ABSTRACT: Because individuals develop dementia as a manifestation of neurodegenerative or neurovascular disorder, there is a need to develop reliable approaches to their identification. We are undertaking an observational study (Ontario Neurodegenerative Disease Research Initiative [ONDRI]) that includes genomics, neuroimaging, and assessments of cognition as well as language, speech, gait, retinal imaging, and eye tracking. Disorders studied include Alzheimer’s disease, amyotrophic lateral sclerosis, frontotemporal dementia, Parkinson’s disease, and vascular cognitive impairment. Data from ONDRI will be collected into the Brain-CODE database to facilitate correlative analysis. ONDRI will provide a repertoire of endophenotyped individuals that will be a unique, publicly available resource.


Keywords: Neurodegeneration, Dementia, Alzheimer’s, Amyotrophic Lateral Sclerosis, Frontotemporal Dementia, Parkinson Disease, vascular cognitive impairment

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Dementia is the single greatest cause of neurological disability in our senior population, with a global incidence of 47.5 million cases. The annual cost of caring for dementia in Canada is $15 billion—a figure expected to grow to nearly $153 billion by 2038— including a tenfold increase in demand for long-term care. The cumulative global cost of Alzheimer’s disease (AD) and...
dementia is currently estimated to be $605 billion, which is equivalent to 1% of the entire world’s gross domestic product. This figure will continue to grow unless disease-modifying interventions are found to alter these alarming trends. Key to any such initiative will be the ability to identify early and accurately those individuals who are at risk for developing a dementia, either as an independent disease process or as a comorbidity of a related neurodegenerative or neurovascular disorder.

Here, we describe the Ontario Neurodegenerative Disease Research Initiative (ONDRI), a prospective cohort study that will use a multimodal approach to predicting the occurrence or progression of cognitive or neuropsychological impairment in a defined patient population. Disease progression will be monitored in 600 patients from across Ontario, Canada, for up to 3 years using rigorous evaluations across multiple assessment platforms, including neuroimaging, detailed neuropsychological evaluations (including comprehensive speech and language assessments), genomics, evaluations of cognitive control of eye movements and retinal layer thickness and morphology, gait performance, and neuropathology.

Patients will be enrolled in the study with either (1) AD or amnestic single or multidomain mild cognitive impairment (MCI), (2) amyotrophic lateral sclerosis (ALS), 3) frontotemporal dementia (FTD), (4) Parkinson’s disease (PD), or (5) vascular cognitive impairment (VCI). These disorders were selected based on their prevalence within the aging population and the frequent occurrence of neuropsychological dysfunction in each at various stages over their course. Amongst these, AD pathology is the most common, underlying approximately 63% of all dementia cases. Although objective memory loss characterizes amnestic MCI, unlike AD, the cognitive impairment does not significantly disrupt daily functioning. Although traditionally considered to be a disorder of upper and lower motor neurons, more than 50% of ALS patients will exhibit neuropsychological deficits that range from subtle syndromes of cognitive or behavioural dysfunction, including impairments in social cognition, to FTD. When present, frontotemporal dysfunction in ALS is associated with a reduction in survival by approximately a year. PD affects approximately 1 in 1000 in the general population and 1 in 100 individuals older than age 65 years. The prevalence of PD is expected to double by the year 2030. Similar to ALS, a significant proportion of PD patients present with or will develop neuropsychological dysfunction and, over time, dementia (PD dementia) develops in more than 80%. FTD, including subtypes of primary progressive aphasia, progressive nonfluent aphasia, semantic dementia, and behavioural variant FTD, accounts for 20% of early-onset dementia cases with symptom onset commencing at 45 to 65 years of age. Finally, VCI is the second most common form of dementia, with 30% of stroke patients developing dementia. The risk of stroke and dementia rises exponentially with each decade after age 65, with one-third of our population expected to have a stroke, dementia, or both in their lifetime.

We hypothesize that this multimodal approach will rapidly detect meaningful neuropsychological change over a short interval, allowing for the early and accurate prediction of the presence of, or progression of, dementia. We further hypothesize that we will identify different forms or profiles of dementia that will map onto specific neural circuits, some shared and some differing across disorders depending on the hubs primarily affected. Further, the study will examine the contribution of small-vessel pathology to each of these disorders given the increasing recognition of the prevalence and potential synergistic effects of this important comorbidity. In this paper, we describe the core components of ONDRI.

**Methods**

**Participants**

Six hundred participants who have one of the following diseases: AD/MCI (150: 75 AD; 75 MCI); ALS (90); FTD (60); PD (150); or VCI (150) will be enrolled into this longitudinal study from multiple centres throughout Ontario (Figure 1). Inclusion and exclusion criteria for the study as a whole, for each disease entity, and for each platform are delineated in the Supplementary material. Ethics approval was obtained from all participating institutions. Each participant will have a study partner and will be evaluated using multiple assessments for a total of 7 to 8 hours annually (unless otherwise specified) (Table 1).

For each platform, the respective assessment tools are listed in Table 1. To be eligible for the study, each patient must be capable of completing each component, with the exception of the neuropsychological evaluation at baseline and at follow-up visits. In addition to their comprehensive demographic information will also be collected, and a detailed medical and family history obtained. Patients with FTD will also undergo electrophysiological studies at baseline and at 1 year to document the presence or absence of lower motor neuron dysfunction. For the ALS cohort, participants will complete a neuromuscular examination and forced vital capacity evaluation at baseline and at follow-up visits. In addition to their annual visits, participants will complete a 6-month telephone visit that will include the clinical questionnaires and the telephone version of the Montreal Cognitive Assessment.

**Neuropsychology**

Eight neurocognitive domains will be evaluated (Table 1 and Supplementary material). These domains are broad-based and include attention, processing speed, memory, speech production, language, intelligence, and visuospatial function, with a particular focus on cognitive domains that reflect frontal network functioning, including complex attention, executive functions, and social cognition. Furthermore, in accordance with the goal of discerning the effect of vascular disease on each neurodegenerative disease under study, the composition of tests reflects the recommendations of the VCI harmonization standards. Participants and their study partners will complete a series of questionnaires that provide measures of neuropsychiatric functioning, meta-cognitive skills, personality, and activities of daily living. The neuropsychological evaluation is being conducted in all participants annually, with the exception of ALS participants who will be evaluated biannually given the nature of the disease and its rapid progression.
Gait

A standardised protocol for assessing balance and gait under single and cognitive demanding dual-task conditions will be used. Static balance (stationary standing) will be assessed using wireless force board technology and accelerometry under eyes open and closed visual conditions during 30-second trials. Estimates of centre of pressure and centre of mass sway will be computed. Gait, which demands dynamic stability, will be assessed using wearable accelerometry (Gulf Coast) bilaterally at ankle and hip or an electronic walkway (GAITRite System or PKMas System). Gait will be assessed under two task conditions: (1) preferred walking alone (single task) and (2) dual-task walking performing a concurrent secondary cognitive task. The secondary tasks include: (a) counting backwards from 100 by ones, (b) subtracting serial sevens from 100, and (c) naming animals. All cognitive tasks will be performed out loud and no instruction to prioritize the gait or cognitive task will be provided, allowing both gait and cognitive tasks to vary naturally. Gait characteristics (e.g. velocity, cadence, step length, step and stride time variability) and dual-task gait cost (%) will be calculated. Dual-task cost will be calculated as ([single-task gait value – dual-task gait value]/simple-task gait value) × 100. Step/stride time variability will be calculated as the coefficient of variation for stride time: Coefficient of variation = (standard deviation of stride time/mean stride time) × 100.

Genomics

Each ONDRI participant will be screened for mutations within a panel of neurodegenerative disease genes that was selected, curated, and reviewed by neurodegeneration researchers (Table 1). Specifically, next-generation sequencing technology is being deployed to identify any genetic variation using ONDRISeq. In conjunction, we are genotyping all participants for >250,000 single-nucleotide polymorphisms (SNPs) associated with neurodegeneration as represented on the NeuroX chip. Apolipoprotein E ε4 allele carrier status, which is a risk factor for not only AD but possibly for poststroke dementia and PD dementia, is being evaluated. All ONDRI participants will be genotyped for the C9ORF72 expansion using amplicon length polymerase chain reaction analysis and repeat-primed polymerase chain reaction as previously described.

Ocular Assessments

For the ocular platform, individuals with glaucoma will be excluded.

Ocular I: Eye Tracking

All eye tracking will be conducted with a portable Eyelink 1000 Plus eye tracker (SR Research, Ottawa, Canada). Participants will perform three specific tasks including a pro-saccade and an anti-saccade task. In the former, simple sensory motor function will be evaluated by the patient looking from a central fixation point to the target, thus eliciting a highly automatic response that is used to determine the shortest latency of visually triggered saccades and saccade metrics to assess the integrity of the visual and motor pathways. In the latter, the participant will be instructed to look away from the stimulus. This task dissociates sensory and motor processes and measures flexible behavioural control. Participants must suppress the automatic pro-saccade, invert the target vector, and then generate a voluntary anti-saccade. Dynamic free viewing will be used to evaluate the relative components of top-down and bottom-up attention to processing scan paths during unstructured free viewing of video clips. The participant will view video clips that switch randomly every 2 to 4 seconds from one scene or event to another (this is similar to watching television where the channel changes are out of their control). Every time the clip changes, the top-down system (willed processes) loses the ability to guide the next two to three saccades and the bottom-up system (reflective processes) takes over.

Ocular II: Spectral Domain Ocular Coherence Tomography

The Heidelberg Spectralis spectral domain ocular coherence tomography (SDOCT) Blue Peak instrument (Heidelberg Engineering GmbH, Heidelberg, Germany) will be used to quantify retinal nerve fibre layer thickness. This instrument allows...
for infrared, fundus autofluorescence, and SDOCT imaging and will include Nsite Axonal Analytics software. The Spectralis uses a 870-nm center wavelength super luminescent diode and it can acquire up to 40,000 A-scans/second with a depth (z-plane) resolution of 7μm and a transversal (x, y-plane) resolution of 14μm in the retina. The number of A-scans, or pixels, within the image determines the transversal resolution and this can be adjusted by the operator. High-resolution mode provides 5μm transversal resolution, whereas high-speed mode provides 11μm resolution because the distance between A-scans is doubled. An online eye-tracking device decreases motion artifacts, whereas the high scanning speed reduces the impact of involuntary eye movements.
protocols (Table 1) are run on each subject in the following order:

- Proton density (PD)/T2-weighted scan (resolution time [TR] resolution) used for volumetric assessment of brain structures,
- Fluid-attenuated inversion recovery (TR = 9000 ms, TI = 2250-2500 ms) for the assessment of white matter hyperintensities,
- Gradient echo (TR = 650 ms, TE = 20 ms) for the assessment of tissue microbleeds,
- Resting state functional MRI (TR = 2400 ms, TE = 30 ms, flip angle = 70°, 3.5 mm isotropic resolution, 250 volumes, 10-minute acquisition time) for the evaluation of brain network activity,
- Diffusion tensor imaging (2 mm isotropic resolution, 30 to 32 directions, b-value = 1000) for the evaluation of white matter structural integrity.

The total time required for all imaging is approximately 45 to 50 minutes. All images are uploaded to the Brain-CODE database and undergo rigorous quality control to assess protocol adherence and evaluate signal-to-noise ratio, contrast-to-noise ratio, and the presence of image artefacts.

An initial volumetric analysis will be made by the imaging platform and the results provided to investigators. These analyses will include volumetric analysis of hippocampal volume, ventricle volume, as well as 26 different volumes of interest using Signal amplification by reversible exchange (SABRE), and Lesion Explorer. Additional measurements are planned to include number of microbleeds, regional measurements of diffusional fractional anisotropy and mean diffusivity, and resting-state network connectivity.

The structural images are reviewed by a board-certified neuroradiologist to detect any incidental findings or exclusion pathology.

Neuropathology

Neuropathology provides the diagnostic gold standard against which the clinical and neuroimaging diagnoses are tested. Such confirmation has not yet been replaced by other diagnostic approaches because recent data indicate that more than 10% of patients entering clinical trials for treatment of AD suffer from other conditions. Beyond the categorical diagnosis, the neuropathological assessment will also document the extent to which multiple neurodegenerative pathologies are present over and above the primary diagnosis. The extent of concomitant vascular disease will also be evaluated. Autopsies will be performed at the local sites, and the neuropathological diagnosis rendered would be entered in the history. Fixed or paraffin-embedded tissue blocks, as well as a limited sample of frozen brain tissue, will be sent to a central laboratory where they will be subjected to uniform staining. After scanning the slides, evaluation will be performed by two different neuropathologists and the diagnosis and quantitative assessment of lesion load will be entered into the database. In this way, the clinical and research use of the autopsy is entirely separate. The fixed and frozen tissue samples will also be made available for further analyses (e.g. genomic, epigenetic, proteomic, metabolomics research to study the molecular pathology underlying neurodegeneration). In addition, the digital slides constitute an inexhaustible resource that can be distributed to as many researchers as necessary.

Neuroinformatics

All data collected across all assessments will be deidentified and uploaded into a central database, Brain-CODE, including MRI and SDOCT images, and will be analyzed across modalities and cohorts using mixed models to identify common and unique predictors of cognitive decline across the five neurodegenerative diseases. Where appropriate, we will use propensity-weighted multivariate regression analysis (which accounts for different sources of selection bias in observational studies) and also partial least squares regression (given limited sample size and multi-collinear variables in some analyses).

Discussion

ONDRI is a unique, prospective multimodality study to improve understanding of the pathogenesis of neuropsychological deficits across a broad range of neurodegenerative disorders (Figure 2). Beyond this, ONDRI has already facilitated the development of standardized assessment protocols, which will allow for direct comparisons to be made across a range of neurodegenerative and neurovascular disorders. These tools will allow for a systems-based approach to identify not only unique clinical, imaging, ocular, genetic, and other biological markers associated with each of these disorders, but also to define where...
there are significant biological overlaps. Although the numbers of patients being studied is small (600) relative to larger prospective studies, patients enrolled in ODNRI will be a unique resource because they will be deeply endophenotyped and their deidentified data publicly available by request through the ODNRI publications and data analysis committee.

Current therapeutic approaches in neurodegenerative diseases, where available, tend to be directed towards single biological mechanisms that may be inadequate given the complexity of these multifaceted diseases in addition to the spectrum of mechanisms by which neurodegeneration is expressed.33 Through this integrated discovery approach, we have the unique opportunity to identify multiple markers of brain health that will contribute to the development of: (1) biomarkers for neurodegenerative diseases that may ultimately be used in the identification of presymptomatic individuals; (2) improved identification of overlap syndromes amongst neurodegenerative diseases for both clinical and research purposes; and (3) personalized treatments, which may require a “cocktail” similar to the approach that has been applied in cancer, and are likely to be more efficacious in halting disease progression than current drug regimens.34 These may vary depending on the stage of the disorder being treated, the genetic predispositions discovered to be contributing to an individual’s disease, and the possible role of mixed pathologies. Hence, this well-structured and integrated longitudinal exploratory study has the potential to contribute to significant effects on health care in the rapidly growing area of neurodegenerative and neurovascular diseases.

Finally, the nature of ONDRI is such that the data obtained will be made available to the wider scientific community as well as ultimately federated with data arising from a range of other studies currently examining neurodegenerative disorders, including comparative cohort studies just getting underway in Canada such as the Brain Eye Amyloid Memory study (www.tdra.ca) and the Canadian Consortium on Neurodegeneration in Aging (www.ccna-ccnv.ca).

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DISCLOSURES

The authors do not have anything to disclose.

SUPPLEMENTARY MATERIAL

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