CENTRE CENTER
LUDMER
NEUROINFORMATIQUE & SANTÉ MENTALE | NEUROINFORMATICS & MENTAL HEALTH

PHASE I REPORT, 2013-2017

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The Ludmer collaboration

McGill | neuro | Hôpital général juif Jewish General Hospital | Douglas Institut universitaire en santé mentale Mental Health University Institute

EXECUTIVE SUMMARY

The **Ludmer Centre for Neuroinformatics & Mental Health** was established in 2013 to exploit new research approaches in the study of normal and abnormal brain development. This research has vast implications for understanding and treating mental illnesses, such as attention deficit, anxiety, bi-polar, depression and schizophrenia, as well as neurodegenerative disorders, such as Alzheimer's, autism, Parkinson's and dementia. During Phase I, from 2013 to 2017, the Ludmer Centre established Montreal as a neuroinformatics hub by propelling a big-data research approach across three strategic and integrated axes.

I. Ensuring access to an interconnected neuroinformatics infrastructure and datasets.

The **McGill Centre for Integrative Neuroscience** (MCIN), which was initially created to process data-heavy and computationally intensive neuroimaging research, represented a solid foundation on which to build Canada's big-data research capacities, hence, its selection as the Ludmer Centre's neuroinformatics pillar. Supported by the Ludmer Centre, MCIN technologies have evolved into a powerful tool to explore the brain, enabling researchers to undertake computationally intensive research that combines clinical, psychological and neuroimaging data with genetic and epigenetic (modifications to gene expression) data.

By the end of 2016, MCIN's user-base had grown to 190 virtual sites encompassing hundreds of users across 24 countries, 69% of them in Canada. MCIN technologies power 22 large-scale data-sharing initiatives nationally (13) and internationally (9), an 83% increase from 2013. These include some of the largest national and international Alzheimer's, autism and mental health studies. Secured research grants ensure a well-funded tool-development pipeline into 2022.

As the global neuroscience community converges towards larger, real-time collaborations, MCIN and the Ludmer Centre are solidifying the position of McGill University and Montreal as part of Canada's national neuroinformatics infrastructure. MCIN is a cornerstone of McGill University's successful $84M grant from the Canada First Research Excellence Fund and provides the neuroinformatics infrastructure for the Tanenbaum Open Science Institute. In 2017, MCIN also received two grants ($12M) to roll out Canada's first national neuroinformatics service, as a proof of concept. MCIN is also collaborating with multiple international initiatives to provide services or ensure interoperability (the ability to exchange and process data) with neuroinformatics initiatives in other countries. Through these and MCIN-supported data-sharing initiatives, MCIN is now strategically positioned to connect Canada's neuroscience community to some of the largest data-sharing research initiatives in the European Union, the United States, and Asia.

II. Leading and supporting a 'big-data' approach to brain research.

Building on its capacity for innovation, the Ludmer Centre's research cadre has grown from three to 12 researchers. From 2015 to 2017, Ludmer Centre researchers delivered over 100 scientific lectures and published over 200 research papers, encompassing hundreds of collaborators from prestigious institutions across 16 countries. Key research outcomes include:

- ✓ Ludmer Centre researchers **identified over a hundred genes and developed a candidate polygenetic risk score (PRS)** identifying susceptibility for poor mental health outcomes**.** Collaborations with 11 cohort studies will help to validate the PRS and align future studies of gene-environment interactions (GxE studies).
- ✓ The Ludmer Centre expanded data collection in two studies to include epigenetic datasets—the **first globally to include measures of early-life adversity** with genetic, neuroimaging and behavioural studies.

- ✓ Ludmer Centre researchers **advanced our understanding of Autism Spectrum Disorder**. They found network inefficiencies were already established in the auditory cortex in six-month-old infants. Prior to this, the earliest diagnosis was at 24 months. The extent of the inefficiency at six months also related to the severity of autistic symptoms at 24 months.
- ✓ Ludmer Centre researchers developed **multifactorial mathematical models of disease progression** that advance early-clinical identification and research into Alzheimer's disease (AD). The first models (i) explained how the brain pathology of AD propagates through white matter pathways, (ii) demonstrated that the build-up of toxic amyloid protein resulted from inadequate clearance, rather than overproduction, and (iii) showed that the earliest elements in AD progression involve damage to cerebral blood vessels, not only to Aβ lesions, as previously believed. ***Discover* magazine ranked the research as 12th among the top 100 scientific discoveries of 2016.**
- ✓ These mathematical models are being translated into a software tool that will **advance research in AD and other brain disorders such as Parkinson's, autism, and schizophrenia.** Current collaborations include a Spain-based Parkinson's study, a Montreal-based autism study, and an Argentina-based brain stimulation study.
- ✓ The mathematical model is also being used to characterize individual multifaceted brain signatures – **brain 'fingerprints'– to explain why drugs work in some patients but not in others.** The model is being validated in drug interventions for AD and depression.

Unique GxE studies and global collaborations have positioned the Ludmer Centre as a global leader in the study of epigenetics, child development and mental health. Through mathematical modelling and brain fingerprints, the Ludmer Centre has demonstrated just a small potential of the power inherent in neuroinformatics and data-sharing initiatives.

III. Mentoring and training tomorrow's innovative researchers in big-data research.

To maximize the potential of its neuroinformatics ecosystem and data-sharing initiatives, the Ludmer Centre mentors and trains new researchers. Leveraging the strengths of its research membership, the Centre has created a strong training environment that exposes young researchers to multifactorial data and neuroinformatics approaches. In Phase I, Ludmer Centre researchers welcomed 14 visiting scholars, mentored 28 post-doctoral fellows, and trained 28 students (PhD, Masters). Drawn from a wide range of academic programs, these researchers represented the best and brightest minds from over 25 countries.

Open to all researchers, the Ludmer Centre delivered 22 meetings aimed at fostering a dynamic peer-exchange learning environment as well as nine training workshops to expand understanding and appropriate application of statistical algorithms and software packages and to foster best practices in reproducible research.

Phase I accomplishments demonstrate that the Ludmer Centre has undertaken critical steps towards establishing itself as a global research centre. It is now strategically positioned to scale up a big-data neuroinformatics approach to brain research, ensuring Montreal's positioning as a hub for neuroinformatics leadership and innovation.

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THE LUDMER CENTRE

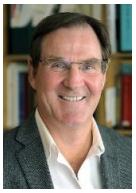
The search for unique genetic causes of specific mental or neurodegenerative disorders has failed. Over the past 30 years, there have been no new treatments. There are no cures. Where they exist, drugs treat only the visible symptoms, not the underlying causal factors. There are still no definitive biological tests (blood, genetic, imagining, etc.) to confirm a diagnosis.

Researchers, across multiple domains, are now challenging illness-specific research approaches and the likelihood of identifying unique genetic causes. Although each individual inherits a genetic blueprint, research shows this blueprint appears to be highly dependent on the response of genes to a complex mix of environmental factors that alter gene expression (epigenetics), including diet, microbiome, social forces and trauma. Today, research is converging towards a holistic approach to human health that combines multimodal datasets including neuroimaging, genetics, epigenetics, and clinical data, among others.

The Ludmer Centre believes **the application of a big-data approach to brain research will revolutionize our understanding of the brain** and our ability to diagnose, treat and prevent neurological diseases and mental illnesses. This approach requires a commitment to increasing data-sharing initiatives, collaborations across longitudinal studies, and open-source access to the tools that make data analytics possible—neuroinformatics—as well as to ensuring researchers have the right skills and support to maximize the potential inherent in big-data research.

Established in 2013 with a generous donation from the Irving Ludmer Family Foundation and officially recognized as a McGill centre in 2016, the Ludmer Centre is a multicentre collaboration encompassing three Montreal-based research institutes: the Douglas Mental Health Hospital Research Centre (the Douglas), the Jewish General Hospital's Lady Davis Institute (JGH/LDI), and McGill University's Montreal Neurological Institute (MNI). A transdisciplinary centre, it brings together researchers across the broad spectrum of neurosciences, engineering, statistics and computer sciences and supports thousands of researchers, nationally and internationally.

The Ludmer Centre is led by three Scientific Directors, world-renowned leaders in their fields, supported by a growing cadre of dynamic researchers that, as of 2017, included nine early-career researchers and 28 post-doctoral fellows.



Dr Alan Evans at the MNI leads the Ludmer Centre's **Neuroimaging and Neuroinformatics** pillars. He is a James McGill Professor of Neurology and Neurosurgery, Psychiatry, and Biomedical Engineering, and the Director of the **McGill Centre for Integrative Neuroscience** (MCIN) at the MNI. In addition to pioneering neuroimaging techniques and advancing research into neurodegenerative diseases, Dr Evans has developed neuroinformatics technologies that now underpin data-sharing initiatives globally — the tools that make big-data analytics possible. The Ludmer Centre would be inconceivable without his innovative infrastructure and unprecedented access to data-sharing initiatives throughout the world.

Dr Michael Meaney at the Douglas Hospital leads the **Genomic and Epigenetics pillar.** He is a James McGill Professor in the departments of Neurology and Neurosurgery and Psychiatry at McGill and the Director of the Sackler Program for Epigenetics and Psychobiology. Dr Meaney's leadership is pivotal. He not only confirmed epigenetics' vital role in brain development but also leads pioneering research and global collaborations into the biological mechanisms through which epigenetic factors alter gene expression to set individuals on a pathway to developing a mental illness.

Dr Celia Greenwood at the JGH/LDI leads the Ludmer Centre's **Genomics, Bioinformatics and Statistical Genetics** pillar. She is a professor in the departments of Oncology, Human Genetics and Epidemiology, Biostatistics and Occupational Health, and the Division of Cancer Epidemiology at McGill, and a Senior Scientist at the JGH/LDI. Dr Greenwood has made significant contributions in genetics, genomics, and genetic epidemiology. She provides the analytical capacity (statistical methods, algorithm development) underpinning the Ludmer Centre's big-data approaches and linkages with other research domains (cancer, genetics) manipulating similar datasets. She also provides the central leadership in the Ludmer Centre's training program for young researchers.

PHASE I ACCOMPLISHMENTS

The Ludmer Centre employs a holistic, transdisciplinary, big-data approach to propel new research into brain development and disorders across three strategic axes:

I. Ensuring access to interoperable neuroinformatics infrastructure and datasets.
II. Leading and supporting a 'big-data' approach to brain research.
III. Mentoring and training tomorrow's innovative researchers to apply a big-data approach.

This report highlights the Ludmer Centre's key accomplishments across these three strategic axes during Phase I, from September 2013 to 2017.

AXIS I, ACCESS TO NEUROINFORMATICS INFRASTRUCTURE & DATASETS

The Ludmer Centre promotes data sharing, open-source tool development, and interoperability between neuroinformatics systems with the goal of one day seeing the emergence of **a common, globally accessible, and cost-effective neuroinformatics infrastructure**.

At the start of Phase I, no Canadian or international initiative could match the neuroinformatics infrastructure and expertise provided by MCIN, which was created to process Dr Evans' data-heavy and computationally intensive neuroimaging research. By the end of Phase I, MCIN's neuroinformatics infrastructure had evolved into a powerful computational platform to explore the brain and to build predictive models of disease risk and progression. MCIN technologies support 22 large-scale data-sharing initiatives encompassing thousands of researchers across Canada, the USA, Asia and Europe.

Ludmer Centre support focused on expanding MCIN's existing capacities to develop an interoperable neuroinformatics service accessible to researchers globally. This included (i) providing leadership in promoting a big-data research approach, (ii) expanding the MCIN technologies and capacity (specifically for epigenetics research), and (iii) positioning MCIN technologies as the infrastructure of choice nationally and internationally.

LEADERSHIP

The Ludmer Centre's Scientific Directors have assumed leadership positions in organizations within their respective domains in order to set standards, propel collaborations and encourage the application of a big-data approach.

- **Dr Evans** co-founded the **International Consortium for Brain Mapping** (1993) and the **Organization for Human Brain Mapping** (OHBM, in 1995), where he is the current Chair. In 2016, he established and currently leads the North American node of the **International Neuroinformatics Coordinating Facility** (INCF). McGill and the Ludmer Centre will host the 2018 INCF and 2020 OHBM conferences.
- **Dr Greenwood** is on the boards of directors of the **Canadian Genetics and Genomics Society** and the **International Genetic Epidemiology Society**. She leads the pan-Ludmer training program and helped to spearhead an interdisciplinary, inter-faculty PhD program for transdisciplinary trainees in big-data research, the McGill **Quantitative Life Sciences** program (commenced Fall 2017), where she is the Director.
- Dr Meaney created the **Canadian Neuroepigenetics Network** in 2013, linking researchers across Canadian universities, to help translate epigenomic studies into clinical practice.

INNOVATIVE NEUROINFORMATICS PLATFORM

The Ludmer Centre's neuroinformatics ecosystem is comprised of two integrated platforms CBRAIN and LORIS (side bar) and related tools (CIVET, MINC, BrainBrowser, BrainWeb, etc.). Together, they enable researchers to manage, manipulate and process extremely large datasets that most computers cannot handled.

Over the course of Phase I, pan-Ludmer collaborations significantly improved and expanded the data-processing and visualization tools. Moving beyond its initial neuroimaging focus, the platform today enables computationally intensive brain research through mathematical and statistical tools that allow researchers to integrate and manipulate clinical, psychological or neuroimaging phenotypes with genotypic and epigenetic data. In keeping with the Centre's mandate to provide neuroinformatics capacities to researchers globally, all tools are accessible as open-source software.

Details on new tools and upgrades to the neuroinformatics platform are available on the MCIN website (www.MCIN.ca). These were the subject of seven publications (with two pending) describing the cyberinfrastructure, best practices and new technologies in open-access peer-reviewed journals.

Among the most notable **additions were an epigenetic toolkit making CBRAIN/LORIS** the first open-source platform to integrate such tools, as well as the development of a new CIVET pipeline enabling foetal/neonatal analyses, NEOCIVET. MNI neurosurgeon Dr Abbas Sadikot and his team, in collaboration with MCIN, also

LORIS is an open-source data-management system for complex studies. It enables researchers from multiple, geographically dispersed locations to integrate multi-modal data into a consistent, searchable datasets within a single web-based informatics platform.

CBRAIN is an open-source science gateway: a web-based research platform providing collaborative and transparent access to remote data sources, distributed computing sites, and an array of processing and visualization tools within a controlled, secure environment.

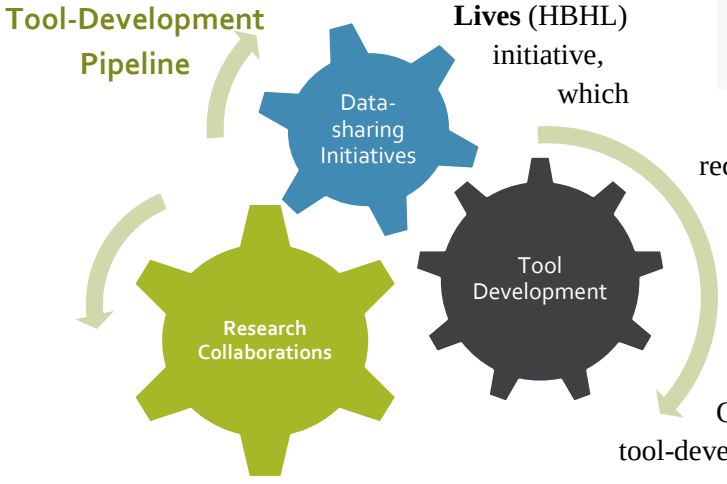
completed the mapping of the basal ganglia in the **BigBrain Atlas** (inset box), which is expected to inform the future of Parkinson's disease surgeries.

Tool-development Pipeline

Maintaining an innovative neuroinformatics platform is reliant on a sustainable tool-development pipeline. This requires the integration of informatics experts into ongoing multi-modal research projects with an established process for creating, validating and moving novel algorithms and tools into an existing neuroinformatics platform. Supported by the Ludmer Centre, MCIN provides this incubator environment through its dedicated 30-member developer team, support for data-sharing initiatives, and extensive network of research collaborations.

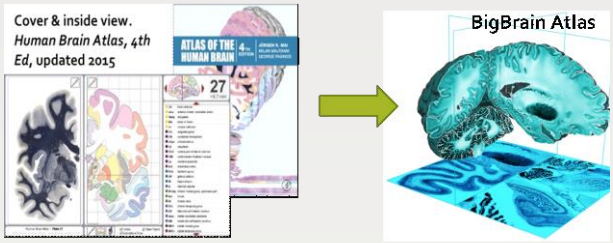
Part of a mutually reinforcing relationship, researchers utilizing MCIN technologies are vital catalysts in and contributors to a dynamic tool-development process (diagram, below). As more researchers utilize MCIN technologies, the type, complexity and breadth of tools expands, drawing in new users and increasing the demand for new tools and support services.

MCIN is providing the neuroinformatics infrastructure for two new McGill initiatives, the **Healthy Brains for Health Lives** (HBHL) initiative, which received $84M from the Canada First Research Excellence Fund, and the **Tanenbaum Open Science Institute** (TOSI, $20M). Ludmer Centre researchers across its four pillars also secured over $20M in new research funding in 2016/17 alone.



Combined, these projects ensure a well-funded tool-development pipeline in support of ongoing research

The Brain Reference Atlas Reimagined



The BigBrain Atlas is the **highest-resolution 3D digital map of the human brain produced to date** — the first major revolution in brain reference atlases since the initial such atlas was introduced in the 1950s. BigBrain was developed on the CBRAIN/LORIS platform by Dr Evans' team in collaboration with the Jülich Research Centre in Germany.

Digitally re-constructed from 7404 human brain slices, it provides a navigable 3D Google-street-view-map equivalent of the human brain. *MIT Technology Review* ranked it among the **top 10 technological breakthroughs of 2014**. It has the potential to revolutionize medical training, neuroscience research and brain surgery.

Swedish-based Interspectral, which creates interactive 3D visualization experiences for education, training and entertainment, has already used the datasets to create six interactive exhibits in science museums across Europe. Once the mapping is completed, brain surgeons will be able to overlay neuro-images of their patients to help guide surgeries in real time.

The goal is to move BigBrain online as an open-access service, creating a platform from which developers, researchers, teaching institutions, and bioscience corporations can contribute to and expand its usability and functionality.

into 2021, allowing MCIN to expand and diversify the types of datasets it supports and the capacity to analyze them.

Data-Sharing Initiatives Powered by MCIN

The growth in CBRAIN/LORIS users also attests to the relevance of the tools. As of the end of 2016, the user-base had increased by 37% to 516 registered users (69% in Canada) across 190 virtual sites representing organizations in 24 countries.

In addition to multiple small studies, as of 2017, the number of **ongoing large-scale data-sharing initiatives powered by MCIN technologies increased** by ten to 22 initiatives (13 national, nine international), covering normal brain development, neurodegenerative diseases and mental health.

These 22 initiatives, which encompass hundreds of researchers globally, have resulted in hundreds of research publications. Key examples include the Canadian Consortium on Neurodegeneration and the (autism) Infant Brain Imaging Study (inset box, left).

These data-sharing initiatives are critical to the challenge of reproducibility in science.[1] They also prevent data loss, increase sample size, and reduce acquisition costs by encouraging data re-use, maximizing returns on public funding.

NEUROINFORMATICS INFRASTRUCTURE OF CHOICE

The Centre's ability to position MCIN technologies as an innovative neuroscience platform capitalized on over two decades of sustained investment from the Canadian government (CIHR CFI, etc.) and foundations (Brain Canada, Compute Canada, etc.), and new funding from philanthropic investors (Jean Coutu Family Foundation, Irving Ludmer Family Foundation). During Phase I, MCIN solidified its position as part of Canada's national neuroinformatics infrastructure, while increasing collaborations and interoperability with international systems.

National Positioning

Among the 22 data-sharing initiatives built on MCIN technologies, 13 are Canadian. MCIN will also providing the neuroinformatics infrastructure for McGill's newly funded NeuroHub (HBHL) and open-science (TOSI) initiatives. Leveraging these initiatives, in 2017, Dr Evans secured key funding and support to expand CBRAIN/LORIS functionality[2] and to roll out, as a proof-of-concept, national neuroinformatics service centres[3] across Canada.

CCNA CCNV

The **Canadian Consortium on Neurodegeneration in Aging** (CCNA) provides the infrastructure and support that facilitates collaboration amongst Canada's top researchers in age-related neurodegenerative diseases: **350+ clinicians and researchers**. MCIN is the data-coordinating centre for the study. By accelerating the discovery, innovation, and the adoption of new knowledge, the CCNA positions Canada as a global research leader in the diagnosis, treatment and prevention of age-related neurodegenerative diseases.

The **Autism Infant Brain Imaging Study** (IBIS) is a collaborative effort of four USA-based university sites. MCIN, the only Canadian partner, is the data-coordinating center. Funded by the National Institutes of Health, the goal is to increase understanding of the timing and pattern of brain development in very young children with autism. The study has already collected close to 10,000 phenotypic and imaging variables, with 4,000 subject time points.

[1] Challenges in Irreproducible Research. (May 2016) Nature international weekly journal of science.
[2] Canadian Fund for Innovation, Cyberinfrastructure Program ($2.9M)
[3] Final confirmation is pending; however, at a Sept. 2016 meeting that convened a broad cross-section of Canadian researchers, the 40 members agreed to and have submit one unified $10M proposal under the leadership of Dr Evans.

The goal is to create a single large-scale, open-science, data-sharing platform to "hardwire" Canadian neuroscience by 2020 and position Canada as a world leader in this area.

MCIN is now strategically positioned to connect Canada's neuroscience community to international research initiatives. For example, in dementia-related research alone, MCIN supports Canada's largest national initiatives (CCNA, CDAN), as well as three Quebec (CIMA-Q, PREVENT-AD, Memory Clinic) and two international (ADNI-Korea, IBRAIN-India) initiatives. MICN also powers some of the largest Canadian (NNCFA[4]), USA (IBIS) and multi-country (ABIDE) autism initiatives.

International Positioning

Concurrent to the initiation of the Ludmer Centre, the European Union and the United States both introduced brain initiatives that sought to develop comparable neuroinformatics infrastructure to MCIN: the USA-based BRAIN Initiative and the EU-based Human Brain Project. Dr Evans successfully leveraged his collaborations and leadership role, as well as MCIN's reputation, to develop strategic partnerships with these initiatives and others. The goal is to encourage the adoption of MCIN technologies or, at a minimum, create interoperable systems.

- **EU Human Brain Project (HBP):** Dr Evans is the HBP's only Canadian partner and a long-time collaborator on two HBP projects. Following the signing of a March 2017 MOU, MCIN commenced the integration of CBRAIN/LORIS technologies into HBP services.
- **USA BRAIN Initiative**: In 2016, Dr Joshua Vogelstein at Johns Hopkins University initiated an MCIN-equivalent neuroinformatics service called the US Brain Hub under the BRAIN Initiative. Dr Evans participated in several BRAIN Initiative consultations and agreed to mentor a PhD student from Dr Vogelstein's lab to facilitate interoperability.
- **Data-sharing initiatives:** Nine of the 22 data-sharing initiatives powered by MCIN are international collaborations (USA, Netherlands, Germany, France, Belgium, Singapore, South Korea, India) in autism, mental health and normal brain development.
- **Emerging markets in Asia**: MCIN technology has a foothold in the two largest emerging markets, India and China. CBRAIN powers India's dementia network, IBRAIN, and a China-Cuba-Canada collaboration built on CBRAIN/LORIS was initiated in 2017 to expand a neuroinformatics approach to neuroscience research across China.

AXIS II, LEADING A 'BIG-DATA' APPROACH TO BRAIN RESEARCH

Ludmer Centre researchers lead and support numerous collaborative and multidisciplinary research studies, nationally and internationally, in the application of neuroinformatics and epigenetic approaches. As well, they contribute to the growing pools of shared datasets. The scientific breakthroughs presented in this section are the culmination of multiple studies, of which only a sampling are represented here (see inset box).

Prolific Output

From 2015 to 2016, Ludmer Centre researchers:

- published over **125 research papers** in peer-reviewed journals,
- encompassing **over a thousand collaborators** from prestigious institutions across five provinces and 16 countries, and
- gave over **100 lectures**.

The Ludmer Centre's research mandate encompasses normal and abnormal brain development, with specific attention to the epigenetic mechanisms underpinning these, the **gene x environment** (GxE) interactions. Further, as part of its

[4] National Neuroinformatics Coordinating Framework for Autism – newly funded in 2017.

commitment to advancing a big-data approach to brain research, the Centre promotes **mathematical modelling** of disease trajectories, and leads research in data-sharing initiatives powered by MCIN. The Ludmer Centre has made significant advances in these areas.

ADVANCING 'GENE X ENVIRONMENT' RESEARCH

The Ludmer Centre believes epigenetics research is vital to understanding normal brain development and to unlocking the genesis of brain disorders. Thus, a major objective is to elucidate the nature of '**gene x environment'** (GxE) interactions that shape individual differences in human development, and the degree to which such influences are mediated by the epigenetic signals that regulate gene expression and brain development. Strategic collaborations and the development of epigenetic neuroinformatics tools combined with the novel research presented below have positioned the Ludmer Centre's Genomic/Epigenomic team as global leaders in the study of the epigenetics of child development and its consequences for mental health.

GxE Studies May Predict Susceptible to Adversity

In Phase I, Ludmer researchers undertook a series of epigenetic studies aimed at characterizing the genetic architecture that explains why some people are extremely sensitive to environmental adversities, while others—seemingly more resilient—are able to thrive. The studies culminated in the creation of a candidate polygenetic risk score (PRS) for susceptibility to adversity as a predictor of poor mental health outcomes. The risk score was developed and validated in two independent human cohort studies (addiction, mental health) and is currently being informed by several studies aimed at distinguishing resilient and susceptible mice. This is an important development as PRS's can be used to detect shared genetic aetiology among traits and as a phenotypic biomarker.[2] Moving forward, the PRS will need to be validated in relation to a range of environmental conditions and health outcomes, which requires access to diverse cohort studies.

The Power of Partnerships

Recognising that GxE interaction studies require replication, validation and adequate statistical power (i.e., significant sample sizes) to elicit meaningful results, throughout Phase I, Dr Meaney's team developed collaborations with a broad array of existing cohort studies: five longitudinal birth cohort studies, three high-risk cohort studies, and three intervention studies, among others. This enabled closer alignment of GxE interaction studies and data collection, as well as studies in which to refine and validate the PRS.

Longitudinal studies of children and their families that document the interplay between environmental conditions (epigenetics) and genetic influences (from conception to adulthood) provide crucial data in the quest to understand the pathways that link the quality of the early environment to specific developmental and mental health outcomes. Supported by the Ludmer Centre, in 2014 and 2015, the Singapore-based GUSTO and Montreal-based MAVAN studies became the first globally to include epigenetics data, providing researchers with data from neuroimaging, genome-wide epigenetic analysis (DNA methylation), genome-wide polymorphism analysis (SNP arrays) and measures of brain-based phenotypes. By 2017, three

more studies had agreed to work together to expand GxE studies: the Netherlands-based GenR, Montreal-based ZEPSOM, and UK-based ALSPAC. Promising findings indicate that variations in a newborn's epigenome are heavily influenced by antenatal maternal mood, but the effect is moderated by the infant's genome.

MATHEMATICAL MODELLING, REVOLUTIONIZING BRAIN RESEARCH

Neurodegenerative and mental disorders are a complex interaction of age and gender, genetics and epigenetics, environment and lifestyle. The Ludmer Centre's goal is to create integrative multifactorial models to explain the interactions that define both normal and abnormal brain development and, ultimately, to develop the tools that will enable doctors to determine which medications will work best for a given individual - personalized medicine approaches. In Phase I, no research better exemplified Ludmer Centre leadership and progress than that of Dr Evans and Dr Yasser Iturria-Medina's groundbreaking work on late-onset Alzheimer's disease (AD).

Through a series of studies, Dr Iturria-Medina developed a mathematical model that explained how the brain pathology of AD propagates through white matter pathways. The model demonstrated that the build-up of toxic amyloid protein resulted from inadequate clearance rather than overproduction. He used this model to analyze data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) databank, demonstrating that the earliest elements in AD progression involves damage to cerebral blood vessels—not only Aβ lesions, as previously believed. These findings have major implications for the design of AD interventions and move the goalpost for both early clinical identification and AD research. The January 2017 edition of ***Discover*** **magazine ranked Dr Iturria-Medina's research as 12th among the top 100 scientific discoveries of 2016.**

Dr Iturria-Medina is finalizing research demonstrating that his mathematical model can be used to characterize individual multifaceted brain signatures – brain 'fingerprints'– to explain why drugs work in some patients but not others. He is also working on translating his mathematical models into a computational research tool (software package) —**the Multifactorial Association Models of Brain (dys)Organization (MAMBO) toolbox** — that will not only advance research in AD but also **other brain disorders such as Parkinson's, autism, schizophrenia, etc.** He is working to identify funding and collaborations to access datasets for AD and other brain disorders. Current collaborations on **multifactorial modelling** include three studies: a Spain-based Parkinson's study, a Montreal-based autism study, and an Argentina-based brain stimulation study. He is also validating his **brain 'fingerprint' model** on a drug intervention for AD and a dissociative anesthetic that holds promise for depression research.

The MAMBO toolbox and 'brain fingerprint' model will not only advance research in Alzheimer's but also research into other brain disorders, such as Parkinson's, autism, schizophrenia, etc.

MCIN's neuroinformatics infrastructure and the 22 data-sharing initiatives it supports, as well as Ludmer Centre collaborations, have been instrumental to advancing this research.

DATA-SHARING ADVANCES AUSTISM RESEARCH

In addition to providing the neuroinformatics infrastructure underpinning large data-sharing initiatives (pg. 7), Ludmer Centre researchers are also leading research utilising the data. Recent

research on Autism Spectrum Disorder by Ludmer Centre researchers Dr Evans and Dr John Lewis demonstrate the potential for such initiatives to revolutionise brain research.

Using data from the MCIN-supported Infant Brain Imaging Study (IBIS, inset box pg.7), the researchers found network inefficiencies were already established in the auditory cortex in six-month-old infants. Prior to this, the earliest diagnosis was at 24 months. Dr Lewis also found the extent of the inefficiency at six months of age was positively related to the severity of autistic symptoms at 24 months. As the children aged, areas involved in processing of vision and touch, as well as a larger set of areas involved in sound and language, also showed a similar relation between inefficiency and symptom severity. The ability to identify the point at which autism begins to take shape in the human brain may allow for diagnosis before behavioural changes appear, leading to earlier intervention and better prospects for a positive treatment outcome.

The origins of autism are still unknown; however, by pinpointing the brain regions involved in processing sensory inputs as the earliest known locations of neural dysfunction related to autism, we can narrow down the genetic factors and mechanisms that could be responsible for its development. The fact that neurological signs are already present at six months also eliminates some environmental factors (epigenetics) as potential causes of the disorder.

AXIS III, INVESTING IN THE FUTURE

The Ludmer Centre aims to develop transdisciplinary research cadres capable of maximizing the potential of its neuroinformatics infrastructure and large multivariate datasets by mentoring and training new researchers—the next generation of brain science innovators and leaders. In Phase I, Ludmer Centre researchers welcomed 14 visiting scholars, mentored 28 post-doctoral fellows, and trained 20 PhDs and 8 MSc/undergraduate students. In addition to drawing researchers from a wide range of programs, these trainees represent the best and brightest intellects from over 25 countries.

As part of its training program to instil a big-data approach, the Ludmer Centre organised training activities aimed at Ludmer Centre research members and the broader research audience.

- **Individualised training:** One-on-one training was provided to researchers and trainees to help identify the best analytical strategies/algorithms for their data and research.
- **Working Groups:** Researchers and trainees participating in two pan-Ludmer working groups were mentored and supported to develop, test and add new software programs (bi-products of their research) to the neuroinformatics platform.
- **Research & Peer Exchange:** The Centre organised 22 meetings aimed at fostering a dynamic peer-exchange learning environment across Montreal-based institutions.
- **Specialised training workshops:** The Centre provided nine workshops aimed at expanding understanding and the appropriate application of statistical algorithms.

The Ludmer Centre's diverse and dynamic Phase I mentorship program successfully leveraged the strengths of its research membership to create a strong multidisciplinary training environment that exposes young researchers, in and outside of the Ludmer Centre, to big-data and neuroinformatics approaches.