*The **Ludmer Centre** leads research in both normal brain development and brain disorders: neurological and mental disorders. This brief focuses on the **Centre's research in Alzheimer's disease and dementia**.*

Alzheimer's & Dementia Research

Big-data in Dementia Research

Dementias affect millions of people across Canada (right) and 46.8 million people worldwide – a number set to double every 20 years (WHO, 2015). The most common cause of dementia, late-onset Alzheimer's disease, is not caused by a single neurological mechanism but is the product of several associated brain mechanisms influenced by an individual's genes and lifestyle.

Neurodegenerative disorders such as dementias are a complex interaction of age and gender, genetics and epigenetics, environment and lifestyle. An understanding of these complex interactions is essential to the identification of early-detection biomarkers and the development of drug treatments that can postpone onset or even avert it, and is now, more than ever, a possibility thanks to transdisciplinary big-data approaches.
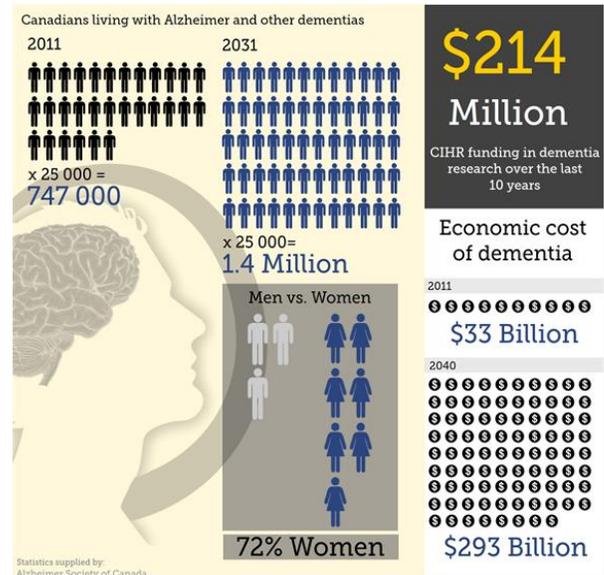
The **Ludmer Centre for Neuroinformatics & Mental Health** aims to advance neuroscience research through the application of big-data analytics. Our goal is to **create integrative multifactorial models** to explain the interactions that define both normal and abnormal brain development and, ultimately, to develop the tools that will enable doctors to determine which medications will work best for a given individual - personalized medicine approaches. This includes **developing the vital data-sharing initiatives** and **neuroinformatics tools** that make big-data analytical research possible.

This brief outlines the leadership and contributions of the Centre's researchers, specifically Dr Alan Evans and Dr Yasser Iturria-Medina at the McGill Neurological Institute (MNI), and the neuroinformatics infrastructure creating a tipping point in our ability to advance Alzheimer's and Dementia research.

Leading Alzheimer's & Dementia Research

Advanced imagining techniques[1] are playing an increasingly important role in basic and clinical dementia research aimed at identifying early-detection signs and disease biomarkers. **Ranked among the top 1% of cited researchers**, Dr Evans is a world authority on imaging technologies, brain mapping and neurological research. In recognition of this body of research in Alzheimer's disease alone, in November 2017, the Senate of Canada awarded him the **Canada 150 medal**. Underpinning this research has been the gradual and systemic construction of a big-data research approach: neuroinformatics.

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[1] e.g., MIR, fMIR, PET

Understanding how neurological diseases interact with the brain's vascular, functional and structural connectivity networks remains a challenge, complicated by the increasing number and complexity of the datasets. Extracting meaningful results is no longer possible without a big-data approach, specifically algorithms that condense complex processes and mathematical modelling that combine these diverse datasets into visual models that help us understand and theorise about disease trajectories – how, when and why they start and progress. **Dr Iturria-Medina** is one of the most promising new researchers in multifactorial mathematical brain modelling.

Big-data - a tipping point in Alzheimer's research

No research better exemplifies the potential inherent in a big-data research approach than the recent ground-breaking work on late-onset Alzheimer's disease led by Dr Evans and Dr Iturria-Medina. Through a series of cumulative studies, Dr Iturria-Medina developed a mathematical model that explained how the brain pathology of Alzheimer's disease propagates through white matter pathways. The model demonstrated that the build-up of toxic amyloid protein resulted from inadequate clearance rather than overproduction. He then used this model to analyse data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) databank, demonstrating that the earliest elements in Alzheimer's progression involves damage to cerebral blood vessels—not only Aβ lesions, as previously believed. Dr Iturria-Medina is currently validating the multifactorial model in collaboration with an Alzheimer's study at the Douglas Hospital.
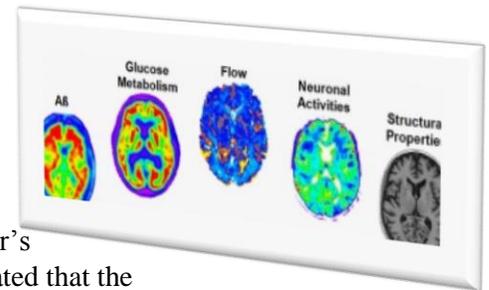
The findings have major implications for the design of Alzheimer's interventions and move the goalpost for both early clinical identification and Alzheimer's research. The January 2017 edition of *Discover* magazine ranked this research as 12th among the **top 100 scientific discoveries of 2016.**

Taking research to the next level

Dr Evans team intends to extend this analysis to the study of tau protein propagation using PET data. This will allow for an understanding of the different pathological processes that are associated with concurrent beta-amyloid and tau transmission as well as the interaction between them.

Dr Iturria-Medina is working on translating his mathematical modelling into a computational research tool (software package) —**the Multifactorial Association Models of Brain (dys)Organization (MAMBO) toolbox** — that will not only advance research in Alzheimer's disease but also other brain disorders such as dementia, Parkinson's, autism, schizophrenia, etc.

Taking this research to the next level, Dr Iturria-Medina is also finalizing research demonstrating that his mathematical model can be used to characterize individual multifaceted brain signatures – **brain fingerprints** (left) **– to explain why drugs work in some patients but not others**. The next step will be to validate the 'brain fingerprint' model on a drug intervention for Alzheimer's disease.
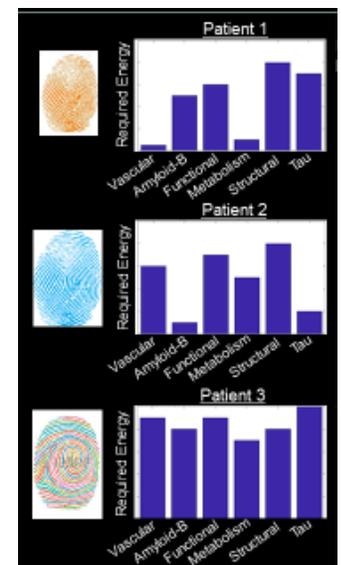
Over the past 30 years, research has increasingly linked moderate and severe traumatic brain injury to a greater risk of developing Alzheimer's disease or other types of dementia years after the original head injury. Dr Iturria-Medina collaborated in a 2017 study led by Dr Sébastien Tremblay that takes the first steps toward developing an objective tool for diagnosing a history of sports concussions in ex-athletes.

To learn more about how Dr Evans, Dr Iturria-Medina and McGill researchers are using big data to advance research, watch the 2017 lecture, **Alzheimer's and Dementia Research Powered by Big Data.**

Unrivalled Neuroinformatics Ecosystem

Neuroinformatics technologies are what makes big-data analytics in neurosciences possible. With over 20 years invested in research and development and a dedicated team of over 30 neuroinformatics experts, no other Canadian or international initiative can match the neuroinformatics ecosystem and expertise of Dr Evans lab, the [McGill Centre for Integrative Neuroscience](#) (MCIN), nor its proven record of accomplishment for high-powered computing and analytics in brain research.

Neuroinformatics systems have to be interoperable

In order to maximise the potential in neuroinformatics technologies, the individual **tools (apps) and platforms** on which they run **have to be interoperable**: able to exchange and automatically interpret data meaningfully and accurately. To achieve this, Dr Evans helped lead the interoperability movement by providing his own neuroinformatics platform as open-source software. He also co-founded international standard-setting bodies: 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.

The MCIN neuroinformatics ecosystem is comprised of two integrated platforms CBRAIN and LORIS and related tools (CIVET, MINC, BrainBrowser, BrainWeb, BigBrain Atlas, etc.). Combined, they enable researchers to manage, manipulate and process neuroimaging, behavioural, genetic and epigenetic datasets. In addition to over 20 data-sharing initiatives, MCIN technologies also underpin major research initiatives at the Montreal Neurological Institute and Hospital, the Ludmer Centre, the Health Brain for Health Lives initiative, and the new Tanenbaum Open Science Institute (TOSI). In 2017, Dr Evans also secured key funding to roll out, as a proof-of-concept, neuroinformatics service centres across Canada.

Data-sharing, the building blocks of research

Working in disciplinary silos, individual researchers, thanks to recent technological advancements, have been amassing critical datasets over a growing number of fields. Although they produce potentially promising results, the number and types of datasets collected by individual researchers are seldom complex or large enough to derive statistically significant findings. The ability to maximise the combined potential of such datasets (neuroimaging, genetics, epigenetics, behavioural, etc.), until recently, was locked away behind a culture of proprietary research and inadequate tools for data analysis.

Shared data repositories prevent data loss, increase sample size, and are critical to [scientific reproducibility](#). They reduce acquisition costs by encouraging data re-use, thereby maximizing returns on research funding. In addition to developing the neuroinformatics platform and tools that enable today's large-scale data-sharing initiatives to occur, for the last 20 years Dr Evans has been a **leading driver of local, national and international data-sharing initiatives in Alzheimer's and dementia research**.

In addition to these data-sharing initiatives (inset box, below), Dr Evans' neuroinformatics ecosystem also underpins multiple large-scale data-sharing initiatives in normal brain development as well as in epigenetics and early childhood development. Although the causes of Alzheimer's disease are ill understood, the involvement of [epigenetic mechanisms in memory formation](#), either under pathological or physiological conditions, is clear. Increased access by research globally to these data-sharing initiatives is propelling rapid innovations and new findings in Alzheimer's and dementia research.

Through MCIN, **McGill and the Montreal Neurological Institute and Hospital (the Neuro) are strategically positioned to connect Canada's neuroscience community in Alzheimer's and dementia-related research,** both nationally and internationally.

Data-sharing powered by MCIN

Canadian Consortium on Neurodegeneration in Aging (CCNA), 2014-ongoing

CCNA is Canada's research hub for all aspects of research involving neurodegenerative diseases that affect cognition in aging.. It is the Canadian component of the largest international dementia study (CIHR's Dementia Research Strategy) for research on preventive, diagnostic and treatment approaches to Alzheimer's disease and related dementia. The CCNA Scientific Director is Dr Howard Chertkow, Director of the Bloomfield Centre for Research in Aging at the Jewish General Hospital.

Consortium pour l'Identification précoce de la Maladie d'Alzheimer–Québec (CIMA-Q), 2013-ongoing

Quebec's Alzheimer's neuroimaging network regroups 90 researchers and clinicians and promotes Québec expertise. It has set up platforms for research on reliable predictive cognitive tests, neuroimaging markers, biomarkers, and the identification of risk and preventive factors. It is recruiting 400 participants.

Korea Alzheimer's Disease Neuroimaging Initiative, an international imitative (K-ADNI), 2013-ongoing

K-ADNI is registry for Alzheimer's disease and subcortical ischemic vascular dementia in Korea. The study and datasets contribute to the international ADNI data-sharing initiative. The study is recruiting five hundred subjects.

PREVENT Alzheimer's Program (PREVENT-AD), Douglas Hospital, Montreal, 2012-ongoing

The PRe-symptomatic EValuation of Experimental or Novel Treatments for Alzheimer's Disease or PREVENT-AD study is the principal clinical research activity of the Centre for Studies on Prevention of Alzheimer's Disease, or StoP-AD Centre. The goal is to identify biomarkers that will provide the best chance of prevention. Dr John Breitner, Director of the Centre for Studies on Prevention of Alzheimer's Disease at the Douglas Hospital.

Indian Brain Imaging Research Network (IBRAIN), National Brain Research Centre, India, 2010-ongoing

IBRAIN is a national multi-center neuroimaging study lead by Dr Prasun Roy promoting nation-wide multi-disciplinary research in neuroscience across 45[+] centres and integration with international imaging networks.

Canadian Dementia Action Network (CDAN), 2010-ongoing

CDAN brings together Canada's world-class biomedical researchers and clinicians for the purpose of quickly identifying promising treatments for Alzheimer's disease and related dementias (ADRD).

Centro de investigación y asistencial de referencia internacional en la enfermedad del Alzheimer (CITA), Spain, 2010-ongoing

CITA has developed a Alzheimer's research platform for CITA researchers in disease, linking Spanish researchers to international initiatives.

Moe Levin Memory Clinic, the Douglas Hospital, Montreal, ongoing

The Program for Dementia with Psychiatric Comorbidity (PDPC) provides highly-specialized clinical care, teaching and research to a clientele with mild to severe cognitive loss, combined with psychiatric and behavioural problems.

AddNeuroMed, Europe, 2005-ongoing

A pan-European multi-centre initiative to help identify and test biomarkers for Alzheimer's disease (brain scan, a blood or spinal fluid test or some other measure of brain activity or function). The AddNeuroMed repository (collection finalized, 2008) is compatible with the ADNI study and available to researchers, on request, since 2009.

NeuGrid 2008-2011; **N4U** 2011-ongoing, Europe

NeuGRID, and its expansion neuGRID for you (N4U), is a web portal to (i) help neuroscientists in Alzheimer's, psychiatric, and white-matter research do high-throughput imaging research, and (ii) provide clinical neurologists automated diagnostic imaging markers of neurodegenerative diseases for individual patient diagnosis.

OutGRID, Europe, 2009-2012

One of the first initiatives to establish a worldwide e-infrastructure for computational neuroscientists through interoperability between the European neuGRID, Canadian CBRAIN (MCIN) and US LONI Alzheimer's initiatives.