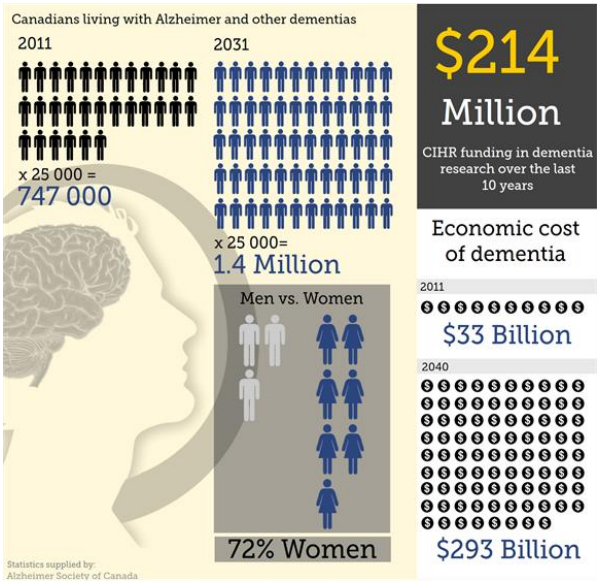
*The **Ludmer Centre for Neuroinformatics & Mental Health** leads research in both normal brain development and brain disorders: neurological and mental disorders. This brief focuses on the **Centre's research in Alzheimer's disease and dementia**.*

Alzheimer's & Dementia Research

Dementias affect millions of people across Canada (right) and some **50 million people worldwide** – a number set to double every 20 years (WHO, 2017). Only 1-in-4 people are diagnosed. The most prevalent types are late-onset Alzheimer's disease, especially in high-income countries, followed by vascular dementia, in mid-to-low income countries.



No cure – current **medications only marginally improve symptoms** and are highly patient dependent; none slow or stop neuronal damage, and prevention is ill understood.

Dementia is not caused by a single neurological mechanism. It is the product of several associated brain mechanisms and the death of neurons, arising from a multitude of largely unknown causes stemming from a complex interaction of age and gender, genetics and epigenetics, environment and lifestyle. **Understanding these interactions is essential to the identification of early-detection biomarkers** and the development of drug treatments that can postpone onset or even avert it, which is now, more than ever, a possibility thanks to transdisciplinary big-data research approaches.

The **Ludmer Centre for Neuroinformatics & Mental Health** advances brain research through the application of big-data analytics to neuroscience research encompassing genetics, epigenetics, imaging and behaviour datasets, among others. Our goal is to **create integrative multifactorial models** to explain the interactions that define both normal and abnormal brain development and, ultimately, to develop personalized medicine approaches: the tools that will enable doctors to determine which medications will work best for a given individual. 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 innovative neuroinformatics infrastructure creating a tipping-point in our ability to advance this research.

Leadership in 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 biomarkers. **Ranked among the top 1% of cited researchers**, **Dr Evans** is a world authority in imaging technologies, brain mapping and neurological research. In recognition of this body of research in Alzheimer's disease alone, in November 2017, the

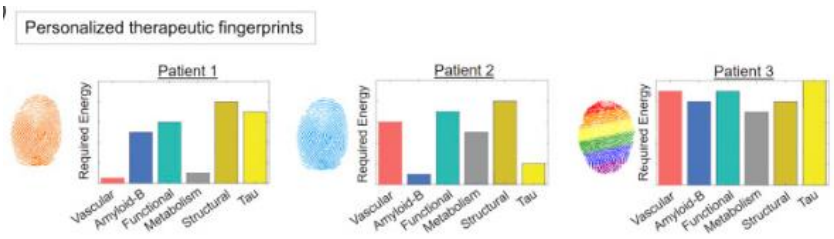
[1] e.g., structural (e.g., MRI), functional (e.g., fMIR, PET, EEG) and multimodal (Connectomics) techniques.

Senate of Canada awarded him the **Canada 150 medal**. Underpinning his research has been the gradual and systemic development of **big-data neuroscience techniques and algorithms: neuroinformatics**. These include computational tools that automate complex mathematical data-processing and modelling so that research results, which previously took years and months to calculate, are rendered in days or hours.

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

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, they 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. Dr Iturria-Medina then used this model to analyse data from the Alzheimer's Disease Neuroimaging Initiative databank, demonstrating that the earliest elements in Alzheimer's progression involves damage to cerebral blood vessels—not only Aβ lesions, as previously believed. The January 2017 edition of ***Discover*** **magazine ranked this research 12th among the top 100 scientific discoveries of 2016.**



Building on this, Dr Iturria-Medina used multimodal neuroimaging data to create the equivalent of therapeutic brain fingerprints - **unique brain signature profiles** (image)- that enable us to separate those diagnosed with Alzheimer's into distinct groups based on their brain 'fingerprint' (published June 2018). The existence of these unique profiles also helps to explain why Alzheimer's drugs work for one person but not another, a critical first step in the ability to implement personalised medicine strategies.

Dr Iturria-Medina also 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. 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.

Companies like Eli Lilly, Eisai, Roche, Pfizer, AstraZeneca, Biogen, and Merck & Co. have devoted billions to research, with almost zero returns. Among the reported 400^{+} clinical trials, there is nearly a 100% failure rate (compared to 81% for cancer) and no new therapies have emerged in the last decade.[2] In addition to having major implications for the design of Alzheimer's interventions and drugs, the research being led by Dr Evans and Dr Iturria-Median, specifically the brain fingerprint findings, moves the goalpost for advancing dementia research and developing drug treatments and early clinical identification tools.

[2] Sai Janani Ganesan. How Close Are We To A Cure For Alzheimer's? Feb 13, 2018 Forbes

Powering data-sharing initiatives

Canada-Cuba-China Initiative, 2018-ongoing

Canadian Consortium on Neurodegeneration in Aging, 2014-ongoing

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

Korea Alzheimer's Disease Neuroimaging Initiative, an international imitative, 2013-ongoing

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

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

Canadian Dementia Action Network, 2010-ongoing

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

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

AddNeuroMed, Europe, 2005-ongoing

NeuGrid 2008-2011; N4U 2011-ongoing, Europe

OutGRID, Europe, 2009-2012

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 25 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) in the MNI, nor its proven record of accomplishment for high-powered computing and big-data analytics in brain research. MCIN is also the neuroinformatics arm of the **Ludmer Centre for Neuroinformatics & Mental Health**.

In lay terms, the neuroinformatics platform, like the Microsoft Office Suite, is a multi-tool, turnkey software solution, albeit more complex, for neuroscience research; one that is linked to unlimited computational processing capacity to store, process and analyse multivariate datasets. Dr Evans' neuroinformatics ecosystem is comprised of the CBRAIN/LORIS platform and a host of specialised tools that enable researchers to manage, manipulate and process neuroimaging, behavioural, genetic and epigenetic data, among others.

Increased access to data-sharing initiatives is also propelling rapid innovations and new findings in Alzheimer's and dementia research. These initiatives prevent data loss, increase sample size, are critical to scientific reproducibility, and are cost effective. Dr Evans has been a **leading driver in over 25 national and international data-sharing initiatives, twelve in Alzheimer's and dementia research** (see list in sidebar).

Dr Evans' neuroinformatics technologies, CBRIAN/LORIS, underpin major research initiatives at McGill, the MNI, and the Ludmer Centre as well as new initiatives, launched in 2017, to roll out national neuroinformatics platforms in Canada, the European Union, and Asia. Ultimately, Dr Evans hopes to link these initiatives through their shared neuroinformatics base (CBRIAN/LORIS) and expand collaborative international research capacity through a Global Brain Consortium of leading neuroscientists.

Supporting the development of a shared-access open-source neuroinformatics platform has become increasing critical in a world where pharmaceutical companies are becoming more risk-averse. The repeated failure of clinical

trials, combined with the overall complexity and cost of developing and maintaining proprietary neuroinformatics platforms, is forcing many pharmaceutical companies to scale back on neuroscience research. Pfizer, with its 2018 decision to abandon decades of research in Alzheimer's and Parkinson's, is the first of what could become an alarming trend.

To maintain the momentum behind Alzheimer's and dementia research, we need to invest in neuroinformatics technologies capable of propelling this research and share them with researchers globally. McGill, the Neuro and the Ludmer Centre are committed to see this happen.

Taking research to the next level

As a next step in the scientific validation process, Dr Iturria-Medina is looking for research **funding to revalidate and expand his 'brain fingerprint' model on other dementia and Alzheimer's datasets**, as well as in clinical trials testing drug interventions.

Dr Iturria-Medina is also 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, among others.

Dr Evans' teams is seeking funding to **expand the capacity of the neuroinformatics platform** to include new functional and multimodal imaging technologies and to ensure researchers globally can access these tools. As more questions about the complexity and functions of the brain arise, so too does the need for more advanced experimental tools, specifically, ones that can be **cost-effectively transitioned to clinical practice (**e.g., EEG: electroencephalography**)**.

Increased **functional imaging capacity** will enable Dr Evans team to extend data analysis to the study of tau protein propagation in Alzheimer's disease using Positron Emission Tomography (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.

Multimodal neuroinformatics capacities, such as those in the emerging field of **connectomics** (such as, EEG**)** will enable researchers to explore, for the first time, the macro architecture of the brain's neuro connectivity and to characterize disturbances of interconnected neural systems in specific brain regions. Researchers believe traumatic stress may impair the integrity of the brain's nerve connections and cause the debilitating problems suffered by those with neurological and a mental health problems. Connectomics research is already yielding new insights into Alzheimer's disease and schizophrenia.

The overarching goal of future research and neuroinformatics-development initiatives is to facilitate global research towards understanding the human brain and the development of neuroimaging biomarkers for Alzheimer's and dementia, which will permit early identification, tailored treatments for individual patients, and, eventually, prevention.

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,** or contact us for a visit.

Contact: Joanne Clark, Administrative Director, Ludmer Centre for Neuroinformatics & Mental Health
E joanne.clark@mcgill.ca | Cell +1 514 265 3408 | C/O Neuro Development Office, McGill University
3661 Rue University, #12 | Montréal, Québec | H3A 2B3