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A Neuroethics Backbone for the Evolving Canadian Brain Research Strategy

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Building on Canada's strong traditions in neuroscience and ethics, neuroethics provides a backbone for the evolving Canadian Brain Research Strategy (CBRS) that, from the outset, incorporates ethically responsible discoveries in brain science into clinical, societal, educational, and commercial innovation.

A Grand Neuroethics Challenge

One in three Canadians will be affected by a brain or nervous system illness, disorder, or injury within their life. These conditions span the life cycle. Mental health conditions often affect young Canadians in the prime of life, with an estimated 75% of mental illnesses beginning before the age of 24. Injuries to the nervous system, such as concussion, occur frequently in adult life and can lead to lifelong disability. Age-associated dementia has surpassed other conditions as the largest financial burden on the Canadian healthcare system today. A 2016 report from the Evaluation Panel from the CIHR Institute of Neurosciences, Mental Health and Addiction (INMHA) placed the overall cost of neurological and mental health disorders to the Canadian economy at $61B CAD annually. In addition to a high economic cost, brain disorders impose staggering personal and societal tolls.

Canadians firmly support the need for ethical health research, innovation and economic advancement in neuroscience. This commitment is underpinned by Canada's multi-million-dollar investment in dedicated funding for neuroethics teams, operating grants, and research chairs and fellowships beginning in early 2000 and carrying on today (Quirion, 2002). The embedding of an already strong neuroethics platform into the new Canadian Brain Research Strategy (CBRS; www.canadianbrain.ca) is the latest and most exciting step forward. The building of CBRS was initiated in 2015 and has been nurtured under the leadership of INMHA. Following a consensus meeting of directors of neuroscience programs across Canada and other key stakeholders in Halifax in September 2018, the CBRS is moving forward as an organizing entity independent of INMHA, with an intersectoral steering committee that will work in continuous liaison with the conference leaders and participants and with a strategic eye on developing and situating Canada as a neuroscience-driven nation.

Here we discuss the proposed key pillars—Understand, Address, Apply, and Build—inspired by the distinguishing and central question of the unfolding CBRS—how does the brain learn, remember, and adapt?—a question that seeks to understand the most fundamental aspects of what defines the self (Figure 1). The powerful ability of the brain to change or rewire itself in response to experience is the foundation of human identity. Understanding the mechanisms underlying this plasticity is at the root of any effort to treat neurological and mental disorders. Neuroethics is a necessary anchor into this question. It intersects with all pillars and forms an explicit foundation for the Apply pillar on which we focus in this paper.

The Apply pillar draws upon Canada's long tradition of pioneering work in neuroethics, beginning with Canadian neurosurgeon and neuroscientist Dr. Wilder Penfield, who founded the Montreal Neurological Institute. Penfield's writings may be viewed as a precursor to neuroethical deliberation. Penfield was a student of Sir William Osler, to whom Canada attributes deep insights into science and the biomedical sciences. Physician-bioethicist Joseph J. Fins quotes a 1919 address by Osler, "The Old Humanities and the New Sciences," to Oxford's Classical Association, in which he "admonished the divide between the sciences and the humanities, observing that … the so-called Humanists have not enough Science, and Science sadly lacks the Humanities" (Fins, 2008). We provide specific examples of neuroethics leadership in this country that bridge the divide that Osler described, highlighting this country's advances in neuroscience and law, mental health and addiction,

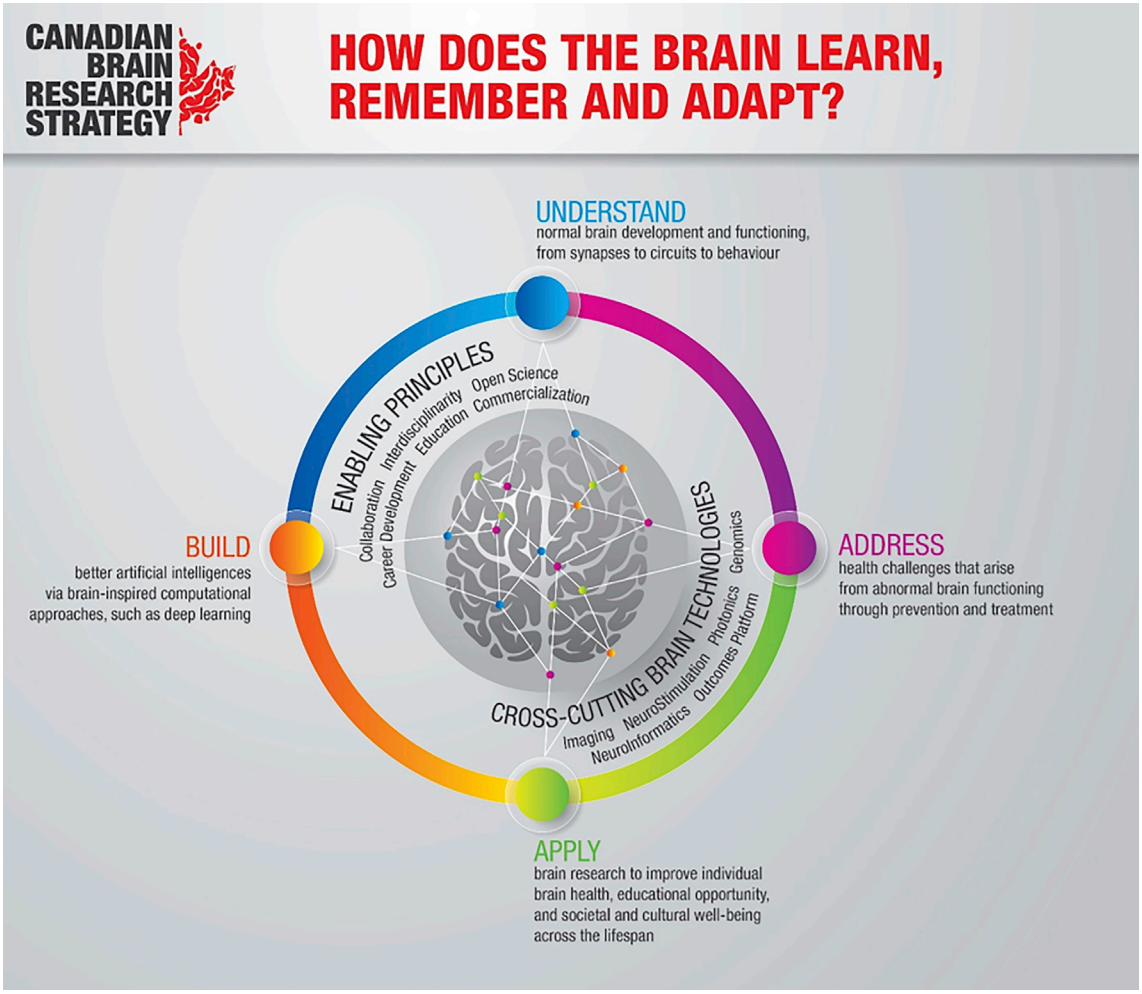

Figure 1. Scientific Framework for the Proposed Canadian Brain Research Strategy (CBRS) as of September 2018

public outreach, and knowledge mobilization through patient engagement. We conclude with a look to the future of international collaboration with the International Brain Initiative (IBI) and Neuroethics Global Summit colleagues and partners.

Co-creation of a CBRS

The CBRS aims to be an integrated national research effort that builds on Canada's strengths and current investments in cutting-edge collaborative neuroscience to drive transformative outcomes in neurological and mental health for Canadians. Its final design will enable Canada to:

- Accelerate the understanding of the brain and translation to clinical treatments that address grand challenges in brain and mental health for Canadians.
- Increase collaboration, data sharing, and technology development and dissemination among Canadian researchers and build on collective strengths.
- Identify targets and milestones for strategic and coordinated investment in Canadian neuroscience and mental health.
- Train the next generation in interdisciplinary brain research, bridging diverse disciplines spanning the physical and computational sciences to anthropology, sociology, and economics.
- Develop meaningful collaborations with other Brain Initiatives on the international stage.

To achieve these goals, the four pillars on which the CBRS is building are collectively supported by six enabling principles: collaboration, interdisciplinarity, open science, career development, education, and commercialization. These principles both guide how research within the CBRS is conducted and set targets to advance a sustainable mission and vision. The principles are interwoven with five specifically identified technology development areas to probe, manipulate, decode how the brain functions—imaging, stimulation, photonics, genomics, and neuroinformatics—that, together with embedded and rigorous experimental trial designs and outcome measurements, serve as platforms for a competitive Canadian neuroscience research world today.

The first pillar, Understand, focuses on normal brain development and functioning, from synapses to circuits to behavior, and neuroplasticity across the lifespan.

Important insights by Canadian neuroscientists have come from explorations of plasticity in a wide range of species, studies of human memory, discoveries in neural stem cells and regenerative medicine, pain research, and interactions among genes and environments during early childhood that guide human development.

From the outset, the Understand pillar embraces the change in culture needed—from traditional siloed disciplines of genetics, neurophysiology, neurocomputing, psychology, ethics, and sociology to cross-disciplinary collaboration—to reveal how the brain evolves over a lifetime.

This approach in turn allows fundamental knowledge to be translated to health challenges arising from dysfunction of these basic brain processes (Address) and informs technology development as well as methods such as artificial intelligence and computational modeling that may have transformative industrial applications and economic impact (Build). For these three pillars, neuroethics is implicit, encompassing both simple and complex phenomena that include, for example, the responsible conduct of research, limiting the numbers and suffering of animals in research, respecting persons and protecting their autonomy and rights, data and privacy protections, and anticipating both beneficial and consequential outcomes. In Apply, the approach focuses on societal and cultural well-being, making it the pillar for which neuroethics plays the most explicit role.

At the Interface of Apply and Neuroethics

The Apply pillar recognizes the imperative of the CBRS to promote individual and societal well-being; evidence-based, informed social and health policy; and education. The scope of the efforts supported by this pillar are broad: developing best practices in early childhood education, enabling the active participation of older adults in society, helping teenagers make smart choices about drug and alcohol use, and supporting people as they navigate escalating demands in the workplace and at home. It includes consideration of the critical role that new regulatory policies or technology play in how people interact, learn, and contribute. It includes, as well, the evolution of new tools and the way that they are adapted to human capabilities to support productive, socially cohesive, and healthy lives on the one hand and to mitigate triggers of distraction, alienation, and burnout on the other.

Learning is possible because brains are plastic and capable of change. Education, therefore, must be tailored to the mechanisms that both enable and constrain underlying brain plasticity. Reciprocally, techniques in cognitive neuroscience allow neuroscientists to study in ever greater depth how human factors, such as education and culture, shape the structure and function of the brain. As scientists and scholars gain a more in-depth understanding of these mechanisms, targeted educational practice and policies that optimize learning can be applied in the classroom and other settings. For example, one program has led paradigm-shifting research in the areas of gene-environment interplay and critical periods of brain development (Anreiter et al., 2017). This effort is now focusing on the understanding of broad group differences in outcomes toward a predictive understanding of individual response to experience. A number of large school-based trials led by Canadian researchers have shown that targeted neurodevelopmental interventions also promote mental health and well-being, indirectly by promoting academic success and directly by supporting important executive and other cognitive functions (e.g., Conrod et al., 2013).

Canadian-led studies of brain plasticity have also revealed the interactive effects of early experience, stress, nutrition, sleep, and exercise on learning outcomes, all of which have important implications for how educational environments are structured. In adulthood, new doors are open to optimizing education in the workplace and to ensuring an environment that supports peak human performance, whether through social supports and technological innovations or general health measures that promote resilience in the adult brain.

The transformation of the fields of psychiatry and neurology with the discovery of biomarkers has led to opportunities for detection and early intervention around vulnerability before disease emerges, advanced diagnostics, and improved follow-up of response to treatment. Canadians have been pioneers in developing novel neurodevelopmental and adult biomarkers for diseases for which diagnosis has historically relied largely on interview data and patient reports. With this transformation comes the significant responsibility both for deliberation and action, especially when applied to pediatric populations, for which prediction is not 100% accurate, and for cases where interventions might modify outcomes.

The management of unexpected interventional consequences or abnormal findings in research and clinical medicine can pose unique human rights challenges for researchers, research participants, healthcare recipients, and third parties. Canadian neuroethicists and others have made pioneering contributions to this landscape (Illes et al., 2006) and continue to review and refine related processes through an open and democratic initiative led by Canada's Secretariat on Responsible Conduct of Research, of the Tri-Agency (Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council, and the Social Sciences and Humanities Research Council) Framework on Responsible Conduct of Research. Systematic neuroethical analyses have also yielded guidance for disclosure of educational and health events that integrate practical and legal considerations with explicit appreciation of human rights along the continuum of decisional capacity. Canadian neuroethics researchers have further created innovative models for conveying critical brain health information that accounts for age, individual values, cross-cultural considerations, variation in ability, and vulnerability. In an era of big data and the growing implementation of open science approaches in Canadian neurosciences (Canadian Open Neuroscience Platform; www.conp.ca), new strategies are continuously needed to ensure scientific standards and cultural sensitivity and to retain scientific, ethical, and legal relevance and responsiveness.

To advance the goals of the CBRS, scholars and scientists working with the Apply pillar have adopted a spiral model of translation to enable iterative, rapid, and positive interactions between researchers and end-users: clinicians, policy-makers, trainees, affected clinical populations and their advocacy, science writers, and news and social media. The

spiral approach per se is novel for neuroethics, but it is well aligned with the pragmatic orientation of Canadian neuroethics that endeavors to:

1. Harness neuroscience insights to maximize the potential of every individual at every life stage.
2. Identify and promote factors that enhance individual and population resilience, prevent brain insults and health vulnerabilities, and promote recovery from brain disorders.
3. Deliver innovative ethical and social frameworks needed to catalyze and protect advances in all aspects of neuroscience that pertain to the CBRS.
4. Encourage the sharing of data, accelerated and systematized discovery, and the implementation, translation, and democratization of technology within the nation and eventually outside.

Overall, the model embraces an evidence-informed approach to determine how research can be optimally synthesized and prioritized for the utmost ethical and social benefit of the citizens of our diverse country.

Applied Neurolaw, Public Discourse, and Patient Engagement

Since approximately 2010, Canadian neurolaw scholarship has taken a comprehensive approach to issues related to the application of the law to neuroscience and to the incorporation of neuroscience evidence in legal disputes. Key neurolaw questions relate, for example, to legal concepts of responsibility, privacy, disability, mental health, human rights, intellectual property rights, and the regulation of healthcare (Chandler et al., 2018). Evidence related to the brain is cited in the context of Canadian civil, criminal, and human rights cases in support of legal arguments about a broad range of matters. Neurolaw implications inform the strategic trajectories of the CBRS Apply pillar today as in, for example, a recent medicolegal dispute over end-of-life decision-making in a patient with a disorder of consciousness. The intersection of law with neuroscience in Canada is also illustrated with the continued debate over the concept of brain death, now 50 years after the landmark Harvard Committee report. This concept is fundamental to high-technology medicine that can now maintain at least some physiological functions artificially for long periods of time. Canadian courts are presently wrestling with multiple challenges to brain death as a purely biomedical concept and in the ways that neuroscience and neurotechnology may alter, but are unlikely to settle, the social, cultural, philosophical, and religious questions at the heart of this issue.

Further providing deep roots for the CBRS Apply pillar, Canadian neuroethics scholarship has delved into the nature and impact of public discourse about neuroscience both in traditional and online media. This scholarship has applied new knowledge to a call for a cultural shift in academic institutions to promote and reward public and policy engagement (Illes et al., 2010) and to pinpoint knowledge gaps and misunderstandings that have the potential to thwart evidence-informed ethics and rational debate. Research on the seductive allure of neuroimages in the media, sometimes called neuro-realism, has investigated the effect of visual information on people's judgments, including in the context of addiction (Racine et al., 2017). Much remains to be explored in this area, and it has special salience for the understanding and dissemination of knowledge about substance-use disorders, the far-reaching impact of the opioid crisis across Canada, and this country's harm-reduction strategies in the face of stigma, blame, and fluctuating political views.

Finally, a uniquely Canadian initiative, the Strategy for Patient-Oriented Research (SPOR), emphasizes support, mutual respect, and a collaborative approach to the generation of knowledge for health and illness. In developing social policy that is responsive to recent advances in sciences, SPOR fosters inclusiveness of patients and their families, caregivers, and healthcare providers in research. Innovative research in ethics and the practice of brain science has harnessed novel tools to support engagement, for example, of participants with Alzheimer's disease and uncovered critical tensions between research ethics board requirements and the values and priorities of patient communities. Research on brain science and social discourse and, in particular, Canadian studies on the representations of brain health and neurotechnologies in social media (Robillard et al., 2015) have laid the foundational work for opportunities in the CBRS to co-build resources with patient communities and apply them to ensure that the needs of end-users are met.

Canada's Next CBRS Neuroethics Steps

At the first meeting of the Global Neuroethics Summit in Daegu, South Korea, the Working Group identified five questions for neuroethicists in the respective Brain Initiatives to take home, contemplate, and address (Global Neuroethics Summit Delegates et al., 2018). As we have described in the framework for the CBRS and through the three specific themes of neurolaw, public discourse, and patient engagement as examples, four questions are in direct sight of the CBRS and its focus on learning, remembering, and adapting: (1) What is the potential impact of a biological model or neuroscientific account of disease on individuals, communities, and society? (2) What are the ethical standards of data collection, and how do local standards compare to those of global collaborators? (3) How could brain interventions impact or reduce autonomy? (4) In which contexts beyond the laboratory bench might an innovative technology be deployed? We emphasize the importance of cross-cultural considerations of privacy, consent, and responsibility as well as training and outreach among many other principles and goals relevant to this neuroethics conversation. We defer the fifth question, pertaining to capabilities that neural cells *in vitro* might reflect or acquire, to later phases of work and ongoing engagement with the International Brain Initiative.

As the full implementation and governance plan of the CBRS unfolds in 2019, it will align with the government of Canada's priorities of knowledge mobilization and translation, innovation capacity building, and a knowledge-based economy. It will build on our existing and many planned global collaborations: for example, with Australia for neurotechnology; with the U.S. for neurodegenerative diseases and disorders in neurodevelopment, including pediatric epilepsy; and with the ERA-NET Neuron Consortium and Human Brain Project for psychiatric neurosurgery and

neuromodulation, among others. Dynamic new initiatives such as the recent Tri-Agency initiative on artificial intelligence and society are on the horizon. The evolution and refinement of the CBRS will follow in the historical footsteps of Canadian neuroethics and be guided actively and collaboratively by the robust and dedicated efforts of contemporary Canadian neuroethics leadership.

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DECLARATION OF INTERESTS

The authors serve pro bono on many advisory boards but declare no financial competing interests.

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