socio-economic position, urbanicity) influences as well as measures of brain health and function. Such analyses should aim to understand how networks of genes in the brain interact with dynamic environmental influences to define the development and function of neural circuits, and how these circuits operate within context to define brain function across the lifespan.
- Web-based approaches to research and intervention in brain health, e.g. development of innovative technologies (e.g., mobile devices) for assessment and enhancement of brain function (neurophenotyping) in real world settings, and web-based, non-pharmacological interventions (e.g., web-assisted cognitive behavioral therapies, mindfulness training, etc.). Such programs should be developed with respect to the needs and distinct features of diverse target populations.

HBHL Platforms

Recognizing that HBHL research efforts are dependent on key platform technologies, the HBHL Research Management Committee (RMC) has established 5 subcommittees to support and develop platform technologies relevant to HBHL's research priorities. Researchers planning to use or further develop such platforms should contact each sub-committee leader. The mandates of each sub-committee are the following:

1. Social Sciences (leader: Laurence Kirmayer): provide input into HBHL theme projects and other activities, oversee training in social science for neuroscientists and foster new approaches to interdisciplinary collaboration through organizing focussed workshops and training programs. Establish interdisciplinary working groups on (i) Social Indicators of Brain Health to systematize and refine existing indicators in available open science data-sets at McGill and beyond; (ii) Social Contexts of Brain Health with a view to refine existing research frameworks and diagnostic tools in psychiatry.

2. NeuroHub and Machine Learning (leaders: Bettina Kemme and Jean-Baptiste Poline): oversee the development of the platform for integrating data across studies and state-of-the-art modelling methodologies by: 1) identifying and addressing the research challenges in extending the current HBHL infrastructure to ensure that it will be able to support the wide range of applications that will be developed in the HBHL context; 2) identifying the community, data, important infrastructure (hardware and software) and needs for enhanced research infrastructure (e.g. storage/capacity, computational/HPC, growing needs etc.); 3) assisting the Neuroinformatics theme with the routine operations of managing a complex HBHL-related data repository, employing the LORIS/CBRAIN data-sharing ecosystem; 4) interacting with and advising the other research themes and facilitating the use of NeuroHub in their research activities; 5)

participating in all HBHL activities, when relevant (e.g. workshops, seminars, development of the Request for Proposals, etc.); and 6) building relationships with external academics, resources, and companies.

3. Clinical Neuroscience (leaders: Gustavo Turecki & Lesley Fellows): ensure that the clinical goals of HBHL are met by: 1) supporting the translation of scientific advances from HBHL to the clinic; 2) ensuring that HBHL priorities consider clinical perspectives; 3) facilitating communication amongst clinical neuroscientists (broadly inclusive of those who study neurological disorders, medical conditions affecting the brain, and clinical and psychosocial mental health researchers) at McGill and at partner organizations; 4) communicating between this clinical research community and the HBHL RMC; and 5) identifying bottlenecks or gaps between fundamental research and potential applications to the clinic, and propose solutions.

4. Animal Models (leader: TBD): promote animal models to achieve HBHL goals by: 1) accelerating large-scale data acquisition from animal models at behavioral, circuit and cellular levels through HBHL funding mechanisms; 2) fostering the development of novel methodologies for the analysis of large datasets from animal experimentation through HBHL funding mechanisms; 3) developing innovative bioinformatics technologies to allow effective and bidirectional knowledge translation from animal to human research through HBHL funding mechanisms; 4) establishing formal relationships with the four themes in order to foster research on normal and pathological brain function across all brain research areas; 5) identifying external partners (academia and industry) with expertise currently unavailable in HBHL to enhance the research potential; and 6) contributing to HBHL activities in general across themes and subthemes to optimize synergy between this subcommittee and other HBHL committees and subcommittees.

5. Cellular and Tissue Models (leader: Edward Fon): support the following types of technologies and platforms across the four HBHL themes: 1) development of novel biomaterials, scaffolds and methods for growing, characterizing (RNASeq, single cell sequencing) and genetically engineering (CRISPR) iPSC-derived neurons, glia and organoids in both 2 and 3 dimensions to better reflect how they behave in the brain; 2) integration of multidimensional clinical, genetic, imaging patient data from the C-BIGR with the comprehensive profiling of patient samples, neurons and organoids generated from iPSCs in close collaboration with the four other HBHL platforms; 3) development of tools for the analysis of large structured and unstructured datasets obtained from assays with iPSC-derived neurons and glia; 4) generation of cell- and tissue-based assays that will be disease-relevant and robust enough to use in open drug screening campaigns in collaboration with Pharma partners.